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Perioperative quality assurance in neurosurgery

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“We must think critically, and not just about the idea of others. Be hard on your beliefs. Take them out onto the veranda and hit them with a cricket bat.”

Tim Minchin, 2016

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Kristin Sjåvik
Tromsø, February 22nd 2018

Perioperativ kvalitetssikring i nevrokirurgi - forord

«I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least part of the work»

Harvey Cushing, 1920

Nevrokirurgi er et fagfelt som innebærer operasjoner med til dels høy risiko. Denne avhandlingen fokuserer på flere av faktorene rundt selve det kirurgiske inngrepet - faktorer som i høy grad påvirker det endelige operasjonsresultatet. Mange av forholdene utenfor operasjonsstuen har stor betydning for pasientforløpet, og er sentrale i kost-nytte analyser. Lykkes man med å optimalisere viktige perioperative faktorer, vil det bidra til tryggere og bedre behandling, og ikke minst til å minimere risiko for komplikasjoner og behov for ytterligere intervensjon.

Prosjektet er et samarbeid mellom nevrokirurger ved tre skandinaviske universitetssykehus. Hvert enkelt sykehus har lang erfaring med nevrokirurgisk behandling, og har sine egne behandlingsmetoder som gjennom tidene har blitt overført i mester-svenn tradisjon. I moderne nevrokirurgi, som i flere andre spesialiteter, ser man et økende fokus på evidensbasert kunnskap. Selv om man behandler de samme lidelsene, finnes det ulike måter å håndtere samme pasientgruppe på. Til tross for at operasjonene stort sett er ensartede, er det viktige systematiske forskjeller fra sted til sted i hvilke prosedyrer man har rundt kirurgiske inngrep, som igjen kan påvirke resultat i form av komplikasjoner og overlevelse.

Målet med dette prosjektet er å fremskaffe evidensbasert kunnskap som kan utfordre sedimenterte kirurgiske dogmer i pasienthåndtering fra 24 timer før et inngrep til 30 dager postoperativt. Kun på den måten kan man sikre et likartet tilbud og resultater av høy kvalitet - uavhengig av hvor man er bosatt og hvilken klinikk man sokner til. Avhandlingen bygger på fire artikler som er en del av en serie tilsvarende prosjekter. Flere av de fremtidige prosjektene er allerede startet – og noen av de tidligere publikasjonene fra samarbeidspartnere i dette prosjektet er allerede ansett som internasjonalt standardsettende.

Metoden vi har brukt i «perioperativ kvalitetssikring i nevrokirurgi» kan brukes vitenskapelig ved evaluering av en rekke nye områder av pasientbehandlingen. Skandinavia med sitt offentlige helsevesen står i en særstilling i verden med god tilgang til populasjonsbaserte helsedata. Her vil det ligge til rette for å etablere fremtidige evidensbaserte perioperative retningslinjer for behandling av nevrokirurgiske tilstander.

Tromsø 22.02.18

Kristin Sjåvik

Abstract

Background

Perioperative treatment for common neurosurgical conditions such as chronic subdural hematomas (CSDH) and meningiomas vary. The perioperative period is by definition the time span from 24 hours before surgery until 30 days postoperatively. Even if the surgical treatment in the operation theater can be exactly the same, complication rates differ, and results vary. The aim of the thesis was to compare recurrences after CSDH burr-hole surgery using three different drainage techniques, to establish the risk of recurrence in CSDH patients using antithrombotic (AT) medication, to clarify the risk/benefit ratio of prophylactic pharmacotherapy initiated the evening before craniotomy for meningioma, and to identify important predictors for complications in meningioma surgery. A future more large-scale aim was to clarify whether this pragmatic research design could be used for further refinement and quality work in practical neurosurgery.

Methods

A comparative effectiveness framework was created to conduct retrospective reviews in different Scandinavian cohorts from three different neurosurgical departments (Karolinska University Hospital, University Hospital of North Norway and St. Olavs University Hospital). The Scandinavian cohorts were all population-based, and all patients treated between 2005 and 2013. Studies included large number of patients ranging from 763 to 1260 patients.

Results

Active subgaleal drainage for 24 hours after surgery seems to be the most efficient and safest treatment strategy for chronic subdural hematoma. Patients with CSDH on antithrombotic therapy at the time of diagnosis, have similar recurrence rates and mortality compared to those without antithrombotic therapy. Early AT resumption is not associated with more recurrence, but with lower thromboembolic frequency. As needed perioperative administration of low molecular weight heparin, reserved for patients with excess risk because of delayed mobilization, is effective and appears to be the safest strategy, rather than routine administration. Severe complications after meningioma resection are more encountered in elderly patients (>70 years old), dependent patients (Karnofsky performance scale <70), and patients who undergo longer lasting surgery (>4 hours). Patient selection, including careful consideration of the individual risk-benefit ratio, is important in improving the safety of intracranial meningioma resection.

Conclusion

The framework with its population-based studies provided valid results for the clinical questions raised. The researchers will continue to work on establishing evidence-based guidelines for common neurosurgical conditions within the established research platform.

List of publications

I. **Assessment of drainage techniques for evacuation of chronic subdural hematoma: a consecutive population-based comparative cohort study.**

Sjåvik K*, Bartek J Jr, Sagberg LM, Henriksen ML, Gulati S, Ståhl FL, Kristiansson H, Solheim O, Förander P, Jakola AS.
*Drs. Sjåvik and Bartek contributed equally to this work (shared 1st authorship)
Journal of Neurosurgery. 2017 Jun;23:1-7.

II. **Role of antithrombotic therapy in the risk of hematoma recurrence and thromboembolism after chronic subdural hematoma evacuation: a population-based consecutive cohort study.**

Fornebo I, Sjåvik K, Alibeck M, Kristiansson H, Ståhl F, Förander P, Jakola AS, Bartek J Jr.
Acta Neurochirurgica (Wien). 2017 Nov;159(11):2045-2052.

III. **Venous Thromboembolism Prophylaxis in Meningioma Surgery: A Population-Based Comparative Effectiveness Study of Routine Mechanical Prophylaxis with or without Preoperative Low-Molecular-Weight Heparin.**

Sjåvik K, Bartek J Jr, Solheim O, Ingebrigtsen T, Gulati S, Sagberg LM, Förander P, Jakola AS.
World Neurosurgery. 2016 Apr;88:320-6.

IV. **Predictors of severe complications in intracranial meningioma surgery: a population-based multicenter study.**

Bartek J Jr*, Sjåvik K, Förander P, Solheim O, Weber C, Ingebrigtsen T, Jakola AS.
*Drs. Sjåvik and Bartek contributed equally to this work (shared 1st authorship)

World Neurosurgery. 2015 May;83(5):673-8.

The papers will be referred to by their Roman numerals in the text.

Abbreviations

AD = Active subgaleal drainage

AT = Antithrombotic treatment (antiplatelets and anticoagulants)

CER = Comparative effectiveness research

CID = Continuous irrigation and drainage

CSDH = Chronic subdural hematoma

CT = Computer Tomography

DVT = Deep vein thrombosis

ICU = Intensive care unit

KPS = Karnofsky Performance Scale

LMWH = Low-molecular-weight heparin

MRI = Magnetic Resonance Imaging

PD = Passive drainage

PE = Pulmonary embolus

RCT = Randomized controlled study

VTE = Venous thromboembolism

Introduction

Historical perspectives

Surgical treatment strategies, and decisions on how and when to perform an operation, have historically largely been based on traditions and the surgeon's own personal experience and preference (1,2,16). Back in the days of neurosurgical pioneer Harvey Cushing (1869-1939), neurosurgical journals were scarce, and seeking advice from colleagues in other parts of the world was not easy (3). Undergoing intracranial tumor surgery at that time, patients faced a mortality rate as high as 50%. Cushing eventually established a large referral base and systematically started to follow his patients. By 1910 he had operated a total of 180 tumor patients and managed to reduce mortality rate to 13%. His registration and follow-up routines were the beginning of modern quality assurance in neurosurgery. In parallel, Norway's pioneering neurosurgeon Vilhelm Magnus (1871-1929) operated 216 tumor patients with equally low mortality rates as Cushing (4,5). The two surgeons met in 1928. Since then, a technical revolution and modern research have brought us into an era where advanced operations are performed on a regular basis with lower morbidity and mortality rates than ever before (6,7). Having reached these low mortality rates, focus has discretely shifted towards patient-reported outcomes, such as functional scores and health related quality of life (8). Surgical patriarchs are being challenged by patient involvement, i.e. shared decision-making, which relies highly on correct preoperative risk-benefit assessments. The need for clinicians to keep updated - critically evaluating and embracing quality research, continuously asking questions about own practice, is essential. In 2018 "the human factor" in surgery and patient treatment is still as crucial as in Cushing's time, and the need for quality assessment of clinical practice sustains.

To Err is Human

In the book "To Err is Human", published in 2000 by the Institute of Medicine (US) Committee on Quality of Health Care in America, the authors found that as many as 98,000 people die each year from medical errors in American hospitals (9). This initiated a national agenda for reducing medical errors and improving patient safety. The initiative was followed by many publications, WHO Guidelines for Safe Surgery were launched in 2009 (10), and in 2009 there was a landmark publication showing that morbidity and mortality rates after surgery went down after implementing a simple "safe surgery" checklist (11). This new method had been adopted from aviation and other industries considered high risk such as space aeronautics, offshore industry and military defense (9).

People and doctors make mistakes. This thesis is partly about minimizing operator error in perioperative neurosurgical care, but most of all to gain scientific knowledge about best practice in everyday patient flow. Safe surgery procedures and increased focus on patient safety has become a natural part of our everyday surgical work, and routines for aberrations and constant improvement in patient care is more streamlined than only a decade ago.

In this thesis, the perioperative time period is defined as the 24 hours before surgery and the first 30 days postoperatively. In paper IV, we expanded the timespan to comprise indications for elective surgery. This often takes place in the outpatient clinic weeks or months prior to surgery. The aim is to optimize outcome and to minimize complications based on a balanced risk-benefit judgement.

A decision to perform or undergo brain surgery is different than many other types of surgical decisions, simply because this organ can be non-forgiving if even the smallest mistake is made.

Neurosurgery, a high-risk endeavor?

In spite of historically low morbidity and mortality rates, neurosurgery is still considered a high-risk field (12,13). The borders are constantly pushed, a surgical "comfort zone" is never reached. As neurosurgeon and author of the populistic bestseller book from 2014 "Do No Harm" (2014) Henry Marsh stated: "As I become more and more experienced, it seems that luck becomes ever more important." Not the most reassuring statement to hear from a surgeon before going through surgery, but an honest description about the borderline of what is technically possible and what is not. The book reached top-selling numbers last year, showing that the public interest in quality of care and awareness of its vulnerability increases.

As neurosurgeons, we are regularly confronted with complications, and constantly reminded to stay alert throughout working hours both in the operation theater and in outpatient clinics where crucial decisions are made. Considering the high demands of treatment quality, evidence-based guidelines for neurosurgical treatment and perioperative quality handling are still surprisingly scarce (14,15).

This is somewhat in contrast to modern *medical* research. Especially in the pharmacological industry, research is often performed in the framework of heavily financed large randomized controlled studies (RCT) where patient homogeneity is essential, ensuring high internal validity. In surgery, RCTs aren't always feasible (17). It needs to be acknowledged that surgical research is different and more complex compared to pharmacological research. Patients constitutes a highly heterogenous group, and treatment decisions are dependent not only on the skills and treatment traditions of each individual surgeon or surgical unit – but also on the preferences of each single patient. In surgical research, patients have also shown to be reluctant to randomization when the treatment is invasive (18) and carries a risk. Particularly in surgery, comparative effectiveness studies have proven to be a helpful supplement to the strict setup of RCTs – combining the strength of the gold-standard RCT but in a more pragmatic clinical real-life setting (19). This ensures high external validity, however with some important limitations that will be further discussed.

A high-risk neurosurgical operation is not finished until you see the patient awake in and through postoperative care. If you remove a meningioma, you can perform beautiful and well-planned surgery. But if you administer pharmacological thromboembolic prophylaxis directly prior to surgery and miss the potential life-threatening hematoma developing in postoperative care, the patients will not benefit from what you just did. If you irrigate a chronic subdural hematoma in the operation theatre, but do not keep a drainage for the coming hours, twice as many patients will have to be re-operated within the coming weeks. These are small but important issues that influence the overall surgical result and perioperative risk. Working together and discussing patient management with colleagues from other hospitals home and abroad, one soon realizes that the variation in perioperative handling of patients is greater than the differences in surgical exposure and craftmanship itself. Giving each patient the best treatment should be defined not only by the operation but by the whole package of care (9).

Patient safety and risk prediction

A minority of the patients are subject to errors or major complications. Hence, prevention and monitoring should be tailored at high-risk patients to be most effective.

In paper IV, we benchmarked risk for complications following meningioma surgery and aimed to predict risk for severe complications. This is essential in ensuring informed patient consent and tailoring of pre-, per- and postoperative care.

How do we measure and monitor perioperative safety? The Landriel Ibañez classification (2010) is a validated tool for evaluating neurosurgical complications (20). It represented a further development of the Clavien-Dindo grading (21) from 1992. The latter classified general surgical complications in four severity levels. The classification gave rise to valuable discussions about complication monitoring and assessment (22,23). The Landriel Ibañez scale was published as a modified, tailored classification system for neurosurgical and spine surgery complications. Therefore, we consequently use this classification to compare complication rates between centers and differences in perioperative treatment. The classification will later be described in detail, along with its strengths and weaknesses.

Chronic subdural hematoma

Evacuation of chronic subdural hematoma is one of the most common neurosurgical procedures. It is most often encountered in the elderly and in the neonates. In neonates, the pathogenesis is different, and they are therefore not included in our study (24). The number of CSDH patients is expected to increase as the oldest segment of the population continues to grow. According to the prognosis for 2030, CSDH is expected to be the most common intracranial neurosurgical condition in the US (25,26). Incident rates for surgical intervention is reported 10-20/100.000 per year in different materials (26,27,28).

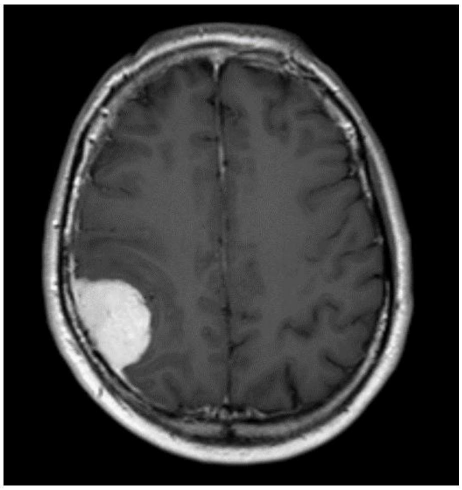
The pathophysiology is still debated and not fully understood (29). What we do know, is that rupture of bridging veins running from the cortical surface into the dura and greater venous intracranial sinuses leads to accumulation of blood in the subdural space. Cerebral atrophy, which comes naturally with age, contributes to "stretching" of the veins - making them prone to rupture with only minor trauma. One supplemental theory is that hyperangiogenesis and micro bleedings in the so-called neomembrane might play a role in the development of, and especially in the recurrence of, CSDH (30).

Treatment is technically not very demanding. However, the patients are often old and carry comorbidity (27,28,29,31). There is practically no upper age limit for going through surgery for CSDH - left untreated the hematoma often cause severe neurological damage and death. The surgery is mini-invasive, mostly done under local anesthesia in combination with sedation. After a 3-4 cm skin incision, a small burr hole in the skull is made. The surgeon then enters the subdural space which is easily reached through the dura mater, and the blood is washed out. The procedure typically takes 20-30 minutes, and the overall outcome is generally good, and the morbidity and mortality rates related to the surgical procedure is low (27). The use of postoperative drainage systems for the first postoperative hours is common (31-36).

Typical perioperative course for CSDH

Clinical symptoms lead to a CT scan/MRI in a local hospital. A neurosurgical unit is contacted if a CSDH is confirmed - and if indication for surgery, transfer to the regional neurosurgical unit is arranged. If the patient is on antithrombotic medication this is typically paused prior to transferal – and if the situation is not critical, there is often a few days delay before surgery is performed. Most patients are treated as emergency cases by on-call surgeons within the first 3-4 days after diagnosis. Critical postoperative events are rare (27). The postoperative treatment strategies still vary, as will be described in paper I and II. The length of stay in a neurosurgical unit is usually of 1-3 days duration before transfer back to a local hospital or discharge to home. Follow up routines after discharge vary. Follow up visit at the neurosurgical unit is usually not necessary if surgery and recovery has been uneventful.

Intracranial meningioma



Intracranial meningioma is a typically benign lesion originating from the meninges. Therefore, serious treatment complications are less acceptable. The incidence is 7-9/100 000, making it the most common primary brain tumor operated, and the most frequent radiological intracranial neoplasm finding (37,38). These tumors are frequently incidental radiological findings connected to assessment for unspecific neurological symptoms or signs, and head trauma.

Meningiomas are usually slow-growing benign tumors, mostly WHO grade I, but sometimes a more malignant clinical course and/or histopathology can be seen (40,41). Many of these patients are followed with «watchful waiting», that is repeated MRI imaging. Treatment is often advocated if growth or development of symptoms occurs. The tumor can be surgical removed, which is the treatment modality of choice. Other treatment options are gamma knife surgery for smaller lesions (<3 cm), or conventional irradiation for more extensive or malignant lesions and if surgery is not an option. Surgery can be time consuming, depending on the location of the tumor, and is normally done under general anesthesia. There can be technical challenges such as closeness to neurovascular structures, eloquent localization or involvement of large parts of the skull base, implying high-risk procedures. For craniotomies surgeons usually use a high-speed drill and saw to gain access to the brain via a larger opening. In meningioma surgery, the ultimate goal is to remove the tumor with the meninges that it originates from, but sometimes only partly resection can be done due to technical challenges already mentioned.

Typical perioperative course for meningiomas

For patients with meningiomas, there is usually an outpatient consultation weeks or months before surgery after diagnostic CT and/or MRI. If indication for invasive treatment, these cases (with a few exceptions) are highly elective. Patients are admitted the day before surgery, go through standard preparations, and undergo well planned surgery the day after. The operation usually lasts for a few hours depending on location and size, and postoperative monitoring focuses on epileptic seizures, neurological deterioration and postoperative hematoma. These patients are typically hospitalized for 3-4 days, but on a regular basis these patients experience transient or permanent neurological disturbances or postoperative complications, as focused on in paper III and IV. Some admissions therefore last longer, and sometimes structured and protracted rehabilitation is necessary after undergoing surgery.

Controversies in current literature

Chronic subdural hematoma and drainage techniques

The benefit of postoperative drain vs no drain after evacuation of CSDH has been established (32). Still, recurrence rates are high, and ways to achieve further improvement should be sought. Drainage technique varies and there are controversies as to what drainage system is most effective and safe (31-36).
Santarius et al. reported a 6 months recurrence rate of 9.3% after postoperative subdural drainage. The no-drain group in the study had a recurrence rate of 24%. In this study, they made two burr holes instead of one, possibly facilitating CSDH evacuation (42). Secondly, the drain was kept in place for 48 hours in contrast to 24-hour drainage, and the potential drawbacks of prolonged drainage time has earlier been discussed by other authors but is not yet clear (43,44). Increasing demands on efficiency and optimization of perioperative patient flow makes it difficult to justify this perhaps more extensive treatment strategy – at least when recurrence rate still is quite high.

In 1999, a publication from one of the centers involved in our current study demonstrated a recurrence rate of 2.6% when using continuous irrigation and drainage postoperatively. This recurrence rate was remarkably low (36). A prospective trial from 1993 had earlier shown no statistical difference in recurrence rate with this technique compared to a closed-system drainage, but the study included only 19 patients in the study group (99). The very low recurrence rate of 2.6% was never confirmed at other centers. The center which published the 1999 study kept on using the irrigation technique despite the potential danger of allowing continuous inflow irrigation to a clotted outflow drain. In general, when departments choose techniques that have a higher risk profile and is more resource demanding, the results should be proven extraordinary good. The retrospective study from Hennig et al was criticized for using only historical controls, and the postoperative CT did not demonstrate any differences between surgical techniques when measuring the residual interposition between the skull and brain. Furthermore, only 77/137 patients were treated with the technique and comparison was done with no less than three other techniques (no drain, passive drain and craniotomy) used in the same population. The study might be severely underpowered as commented by Avezaat in Acta Neurochirurgica the same issue (36).

Gazzeri et al published a large study in 2007 on the use of subgaleal active drainage instead of the more common subdural passive drainage. They reported 7.6% recurrence in need of a repeated procedure (35). In their study, the intraoperative irrigation was done through a 3 cm mini-craniotomy and postoperative drainage time was 48-72 hours. It seems unfeasible to choose a technique that is more time consuming and resource demanding, yet does not give significantly better results than in the Santorius study, hence the practice changing potential of their study was limited.

With the exception of a randomized controlled trial reporting that postoperative drainage was better than no drainage (32), still there is a lack of high quality evidence in CSDH management. Another RCT did not replicate the benefits of a drainage system, but the study was severely underpowered (46).

Still, there is no consensus as to what drainage technique is most efficient and safe – and only in Scandinavia, there are several different techniques in use even today.

Chronic subdural hematoma and antithrombotic therapy

Other controversies around CSDH treatment have been antithrombotic therapy and the influence on incidence and recurrence rate. The literature provides little or no evidence for an association between the risk of CSDH recurrence and use of AT therapy (46-48). Guha et al demonstrated a postoperative risk of 2.6% for VTE in pausing AT treatment the first 30 days after surgery for CSDH – claiming it could be quite safe to pause AT therapy perioperatively (48). But for how long? The debate is still ongoing and there are no current guidelines for when to resume AT after CSDH evacuation. The question when to resume AT after CSDH evacuation is a frequent one in neurosurgical daily practice, with a recent study (49) revealing that most surgeons relied on their «own intuition and past experiences» when making their decision. The issue is however important since timely resumption may save lives in this setting, e.g. for patients with coronary artery disease, use of ASA can reduce mortality by >20% (50). On the other hand, too early resumption may increase recurrence rates.
Few studies have linked early or late resumption of AT to recurrence rate of CSDH. Only weak evidence suggests no association (48,51). A major concern is that most of these studies might have been underpowered considering their relatively small sample size, and there are also no prospective controlled studies on this topic (46,48,51).

A recent study reported increased thromboembolic events (11.5% vs 6.4%) in the late resumption group (52), but no difference in repeat surgery for CSDH. This finding would indicate that early resumption should be the norm unless clear contraindications are present. The latest publication of interest, published Jan 2018, is a systematic review and meta-analysis (53). Phan et al included eight studies for analysis following PRISMA guidelines for systematic reviews, and concluded that decision to resume antithrombotic medication postoperatively is complex and should be individualized.

The lack of evidence in this matter is not at all surprising. The number of variables, including the individual risk profile, potency of the drug in question, dosage and time of resumption, makes it challenging to perform an RCT, as pointed out in the 2014 review of Chari et al. (54). The authors suggested to use prospective data from clinical registries instead. Until such data become available, the authors conclude that each patient should be assessed individually by the surgeon based on current best evidence concerning the risk of VTE without anticoagulation (55,56).
In paper II we aimed to study both the risk-benefit of early and late re-insertion of AT medication, and if patients of AT therapy have a higher risk of recurrent CSDH.

Intracranial meningioma and venous thromboembolic prophylaxis

Surgery for meningiomas is often long-lasting, and duration of surgery is a known risk factor for thromboembolic events (57). It is unclear whether perioperative antithrombotic prophylaxis such as LMWH can reduce the risk of VTE, or increase perioperative blood loss and the frequencies of postoperative hematomas (58,59).
Postoperative venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism (PE), after intracranial tumor surgery is reported as high as 26% with 1.5-5% risk of PE (12,60-62). PE is a serious complication and reported mortality was 23% in a recent study of patients with meningioma (63).

The efficacy of perioperative pharmacological prophylaxis with LMWH in patients with intracranial tumor has been assessed in two randomized controlled trials (59,60). One study including 307 patients found a reduced incidence of VTE with no increased risk of postoperative hemorrhage among patients receiving LMWH the morning after surgery. However, this study did not have enough power to detect potential differences in postoperative hematomas. The patients were all screened for VTE, and only 10 of 65 patients with VTE were symptomatic. The clinical relevance of asymptomatic DVT can be debated – so for clinical endpoints the study was underpowered and consequently the clinical relevance of the result less clear. Agnelli et al also excluded patients with expected hospital stay less than 7 days. The expected length of stay ≥ 7 days in the study group is clearly longer than the average meningioma patient in Scandinavian centers, and in that setting the clinical value can be questionable.

Another study (59) that randomized 68 patients to placebo or LMWH at the onset of surgery was stopped early because of high frequency (11%) postoperative hematoma in the LMWH group. A more recent systematic review recommended mechanical prophylaxis alone, referring to these studies and potentially devastating consequences of a postoperative hematoma (64).

Definitions of postoperative hematoma vary between studies. It may seem more relevant to compare rates of *reoperations* for hematoma. A recent, large single-center study reported 2.9% of the patients were operated for postoperative hematomas after meningioma surgery (63). In summary, there is still no consensus on the overall use and timing of pharmacological prophylaxis (65-67).

Intracranial meningioma and prediction of complications

For meningioma surgery, standardized reports on complications are so far lacking. Most studies on complications and adverse effects after meningioma surgery are single-institution series spanning previous decades with limited external validity and questionable relevance to contemporary microsurgical approaches (68-74). As people live longer and have higher expectations to quality of life, the literature is limited in the guidance of clinical decision making in meningioma patients.

Old age and reduced functional status have often been considered predisposing factors to poor outcome after intracranial meningioma surgery (75). However, in younger patients, surgical resection is often recommended even for smaller and non-symptomatic meningiomas – especially if growth is demonstrated on subsequent imaging. In elderly patients, conservative treatment is often recommended even in cases of larger, symptomatic meningiomas. If conservative treatment fails (i.e. severe symptoms develop), surgery is offered. But how can we know for certain if the case is not that the increased surgical risk reported in elderly patients may at least be partially explained by the higher incidence of large, symptomatic meningiomas in this group? The previous literature offers no adequate answer to if we in fact are denying a large patient group access to treatment that does not have as skewed risk-benefit perioperative profile as one could believe. There is a need for identifying valid predictors of severe complications in meningioma surgery.

Existing guidelines

In 2016, the publication "Appraisal of the Quality of Neurosurgery Clinical Practice Guidelines" by Ducis et al compared the rate of neurosurgical guideline publications over time with all other specialties (14). Guidelines and quality of supporting evidence were then analyzed. There were 49 guidelines found based on 2733 studies, with only 9% considered highest class of evidence. The guidelines contained 697 recommendations, of which only 24% were considered "Level 1" recommendations. Four years earlier, Yarascavitch et al published the article "Levels of evidence in neurosurgical literature: more tribulations than trials" (15), underlining the lack of high quality evidence in our field.

Recommendations for thromboembolic prophylaxis in neurosurgery were made in 2012. The recommendations are that stand-alone mechanical prophylaxis is provided to patients undergoing craniotomy, but with add-on pharmacoprophylaxis to high-risk patients (e.g., malignant disease with a hypercoagulable state) (76).

There are no guidelines for the treatment strategy of chronic subdural hematoma, nor are there clear guidelines or recommendations for when to resume AT therapy after surgery for CSDH, only recommendations to do individual assessment for each single patient.

Aims of the thesis

- To compare recurrences after chronic subdural hematoma burr-hole surgery in regions served by neurosurgical centers using three different postoperative drainage techniques (Paper I).

- To establish the risk of recurrence in patients with chronic subdural hematoma on antithrombotic treatment, and explore if timing of resumption of antithrombotic treatment influence the occurrence of thromboembolism and hematoma recurrence (Paper II).

- To clarify the risk/benefit ratio of prophylactic pharmacotherapy initiated the evening before craniotomy for meningioma (Paper III).

- To investigate predictors of complications after intracranial meningioma resection using a standardized reporting system for adverse events (Paper IV).

Material and methods

Study population

Scandinavian health care system

The health care system in Norway and Sweden is divided into different geographic regions with compliant referral patterns for intracranial neurosurgery within these regions. There are four neurosurgical centers in Norway (Tromsø, Trondheim, Bergen and Oslo) and six neurosurgical units in Sweden (Linköping, Lund, Uppsala, Umeå, Stockholm and Gothenburg). A patient with an intracranial meningioma in the greater Stockholm region is referred to and cared for at the Neurosurgical Department at Karolinska University Hospital. Similarly, patients with meningioma in northern and central Norway will be referred to the University Hospital of North Norway and St. Olavs University Hospital, respectively. The initial radiological imaging is most often carried out in general local hospitals after referral from a primary physician. There are 39 local hospitals in Norway and 95 local hospitals or health centers in Sweden. Because no private health care alternative exists for patients with meningiomas and chronic subdural hematomas and a strict regional referral is used, it is highly unusual that patients actively seek health care outside their region of residence - in practice eliminating risk of referral bias (6). Data from Statistics Norway (http://www.ssb.no) and Statistics Sweden (http://www.scb.se) were used to estimate the mean population of the respective hospital catchment areas during the study period.

In **paper I** the included patients were all adult patients (18 years or older) treated with evacuation of primary CSDH in the period from 2005 through 2010, at the neurosurgical departments of Karolinska University Hospital (Stockholm, Sweden), the University Hospital of North Norway (Tromsø, Norway) and St. Olavs University Hospital (Trondheim, Norway). The time period was chosen because of the time the current electronical health record and images systems were introduced in Stockholm. This facilitated data collection and secured easy access to radiological imaging. The length of the time period for data collection was decided after power calculations had been done – to ensure adequate statistical power.

The patients were identified using the hospitals' patient administrative databases and operating room logs. Patients who underwent any other form of intracranial surgery during the last 6 months prior to CSDH intervention and those having CSDH in relation to arachnoid cysts were excluded. In total, 1260 patients were included in the study.

All patients in **paper II** were included from Karolinska University Hospital only. We used the same patient data material as in paper I, in the same period of time, with the same inclusion and exclusion criteria. However, Karolinska University Hospital was the only hospital in this time period with electronic medication journals. To ensure high-quality data for primary endpoints which now focused on antithrombotic therapy and the timing of resumption of AT medication as potential factors influencing recurrence rate and complications, we therefore included only the Swedish CSDH patients. 763 patients were included.

In **paper III and IV**, all patients undergoing resection of intracranial meningioma between 2007 and 2013 at Karolinska University Hospital, the University Hospital of North Norway and St. Olavs University Hospital were identified using the hospitals patient administrative databases. This time span was chosen because of introduction of the current electronical operation planning- and surveillance program in Tromsø in 2007. In this study, duration of surgery and blood loss was crucial variables that could not easily be extracted from the old manual operation logs. The data collection took place in 2014, and patients were included up until 3 months prior to collection of data. In total, 979 craniotomies and meningioma resections were performed in patients aged 18 years or older. All cases were histopathologically verified. Biopsies only, transsphenoidal surgery, and patients having undergone intracranial procedures or having experienced thromboembolic events within 3 months before meningioma surgery were excluded. Also, patients from abroad, actively seeking care and operated at the study centers (Karolinska University Hospital), were excluded from the study due to perceived problems with lack of follow-up data.

Interobserver variability

More than one researcher did the data collection. Internal validity was secured by doing random selected double registration of patient data, without any systematic registration difference. Hard endpoints were checked towards death registry. Establishment of two databases using SPSS and input of data material was done by the main author. Regular meetings with researchers from all three centers were conducted to discuss controversial data. Primary endpoints in paper III were double checked for all patients with clinically significant hematomas.

Statistics

All analyses were performed using SPSS (version 21.0 IBM Corp., version 18.0 + 24.0 (Chicago, IL, USA)). The statistical significance level was set to $p \leq 0.05$. All analyses were decided a priori (per protocol) unless otherwise specified.

Paper I: All tests were 2-sided. Central tendencies presented were presented as means ± SD. Categorical data were analyzed using Pearson's chi-square test. Comparisons of means between departments were analyzed using ANOVA statistics. Overall survival was presented as Kaplan-Meier curves and compared using a log-rank test. The post hoc adjusted logistic regression analyses were created due to baseline imbalances between groups.

Paper II: All tests were two-sided. Central tendencies were presented as means ± SD or medians (interquartile range) in case of skewed distribution. Comparisons of groups when the dependent variable was continuous and there was a dichotomous grouping variable were analyzed with an independent sample t-test when data were normally distributed and with the Mann-Whitney U test when data were skewed. Categorical data were analyzed with Pearson's chi-square test. Comparisons of means between groups were analyzed using independent samples Student's t-test.

Paper III: Comparisons of dichotomous data were analyzed with Pearson's chi square test. Distributions of continuous variables were analyzed with independent sample t-test if normally distributed or with Mann-Whitney U test if skewed.

Paper IV: We used q-q plots to test whether data were normally distributed. Categorical variables were assessed with chi-square test. Univariate analysis included screening of all gathered outcome predictors, with age as a continuous variable, whereas all other predictors were categorical. Outcome predictors with a P value ≤ 0.1 were included in a final multivariable regression model. To test if the model was robust, the variables were also analyzed with full information (i.e., no categorization). $P \leq 0.05$ was considered statistically significant.

Ethical considerations

All studies were approved by the Regional Committee for Medical and Health Research Ethics in Central Norway, and by the Stockholm regional ethical review board in Sweden.

All studies were registered in clinicaltrials.gov prior to data collection. Reporting is consistent with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Outcome measures

The Landriel Ibañez classification

The Landriel Ibañez classification has been used as the main complication assessment in our four papers. This standardized way of reporting perioperative (within 30 days after surgery) adverse events was introduced for neurosurgical procedures in 2011 (20). It has raised important discussions about how to compare clinical results of different neurosurgical centers, and about whether a classification of complications in neurosurgery is necessary (77).

Table 1. Classification of Neurosurgical Complications

Grade I	Any non–life-threatening deviation from normal postoperative course, not requiring invasive treatment
Grade Ia	Complication requiring no drug treatment
Grade Ib	Complication requiring drug treatment
Grade II	Complication requiring invasive treatment such as surgical, endoscopic, or endovascular interventions
Grade IIa	Complication requiring intervention without general anesthesia
Grade IIb	Complication requiring intervention with general anesthesia
Grade III	Life-threatening complications requiring management in ICU
Grade IIIa	Complication involving single organ failure
Grade IIIb	Complication involving multiple organ failure
Grade IV	Complication resulting in death
Surgical Complications	Adverse events that are directly related to surgery or surgical technique
Medical Complications	Adverse events that are not directly related to surgery or surgical technique

ICU, intensive care unit.

(Courtesy of dr. Federico Alfonso Landriel Ibañez)

A standardized way of reporting adverse events may not reveal the entire spectrum of disability induced by surgery. For example, cerebral infarction causing significant disability may be classified as a grade I complication, whereas an otherwise uncomplicated cerebrospinal fluid leak treated with extra stitches or lumbar drain is a grade II complication. If the infarction is extensive enough and considered life-threatening – i.e. demanding aggressive ICP-tailored treatment in intensive care unit and/or surgical craniectomy, it will be classified as a grade III complication. The classification gives ordinal categorical data for complications. When more than one complication was present in a single patient, the major complication was assessed. We believe that the drawbacks of this reporting system are outweighed by the advantages of a standardized assessment allowing more reliable comparisons. For serious life-threatening adverse events, as is our focus in Paper IV, the classification seems robust as we will discuss further.

Recurrence of chronic subdural hematoma

We defined the index operation as the first surgical procedure on the affected side. Bilateral hematomas were registered as one index operation is both sides were treated as part of the same procedure. A recurrent CSDH was defined as same-sided CSDH recurrence treated with surgery within 6 months of the index operation. In the cases in which a one-sided index-operation was followed by a bilateral recurrent procedure (i.e., one recurrent side and one untreated side), the patient was still registered as having only one index operation and one reoperation.

Clinically relevant postoperative hematoma

A clinically relevant postoperative hematoma was defined as radiologically detected hematoma having any possible association with postoperative course/events, including prolonged observation in intensive care unit, delayed mobilization, possibly related neurological deficits including transient deficits, or more severe related events like impaired consciousness or death. All reoperations for postoperative hematomas were obviously registered as such, being one of the secondary end points.

Venous thromboembolic events

At all institutions in these studies, the first-line diagnosis of DVT and PE is lower extremity ultrasonography and contrast-enhanced spiral chest computed tomography, respectively. None of the centers performed VTE screening in asymptomatic patients.

Summary of Results

Paper I

Assessment of drainage techniques for evacuation of chronic subdural hematoma: a consecutive population-based comparative cohort study.

Sjåvik K *, Bartek J Jr, Sagberg LM, Henriksen ML, Gulati S, Ståhl FL, Kristiansson H, Solheim O, Förander P, Jakola AS.
*Drs. Sjåvik and Bartek contributed equally to this work (shared 1st authorship)

Journal of Neurosurgery. 2017 Jun 23:1-7.

Recurrence in need of surgery was observed in 10.8% in the continuous irrigation and drainage cohort (CID), in 20.0% in the passive drainage cohort (PD), and in 11.1% in the active drainage cohort (AD) (p<0.001). Complications were more common in the CID cohort (14.5%) compared with the PD (7.3%) and AD cohorts (p=0.019). Perioperative mortality rates were similar between cohorts (p=0.621). After adjusting for differences in baseline and treatment characteristics in a regression model, the drainage techniques were still significantly associated with clinical outcome (p<0.001 for recurrence, p=0.017 for complications).

Although one cannot exclude unmeasured confounding factors when comparing centers, active subgaleal drainage seems to be superior to the more common passive drainage - and safer than continuous irrigation.

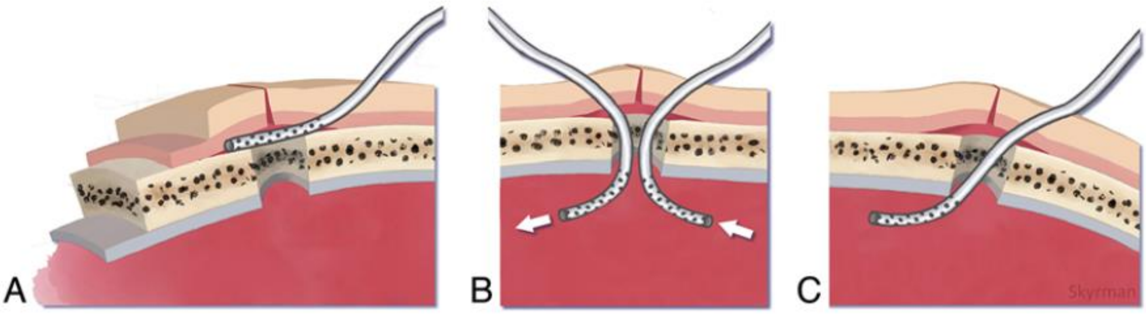


FIG. 1. Illustration of the 3 different drainage techniques. **A:** AD technique with active/suction drainage placed in a subgaleal position overlying the burr hole. **B:** CID technique with active inflow and passive outflow drainage placed in the subdural space. **C:** PD technique with passive drainage in the subdural space. Copyright Simon Skyrman. Published with permission. Figure is available in color online only.

Paper II

Role of antithrombotic therapy in the risk of hematoma recurrence and thromboembolism after chronic subdural hematoma evacuation: a population-based consecutive cohort study.

Fornebo I, Sjåvik K, Alibeck M, Kristiansson H, Ståhl F, Förander P, Jakola AS, Bartek J Jr.

Acta Neurochirurgica (Wien). 2017 Nov;159(11):2045-2052.

There was no difference in CSDH recurrence within 3 months (11.0% vs. 12.0%, p=0.69), nor was there any difference in perioperative mortality (4.0 % vs. 2.0%, p=0.16) between those using antithrombotic therapy (AT) compared to those who were not. Perioperative morbidity was more common in the AT group compared to no-AT group (10.7% vs. 5.1%, p<0.01). Comparing early (<30 days) vs. late (>30 days) AT resumption, there was no difference with respect to recurrence (7.0% vs. 13.9%, p=0.08), but more thromboembolism in the late AT resumption group (2.0% vs 7.0%, p<0.01).

In clinical practice, CSDH patients on AT therapy at the time of diagnosis have similar recurrence rates and mortality compared to those without AT therapy, but with higher morbidity. Early resumption was not associated with more recurrence, but with lower thromboembolic frequency. Early AT resumption seems favorable.

Paper III

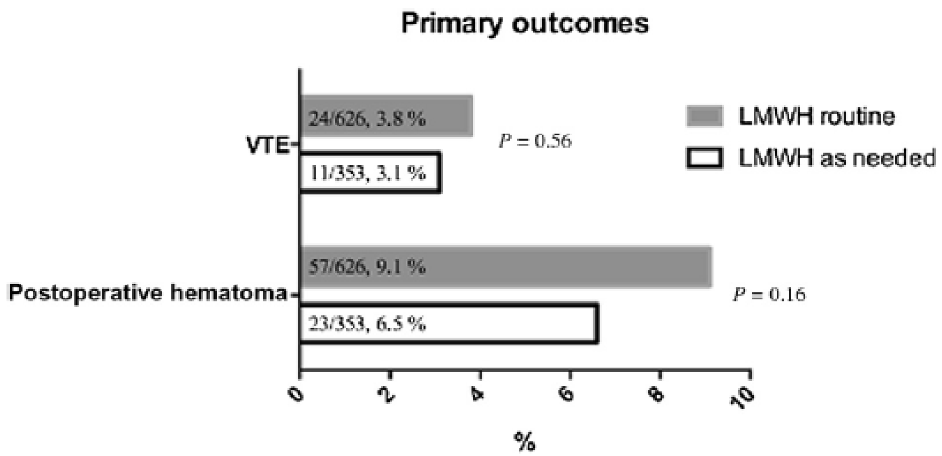
Venous Thromboembolism Prophylaxis in Meningioma Surgery: A Population-Based Comparative Effectiveness Study of Routine Mechanical Prophylaxis with or without Preoperative Low-Molecular-Weight Heparin.

Sjåvik K, Bartek J Jr, Solheim O, Ingebrigtsen T, Gulati S, Sagberg LM, Förander P, Jakola AS.

World Neurosurgery. 2016 Apr;88:320-6.

In the LMWH routine group, VTE was diagnosed after 3.9% of operations compared to 3.1% after operations in the LMWH as needed group (p=0.56). Clinically relevant postoperative hematomas occurred in 9.1% in the LMWH routine group vs. 6.5% in the LMWH as needed group (p=0.16). Surgically evacuated postoperative hematomas occurred after 3.0% of operations in the LMWH routine group vs. 2.3% in the LMWH as needed group (p=0.26).

There is no benefit of routine preoperative LMWH starting before intracranial meningioma surgery. Neither could we detect a significant increase in clinically relevant postoperative hematomas secondary to this regimen. We suggest that as needed perioperative administration of LMWH, reserved for patients with excess risk because of delayed mobilization, is effective and also appears to be the safest strategy.



Postoperative hematoma was defined as intracranial hematoma detected by computed tomography and/or magnetic resonance imaging that complicated the postoperative course.

VTE denotes postoperative deep-vein thrombosis and/or pulmonary embolism verified with diagnostic imaging.

Figure 1. Primary end points. LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

Paper IV

Predictors of severe complications in intracranial meningioma surgery: a population-based multicenter study.

Bartek J Jr*, Sjåvik K, Förander P, Solheim O, Weber C, Ingebrigtsen T, Jakola AS.
*Drs. Sjåvik and Bartek contributed equally to this work (shared 1st authorship)

World Neurosurgery. 2015 May;83(5):673-8.

Severe complications after meningioma resection are more often encountered in elderly patients (>70 years old), dependent patients (Karnofsky performance scale score <70), and patients who underwent longer lasting surgery (>4 hours). Patient selection, including careful consideration of the individual risk-benefit ratio, is important in improving the safety of intracranial meningioma resection.

Based on our results, we created a risk score prediction model encompassing the variables 1) age >70 years, 2) duration of surgery >4 hours, and 3) KPS score <70, with each individual variable having equal significance giving a 4-tier scoring system. The analysis revealed a risk of encountering severe complications when none of the variable were present of 2.2%, with one variable present 7.6%, with two variables present 14.2%, and with all three variables present 46.7% risk.

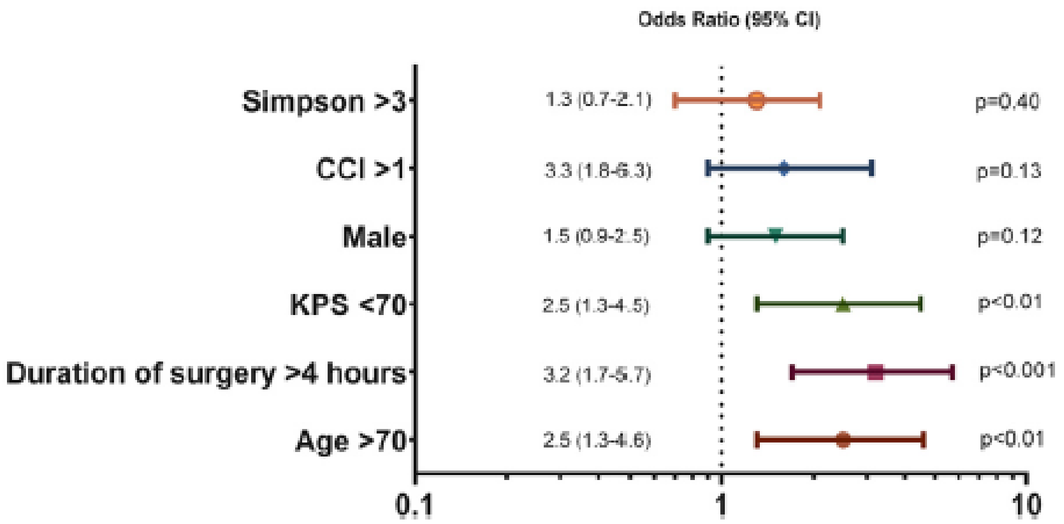
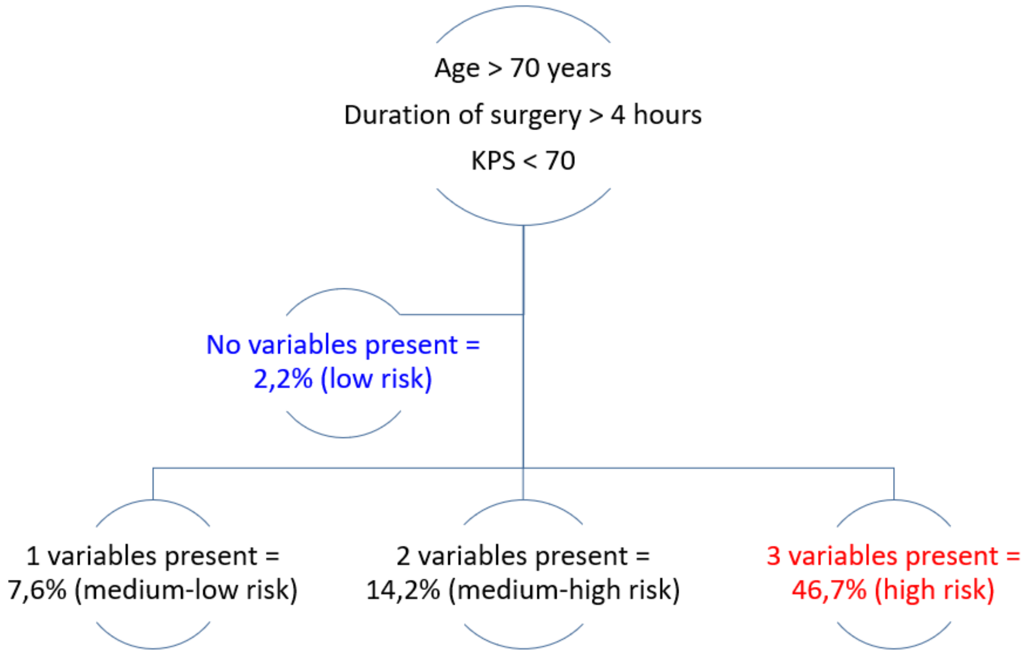


Figure 1. Multivariable regression analysis, including univariable predictors with *P* value ≤ 0.1. CCI, Charlson comorbidity index; KPS, Karnofsky performance scale. . GraphPad Prism version 5.0 (GraphPad Software, Inc., La Jolla, California, USA) was used to construct this figure.

Risk score prediction model for severe complications



Discussion

Patient centered research – the role of the clinician

Patient centered research is described to provide a venue for scientifically and relevant research to promote the development, evaluation and implementation of therapies for each patient. The combination of being both clinician and researcher gives a particular ability to ask relevant clinical questions. This type of research is not in opposition to basic science but an add-on, ensuring practical implementation of findings. “User participation” is now considered mandatory when applying for funding in clinical research, and this means that patients and patient organizations are involved in all or part of the process. In funding for translational research, there is now even an increased demand that clinicians should be involved as “user participation” to ensure clinical relevance of the research.

In 2012, the Methodology Committee of the Patient-Centered Outcomes Research Institute in America published its first recommendation for the conduct of research leading to evidence-based, patient-centered health interventions (78). The report was published in New England Journal of Medicine, and focused on connecting research results to patients’ health care needs. Selected methodological milestones in research were described from the first large-scale RCTs in the 1940s, through propensity score and meta-analysis and ascendancy of registries in the 1980s and 1990s. After year 2000, comparative-effectiveness research and patient-centered outcomes research have been mostly influential with its widespread use in scientific literature (78).

The number and types of available treatment options for a given condition have increased dramatically, and a subtle change of focus from asking “*what is the matter with you”* to *“what matters to you”* is ongoing (8). In intracranial glioma surgery today, perioperative risk assessment includes decision making about awake surgery or not, the necessity of intraoperative use of 5-ALA, 3D ultrasound navigational tool, preoperative functional mapping, and the use of intraoperative neurophysiology including direct cortical stimulation. The clinical benefit of each new tool to a steadily increasing number of possibilities is no longer as obvious as perhaps was the situation with earlier innovations like e.g. electrocautery and endoscopic equipment (79,80). Obviously, sophisticated research methods are required to compare the benefits and potential harms of any given treatment option and perioperative aspects.

As modern health care systems are under pressure to continuously improve the quality and efficiency of care, cost-effectiveness analysis is crucial as more technology and more expensive treatment modalities evolve. Some will claim that when several presumably equally good options exist, none of the options are actually good nor superior to the other. However, to reach such conclusions the hypothesis should be subject to rigorous investigation. Especially when treatment is more expensive and deviates from main stream with potential more risk, there is a particular need for demonstrating good results.
In surgery, the exact cost for one minute of operation time is dependent on so many different factors that there is no straight-forward answer to the question (81). A 2005 study of 100 US Hospitals found that OR charges averaged USD 62/min, and these figures did not include

resources specific to the procedure (e.g., clip for an intracranial aneurysm) and did not include surgeon and anesthesia provider fees (82).
The cost of a four-day administration of LMWH administration for 1000 patients in Norway is nearly USD 30.000. If a CSDH patient keeps a drain for 48 vs 24 hours, making the hospital stay one day longer, the cost for each patient treatment increases with estimated USD 2.000 (numbers from health authorities in Norway).

Based on one of our CSDH studies, we can no longer justify the use of one of the more resource-demanding techniques after not being able to reproduce the particularly good results published in 1999 (36). Also, routine preoperative LMWH seems of no additional value in preventing venous thromboembolism for patients with meningioma undergoing surgery. Practical implementation of such theoretical knowledge is essential not only for each single patient, but for securing best quality treatment in the safest way possible, at the same time as keeping necessary treatment costs at a low.
Taking all these considerations and bringing them into the operation rooms, quite simply - each future surgeon has to gain interest in academia to reach their full potential and to serve not only this patient, but also future patients.

Changing clinical practice – a turtle race

The main goal of this thesis was to gain evidence-based knowledge that could challenge everyday perioperative neurosurgical dogmas. Only in that way can overall equal treatment be ensured – independent of where patients live or which surgical unit they are referred to. This is especially important in public health systems like in Scandinavia with deeply rooted regional referral practice. Patients have less choice as to where, when and how treatment will be given. Ensuring high quality care and concordant indications for surgery, is essential in providing equal health care opportunities.

Change in clinical practice, however, is known to occur slowly (16,83). Implementing new techniques and perioperative treatment strategies in traditional surgical fields, can be a challenging task. In 2015, an online survey of 534 neurosurgeons was conducted using the Congress of Neurological Surgeons member list (16). One sought to understand what decides a neurosurgeon's clinical recommendations for their patients. Interestingly, the basis for the decision making in modern neurosurgery, still greatly consists of cognitive biases, previous training and personal values. Tanweer et al also went further, showing that in many cases the surgeons would potentially choose a different treatment for themselves than the recommendation they gave to their patients.

The surgeon's own evaluation of whether an intervention has been successful or not, has a tendency to be biased in a too positive manner. In studies assessing residual tumor volume in patients with malignant glioma, comparing postoperative MRI with the surgeons subjective peroperative estimate, surgeons consequently overestimate the resection grade (84). In another prospective single-center study from 2017, Sagberg et al (85) showed that when asked directly postoperative the operating neurosurgeons underestimated their patient's functional level at 30 days post-surgery in 15% of all cases, accurately estimated their functional level in 23% and overestimated their functional level in 62% of all cases. This tendency to

overestimate surgical outcomes may have implications for clinical decision making and for the accuracy of patient information.
In paper IV, we identified predictors for severe complications in intracranial meningioma surgery. If a patient's age is >70 years, KPS score is <70, and expected duration of surgery is >4 hours, the risk of encountering severe perioperative complications is near 47%. Such scores, based on simple criteria, may aid surgeons gut feeling. The question is, do surgeons acquire and adopt this new knowledge? In the future, cognitive assistants based on machine learning, using computer technology such as IBM supercomputer Watson, may help us predict clinical course more accurately and also prevent aberrations in perioperative care (86,87).

In a Canadian prospective study from 2008, Cadili et al aimed to establish whether giving access to current scientific evidence to surgeons, could change their practice to bring it in line with current evidence (88). There was no significant change in practice. Even though one could argue that the design of the latter study was poor with a short time-span from exposure to assessment, the finding is still interesting.
The same challenge clearly exists in Scandinavia. The Scandinavian Guidelines for management of minimal, mild and moderate head injury were published in 2000 by The Scandinavian Neurotrauma Committee (SNC) to provide safe and cost-effective assessment of head injury patients (89). The publication of the SNC guidelines was followed by a national implementation process in Norway. Studies in 2003 (90) showed compliance with the guidelines in only 51% of the cases at that point of time, increasing to 54% in 2007 and 64% in 2009 (91). Still, ten years after the initial publication, 36% of the patients with minimal, mild and moderate head injury were subject to management not in compliance with the guidelines.

Having knowledge about these barriers, how can it be explained that the papers in this thesis already led to change of practice in several neurosurgical departments in Norway and Sweden? Could one speculate that creating professional networks and building trust by working in several different units could be one of the criteria for succeeding, in combination with high-quality scientific work? In that case, one could argue that rotation in a different neurosurgical unit should be a mandatory part of the surgical training – both for identifying non-scientific based differences in practice, and getting to know potential future research partners. The combination of clinical work and scientific skills seem to act as a catalyst for implementation. Identifying key persons with influential skills as research partners, and anchoring scientific projects in hospital management, clearly helped our research team. All four projects were fully supported by head of staff in all three neurosurgical departments, which seems to be of great importance if one would like to take on the role of the hare and not the turtle in the ever-ongoing scientific race.

Comparative studies in neurosurgery

Randomized controlled trials often have high internal validity. This well-established, highly ranked study design can sometimes have limitations in practical use - as they generally have less external validity except for small homogenous well-defined groups of patients (17). Comparative effectiveness research (CER) aims to identify what clinical and public health interventions work best for improving health (92). The method has its strengths and weaknesses. At its best, CER can provide useful information to guide clinical decision making, incorporating patient preferences and patient-centered perspectives (19). It allows real-time comparison of treatment in real patients. This ensures a high external validity in a clinical setting, which is one of the key features of CER.

In 2011, it was stated in the New England Journal of Medicine that patients with multiple chronic conditions accounted for more than 80% of Medicare costs, but ironically also was the least studied population because of its complexity (17,93,94) CER is said to provide an opportunity to correct this disparity. For patients with comorbidity, in this thesis exemplified by the elderly CSDH patients, RCTs are not always well suited because of a highly heterogenous patient group. Thus, even well conducted large-scale RCTs with significant results do not always change clinical decision making.

In 2012, JAMA devoted a whole issue to CER, where its pros and cons were discussed in detail. Despite many positive qualities, the study design clearly has its disadvantages.
Most CER are observational studies using administrative data to evaluate harm and benefits. The observational nature of these studies can obviously preclude causal interference. The quality of electronic health journals can be variable, representing a challenge to the quality of retrospective assessment. Confounding by indication and other aspects of care can lead to wrong conclusions – findings in CER must always be used with care in making treatment decisions. To isolate treatment effects, a great number of personal and provider characteristics associated with the different study treatments or the target health outcomes, must be considered.

Neurosurgery in Norway and Sweden is in a particular beneficial position, combining geographically defined health regions with strict patient referral patterns and catchment areas in a public health system without private alternatives. This provides an opportunity to conduct CER within the frames of pseudo-randomization. The study design can provide guidance in risk-benefit discussions with the single patient prior to clinical decision making.

Finally, there are some ethical problems with CER. Studies typically report aggregate effects like proportions of VTE and average intraoperative blood loss – most patients will however experience more or less benefit and harm than average. Looking at specific subgroups like we did in paper II can partly compensate for this, where we for instance extracted the subgroup on antithrombotic medication at diagnosis for further analyzes. Still, bold conclusions in CER must be drawn with great caution, and its main role is to guide in clinical treatment strategies in everyday life.

Strengths and limitations

The chronic subdural hematoma studies

In **paper I**, we found that AD and CID were associated with a lower chance of reoperation due to CSDH recurrence compared with only PD postoperatively. More complications were observed in the cohort treated with CID. The differences in outcomes across cohorts remained following adjustments for baseline characteristics.

The major strength of this study is a very high compliance with treatment strategy in combination with the population-based approach. The study included large number of patients with low rates of missing data. Comparative effectiveness research is prone to confounding factors. To minimize the risk of confounding, registration of data included variables known to potentially influence primary endpoint, such as the indication for repeat surgery. However, we did not use propensity score matching or other advanced statistical methods in further attempts to control confounding.

Limitations inherent to retrospective assessment are present in this study. The difference in outcomes may be at least in part due to the fact that each type of procedure was performed at different hospitals and by different surgical teams. Differences in general postoperative management is a concern, and the way it could contribute to differences between groups. These differences are difficult to control, especially in retrospect, and are complex and dependent on other non-controllable factors like available hospital beds and the constant need for patient turn-over in highly specialized regional centers.

For the CSDH series, there were differences in incidence rates across the three geographical regions. We therefore cannot exclude the possibility that regional differences in treatment indications, follow-up routine, or indications for reoperations may have affected our findings. In the PD cohort, patients were routinely screened 4 weeks postoperatively with a visit in the outpatient clinic and a CT scan, while radiology controls were performed based on clinical symptoms in the CID and AD cohort. The risk of detection bias is present, but the indications for reoperations showed not to be different between cohorts based on our retrospective review, as patients had to present with relevant clinical symptoms in addition to radiological findings. The difference in recurrences between cohorts was large, and although the above-mentioned may have influenced our results, given the magnitude of recurrence rate, bias alone is unlikely to fully explain the observed difference.

Safety around continuous inflow-and outflow irrigation has always been a concern. We did find increased morbidity in the CID cohort. However, in this cohort a higher percentage of the patients had general anesthesia, and in some cases, there was also delayed mobilization. Two recent studies reported that general anesthesia was associated with higher morbidity and longer hospital stays that sedation combined with local anesthesia (95).

This CID cohort was also more frequent users of antithrombotic treatment, which theoretically could explain the higher morbidity rate as well as the fact that the recurrence rate in this time period was surprisingly higher than reported in the Hennig article in 1999 that described a residual rate of remarkably low 2,6% (36). The results from **paper II** however, dismisses this theory as perioperative morbidity was the same in both groups and AT treatment did not affect recurrence rates. We have no good explanation as to why the current CID cohort performed worse than the earlier series except the design of the 1999 study which can be questioned concerning power and setup. The CID technique was introduced only a few years before the publication. If looking at the IDEAL framework for surgical innovation (80), early adopters and pioneers tend to be extra enthusiastic of techniques. Patients may therefore be treated in expert hand with enthusiastic team. However, with dissemination to other caregivers, external validity increases and results usually drop.

In **paper II**, we found that in clinical practice, CSDH patients on AT therapy at the time of diagnosis have similar recurrence rates and mortality compared to those without AT therapy, but with higher morbidity. Early resumption was not associated with more recurrence, but with lower thromboembolic frequency. Early AT resumption seems favorable.

Some of the limitations in paper II are similar to paper I because of its retrospective assessment. The data on CSDH recurrence and postoperative thromboembolism frequency after pausing antithrombotic treatment remain indisputable, but a limitation exists in the lack of long-term follow-up data. The validity of the study is limited by the surgeons often subjective decision on when to resume AT therapy. Resumption may be confounded by indication since AT may be withheld in presumed high-risk patients for reasons we cannot control in retrospect despite having comparable baseline characteristics.

The external validity is limited in the sense that “early” resumption on AT therapy is defined as within 30 days. Even if the median number of days post surgery in the early group for resumption was 16, one could still debate whether this finding could change clinical policy. However, the findings justify an RCT that can push the borders for resuming AT therapy even earlier – as one now knows that there is an increased risk of VTE with late resumption at the same time there was no increased recurrence rate if early resumed.

The quality of data from well-established digital patient medication charts ensures the highest precision in data collection for this paper.

The meningioma studies

Paper III is to our knowledge the largest study to date assessing the risk/benefit of routine prophylactic administration on LMWH in meningioma surgery. The multicenter, population-based approach with the parallel cohorts instead of historical controls provides a valid result for neurosurgical practice. The high compliance to treatment policy in our study ensures representative findings – and we carefully designed the study to eliminate potential selection bias that is a concern in retrospective studies by analyzing according to department policy instead of treatment. There was no statistical significant increase in postoperative hematomas with preoperative LMWH administration. Including early postoperative (within 24 hours) LMWH administration did not alter the results. There was no difference in VTE in the different groups.

The main concern is the possibility for detection bias and confounding factors associated with CER. There may be a difference in groups in the postoperative alertness and thresholds for effectuating radiologic examinations for suspected VTE. This may be one reason for the observed difference in DVT, because it is unlikely that LMWH add-on is associated with increased VTE risk. One could also imagine the possibility that routine administration of LMWH could make the postoperative care less pro-active towards early mobilization, these are factors that are hard to fully exclude.

Concerning postoperative hematomas, different traditions clearly existed between study centers with respect to routine postoperative radiologic assessment. In one center, postoperative CT or MRI was routinely performed in all meningioma patients within three days after surgery. However, in this study, we assessed only clinical relevant postoperative hematomas, which argues for a limited potential bias. If affecting our result, the difference in routines for postoperative imaging is in favor of the LMWH routine group, which makes the small difference between groups concerning hematomas a conservative estimate.

Additional limitations that could be of importance, are the use of topical hemostatic agents previously found to be associated with VTE, and various biological factors. In particular, body mass index is a factor that could influence risk for thromboembolic events that was not possible to extract retrospectively from the patient charts. However, a population-based approach in the homogenous Scandinavian countries reduces the chance of major differences in predisposing factors.

For the interobserver variability assessment, we agreed on the significance of all intracranial hematomas that were registered. We cannot fully exclude the possibility that some hematomas that were not registered still had a slight impact of postoperative course not documented in the patient's electronic health journal. This still would not have any impact of number of reoperations which is perhaps the most robust outcome measure, and this proportion was not significantly different between treatment groups.

Most VTE after intracranial surgery occur within 30 days, and 30 days is also by convention the period considered for postoperative complications and perioperative events (20-22). In this time frame, we had 3 deaths (0.8%) in the LMWH as needed group and 3 in the LMWH routine group (0.5%). There was 1 death in which PE played a causative role, and this was in the LMWH routine group. In the Agnelli studies, there was apparently no cross-over (before the diagnosis of VTE), and patients with expected hospital stay less than 7 days were excluded (60). Despite providing the highest level of evidence, the generalizability of results in RCTs may be questionable. The present study provides a real-life scenario and focus on clinical end points by comparing strategies and allowing for cross-over when indicated. This strategy better reflects the dynamics of clinical decision making and improves external validity of our results.

To examine the possible effect on hemostasis, we analyzed the difference in estimated blood loss and found a significant difference where the LMWH as needed group had less blood loss than the LMWH routine group (300 mL vs. 450 mL, $p<0.001$). Duration of surgery was also significantly longer in the LMWH routine group, this could be a confounding factor. The reason behind longer duration of surgery are probably multifactorial, and possible explanations may be more problematic hemostasis or different surgical traditions in surgical exposure and approaches (57).

In **paper IV** the aim was to investigate predictors of complications after intracranial meningioma resection. In this large, multicenter, population-based study, we found that 7% of patients experienced severe complications (Landriel Ibañez grade III and IV). In a multivariate regression analysis, we found that age >70 years, KPS score <70, and duration of surgery >4 hours were independent risk factors for severe perioperative complications.

Further, because of homogenous data in a large multi-institutional dataset, we decided to create a score predicting severe complications. Based on this simple score, there seems to be a large and synergistic effect of the three factors age>70 years, KPS score <70, and duration of surgery >4 hours. The presence of one factor increased the risk of experiencing a severe complication from 2.2% to 7.6%, whereas the presence of two factors increased the risk to 14.2%, and the risk for severe complications if all three factors were present 46.7%. This should serve as an explorative dataset, and the risk score should be validated in an independent dataset. If this score is validated, it would be a simple and useful score to improve patient selection to minimize serious adverse events.

The paper is to our knowledge the first study to implement the standardized Landriel Ibañez classification of perioperative complications in meningioma surgery. However, a standardized way of reporting adverse events may not reveal the entire spectrum of disability induced by surgery. We still believe that the drawbacks of this reporting system are outweighed by the advantages of a standardized assessment allowing more reliable comparisons between centers.

The study gives a reliable population-based estimate of severe complications in need of intensive care unit treatment. The defined geographical catchment areas and a strong tradition of regional referral practice once again ensure population-based data. The main limitation in paper IV is its retrospective nature and the short follow-up time as the first 30 days postoperatively was defined as the perioperative time of interest.

To our knowledge, no other studies have evaluated the risk of meningioma surgery using a standardized reporting system. However, increasing age, reduced functional status and comorbidity was previously reported to increase risk of bad outcome of meningioma resection (61,68-72). We additionally report that the duration of surgical procedures seems to be important. In this study, we considered duration of surgery as a marker for surgical difficulty, an important factor that is otherwise difficult to control for. However – we appreciate that a potential important confounder equally difficult to control is surgeon skill. Because we are unable to distinguish between factors prolonging surgery, we think that further speculation on these factors are not indicated. Given the strong association with complications (57), anticipated duration of surgery should be considered as an important risk factor in preoperative risk assessment, and if the benefit of surgery is not obvious, one should reconsider surgery or the surgical strategy in elderly patients with surgical challenging meningiomas. Conventional radiotherapy or radiosurgery could be considered the primary therapeutic option in selected elderly patients without symptoms related to local or global mass effect, with promising results reported in the literature for tumor control and the risk of complications (96-98). Because the results are in accordance with most of the existing relevant literature, we also validated the Landriel Ibañez classification for this purpose.

Practical implications of this thesis

- Two departments of neurosurgery with > 1000 surgical procedures every year have changed drainage technique for evacuating CSDH from continuous irrigation and drainage and from passive subdural drainage to active subgaleal drainage. The research results have been presented at international meetings, but we are not yet certain if more clinics have made technical adjustments. There is ongoing quality control.
- Early resumption (<30 days) of antithrombotic therapy after surgery for CSDH seems beneficial, and a RCT is justified and planned for further clarification as to how early this can be done safely. Protocol is in writing.
- LMWH routinely to meningioma patients is not recommended. The largest neurosurgical unit involved in the study with >2000 operations every year have stopped giving LMWH routinely to all patients undergoing elective craniotomy for tumors.
- With simple variables available to all neurosurgeons, the prediction of immediate postoperative course may be improved. The prediction model for severe complications in meningioma surgery can help guide decision making in outpatient setting.

Ongoing quality monitoring

After the results in the chronic subdural hematoma studies, treatment adjustments were done in two of the centers involved. After changing technique for postoperative drainage in CSDH patients in one of the three centers, there was a transient increase in recurrent hematomas the first year. The technique was refined in collaboration with the other center with the longest experience in that particular technique, after which one succeeded in attaining equally low numbers of recurrences. Whenever a change in surgical routine is done, we recommend assessment of the change according to the IDEAL framework for surgical innovation (80).

Future perspectives

Scandinavian neurosurgeons, with our public health care system, is in a particularly beneficial position regarding population-based health information and research. Knowing your neurosurgical colleagues at home and abroad, and learning about different neurosurgical treatment traditions, give rise to adequate clinical questions. The setup is a valuable platform for academics.

If we can establish evidence-based perioperative recommendations for the most common neurosurgical conditions, it will be an unimpeachable way to meet safety and quality demands in everyday ward logistics with its high expectations in patient turn-over and results.

For further refinement, comparative effectiveness research such as the scientific work we have presented, can provide the necessary basis for conducting future RCTs. Pushing the borders is easier when you stand on rock and not in swamp. We now suggest a large-scale RCT for establishment of optimal timely resumption of antithrombotic medication in CSDH patients after undergoing surgery.

To better illuminate perioperative risks and benefits associated with neurosurgical procedures, we also need sensitive and reliable outcome measures. The Landriel Ibañez scale seems promising in streamlining comparison between centers and should be used also in future projects. Still, new validated neurosurgical classifications tools should be sought. Avoidance of complications starts by risk-benefit assessment prior to decision to perform surgery, and identifying important predictors for complications is crucial for keeping morbidity and mortality rates at a low.

The bridge between academic research and surgery needs to become more obvious, it will encourage young neurosurgeons to incorporate scientific work into their everyday workload. International and multidisciplinary collaboration are key elements to the projects in which past dogmas will be left behind and innovative approaches undertaken. Ongoing major international multicenter prospective studies like "Center-TBI" (100), are modern examples of facilitating future research on i.e. perioperative care for head trauma patients. Databases and registries like the NORspine registry can guide our future choices of best treatment and care for our spine patients, choosing from the ever-increasing abundant selection of high-technological equipment and tools for both patient monitoring and surgery. IBM supercomputer Watson or equivalent technology might guide outpatient decision-making if we "feed" such cognitive assistants with up-to-date risk predictor scores.

But future research always starts with asking the right questions.

As the American physicist Lisa Randall (1962-) stated: "Scientific research involves going beyond the well-trodden and well-tested ideas and theories that form the core of scientific knowledge. During the time scientists are working things out, some results will be right, and others will be wrong. Over time, the right results will emerge."

Conclusions

This thesis investigated several perioperative strategies for the treatment of common neurosurgical conditions.

The following conclusions can be drawn:

- Active subgaleal drainage for 24 hours after surgery seems to be the most efficient and safest treatment strategy for chronic subdural hematoma.

- Patients with CSDH on antithrombotic therapy at the time of diagnosis, have similar recurrence rates and mortality compared to those without antithrombotic therapy. Early resumption is not associated with more recurrence, but with lower thromboembolic frequency.

- As needed perioperative administration of low molecular weight heparin, reserved for patients with excess risk because of delayed mobilization, is effective and appears to be the safest strategy, rather than routine administration.

- Severe complications after meningioma resection are more encountered in elderly patients (>70 years old), dependent patients (Karnofsky performance scale <70), and patients who undergo longer lasting surgery (>4 hours). Patient selection, including careful consideration of the individual risk-benefit ratio, is important in improving the safety of intracranial meningioma resection.

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