Chronic subdural hematoma: tailoring treatment

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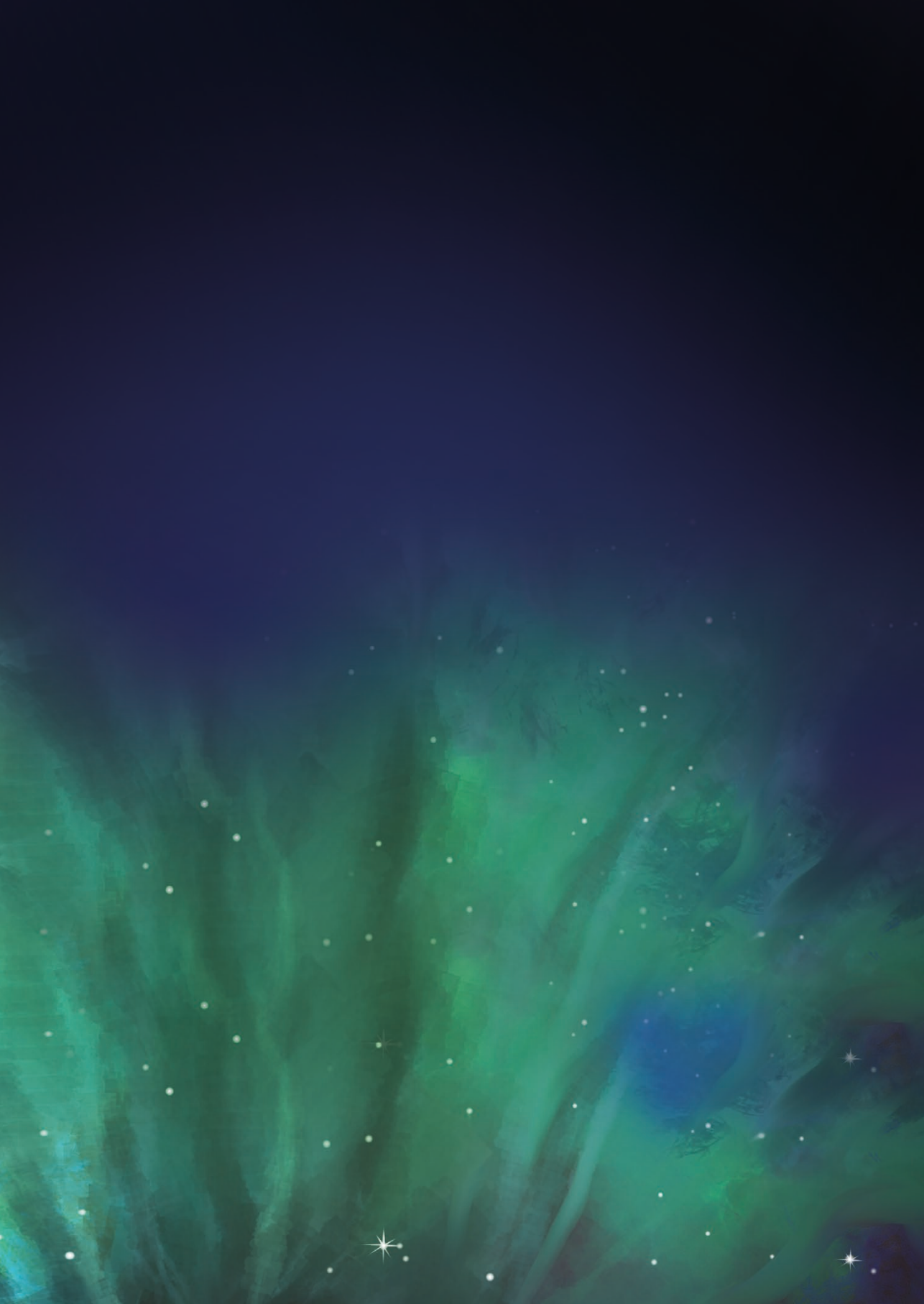

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Summary, general discussion and future perspectives

Summary

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

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

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

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

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

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

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

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

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

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

At three months fewer patients in the dexamethasone group had a favorable functional outcome (modified Rankin Scale score 0-2) than in the surgery group; 102 of 124 patients (82.3%) and 110 of 124 (88.7%) respectively. The adjusted common odds ratio (acOR) for a worse functional outcome (modified Rankin Scale score) associated with dexamethasone therapy at three months was 2.28 (95% CI, 1.43 to 3.64). More complications were observed in the dexamethasone group compared to the surgical group (67% versus 33%). The risk of any infection was 22.8% in the dexamethasone group and 19.2% in the surgery group, for hyperglycemia 19.7% and 4.0%, and for delirium 15.7% and 5.6% respectively. The mean total length of hospital stay within 3 months was 12.0 days (SD 10.6) in the dexamethasone group and 6.8 (SD 6.7) in the surgery group. Mortality was observed in 6% in dexamethasone and 2% in surgical group (aOR 2.63, 95% CI 0.43 to 16.67).

Based on the results of this trial, we concluded that dexamethasone therapy resulted in worse functional outcome at three months compared to surgery by burr-hole craniostomy. Furthermore, patients treated with dexamethasone frequently required additional surgery, had higher mortality, more adverse events, and longer length of hospital stay. The results showed there is no indication for dexamethasone therapy in symptomatic patients with chronic subdural hematoma.

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

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

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

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

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

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

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

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

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

In conclusion, the largest reduction in hematoma size was achieved in symptomatic patients with chronic subdural hematoma without hyperdense components after two weeks of dexamethasone treatment. The need for additional surgery was highest in patients with separated hematoma and this subtype, together with homogeneous hyperdense hematoma, showed lower rates of clinical improvement compared to other hematoma subtypes. The presence of hyperdense components in chronic subdural hematoma could therefore be of prognostic value for poor response to dexamethasone treatment.

General discussion

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

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

Dexamethasone as alternative to surgery

Functional outcome

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

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

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

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

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

Complications

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

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

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

Radiological prognostic markers for treatment outcome

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

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

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

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

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

Conclusion

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

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

Future perspectives

Optimizing treatment

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

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

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

Data improvement

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

Prognostic radiological markers

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

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

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

Prognostic clinical markers

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

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

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

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

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