Surgical treatment strategies of chronic subdural hematoma

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In loving memory of my mother.

ABSTRACT

Background: A subdural collection of old blood is called a chronic subdural hematoma (cSDH). A cSDH of sufficient volume becomes symptomatic and neurosurgical evacuation is then necessary. The recurrence rate (5-21%) after surgery is high and evidence-based guidelines regarding the optimal treatment to diminish recurrence is lacking. The aim of this thesis was to explore whether different irrigation fluid temperatures used in cSDH-surgery as well as different postoperative drainage times had an impact on recurrence, mortality or complication frequency.

Patients and Methods: Adult patients undergoing burr-hole evacuation for cSDH were screened for study inclusion. Study I retrospectively compared the intraoperative use of irrigation fluid at room temperature vs. irrigation at body temperature. Endpoints were recurrence, mortality, and complications. Paper II is the study protocol for study III. Study III was a multicentre randomised controlled trial (RCT) in which we compared irrigation at room temperature vs. body temperature. The endpoints were the same as in study I but with the addition of health-related quality of life (HRQL). Study IV was a retrospective study exploring postoperative drainage times of more or less than 24 hours after cSDH-surgery. The endpoints were length of hospital stay, recurrence, complications, and mortality. All studies had a follow-up of 6 months. In study IV, a separate cohort consisting of 10 patients were also prospectively observed regarding drainage volume per hour after surgery.

Results: Both study I and III demonstrated a significant reduction of recurrence when irrigation fluid at body temperature was used compared to irrigation at room temperature. No significant difference was seen regarding HRQL, complications or mortality. The retrospective cohort of study IV showed no difference between the study groups related to recurrence, complications or mortality. However, length of hospital stay was significantly shorter in the group with < 24 hours of drainage. The prospective cohort in study IV revealed that most drainage occurred within 9 hours after burr-hole evacuation for cSDH.

Conclusion: The results from study I and III provide high level evidence that irrigation fluid at body temperature is superior to irrigation at room temperature in the surgical evacuation of cSDH. Study IV showed that a drainage time < 24 hours did not lead to more cases of recurrence, mortality or complications compared to a drainage time > 24 hours. Length of hospital stay was reduced with a drainage time of less than 24 hours. Evidence from a RCT is needed to confirm the results of study IV.

Keywords: chronic subdural hematoma, irrigation, recurrence, temperature, drainage time, drainage duration, surgery

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Ett kroniskt subdural hematom (kSDH) är en ansamling mellan hårda hjärnhinnan (dura mater) och hjärnan som består av gammalt blod och vätska. Om ett kSDH uppnår en tillräcklig volym utövar det ett tryck på den underliggande hjärnan och symptom uppstår. Det är en sjukdom som framför allt drabbar personer som är äldre än 65 år. Den neurokirurgiska behandlingen består vanligen av att man anlägger 1–2 borrhål i kraniet och spolar ut blödningsvätskan med hjälp av spolvätska. För att minska risken för återfall anläggs även ett drän, vilket möjliggör fortsatt dränage av vätska efter operation. Risken för återfall som kräver reoperation är dock fortsatt hög, uppskattningsvis 5–20 %. Varje reoperation innebär inte bara ökade risker och obehag för den enskilda patienten utan även en ökad belastning för sjukvården. Operation för kSDH är ett av de vanligaste neurokirurgiska ingreppen som utförs och antalet fall i befolkningen med kSDH förväntas öka ytterligare. Riktlinjer baserade på forskning med hög evidensgrad saknas för flera områden rörande behandling av kSDH. Det gör att man idag inte kan säga vad som är den bästa behandlingsstrategin för att få så få återfall som möjligt.

Metod

I denna avhandling undersöktes två olika aspekter av kirurgisk teknik vid operation för kSDH hos vuxna patienter; dels olika spolvätsketemperaturer under operation dels en dräntid längre eller kortare än 24 timmar efter operation. I delarbete I och III jämfördes kroppsvarm med rumsvarm spolvätska som används under operation för att spola ut ett kSDH. Utfallsmåtten var återfall (reoperation), dödlighet och komplikationsfrekvens under en uppföljningstid på 6 månader. Delarbete I utfördes som en retrospektiv (tillbakablickande) studie vid Sahlgrenska Universitetssjukhuset. Delarbete II är studieplanen för studie III. Delarbete III utfördes som en prospektiv (framåtblickande) studie där patienterna randomiserades (slumpmässig tilldelning av behandling) mellan kroppsvarm och rumsvarm spolvätska i samband med operation. Studie III utfördes vid Sahlgrenska Universitetssjukhuset (Göteborg), Akademiska sjukhuset (Uppsala) och Karolinska Universitetssjukhuset (Stockholm). Delarbete IV, utförd vid Sahlgrenska Universitetssjukhuset, var en retrospektiv studie där en dränagetid kortare än 24 timmar jämfördes med en dränagetid längre än 24 timmar. Utfallsmåtten var antal vårddygn på sjukhus, dödlighet,

komplikationer och återfall. Som ett tillägg i studie IV observerades även dränmängden per timma efter kSDH operation hos en mindre grupp patienter prospektivt efter operation.

Resultat

I delarbete I påvisade vi en lägre återfallsfrekvens (4,5 % jämfört med 13,1 %) när kroppsvarm spolvätska användes jämfört med rumsvarm. Dessa resultat bekräftades i studie III där patienter lottades mellan behandling med kroppsvarm eller rumsvarm spolvätska under operation. 541 patienter hade en fullständig uppföljning efter 6 månader. Återfallsfrekvensen skiljde sig tydligt och var 6 % i gruppen med kroppsvarm spolvätska jämfört med 14 % i gruppen med rumsvarm spolvätska. Dödligheten och antalet komplikationer skiljde sig inte åt mellan grupperna med olika spolvätsketemperatur, varken i studie I eller III. Studie IV visade att en dräntid kortare än 24 timmar inte resulterade i fler återfall, dödsfall eller komplikationer jämfört med en dräntid längre än 24 timmar. Dock var vårdtiden kortare i gruppen med en dräntid kortare än 24 timmar (2,7 jämfört med 3,6 vårddygn). Dränmängden per timma hos 10 patienter som genomgått operation för kSDH observerades även. Resultaten från denna mindre observationsstudie visade att nästan allt dränage skedde inom de första timmarna efter operation, vilket i sin tur stödjer de retrospektiva fynden.

Slutsats

De kombinerade resultaten från studie I och III gör att man med högsta vetenskapliga bevisvärde kan säga att kroppsvarm spolvätska bör användas i stället för rumsvarm spolvätska vid urspolning av kSDH, då det tydligt minskar andelen återfall. Resultaten från studie IV antyder att en dräntid kortare än 24 timmar är tillräckligt vid behandling av kSDH. Dock behöver de retrospektiva resultaten från studie IV bekräftas genom en kontrollerad randomiserad studie innan någon behandlingsrekommendation kan ges.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Bartley A, Jakola A S, Tisell M. The influence of irrigation fluid temperature on recurrence in the evacuation of chronic subdural hematoma. Acta Neurochirurgica (Wien). 2020; 162(3): 485-8

II. Bartley A, Jakola A S, Bartek Jr J, Sundblom J, Förander P, Marklund N, Tisell M. The Swedish study of Irrigation-fluid temperature in the evacuation of Chronic subdural hematoma (SIC!): study protocol for a multicenter randomized controlled trial. Trials. 2017; 18(1): 471

III. Bartley A, Bartek Jr J, Jakola A S, Sundblom J, Fält M, Förander P, Marklund N, Tisell M. Effect of irrigation fluid temperature on recurrence in the evacuation of chronic subdural hematoma – a randomized clinical trial. Manuscript, accepted for publication in JAMA Neurology (Sept 23, 2022).

IV. Bartley A, Hallén T, Tisell M. A drainage time of less than 24 hours is sufficient after chronic subdural hematoma evacuation. Manuscript, submitted to Acta Neurochirurgica (Oct 3, 2022).

CONTENT

ABBREVIATIONS

aSDH	acute Subdural Hematoma
ACE	Angiotensin Converting Enzyme
Ang	Angiopoietin
BHC	Burr-Hole Craniostomy
BT	Body Temperature
CI	Confidence Interval
CRF	Case Report Form
cSDH	chronic Subdural Hematoma
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DBC	Dural Border Cells
GCS	Glasgow Coma Scale
HRQL	Health Related Quality of Life
HU	Houndsfield Unit
ICP	Intracranial Pressure
IL	Interleukin
iNPH	idiopathic Normal Pressure Hydrocephalus
INR	International Normalised Ratio
LDT	Long Drainage Time
LP	Lumbar Puncture

MMA	Middle Meningeal Artery
MRI	Magnetic Resonance Imaging
NOAC	New Oral Anticoagulants
OR	Odds Ratio
PCC	Prothrombin Complex Concentrate
PlGF	Placental Growth Factor
RCT	Randomised Controlled Trial
RT	Room Temperature
SD	Standard Deviation
SDT	Short Drainage Time
TDC	Twist Drill Craniostomy
TGF	Transforming Growth Factor
TXA	Tranexamic Acid
VEGF	Vascular Endothelial Growth Factor

1 INTRODUCTION

A chronic subdural hematoma (cSDH) is a collection of old blood and degrading blood products located in the subdural space. In contrast to an acute subdural hematoma (aSDH), where an acute haemorrhage causes fresh blood clots to fill up the subdural space, a chronic subdural hematoma is largely liquified and has often progressed slowly over time. The exact definition of when a subdural hematoma can be termed chronic is not uniformly defined but the cSDH is usually at least 2-3 weeks old. From a pathophysiological aspect the formation of membranes that encapsulate the hematoma may define when the hematoma becomes a chronic subdural hematoma [1].

Historically, the first detailed description of a cSDH was made by Johann J. Wepfer in 1675, recognizing it as a "serum accumulation" under the dura mater in two postmortem cases [2]. In an often-cited publication from 1857 by Rudolph Virchow, inflammation was identified as a possible mechanism in cSDH pathophysiology. However, he did not recognize trauma as a potential trigger but instead thought that the inflammation was caused by infection and termed the condition "pachymeningitis haemorragicha interna" [3]. Wilfred Trotter on the other hand stressed the traumatic origin in a publication from 1914 [4].

Chronic subdural hematoma is one of the most frequent afflictions treated in neurosurgical practice and is typically seen in elderly (> 65 years) patients. Despite being so common many areas of controversy remain regarding the optimal management and there are still considerable differences regarding the treatment strategies employed. Recurrence after surgery in need of reoperation is still a clinical challenge with an estimated range between 5-21 % [5]. Improved guidelines based on level I evidence (evidence from at least one large randomised controlled trial) are needed to optimize treatment of cSDH. The focus of this thesis is mainly different surgical strategies used in cSDH treatment and the evidence supporting them.

1.1 Epidemiology

Patients requiring surgical treatment due to cSDH are seen almost daily in neurosurgical practice. In 1992 Kudo *et al* explored the incidence of cSDH in a large Japanese cohort and found an overall incidence of 13 per 100.000 persons per year. The highest incidence was seen in patients older than 65 years, with an incidence of 58 per 100.000 persons per year [6].

More recent studies clearly show that the incidence of cSDH has increased. A Finnish study from 2019, exploring a cohort of more than 1000 patients, revealed that the overall incidence had doubled the last 25-30 years from 8.2 to 17.6/100.000/year. In the oldest age group with patients older than 80 years, the incidence had almost tripled [7]. Similarly, in a study of cSDH incidence among U.S veterans such high rates as 79.4/100.000/year were found. However, the U.S veteran population showed a 10-fold difference in comparison to the general US population, probably due to increased risk factors in the former group. Regardless, a prediction model from the same study estimated an incidence of 17 per 100.000 in the general US population by the year 2030 [8]. In a study from North Wales the difference in incidence of cSDH in patients older than 65 years was explored. The authors found an increased incidence of 48/100.000/year in 2017 compared with 8.2/100.000/year in 2002 [9]. Furthermore, in Sweden the number of surgeries for cSDH has doubled in the last 18-20 years [10].

Mainly two factors have been identified explaining the increase of cSDH. The first factor is demographic changes with an ageing population. The world population older than 80 years is expected to triple until the year 2050 [11]. The second factor is the increased use of anticoagulant and antithrombotic medications. Approximately 40-60 % of patients with cSDH are on these medications [12]

It is well known that there is a male predominance of cSDH with a 3:1-4:1 male-to-female ratio [6, 7, 13, 14].

1.2 Clinical presentation

If a cSDH progresses and reaches a large enough volume it will become symptomatic. Depending on how fast the cSDH is expanding, it can take days to several weeks before onset of symptoms. The symptoms are either caused by direct compression of the brain (mass effect) and/or raised intracranial pressure (*Figure 1*). Symptoms of cSDH can be diverse and can often be seen in combination. The clinical panorama of symptoms ranges from minimal symptoms to coma and death.

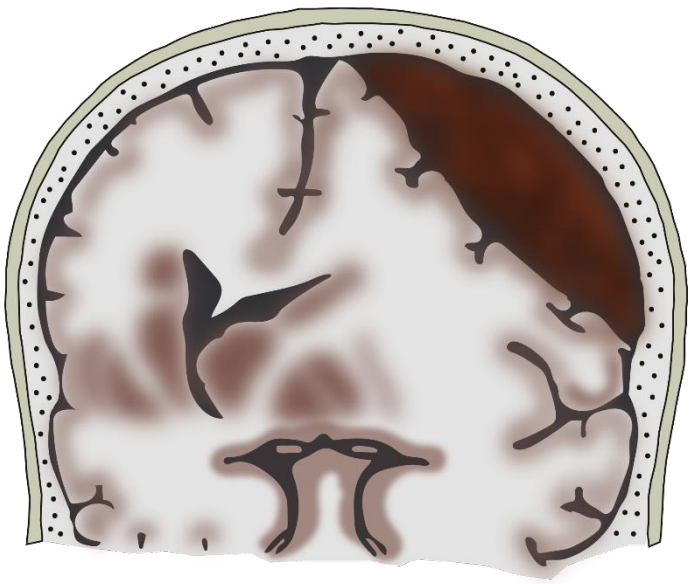

Figure 1. Coronal animation of a chronic subdural hematoma causing significant mass effect with compression of the brain and secondary midline shift. © Victoria Edström Bartley.

In an often-cited randomised controlled trial (RCT) by Santarius *et al* presenting symptoms of more than 250 adult patients were registered at study inclusion [15]. In a retrospective study from Norway by Bartek *et al* preoperative symptoms were registered and compared between the age groups 18-49 and > 50 years in over 1000 patients [16]. Rauhala *et al* also retrospectively registered symptoms at admission of 965 patients undergoing

cSDH surgery in Finland [17]. Some common symptoms of cSDH and their frequency based on these studies are listed below:

Headache

Headache is probably caused by increased intracranial pressure due to mass effect from a cSDH. Rauhala and colleagues reported a 32 % frequency of headache prior to surgery [17]. Bartek *et al* found an overall occurrence of headache in 40 % of patients. A higher prevalence of 87 % was seen in the younger age group (18-49 years) compared with 38 % in patients older than 50 years [16]. Younger people have less space between the dura mater and the brain compared to older people related to normal physiological brain atrophy in the latter group [18]. This explains why cSDH in younger patients more rapidly causes raised intracranial pressure and related headache. Younger people can often present with only headache and are more at risk of rapid deterioration [19].

Disorientation

A newly developed disorientation was reported in 21-33 % of cases [15-17]. As one might expect elderly patients seem to be more susceptible, and confusion was less prevalent (11.5 %) in patients younger than 50 years [16].

Gait disturbance

Gait disturbance or postural instability is a common finding in patients with symptomatic cSDH with a frequency in the range of 38-57 % [15-17]. The gait disturbance may lead to repeated falls that in turn aggravates the cSDH.

Paresis

Paresis of the extremities is also a very common symptom of cSDH with a reported preoperative frequency of 35-45 % [15-17].

Dysphasia

Speech difficulties most often occur with a cSDH causing compression of the left cerebral hemisphere, since 95 % of the general population have a left sided dominance for language [20, 21]. Preoperative dysphasia was seen in 6 % of patients in the Santarius cohort in comparison with 24-26 % in the studies by Bartek *et al* and Rauhala *et al* [15-17]. However, in patients younger than 50 years Bartek *et al* found a lower dysphasia occurrence of 5.8 % [16].

Seizure

Preoperative seizures seem to be relatively rare. Bartek *et al* and Santarius *et al* report a low frequency of 1-3 % while Rauhala *et al* report a somewhat higher frequency of 9.2 % [15-17].

Decreased level of consciousness

The Glasgow Coma Scale (GCS), originally described in 1974 by Teasdale and colleagues is most often used for assessment of coma and decreased consciousness (*Appendix A1*) [22]. Few patients with cSDH are unconscious (GCS 3-8) at admission with a reported frequency of 3-7 % [15-17]. A GCS score of 9-12 were seen in 7-12 % [15-17]. Accordingly, the majority (> 80 %) of patients presented awake with a GCS of 13-15 [15-17].

The Markwalder grading scale was introduced in 1981 and can be used to classify the severity of symptoms caused by cSDH (*Table 1*) [23].

Table 1. The Markwalder grading scale of symptom severity.

Grade	Symptom severity
0	Neurologically normal
1	Alert and oriented; mild symptoms such as headache, absent or mild neurological deficit, such as reflex asymmetry.
2	Drowsy or disoriented with variable neurological deficit, such as hemiparesis.
3	Stuporous but responding appropriately to noxious stimuli; severe focal signs, such as hemiplegia.
4	Patient comatose with absent motor responses to painful stimuli; decerebrate or decorticate posturing.

Adapted from Markwalder, T.M., et al., *The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage.* J Neurosurg, 1981. **55**(3): p. 390-6.

1.3 Pathophysiology

The understanding of the pathophysiology involved in cSDH formation and progression has evolved from a simplistic view that cSDH expansion is merely caused by repeated bleeding from bridging veins to a complex process involving inflammation, angiogenesis, and fibrinolysis [24, 25].

The so called dural border cells (DBC) seem to be the Achilles heel involved in cSDH formation. This cell layer creates the innermost layer of the dura mater. The DBC consist of flattened fibroblasts with little extracellular collagen and few intracellular connections making the cell layer vulnerable to separation [26, 27]. The subdural space does not normally exist but is a potential space created when the DBC layer is split.

It has been postulated that the triggering event, cleavage of the DBC layer, can occur in two ways. The first is that a haemorrhage occurs within the DBC, which is the same as an acute subdural hematoma (aSDH), and that it precedes the formation of a cSDH. The bridging veins are thinnest where they traverse the DBC [28]. The second mechanism is that splitting of the dural border cells happens without evidence of bleeding. Instead, it is thought that there is ingress of cerebrospinal fluid (CSF) from the adjacent arachnoid space into the DBC (this is also called a subdural hygroma) [19, 24, 29]. In the vast majority of cSDH collections CSF can be detected [30]. The traumatic event involved in the second mechanism can probably be minimal, which might explain why many cSDH patients do not remember a prior trauma [17, 31, 32]. The second mechanism seem to be the more common. As shown in previous studies, only 18-20 % of aSDH eventually transform to a cSDH [33-36]. In a recent study by Edlmann *et al*, baseline imaging with computed tomography (CT) was studied in a cohort of 41 patients who eventually developed cSDH after trauma and 63 % had no sign of bleeding on their initial CT [29]. Interestingly, cSDH that transforms from an aSDH seem to progress more rapidly than cSDH without signs of prior bleeding, with symptoms occurring within 1-3 weeks in the former group compared to approximately 8 weeks in the latter [29].

Regardless of the initial event causing splitting of the dural border cells, an inflammatory response follows in an effort to heal the damaged cell layer. The dural border cells start to proliferate and inflammatory cells are recruited to the area. The proliferation and activation of dural border cells lead to fibrin exudation, in turn leading to the formation the inner and outer neomembranes characteristic for a cSDH [24, 25]. The expression of transforming growth factor (TGF-β) by eosinophils seems to be fundamental for driving the persisting fibrosis that forms membranes [37]. The outer membrane, in contrast

to the inner membrane, appears to be driving the progression of cSDH. The inner membrane mostly consists of collagen and fibroblast while the outer membrane in addition contains many types of inflammatory cells [24].

In an expanding cSDH there is an exaggerated inflammatory response with an uneven balance between anti-inflammatory and pro-inflammatory cytokines, with more of the latter [38]. The overall cytokine levels in fluid from cSDH is clearly elevated compared to serum levels [24, 39]. The inflammatory process is complex with many mediators involved, including many different cytokines. The individual contribution of these factors to cSDH pathophysiology is hard to determine but some of them are worth mentioning as they play an apparent role in the progression of cSDH. Interleukin-6 (IL-6) is an important pro-inflammatory cytokine released by many cells. IL-6 activates fibroblasts and thereby is an activator of the pathological membrane formation seen in cSDH [40]. In addition, IL-6 increases the vascular permeability of newly formed vessels in the outer membrane [41]. IL-8 is often released at the same time as IL-6 and is a potent neutrophil attractant but is also involved as an important mediator of angiogenesis [24, 42].

Furthermore, the inflammatory cells in the outer membrane also produce several other potent angiogenic factors such as vascular endothelial growth factor (VEGF), angiopoietin-2 (Ang-2), and placental growth factor (PlGF) leading to the sprouting of immature vessels in the outer membrane [24, 25]. These vessels are both prone to recurrent microhaemorrhages but are also "leaky" due to an induced increased vascular permeability by VEGF and IL-6 [41, 43, 44]. This explains why a cSDH may expand both via rebleeding but also exudation from the immature vascular bed of the outer membrane.

In addition to the inflammation and angiogenesis taking part in the expansion of a chronic subdural hematoma, there is also a state of increased fibrinolysis [24]. Fibrinolysis promotes clot breakdown and sustains intermittent bleeding from the outer membrane into the subdural space. Several factors of fibrinolysis are elevated in chronic subdural hematomas such as plasminogen, thrombomodulin and degradation products of fibrin [24, 45]. Ito and colleagues proved that sporadic bleeding indeed occurs within a cSDH, using labelled erythrocytes [46].

Age may influence several of the mechanisms described above. Newly formed vessels in the elderly often show signs of immaturity and decreased stability as seen in the vascular bed of the outer membrane [25]. Old age also influences the inflammatory response, often as an exaggerated inflammation with an overexpression of IL-6 [25, 47].

To recapitulate this complex multifactorial process: if the initial inflammatory response and subsequent repair of the damaged dural border cell layer would be successful no progression towards a large cSDH would happen. However, in an expanding cSDH a sustained vicious cycle of inflammation, fibrinolysis and angiogenesis occurs (*Figure 2*).

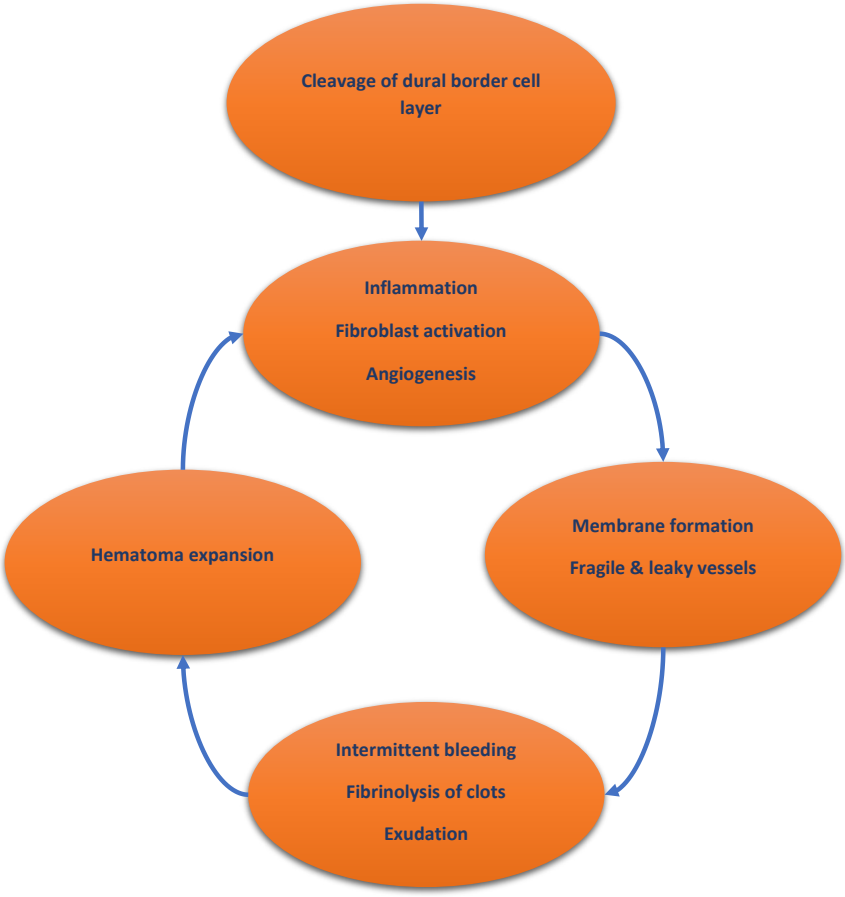

Figure 2. The vicious cycle of cSDH-progression.

1.4 Diagnostic imaging

The main modality for diagnosing cSDH is a CT without contrast enhancement. The most common form of cSDH is a hypodense (< 30 Hounsfield units, HU) subdural collection. However, isodense (30-60 HU, similar to the brain parenchyma) and cSDH with hyperdense parts (> 60 HU) are also seen [48]. The presence of membranes can often be detected by CT as well. Nakaguchi *et al* have proposed four different categories of cSDH seen on CT; homogenous, trabecular, laminar, and separated [49]. Some examples of different CT appearances are shown in *Figure 3.*

The hematomas are bilateral in approximately 20 % of cases [7, 15, 16, 32]. The role of magnetic resonance imaging (MRI) in clinical practice is mainly to differentiate a cSDH from an infection with a subdural collection of pus (empyema) [50].

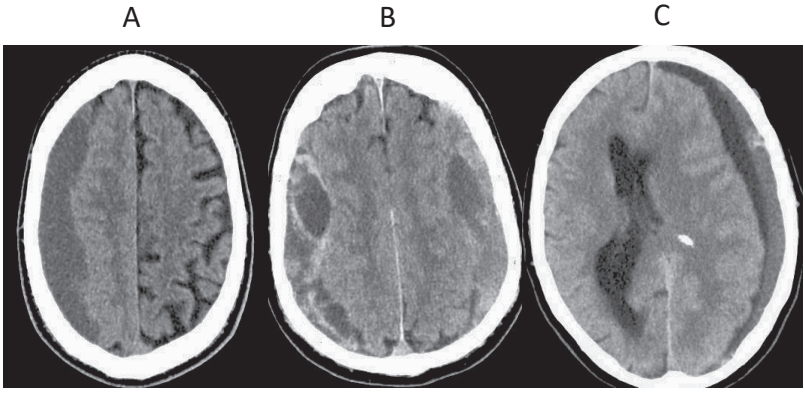

Figure 3. Examples of different CT appearances of cSDH. A) homogenous hypodense B) Trabecular/membranous with several visible membranes C) Separated, a membrane separates the cSDH into two compartments with a hypodense and an isodense part.

1.5 Risk factors

A variety of risk factors have been associated with cSDH formation, the most common are listed below:

Age

Advanced age is a strong risk factor for cSDH. As previously discussed in the epidemiology section (subchapter 1.1), chronic subdural hematoma occurs most often in elderly people with an estimated mean age of 70-76 years [7, 9, 15, 16, 19, 51]. One possible cause is physiological atrophy of the brain related to increased age. In turn, this puts the bridging veins running between the brain surface and the dura under traction, making them more susceptible to rupture. Furthermore, the disproportion between the brain and the skull caused by atrophy probably also increases the risk of splitting the dural border cell layer even without haemorrhage [18, 19, 28].

Sex

Men account for the majority of cSDH patients [5-7, 9, 13, 14, 16, 51]. The higher proportion of males is not entirely clarified. A possible explanation could be increased exposure to trauma seen in the male population and/or the higher frequency of alcohol abuse compared with women [14, 52]. However, this was disputed in a study by Marshman *et al* who found no significant difference between men and women regarding trauma exposure, alcohol abuse or cerebral atrophy in a cohort of 155 cSDH-patients [53]. Studies of differences between men and women regarding age-related brain atrophy investigated with MRI have to date showed ambiguous results [54]. Oestrogen has been demonstrated to have anti-inflammatory properties and may thereby play a role in reducing the risk of cSDH in women [25, 55, 56].

Trauma

A history of trauma can be recollected by a majority (50-75 %) of patients with symptomatic cSDH [17, 31, 32]. However, the trauma triggering the development of cSDH might be so trivial that it is not remembered. Trauma due to falls is the most common form of injury mechanism seen in patients with cSDH [32, 57].

Alcohol abuse

Alcohol abuse may increase the risk of cSDH in three different ways. Firstly, alcoholism is a known cause of cerebral atrophy [58, 59]. Secondly, exposure to trauma is more frequent with alcohol use [60, 61]. Finally, alcohol can cause impaired coagulation [62, 63].

Antithrombotic medications

Together with an aging population the common use of antithrombotic medications is believed to explain the increased occurrence of cSDH. It is estimated that 40-60 % of patients suffering from cSDH are on these medications [12, 16, 32, 64]. Although these medications are also common in the same age group of the general population, several studies have verified that patients with anticoagulant and antithrombotic medications have an increased risk of developing cSDH [12, 64-66].

Intracranial hypotension

States that cause low intracranial pressure increase the risk of cSDH due to a relative lack of cerebrospinal fluid (CSF). This in turn causes the brain to displace caudally from the cranial vault. Analogous to what happens in brain atrophy, this puts the bridging veins under stretch and increases the risk for cleavage of the dural border cell layer. A CSF leak leading to a cSDH can be either iatrogenic (most often after surgery) or spontaneous, but seems to be a rather rare cause of cSDH [67]. However, it might be more common in the younger age group than in geriatric patients. In a rather small study of 27 nongeriatric patients with cSDH a spinal CSF leak was found in 25 % of cases [68]. Much more common is cSDH caused by overdrainage of CSF by shunts. 5-10 % of patients shunted for idiopathic normal pressure hydrocephalus (iNPH) develop cSDH [69-71]. In contrast, chronic subdural hematomas after lumbar puncture (LP) seem to be very rare and in a study by Zetterberg *et al* no cases were seen in over 1000 patients undergoing LP [72].

1.6 Surgical treatment

Surgery is the main modality used for treatment of cSDH. There is little controversy that patients with symptoms correlating with a cSDH causing mass effect are candidates for surgical treatment. Small asymptomatic cSDH can often be treated conservatively with a watch-and-wait strategy with vigilance of eventual symptoms developing.

Many areas of controversy remain regarding the optimal surgical treatment strategy. Despite being such a common entity in neurosurgical practice, treatment recommendations based on level I evidence (good quality RCT-studies) are still few. Three different surgical methods are mainly used today; twist drill craniostomy (TDC), burr-hole craniostomy (BHC) and mini-craniotomy [19].

Optimization of coagulation prior to surgery

Since 4-6 out of 10 cSDH patients are on antiplatelet or anticoagulant therapy it is often necessary to optimize the coagulation prior to surgery [12]. If the patient has mild symptoms (Markwalder grade 1) the best strategy to normalise coagulation is often to delay surgery.

For new oral anticoagulants (NOAC) the recommendation is to delay surgery for at least 24 hours, and for at least 48 hours if the patient has renal failure [73]. If surgery cannot be postponed due to more severe symptoms PraxBind, an antidote for Dabigatran (PraDaxa), can be used for immediate reversal. Since there are no specific antidotes for the other NOACs, administration of prothrombin complex concentrate (PCC) is proposed in these cases instead [73]. For non-urgent surgery in patients on vitamin K antagonists (such as Warfarin) delaying surgery for at least 2-3 days with subsequent checking of the international normalised ratio (INR) is recommended. If needed the administration of vitamin K can normalise the INR more quickly and in urgent cases the addition of PCC is recommended for direct reversal [74, 75]. Regarding antiplatelets the recommendation is to defer surgery for 5-10 days in non-acute cases [19]. Platelet transfusion is warranted in cases in need of urgent surgery [76].

Twist drill craniostomy (TDC)

This method was first described in 1977 in a cohort of 21 patients [77]. In TDC a small opening (< 2 mm) is made in the cranium with a handheld drill. One of the main advantages of this method is that it can be performed at the bedside

using local anaesthetic [77]. The procedure is combined with the insertion of a subdural catheter connected to a closed system drainage. A disadvantage of the original method was that it involved the blind placement of a subdural drain, which in turn increased the risk of brain laceration and bleeding [78]. However, improvements of the technique have been made with the insertion of hollow screws in the cranium instead of the subdural drain, thereby preventing the risks of blind catheter placement [79].

Burr-hole craniostomy (BHC)

In BHC 1-2 burr-holes (10-30 mm) are drilled in the cranium over the maximum width of the hematoma. There seems to be no difference regarding recurrence between using one or two burr-holes, according to a meta-analysis of a large cohort of cSDH-patients [5]. After the burr-holes have been placed, a durotomy is made and the subdural space is often rinsed with irrigation fluid until the return of fluid looks clear. Finally, a postoperative drain is placed either in the subdural space or in a subgaleal location [15, 19, 80]. The procedure is performed in the operating theatre. However, the procedure can be done under conscious sedation combined with local anaesthesia as an alternative to general anaesthesia. BHC gained popularity in the neurosurgical community after a publication by Markwalder *et al* in 1981, describing its use as a successful alternative to the larger craniotomies that previously had been performed in cSDH surgery [67]. Currently, BHC seems to be the most commonly used technique for cSDH evacuation [19, 81, 82].

Mini-craniotomy

In contrast to the large craniotomies used historically for cSDH evacuation, a mini-craniotomy with a bone flap of less than 30 mm has gained interest as an alternative to TDC and BHC [83, 84]. The procedure can be combined with intraoperative irrigation and a postoperative drain. An advantage of the technique is the better visualisation provided compared with BHC and TDC. This facilitates the evacuation of hematoma compartments that are separated by membranes. Disadvantages may be a longer operating time and longer hospital stay [85]. The benefits of performing an extensive membranectomy during the procedure has been debated. However, current evidence does not support extensive membranectomy due to the increased risk of bleeding from the membranes [86, 87].

Comparison of surgical techniques

Relatively few studies have compared TDC, BHC and craniotomy and recommendations are limited due to the lack of level I evidence. Weigel *et al* reviewed the three different surgical techniques and concluded that TDC had a significantly higher recurrence rate (33 %) compared to BHC (12.1%) and craniotomy (10.8 %). They also found a significantly increased morbidity for craniotomy (12.3 %) compared to TDC (3 %) and BHC (4 %). No difference in mortality between the three methods was seen. Weigel *et al* concluded that BHC is to be recommended due to the best ratio between cure and complications [88]. In a review by Ducruet and colleagues significantly lower recurrence rates for BHC (11.7 %) compared with TDC (28 %) and craniotomy (19 %) were described. However, they also found a significantly higher complication frequency for BHC (9.3 %) compared with TDC (2.5 %) and craniotomy (4 %). Despite the finding that BHC had the lowest recurrence rate, the authors suggested TDC to be the primary treatment choice due to the lower complication rate. In addition, they proposed craniotomy as the primary choice for trabecular/membranous cSDH [89].

In a meta-analysis of 34.829 patients by Almenawer *et al*, significantly more complications associated with craniotomy was demonstrated with a higher relative risk (RR 1.39, 95 % CI 1.04-1.74) compared with BHC and TDC. No significant difference in recurrence rate or mortality were seen between the three techniques. However craniotomy proved to be more effective than TDC and BHC in treating recurrences of cSDH [5]. Lega *et al* performed a decision analysis model (Monte Carlo utility simulation) comparing all three surgical techniques. The analysis supported BHC as the best choice due to a significantly higher utility rating giving BHC the best ratio between recurrence and complications [90].

To conclude, the results from the studies described above are ambiguous and the meta-analyses and reviews are also limited by the lack of level I evidence. Another limitation is that craniotomy in these studies is not uniformly defined and could be a bone flap of varying size. Furthermore, there is also a variation in measures and definitions of outcome between different studies. Put together, this limits the evidence-based conclusions and recommendations that can be made regarding the choice of surgical technique. Interestingly, a multicentre RCT from Belgium comparing TDC, BHC and mini-craniotomy has been published as recently as 2022 [91]. The authors found no difference regarding the frequency of recurrence, complications, or mortality between the three treatment modalities. The recurrence rate was 13.1 % for mini-craniotomy, 7.6 % for BHC and 19.5 % TDC. The difference was not statistically significant

(p=0.07) [91]. However, there are some limitations of the study. Firstly, the follow-up time for the outcome measures was only 30 days. Secondly, the study seems to have a too small sample size to provide enough statistical power. For the 3-arm comparison in the study the total sample size was only 250 patients [91]. Therefore, more RCT-studies comparing the surgical techniques are needed.

Postoperative drains

In contrast to which surgical method is optimal for cSDH treatment, the evidence for using a postoperative drain is solid. An often-cited RCT by Santarius *et al* provided level I evidence that the use of a postoperative drain after cSDH evacuation leads to fewer recurrences. The reported recurrence was reduced from 24 % in patients without a drain to 9 % with a drain [15]. These findings have since then been supported by other studies and meta-analyses [5, 92, 93]. A post-hoc analysis of the same cohort as in Santarius study showed that long-term survival was improved 5 years after surgery for the drain group, however after 10 years there was no difference of survival detected between the two groups [94].

The drain used after cSDH-surgery can either be placed as a passive (without suction) subdural drain or as a subgaleal/subperiosteal drain. The latter can be either passive or active (with suction) [80]. In a retrospective study investigating risk factors for recurrence, subgaleal drains were associated with higher rates of recurrence compared with a subdural drain. It was not stated in the study if the subgaleal drain was with suction or without suction [95]. A recent multicentre RCT by Soleman *et al,* in which the two drain types were compared, significantly less complications were found for the subgaleal/subperiosteal drain type. In addition, the authors also found fewer recurrences in the subgaleal/subperiosteal group (8.3 %) compared with the subdural drain group (12 %), however the study had a predefined non-inferiority criterion that was not met for the difference in recurrence [96]. In a study by Gazzeri and colleagues no significant differences between the different drain types regarding recurrence were found [97]. In contrast, in a meta-analysis by Greuter *et al* a significant difference with more cases of recurrence as well as drain misplacement was found when subdural drains were used [98]. Put together, subgaleal/subperiosteal drains seem to be at least as effective as subdural drains but with less complications.

The optimal duration of drainage after cSDH surgery is an area of debate. A drain duration of at least 24-48 hours seems to be common [94, 99-102]. Some retrospective studies even advocate that a drainage time of several days is

required to reduce recurrence rates [100, 102]. However, the best available evidence regarding drainage time comes from a Danish multicentre RCT concluding that a drainage time of 24 hours was equal to 48 hours, with no significant difference in mortality or recurrence [103]. Likewise, an analysis of a subgroup in a UK multicentre prospective cohort of cSDH patients showed no difference in recurrence between 1 or 2 days of postoperative drainage [104].

Intraoperative irrigation

Irrigation of the subdural space during cSDH evacuation is common but is another area of controversy. Given the pathophysiology of cSDH progression, with mediators in the subdural space sustaining an angiogenic, inflammatory and fibrinolytic response, it seems theoretically sound to rinse the subdural space of these factors [24, 25]. Some studies and metanalysis are in favour of the positive effects of irrigation on recurrence [88, 101, 105-107]. On the other hand, other studies found no difference in recurrence with or without intraoperative irrigation [90, 108, 109]. In conclusion, the advantage of irrigation remains unclear. The existing evidence for intraoperative irrigation is mainly based on retrospective studies with conflicting results and the evidence provided is limited by the lack of RCT-studies. However, a multicentre RCT comparing cSDH evacuation with or without irrigation is underway and may shed some light on this matter [110].

In neurosurgical practice both irrigation fluid at room temperature and at body temperature are used routinely in cSDH-surgery. In 2017 an internet-based poll on the site neurosurgic.com (no longer active) regarding the use of irrigation as well as the use of different irrigation fluid temperatures was performed. The results revealed that of 620 responding neurosurgeons 97 % used irrigation for cSDH evacuation. 57 % used irrigation at body temperature and 40 % used irrigation fluid at room temperature [111]. However, the influence of different irrigation fluid temperatures on cSDH outcome has not previously been studied.

Endoscope-assisted cSDH-surgery

Endoscope assisted evacuation may have a role in removing membranes and solid clots as shown in a prospective study evaluating the technique [112]. However, the benefits of endoscope assisted cSDH-surgery are presently not clear. Some researchers have shown a reduction of recurrence compared to ordinary BHC [113, 114], while others have found no difference in recurrence

[115]. Since evidence based on RCT-studies is presently lacking the exact role of endoscope assisted cSDH-surgery remains unclear.

1.7 Non-Surgical treatment

Although the focus of this thesis is on different surgical treatment strategies, it is important to also describe non-surgical treatment options. The main drawback of the non-surgical methods is that none of them can promptly reduce the mass effect caused by a cSDH as surgical evacuation can. Therefore, the role of non-surgical treatment is either as an adjunct to surgery, in an effort to reduce postoperative recurrence rates, or to prevent hematoma progression in patients with smaller cSDH with no or mild symptoms.

Corticosteroids

Since cSDH is in part an inflammatory disease it is logical that corticosteroids have been studied as a possible medical treatment. Mediators known to be involved in the progression of cSDH such as IL-6, IL-8 and VEGF are all inhibited by corticosteroids [25]. Some retrospective and non-randomised prospective studies have reported reduced recurrence with surgery combined with postoperative steroids but also hematoma resorption when used as primary treatment of smaller cSDH [116-118]. However, in a large RCT by Hutchinson *et al* patients were randomised to either placebo or dexamethasone after surgery. Although recurrences were fewer with adjunct corticosteroids the number of adverse outcomes in the dexamethasone group was higher 6 months after cSDH surgery [119]. The authors therefore could not recommend the use of dexamethasone after cSDH surgery in clinical practice. Similarly, in another recent RCT (unpublished manuscript but part of publicly defended thesis by Miah I P; ISBN978-94-6421-817-6) patients were randomised to either surgery or dexamethasone treatment [120]. However, the study was terminated early due to adverse events in the corticosteroid group. The outcome was in line with a previously published retrospective study by the same research group, showing higher frequency of complications and prolonged hospital stay in the group treated with dexamethasone instead of surgery [121]. Presently the best evidence of corticosteroid treatment in cSDH comes from these two RCT-studies [119, 120]. Therefore, due to issues of safety, corticosteroids cannot be recommended as a treatment option of cSDH. However, it may be a question of finding the optimal corticosteroid dose for an acceptable ratio between complications and recurrence rate. Further studies are warranted.

Angiotensin-converting enzyme (ACE) inhibitors

ACE-inhibitors can theoretically affect cSDH progression by inhibition of angiogenesis [24, 25]. However, results from a prospective randomised study and retrospectives studies have failed to establish any benefit of ACE-inhibitors in the treatment of cSDH [122-124].

Atorvastatin

Atorvastatin has been described to have both anti-inflammatory and anti-angiogenic properties [24]. Retrospective studies reporting positive effects of atorvastatin on hematoma resolution in cSDH are limited by their small study size [125, 126]. A larger prospective study also demonstrated augmented hematoma resolution mediated by atorvastatin, however it was retracted due to research fraud [127]. A recently published meta-analysis of 6 studies demonstrated a reduction of recurrence when atorvastatin was used as an adjunct after surgery [128]. However, evidence from RCT-studies is needed to be able to give recommendations regarding the role of statins in cSDH management. At least two RCT-studies exploring atorvastatin in the treatment of cSDH are ongoing [129].

Tranexamic acid

Tranexamic acid (TXA) inhibits fibrinolysis and has been demonstrated to reduce the hematoma size of non-surgically treated cSDH in a small observational study of 21 patients [130]. There is a strong interest concerning TXA in cSDH treatment and 5 RCT-studies are currently ongoing [129].

Middle meningeal artery embolization

Endovascular embolization of the middle meningeal artery (MMA) targets the frail newly formed vessels of the outer membrane. The technique seems to have promise in the treatment of cSDH. However, the evidence as to which patient group would benefit most from MMA-embolization is presently too limited to give a strong recommendation. Currently, the best available evidence comes from different meta-analysis. Haldrup *et al* performed a meta-anlysis of 18 studies. However, the total number of patients were only 191 in the studies analysed. They found a recurrence rate of previously surgically treated patients to be 2.4 % and the recurrence rate after primary MMA-embolization for cSDH to be 4.1 % [131]. Ironside *et al* included 20 studies in their meta-analysis. In contrast with Haldrup *et al* the total patient cohort was large. In total 1416 patients, of which 778 underwent MMA-embolization and

698 had conventional surgical treatment, were included in the meta-analysis. The pooled recurrence rate in the MMA-cohort was 4.8 % compared with 21.5 % with conventional surgical treatment. The overall complication frequency for MMA-embolization was 1.7 %, showing the safety of the technique [132]. However, a major limitation of these meta-analysis is that neither hematoma size nor midline shift were presented. Since surgery is the only method that can alleviate a large cSDH with significant mass effect it is likely that the cSDH treated by surgery were larger than those treated by MMA-embolization alone. This could explain the differences in recurrence rate reported. Another limitation is the often small size and heterogenous outcome measures of the studies included in the meta-analyses [131, 132]. Regardless, it is very likely that this promising technique has a place in the treatment of cSDH. If MMA-embolization is best used as an adjunct to surgery to diminish recurrence rates or as a primary treatment to hinder progression of smaller cSDH, or maybe both, remains to be decided. Several RCT-studies are ongoing and will hopefully lead to recommendations concerning the role of MMA-embolization in the management of cSDH [129].

1.8 Postoperative management

Recommencement of antithrombotic treatment

As described earlier almost half of patients with cSDH are on antiplatelet or anticoagulant medication [12, 16, 32, 64]. Recommencement of these medications after cSDH surgery are often done on a case-to-case basis and evidence-based recommendations are lacking. Limited evidence has indicated that resumption of Warfarin can be safely done 3 days after cSDH evacuation [133]. However, it is recommended to make individual decisions of resumption based on a comparison between risk scores for bleeding (HAS-BLED) and thromboembolism (CHAD2DS-VASc) [19, 134-136]. Regarding NOACS, the European Heart Rhythm Association has a general recommendation for resumption 10-14 days after intracranial bleeding (not specifically for cSDH)[137]. The optimal time for recommencement of antiplatelets is largely unknown. In a review by Nathan *et al* there was no increased risk of rebleeding reported regardless of when antiplatelet therapy was resumed after cSDH-surgery [138]. But again, the decision to resume antiplatelets is probably most often based on individual risk factors of thrombosis contra bleeding. At our department antiplatelet therapy is often withheld 7-14 days after cSDH-evacuation. Delaying the resumption of antithrombotic medications longer than 30 days may lead to more thromboembolic events [139].

Postoperative radiology

Routinely performing a postoperative CT within 24 hours or not varies between different neurosurgical departments. Santarius *et al* showed in a survey done in Ireland and the United Kingdom that 32 % of the responding neurosurgeons performed a routine CT-scan postoperatively [81]. Hulsbergen *et al* compared a hospital in Boston, USA, that routinely performed CT after cSDH-surgery to a hospital in Utrecht, the Netherlands, that did not routinely order a postoperative CT. There was no difference in outcome between the two hospitals and the authors therefore concluded that there was no benefit of a routine CT after cSDH-surgery [140]. A concern with routinely performing a CT after surgery is that patients may be reoperated unnecessarily based solely on a residual hematoma seen on CT. This concern was supported in a study by Frechon and colleagues, showing that in their cohort of 21 recurrences, 7 were operated even though they had no symptoms [141]. A residual collection of fluid after cSDH-surgery is common and is seen in 75 % 10 days after surgery and in 15 % after 40 days. Importantly, the presence of such a residual fluid collection did not correlate with recurrence or long term outcome [23]. Furthermore, a recent RCT demonstrated that performing a postoperative CT only in patients who develop symptoms of cSDH did not alter outcome, instead it reduced the number of reoperations and medical costs [142]. In conclusion, an evidence-based recommendation can be made as to not routinely performing a postoperative CT after cSDH surgery but only in symptomatic patients.

1.9 Outcome

The reported overall outcome after surgical cSDH evacuation is favourable with a good postoperative modified Rankin Scale score (mRS) of 0-3 in 84-90% of patients 6 months after surgery [15, 119]. The mRS score ranges from 0-6 (0= no symptoms, 6 = dead) and measures the degree of dependence and disability in everyday activities [143]. A score of 0-3 is often considered a favourable outcome (*Appendix A2*). As one might expect, a lower mRS score at admission prior to surgery is associated with a better outcome [144].

Complications

Recurrence is without a doubt the most common complication after surgery for cSDH. The estimated recurrence rate is 5-21 % [5]. Complications can be directly related to the surgical procedure but medical complications after surgery are also common in the frail cSDH-population. Examples of postoperative surgical complications are pneumocephalus, acute hematoma,

surgical site infections, seizures and empyema. Examples of non-surgical complications are infections (pneumonia, urinary tract infection), stroke, myocardial infarction and thromboembolism. In a retrospective study from Sweden (Karolinska University Hospital, Stockholm) of 758 patients an overall complication rate of 7.9 % was reported. The most common type of complication (2.8%) was extracranial infections (pneumonia, urinary tract infection). A decreased level of consciousness (GCS 3-12) as well as severe comorbidity were risk factors of more severe complications [145]. In a study of 1252 patients from three neurosurgical departments in Scandinavia an overall complication frequency was seen in 9 % of patients older than 50 years and in 3 % of patients younger than 50 years of age. However, due to the rather small cohort (n=52) of patients younger than 50 years the difference between the age groups was not statistically significant [16]. In another recently published Swedish study (Uppsala University Hospital), a cohort of 551 patients older than 70 years of age demonstrated a 11.7 % complication frequency. The most common complications were postoperative hematomas (2.6%), seizures (1.7%) and infections (1.9%). The authors also noted alcohol abuse as a significant risk factor for postoperative complications [32]. Rauhala *et al* demonstrated a 15% overall frequency of complications in a large retrospective cohort of 1148 patients with cSDH in Finland (1990-2015) [146]. Put together, a fair estimate of the overall postoperative complication frequency in patients with cSDH is in the range of 3-15 %.

Mortality

As described previously, studies have shown an overall favourable outcome 6 months after cSDH surgery in the vast majority of patients. At the same time, an excessive 1-year mortality has been demonstrated compared to age-matched controls. Miranda and colleges recorded a mortality as high as 32 % in patients with cSDH older than 65 years [147]. However, in a more recent study of a large cohort by Rauhala *et al* the 1-year mortality was 13.7 %. Nonetheless, the excess 1-year mortality in patients with cSDH was 9 %. Furthermore, the cSDH patients had a continuous and increasing excess mortality up to 20 years after the cSDH diagnosis [17]. It is important to note that in both these studies patients treated with or without surgery for cSDH were included.

In patients surgically treated for cSDH 6-month mortality rates of 8.6-12 % has been reported [17, 94]. Bartek *et al* recorded a 90-day mortality of 6.3 % in patients older than 50 years and 1.9 % in patients younger than 50 years [16]. Sundblom et al reported a 30-day mortality rate of 3.1 % after surgery in a patient cohort of 511 patients older than 70-years [32].

The excess mortality seen in patients diagnosed with cSDH seems to be related to concomitant comorbidity rather than the cSDH per se or the treatment given. This would explain the continuous excess mortality several years after the diagnosis of cSDH. In the study by Rauhala *et al*, demonstrating excess mortality after cSDH-diagnosis, a subgroup without any comorbidity had no excess mortality. Non-operative treatment of cSDH was associated with an increased risk of excess mortality. This might be explained by a very high surgical risk related to severe comorbidities in the non-operated patients [17]. Sundblom *et al* reported an overall comorbidity in 378 of 511 (74%) in patients older than 70 years. Cardiovascular disease was seen in 43 %, diabetes mellitus in 18 %, previous stroke in 14 % and dementia in 12 % of patients [32].

1.10 Risk factors for recurrence

Several factors have been identified as risk factors for recurrence after cSDH evacuation. Age or gender does not seem to be independent risk factors of recurrence [145, 148, 149]. However, one study by Han *et* al identified age as a risk factor [150]. Miah *et al* performed a meta-analysis of 22 studies concerning radiological risk factors for recurrence and found that hyperdense parts in a cSDH was the strongest risk factor. Laminar and separated cSDH on CT were also associated with recurrence as well as a preoperative hematoma size larger than 20 mm and midline shift above 10 mm. Bilateral hematomas were related to an increased recurrence risk as well [151]. Similarly, in a Scandinavian cohort, bilateral hematomas, preoperative hematoma size and membranous CT-appearance were identified as independent risk factors of recurrence [145]. The size of an eventual residual subdural cavity after surgery (indicating poor brain expansion) is also linked to recurrence [149]. Stanisic *et al* developed the Oslo chronic subdural hematoma grading system for predicting recurrence after cSDH-surgery (*table 2*). They identified laminar and hyper-/isodense cSDH as well as a postoperative cavity > 200 millilitres to be the strongest prognosticators of recurrence [148]. The main drawback of the grading system is that it requires a routine postoperative CT while recent level I evidence advices against the routine use of postoperative CT after cSDH evacuation [142]. Several studies have shown that preoperative use of antithrombotic-/anticoagulant medications does not increase the risk of postoperative recurrence [145, 148, 149, 152]. It seems logical since efforts are made to normalize any suspected coagulation disturbance prior to surgery. However, other studies have found an increased risk for recurrence related to preoperative medication with antiplatelets and anticoagulants [65, 153].

Table 2. The Oslo cSDH grading system for predicting recurrence.

CT appearance	
Iso-/hyperdense subtypes and laminar or separated types	2
Hypodense or gradation subtypes and trabecular type	0
Preoperative volume, > 130 ml	1
Preoperative volume, ≤ 130 ml	0
Postoperative cavity volume, > 200 ml	2
Postop. cavity volume, 80-200 ml	1
Postop. cavity volume, < 80 ml	0
Total score	0-5

Total score points	Non-recurrence (n)	Recurrence (n)	Rate of recurrence requiring reoperation (95% CI)
0	18	0	0% (0-18%)
1-2	48	3	6% (1-16%)
3-4	21	9	30 (15-49%)
5	3	5	63% (25-92%)

Adapted from Stanisic, M. and A.H. Pripp, *A Reliable Grading System for Prediction of Chronic Subdural Hematoma Recurrence Requiring Reoperation After Initial Burr-Hole Surgery.* Neurosurgery, 2017. **81**(5): p. 752-760.

2 AIM

Study I-III

The primary aim was to study if the recurrence rate after cSDH surgery is affected by different irrigation fluid temperatures. A secondary aim was to investigate the postoperative mortality 6 months after surgery. Complication frequency and type was also recorded as secondary aims. An additional secondary aim, in study II-III, was to evaluate the health-related quality of life (HRQL) at 6 months after surgical evacuation of cSDH.

Study IV

The aim of this study was to compare postoperative drainage times shorter or longer than 24 hours after cSDH surgery and investigate the impact on recurrence frequency, length of hospital stay as well as complication and mortality rate. Additionally, another aim was to perform a prospective observation of drainage volume per hour after cSDH evacuation.

3 PATIENTS AND METHODS

3.1 Study design

Study I

Study I was performed as a single centre retrospective study. As a primary endpoint the difference in recurrence rate was compared between a cohort of patients treated with intraoperative irrigation fluid at room temperature (RT, 22 °C) and a cohort with irrigation fluid at body temperature (BT, 37 °C) during cSDH evacuation. The incidence of complications requiring hospital admission and mortality was also recorded as secondary endpoints. The follow-up time was 6 months for all endpoints. The study participants were adult patients consecutively treated with burr-hole craniostomy combined with irrigation for cSDH at the Sahlgrenska University Hospital. The hospital is located in Gothenburg, western Sweden, and has a catchment area of approximately 1.9 million inhabitants. The neurosurgical department at the Sahlgrenska University Hospital is the only neurosurgical department in western Sweden so all cSDH surgeries within the catchment area are performed at the department. About 150-190 surgeries for cSDH are performed annually.

The study was conducted September 2013-November 2014. During a 6-month period, irrigation fluid at body temperature was used during cSDH evacuation (BT-group). A comparison regarding the different endpoints was then made with the preceding 6-month period when all patients had been treated with irrigation fluid at room temperature (RT-group).

Study II-III

Paper II is the study protocol for the RCT performed in study III. The SPIRIT-guidelines for RCT study protocols were followed in the making of the study protocol [154]. The CONSORT-checklist for reporting a RCT was used for study III [155]. The study is registered in clinicaltrials.gov (identifier NCT02757235).

In study III intraoperative irrigation at body temperature (37 °, BT-group) was compared with irrigation at room temperature (22 °C, RT-group). The primary endpoint was recurrence (reoperation of ipsilateral cSDH) during a postoperative follow-up of 6 months. Secondary endpoints were mortality and health related quality of life (HRQL) at 6 months and complication frequency and profile within 30-days after surgical cSDH evacuation. In addition to the

assessment of the primary and secondary endpoints a planned CT scan was scheduled at 2 months (or earlier if the patient developed symptoms of cSDH recurrence) after cSDH evacuation. The purpose was to record any residual hematoma and its size.

HRQL was measured with the EuroQol 5D-3L (EQ5D-3L) questionnaire (*Appendix A3*). The EQ5D-3L has questions regarding the 5 dimensions 1. self-care 2. mobility 3. pain/discomfort 4. usual activities 5. anxiety/depression. Each question can be answered with one of the 3 levels: "major problem", "slight/moderate problem" or "no problem". A score of 1 is given for "no problem", 2 for "slight/moderate problem" and 3 for "major problem". Based on the scores, an utility index score can be calculated. This in turn gives a measure of HRQL ranging from index score -0.62 (health state worse than death) to index score 1 (perfect health) [156]. The HRQL in study III is presented as utility index scores.

The study was designed as a multicentre randomised controlled trial with 3 participating neurosurgical departments in Sweden: Sahlgrenska University Hospital (Gothenburg), Uppsala University Hospital (Uppsala) and Karolinska University Hospital (Stockholm). The catchment area of the three hospitals covers 60 % of the population in Sweden. The study was conducted between March 2016 and May 2020. The same surgical technique for cSDH evacuation was employed by all the participating departments. A detailed description of the surgical technique can be found in subchapter 3.2.

Patients with an indication for surgical evacuation of cSDH were screened for study inclusion. Inclusion criteria were: 1. adult patients (older than 18 years) 2. cSDH requiring burr-hole evacuation. Exclusion criteria were: 1. Patients with CSF-shunt 2. Patients with an intracranial arachnoidal cyst 3. cSDH requiring other surgical evacuation than by burr-hole craniostomy 4. Patients who had undergone previous intracranial surgery. Informed consent was obtained for each participant in the study. Consent could also be obtained from next of kin if the patient was unable to give consent. It was possible to withdraw from the study at any time. The calculated sample size needed, for a statistical power of 80 %, was 496 patients. The sample size calculation was based on the recurrence rates reported in Study I. To achieve a homogenous recruitment among the participating departments, but also to compensate for an anticipated loss of follow-up, 200 randomisation envelopes were prepared for each study site (for a total of 600 envelopes). The randomisation envelopes were prepared by an independent statistician. The envelopes had consecutive study numbers containing the randomly assigned intervention of either intraoperative irrigation at body temperature or at room temperature. A block randomisation of 1:1 was applied in the study.

The neurosurgeon performing the cSDH evacuation could not be blinded regarding the randomised treatment intervention. To reduce bias, the patient was not informed of the intervention used. Only the study number for each patient and not the used treatment allocation was registered in the medical records. Furthermore, the researchers of the study were blinded concerning the intervention until the final analysis when the study was completed. An independent statistician then provided decoding of the treatment interventions.

A case report form (CRF) for each patient was used to record variables during the study. In addition to the endpoints and the variables recorded at the 2-month follow-up variables were registered before surgery, during surgery and within 24 hours after surgery (listed below).

Preoperative variables: arm/leg paresis, GCS, age, sex, confusion, seizure, headache, gait disturbance, dysphasia, midline-shift on CT, max hematoma size, hematoma density (hypodense, isodense, hyperdense parts, membranous) bilateral or unilateral cSDH, medications (aspirin, clopidogrel, warfarin, NOAC).

Intraoperative variables: bilateral or unilateral surgery, local or general anaesthesia, duration of the operation (skin-to-skin), volume of the irrigation fluid.

Postoperative variables: arm/leg paresis, GCS, confusion, dysphasia, seizure, gait disturbance, headache,

There are some deviations between the original study protocol (paper II) and the methods used in the RCT (study III). In study III we did not rank complications according to the Landriel-Ibanez classification as proposed in study II [157]. Instead, the overall frequency and type of complications for each group were registered. Kaplan-Meier plots for survival analysis were not used in study III as proposed in paper II. Also, we did not perform an interim analysis by an independent statistician when 100 patients at each site had a complete follow-up as suggested in paper II. This proved to be too costly and was therefore not implemented. Nevertheless, the investigators at the participating departments cross-monitored each other regarding the data collected and consents obtained after the inclusion of 100 patients at each study site.

Study IV

Study IV was a single centre retrospective study comparing drainage times longer (long drainage time, LDT) or shorter than 24 hours (short drainage time,

SDT) after cSDH surgery. Recurrence within 6 months was the primary endpoint. Mortality within 6 months, duration of hospital stay (at the neurosurgical department) and complications within 30 days after surgery were secondary endpoints. A cohort with a drainage time > 24 hours (January-September 2010) was compared with a cohort with a drainage time < 24 hours (January-September 2011). Criteria for study inclusion were patients older than 18 years undergoing cSDH-evacuation combined with an active subgaleal drain postoperatively. Criteria for exclusion from the study were if other surgery than burr-hole craniostomy was performed or if a drain was not inserted.

As a second, independent part of study IV, we observed the volume drained per hour in a prospective cohort of 10 patients (November-December 2021). The inclusion and exclusion criteria were the same as in the retrospective cohort. The volume of drainage was recorded hourly until the drain was removed. In accordance with our regular clinical routine, the drain was removed when no further drainage was recorded during a period of at least 4 hours. Since the drain used had an active suction the drain was also checked every hour to ensure that suction was maintained.

3.2 Surgical technique

The same surgical technique for evacuation of cSDH was used in all the studies described in this thesis. The technique involves creating 1-2 cranial burr-holes, followed by durotomy and bipolar coagulation of the dural edges. Irrigation of the subdural space with Ringers Lactate is then performed. A soft catheter and a 50-ml syringe are used for the intraoperative irrigation. An active subgaleal drain (Abdovac FG 10 with troacar, 25 mm Hg, Wellspect Healthcare) is then placed over the burr-hole and connected to a collection bag with suction. This method was originally described by Gazerri *et al* [80]. Until the drain is removed, the patient is kept in the supine position. Except for the planned 2-month postoperative CT described in study III, CT was not performed as a routine after surgery. Instead, CT was warranted if the patient failed to demonstrate improvement or developed recurrent symptoms after hematoma evacuation.

In study I and III the only difference regarding surgical technique between the two study groups was the temperature of the irrigation fluid used (either 37 °C or 22 °C). Measures were taken to avoid unintentional cooling of the irrigation fluid at body temperature. The irrigation fluid was stored in a heating cabinet and was brought into the operating theatre first when the durotomy was

completed. In study IV the only difference regarding the surgical method was a drainage time shorter or longer than 24 hours after surgery.

The indication to reoperate was the same for the all the studies in this thesis. Reoperation was justified if the patient had persisting symptoms or developed recurrent symptoms in combination with a correlative cSDH on CT.

3.3 Statistical methods

Statistical analyses were performed according to the intention-to-treat principle. For comparison of study groups, x^2-test was used for categorical data. Numerical data was analysed with Student´s t-test if normally distributed and if skewed with Mann-Whitney U-test. The statistical tests were two-sided and statistical significance was set to a p-value of ≤ 0.05. The software used for data collection and statistical analysis were SPSS Statistics (version 25, IBM) and Excel (version 2202, 14931.20660, Microsoft).

3.4 Research ethics

Common to all studies of this thesis is that the research methods used adhere to the Helsinki declaration regarding ethics in research involving human subjects [158].

Study I

The study was reviewed by the Regional Ethics Committee in Gothenburg. Because of the retrospective observational character of the study, it was decided that no formal ethical approval was needed.

Studies II-III

The Regional Ethics Committee in Gothenburg approved the study on the 19th of January 2016 (reference: 932-15). Since both forms of irrigation fluid temperature have been used in neurosurgical practice for a long time the intervention was considered low risk.

Study IV

The Swedish Ethical Review Authority decided that no formal ethical approval was needed. However, they made a statement that no ethical concerns were found with the study (DNR 2021-00048).

4 RESULTS

4.1 Study I

Baseline characteristics of the study population are shown together with the baseline data for study III and IV in *table 5*. The RT-group and the BT-group were well matched without any significant difference regarding sex, age, use of anticoagulant-/antiplatelet medications, bilateral hematomas, hematoma size, duration of surgery or hematoma density. 4 out of 88 (4.5 %) in the BT-group compared with 11 of 84 (13.1 %) in the RT-group had a recurrence within six months (*p=0.013)*. Mortality was 4.5 % (4/88) in the BT-group and 3,5 % (3/84) in the RT-group (*p=0.55).* The overall complication rate was 6.8 % (6/88) compared with 5.9 % (5/84) in RT-group (*p=0.59).* The different types of complications that occurred are listed in *table 3*.

Table 3. Complication profile for study I.

No.	RT-group (N=84)	BT-group (N=88)
1	Intracerebral hematoma	Cerebral infarction (basal ganglia)
2	Pneumocefalus (symptomatic but did not require reoperation)	Pneumonia
3	Acute postoperative SDH (requiring reoperation)	Pneumocefalus (symptomatic but did not require reoperation)
4	Postoperative seizures	Acute postoperative SDH (requiring reoperation)
5	Wound infection (superficial)	Urosepsis
6		Myocardial infarction

4.2 Study III

A total of 1900 patients were screened for inclusion in the study. Because 30 of the 600 randomisation envelopes were lost at one of the study sites, a total of 570 patients were finally included in the study. 19 study participants were excluded directly after randomisation (but before receiving the intervention)

due to either an incorrect randomisation procedure or disqualification regarding the inclusion criteria. An incorrect randomisation applied to 4 patients with bilateral cSDH where surgery was performed in two sessions. Randomisation envelopes were unintentionally opened during both surgical sessions. However, the 4 patients were all treated bilaterally in accordance with the result from the first randomisation. Withdrawal of consent occurred in 5 patients. Another 5 patients were lost during follow-up (3 emigrated from Sweden and 2 were foreign citizens). In the end, 264 in the BT-group and 277 in the RT-group had complete follow-up and final analysis. A detailed overview of symptoms at admission for both groups are shown in *table 4*. Other characteristics pre- and intraoperatively for study III are shown in comparison with the other studies of this thesis in *table 5* (subchapter 4.3). Significantly more cases of disorientation were recorded at admission in the RT-group (43%) compared with 33% in the BT-group (*p=0.05)*. Otherwise, the groups showed no significant difference regarding the preoperative and intraoperative variables.

Table 4. Symptoms at admission in study III.

Variable	BT-group (N=264)	RT-group (N=277)
GCS 13-15	255 (97%)	263 (95%)
GCS 9-12	9 (3%)	14 (5%)
GCS 3-8	0 (0%)	0 (0%)
Disorientation *(p=0.05)*	88 (33%)	119 (43%)
Headache	129 (49%)	118 (42%)
Paresis leg	151 (58%)	161 (58%)
Paresis arm	143 (54%)	155 (56%)
Seizure	7 (3%)	10 (4%)
Dysphasia	70 (26%)	74 (27%)
Gait disturbance	217 (82%)	231 (83%)

Data presented as n (%). BT, body temperature, RT, room temperature. p≤0.05 in bold.

Postoperative assessment within 24 hours revealed an improvement or complete regression of symptoms in more than 95 % of the patients in both study groups. A detailed overview of the results from the first postoperative evaluation can be found as supplementary material (*Appendix A4*).

The planned CT at 2 months after surgery was performed in 219 (83 %) and 235 (85 %) patients in the BT-group and RT-group respectively. As described previously, the CT scan could be performed earlier if the patient developed symptoms consistent with cSDH recurrence. All in all, 54 % (118/219) in the BT-group and 63 % (148/235) in the RT-group had a visible residual hematoma. However, most of the residual cSDH were small without symptoms. Symptomatic hematomas requiring reoperation were, as expected, larger with a mean size of 18 mm in the RT-group compared with 19 mm in the BT-group. Non-symptomatic residual hematomas were smaller; with a mean size of 7.5 mm and 7 mm in the RT-group and BT-group respectively.

Regarding the primary endpoint, 39 of 277 (14 %) patients in the RT-group and 16 of 264 (6 %) in the BT-group had a recurrence ($p<0.001$, OR 2.56 [95% CI 1.38-4.66]). Although the individual odds ratios for each site did not reach statistical significance, there was a trend in favour for irrigation fluid at body temperature seen at all sites. The 15 patients (9 from the RT-group, 6 from the BT-group) that were excluded immediately after randomisation were analysed according to the intention-to-treat principle. The analysis showed that significantly more recurrences occurred in the RT-group compared to the BT-group ($p<0.001$, OR 2.57 [95% CI 1.40-4.71]). Furthermore, a significant difference between groups were still seen if we would calculate the 5 patients lost to follow-up as recurrences. The results also revealed that most recurrences occurred within 2 months after cSDH evacuation; 79 % in the RT-group and 75 % in the BT-group.

Complications requiring hospital admission within 30 days were recorded in 25 of 277 (9 %) patients in the RT-group and in 20 of 264 (7.5 %) in the BT-group. The difference regarding complication rate was not significant ($p=0.39$, OR 1.2 [95 % CI 0.66-2.2]). A detailed complication profile can be found as a supplement (*Appendix A5*). The difference in health-related quality of life estimated with EQ5-3L was not significant. The index score (SD) was 0.749 (0.24) for the RT-group and 0.761 (0.21) for the BT-group ($p=0.48$). The index scores are comparable to the index score of 0.74 reported for the same age group in the general Swedish population [159]. Mortality did not differ significantly between groups. 14 cases (5 %) of mortality were recorded in the BT-group compared with 20 cases (7 %) in the RT-group ($p=0.27$, OR 1.39 [95% CI 0.75-2.55]).

4.3 Study IV

Retrospective cohort

In the LDT-group 96 patients and 113 in the SDT-group were identified and screened for inclusion. Two patients in the SDT-group were excluded because mini-craniotomy had been performed instead of burr-hole craniostomy. The 2 excluded patients had no recurrence within 6 months, however. Finally, 96 patients in the LDT-group and 111 patients in the SDT-group had a complete follow-up. No significant difference was seen between the two study groups regarding preoperative or intraoperative variables *(table 5*).

The LDT-group had a mean (range) drainage time of 24.8 (24-32) and the SDT-group 12.0 (7-20) hours ($p < 0.001$). The recurrence rate was 12.5 % (12/96) in the LDT-group compared with 11.7 % (13/111) in the SDT-group within 6 months after cSDH surgery. The recurrence frequency was not significantly different between the study groups (OR 0.92 [0.5-1.7], p=0.15). The frequency of complications requiring hospital admission within 30 days were 4.2 % (4/96) in the LDT-group compared with 4.5 % (5/111) in the SDT-group (p=0.15). In the LDT-group the complications recorded were one case each of postoperative seizure, postoperative aSDH, pneumonia and sepsis of unknown origin. The complications seen in the SDT-group were one case each of acute myocardial infarction, urinary infection, pneumonia, heart failure and atrial fibrillation. Mortality was 3.6 % (4/111) and 6.3% (6/96) for the SDT- and LDT-group respectively (p=0.10). Length of hospital stay was significantly shorter in the SDT-group with a mean of 2.7 days compared with 3.6 days for the LDT-group (p=0.01).

Prospective cohort

Ten consecutive patients were observed regarding drainage volume per hour after burr-hole craniostomy combined with an active subgaleal drain. The mean (range) drainage time was 13.3 hours (9-17), and the mean (range) drained volume was 121 ml (20-210). A detailed overview of the individual postoperative drainage volumes and times can be found in paper IV. The cohort consisted of 2 women and 8 men, and the mean (range) age was 81 (64-91). The observation showed that in 8 out of 10 patients 90-95 % of the total drainage occurred within 5-6 hours after surgery. The other 2 patients had drained 95 % of their total volume after 9 hours. Recurrence occurred in one patient with a drainage volume of 170 ml and a drainage time of 16 hours. No complications or deaths were recorded during the 6-month follow-up in the prospective cohort.

Table 5. Pre- and intraoperative variables for study I, III and IV.

Variable	**Study I**		**Study III**		**Study IV**	
Cohort	**BT**	**RT**	**BT**	**RT**	**> 24 h**	**< 24 h**
	N = 88	**N= 84**	**N = 264**	**N = 277**	**N = 96**	**N = 111**
Age - yr	74.5 (12)	75.1 (13)	75.4 (10)	76.2 (9.5)	75.6 (10)	75.3 (11)
Women	21 (24%)	24 (28%)	74 (28%)	72 (26%)	32 (33%)	34 (30%)
Operation time - min	44 (20.6)	46 (15.1)	40 (14.6)	39 (14.5)	43.9 (9.6)	42.3 (5.4)
Irrigation volume - ml	N/A	N/A	1717(790)	1620(748)	N/A	N/A
Antithromb. medications	40 (45%)	40 (47%)	134 (51%)	135 (49%)	40 (41%)	48 (43%)
Maximum hematoma width - mm	19 (7.1)	18 (6.7)	20.3(4.6)	21.0 (5.2)	20.1 (4.9)	21.4 (4.1)
Midline shift - mm	N/A	N/A	6.6 (4.1)	6.7 (4.2)	8 (4.8)	9.1 (4.5)
Bilateral hematoma	18 (20%)	15 (18%)	42 (16%)	39 (14%)	21 (22%)	22 (20%)
Hypodense *	38 (43%)	35 (42%)	168 (64%)	187 (68%)	N/A	N/A
Isodense *	25 (28%)	19 (24%)	97 (37%)	96 (35%)	N/A	N/A
Hyperdense parts *	10 (12%)	11 (13%)	26 (10%)	33 (12%)	N/A	N/A
Membranous *	15 (17%)	18 (21%)	37 (14%)	44 (16%)	12 (12%)	17 (15%)

*Data presented as mean (SD) or n (%). Abbreviations: BT, body temperature, RT, room temperature. N/A, not applicable. * In study III combinations of CT-appearance could occur.*

5 DISCUSSION

Despite being such a common entity in neurosurgical practice the high recurrence rate of cSDH remains a challenge. Every recurrence in need of reoperation increases the risk of complications and suffering for the individual patient [94, 146]. In addition, as shown by Rauhala and colleagues in Finland, the healthcare cost increased with 132 % for patients with recurrence compared with those without any recurrence [146]. There is a significant heterogeneity regarding the treatment strategies used and guidelines based on level I evidence are presently few. Since cSDH incidence is increasing there is an urgent need to reduce recurrence rates with the aid of guidelines based on solid evidence.

To date, treatment recommendations based on evidence from large RCT-studies can be made regarding postoperative drains, corticosteroids, routine CT follow-up and drain location. The use of postoperative drains significantly reduces recurrence rates, as convincingly shown by Santarius *et al* [15]. Currently, corticosteroids cannot be recommended as part of the treatment arsenal for cSDH due to an unfavorable ratio between complications and recurrence as shown in a RCT by Hutchinson *et al* [119]. These findings were recently confirmed in a Dutch RCT by Miah and colleagues (submitted manuscript, part of a recently defended thesis by Miah I P; ISBN978-94-6421-817-6) [120]. A RCT comparing routine CT with no routine CT after cSDH surgery found that there was no benefit of routinely performing a postoperative CT, and it is consequently not recommended [142]. Based on their RCT, Soleman *et al* recommend a subgaleal/subperiosteal drain location instead of a subdural location due to a better ratio between adverse events and recurrence [96].

The studies of this thesis explored two aspects of cSDH-surgery, namely different irrigation fluid temperatures used during cSDH evacuation (study I & III) and a postoperative drainage time of more or less than 24 hours (study IV).

Study I & III

In study I and III intraoperative irrigation fluid at body temperature was compared with irrigation fluid at room temperature to explore the influence on recurrence as a primary endpoint. We could show in both study I and III that intraoperative irrigation fluid at body temperature significantly diminishes the recurrence rate compared with irrigation at room temperature. Mortality, HRQL and complication rate did not differ significantly between the study groups. In study III, the RT-group had more cases of disorientation at baseline

compared with the BT-group (p=0.05). Otherwise, the study groups in both study I and III were well matched. Since hematoma size, midline shift, bilateral hematomas and hematoma density showed no difference between the RT- and BT-groups in study III, we do not believe the difference regarding disorientation may have affected the results.

To the best of our knowledge, study I and III are the first studies investigating the effects of irrigation fluid temperature in cSDH-surgery. We cannot fully explain the effect on recurrence seen when irrigation at body temperature is used compared with irrigation at room temperature. Theoretically, irrigation fluid at room temperature may have a negative impact on intraoperative coagulation and thereby cause increased microbleeding during the surgical evacuation [160]. In ENT-surgery (ear-nose-throat) irrigation with 50 °C saline has been shown to reduce bleeding compared with irrigation at room temperature [161, 162]. Furthermore, irrigation of the subdural space seems to be a logical measure to rinse the subdural cavity from mediators of inflammation, angiogenesis and fibrinolysis that cause hematoma expansion. One possible effect of irrigation fluid at body temperature compared to irrigation at room temperature may be increased solubility of the cSDH. For every 20 °C increase in temperature the aqueous solubility of organic materials is doubled [163].

The reduction of recurrence seen in the studies was not only statistically significant but also clinically relevant. Therefore, we provide level I evidence for the intraoperative use of irrigation fluid at body temperature instead of irrigation at room temperature. This evidence-based recommendation is safe and can easily be applied as standard of care in surgical cSDH treatment.

Study IV

The optimal drainage time after cSDH evacuation remains uncertain and the existing evidence is conflicting. It seems common to keep a postoperative drain for at least 24-48 hours. Some authors even advocate for the benefits of a drainage time of several days [100, 102]. However, a recent Danish RCT found no difference regarding recurrence or mortality when comparing drainage times of 24 hours vs. 48 hours [103].

In study IV we retrospectively compared drainage times of less or more than 24 hours after surgical evacuation of cSDH and evaluated the impact on recurrence, hospital stay, mortality and complications. No significant difference was seen between the study groups concerning mortality, complications, or recurrence. Hospital stay was significantly shorter in the

group with a drainage time < 24 hours compared with > 24 hours due to earlier patient mobilization. As a separate part of study IV, we observed drainage volume per hour in a prospective group of 10 patients. Almost all the postoperative drainage occurred within the first hours after surgery in all patients. Therefore, the results from the prospective cohort supported our retrospective data that a drainage time of less than 24 hours may be sufficient after cSDH evacuation.

It is possible that the drain used might have an influence on the drainage time needed. In the Danish RCT a passive subdural drain was used and although there was no difference in recurrence rate between 24 vs. 48 hours, the authors concluded that the drained volume was significantly more after 48 hours. After 24 hours they recorded a mean drained volume of 88 ml compared with 146 ml after 48 hours [103]. In comparison, a subgaleal drain with suction was used in study IV and the mean drainage was already 121 ml after a mean drainage time of 13 hours. As stated previously, present evidence suggests that a subgaleal/subperosteal drain location is preferable due to the better recurrence/complication ratio [96, 164]. The results from study IV suggest that a postoperative drainage time of less than 24 hours is sufficient when an active subgaleal drain is used after cSDH evacuation.

5.1 Strengths

The baseline characteristics of the study populations in study I, III and IV are comparable (*table 5)*. Furthermore, they are also similar to what has been presented in other studies [15, 16, 29, 32, 96, 103, 119, 142, 146, 148, 164]. This shows that the study populations of this thesis are representative of the cSDH-population as a whole. An additional shared strength of studies I, III and IV is that the enrolled study populations came from well-defined geographical catchment areas. All neurosurgical treatment within the catchment areas was performed at the involved neurosurgical departments. The same digitalized medical records were used at the local hospitals as well as the participating departments. Therefore, a straight-forward follow-up of all endpoints was possible. Another common strength was that the same surgical technique was used by all neurosurgeons at the involved study sites. All studies also had a follow-up time of 6 months. The multicentre RCT study design with sufficient statistical power was a strength of study III.

5.2 Limitations

Study I and IV are limited by their single centre retrospective study design. Data regarding the retrospective cohort in study IV is also rather old (2010-

2011). However, during that time the routine regarding drainage time was changed at our department from a drainage of more than 24 hours to less than 24 hours. The routine at our department has since then been to keep a drain for less than 24 hours after burr-hole craniostomy. Consequently, we believe the comparison of the cohorts from 2010-2011 is justified.

Common to all the studies of this thesis is that the surgical behaviour of individual neurosurgeons may change when they are part of a study. Another limitation of study III was that the neurosurgeon performing the cSDH-surgery could not be blinded regarding the randomised treatment (different irrigation fluid temperature). However, as a surrogate marker of an unchanged surgical technique the duration of surgery was unchanged between the study groups in study I, III and IV. Additionally, in study III the volume of irrigation fluid used during surgery did not differ between the BT- and RT-group. Even though the same surgical technique was employed by all the participating departments in study III, it cannot be ruled out that small differences in technique may occur.

In study III 30 envelopes were lost before randomisation and could not be part of the study. The study numbers of these randomisation envelopes came equally from both the BT- and RT-group. Importantly, the lost envelopes did not influence the sample size needed for enough statistical power. Another limitation of study III was that reasons for non-inclusion was not recorded. This was in accordance with the study protocol (study II), however.

6 CONCLUSIONS

- If irrigation is used during burr-hole craniostomy for cSDH, the results from study I and III show that irrigation at body temperature leads to significantly fewer recurrences compared with irrigation fluid at room temperature. Therefore, a recommendation based on level I evidence can be made for the use of irrigation fluid at body temperature as standard of care in neurosurgical clinical practice.

- A postoperative drainage time shorter than 24 hours after burr- hole evacuation for cSDH with an active subgaleal drain did not increase the incidence of recurrence, mortality, or complications as compared with a drainage time longer than 24 hours. However, higher level of evidence needs to be provided by a good-quality randomised controlled trial before a treatment recommendation can be made.

7 FUTURE PERSPECTIVES

Recurrence after cSDH-surgery remains a challenge in neurosurgical practice. It is evident that there are many gaps of knowledge regarding the optimal treatment strategy and additional treatment recommendations based on good-quality evidence are needed. However, the future of cSDH-research looks bright. There is an increased interest in the field, as is shown by the increasing number of publications [129]. Additionally, in contrast to many other neurosurgical conditions the relatively high incidence of cSDH makes RCT-studies with sufficient sample size possible. This is especially true when different neurosurgical departments collaborate. An international collaboration regarding cSDH-research (iCORIC) has recently been proposed [129].

An optimisation of surgical technique is necessary to diminish postoperative recurrences and complications. Additionally, to be able to reduce recurrence further after cSDH-surgery, non-surgical treatment modalities will most likely also play an important role. RCT-studies of high quality are needed to shed light on these issues. Fortunately, many RCT-studies exploring different aspects of cSDH-treatment are underway [129].

More specific to the results of this thesis, we have presented level I evidence that if irrigation is used during burr-hole craniostomy for cSDH irrigation fluid at body temperature should be used instead of irrigation at room temperature. However, further studies on whether irrigation during cSDH evacuation is necessary at all would be of interest. At present, the evidence concerning irrigation is contradicting and limited by non-RCT studies. Interestingly, a Finish multicentre RCT exploring irrigation versus drain alone in cSDH-surgery is ongoing [110]. We have explored the benefits of a physical property such as irrigation fluid temperature during cSDH-surgery, but it is possible that irrigation fluid temperature may have an impact in other surgical procedures as well. As previously described warm irrigation has been shown to reduce bleeding in ENT-surgery [161, 162]. However, the irrigation temperature used in ENT-surgery was 50 °C which is probably not suitable in neurosurgery. Comparative studies of irrigation at room temperature versus body temperature has also been conducted in arthroscopic surgery and urological surgery. The focus of these studies was the effect of irrigation temperature on core body temperature. Irrigation at body temperature was shown to inhibit a decline in core body temperature and reduce postoperative shivering [165-167]. It is possible that irrigation at room temperature during cSDH-surgery may have a negative impact on core body temperature, but it has not yet been studied.

In study IV we explored the influence of a postoperative drainage time of more or less than 24 hours after cSDH evacuation. We found a significantly shorter hospital stay in the < 24 hour-cohort but no difference regarding mortality, complications or recurrence. Our results indicate that a drainage time less than 24 hours after burr-hole craniostomy with an active subgaleal drain may be sufficient. However, the results need to be verified by a RCT. A study protocol for a RCT comparing drainage times of 24, 12 or 6 hours has recently been published [168]. However, since the drain type used in the proposed study is a passive subdural drain, a RCT exploring different drainage times with an active subgaleal drain would also be interesting.

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APPENDIX

A1 – Glasgow Coma Scale *(adapted from Teasdale et al [22])*

Behaviour	**Response**	**Score**
Eye opening response	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Oriented to time, place, and person	5
	Confused	4
	Inappropriate words	3
	Incomprehensive words	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion (decorticate)	3
	Abnormal extension (decerebrate)	2
	No response	1
Total score	Best response	15
	Comatose patient	≤ 8
	Totally unresponsive	3

A2 – modified Rankin Scale *(adapted from Wilson et al [143])*

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

A3 – EQ5D-3L *(adapted from Rabin et al [156])*

Dimension	Description	Score
Mobility	I have no problems walking about	1
	I have some problems in walking about	2
	I am confined to bed	3
Self-care	I have no problems with self-care	1
	I have some problems with self-care	2
	I am unable to wash or dress myself	3
Usual activities	I have no problems with performing my usual activities	1
	I have some problems with performing my usual activities	2
	I am unable to perform my usual activities	3
Pain/Discomfort	I have no pain or discomfort	1
	I have moderate pain or discomfort	2
	I have extreme pain or discomfort	3
Anxiety/Depression	I am not anxious or depressed	1
	I am moderately anxious or depressed	2
	I am extremely anxious or depressed	3

A4 – Postoperative evaluation (< 24 h) for study III.

Variable	BT-group (N=264)	RT-group (N=277)	p-value
Persistent paresis - n/N (%)	30/264 (11%)	42/277 (16%)	p=0.13
- improved	20/30 (67%)	27/42(64%)	
- same	6/30 (20%)	8/42 (19%)	
- worse	4/30 (13%)	7/42 (17%)	
Persist. dysphasia – n/N (%)	16/264 (6%)	22/277 (8%)	p=0.29
- improved	9/16 (56%)	13/22 (59%)	
- same	3/16 (19%)	3/22 (14%)	
- worse	4/16 (25%)	6/22 (27%)	
Persist. Confusion – n/N (%)	50/264 (19%)	66/277 (24%)	p=0.10
- improved	21/50 (42%)	29/66 (44%)	
- same	22/50 (44%)	21/66 (32%)	
- worse	7/50 (14%)	16/66 (24%)	
GCS – median (range)	15 (15-10)	15 (15-9)	

A5 – Complication profile for study III.

Case	BT-group	RT-group
1	Seizure postop.	Seizure postop
2	Insular infarction, permanent neurological deficit.	Urinary tract infection
3	Pneumonia	Urinary tract infection
4	Small ICH, no surgical intervention, no permanent deficit.	Deep venous thrombosis
5	Pneumonia	Myocardial infarction
6	Deep venous thrombosis	Wound infection, treated with antibiotics, no surgical revision
7	Small ICH, no surgical intervention, no permanent deficit.	Ischemic stroke, permanent neurological deficit
8	Severe confusion with psychosis	Wound infection, treated with antibiotics, no surgical revision
9	Seizure postop.	Ischemic stroke, permanent neurological deficit
10	Deep venous thrombosis	Ischemic stroke, permanent neurological deficit
11	Urinary tract infection	Small ICH, no surgical intervention, no permanent deficit.
12	Urinary tract infection	Acute subdural hematoma, reoperation.
13	Acute subdural hematoma, requiring reoperation	Sepsis of unknown origin.
14	Urinary tract infection	Myocardial infarction
15	Seizure postop.	Urinary tract infecion
16	Wound infection, treated with antibiotics, no revision surgery	Ischemic stroke, no permanent neurological deficit
17	Urinary tract infection	Urinary tract infecion
18	Pneumonia with sepsis, fatality.	Pneumonia
19	Acute subdural hematoma, requiring reoperation	Urinary tract infecion
20	Wound infection, treated with antibiotics, no revision surgery.	Urinary tract infecion
21		Ischemic stroke, permanent neurological deficit
22		Wound infection, treated with antibiotics, no surgical revision
23		Pneumonia
24		Renal failure
25		Seizure postop.