Comparative effectiveness of surgery for traumatic acute subdural hematoma

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Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Traumatic brain injury

Traumatic brain injury (TBI) has a devastating impact on patients and their families. TBI, defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force,[1] is one of the greatest global healthcare problems. The yearly incidence varies widely per country with estimates ranging between 344 and 103 per 100,000 population (respectively in Asia and in the United States). TBI is the most important cause of death and disability in young adults and is one of the leading causes of injury-related death and disability across all other ages and in all countries. TBI represents 30–40% of all injury-related deaths, and neurological injury is projected to remain the most important cause of disability from neurological diseases until 2030 (2–3 times higher than the contribution from cerebrovascular disorders or Alzheimer's disease).[2-5]

TBI is typically categorized as primary or secondary brain injury. Primary brain injury describes the irreversible damage of the accident, before any emergency care has been given. Secondary brain injury describes the ensuing pathophysiological cascade which is not yet completely clarified but at least involves a complex interplay of neuroinflammation, hematological disturbances, metabolic disarray and neuronal cell death.[6]

Acute subdural hematoma

Sixty percent of patients with TBI needing hospitalization have intracranial hemorrhage. The most prevalent hemorrhages are focal hematomas, with acute subdural hematomas (ASDH) and intracerebral hematomas (ICH) being most prevalent (Figure 1). Another focal hematoma, the epidural hematoma (EDH) is rare. An ASDH after a traumatic head injury is the most lethal TBI despite treatment.[2,7,8]

Patients with an ASDH can experience a diverse array of symptoms, from deep coma or progressive neurological deterioration to slight headache with a focal deficit, and anything in between (Figure 2). This heterogeneity reflects a complex pathophysiology with many different injury types that may accompany ASDH.

Several terms have been used throughout history to describe ASDH such as pachymeningitis haemorrhagica, intradural hemorrhage, subdural hematoma, subacute subdural hematoma (as opposed to ASDH). While this terms all describe certain distinct characteristics, the expert consensus is to divide chronic and acute lesions. ASDH is herein defined as a subdural hematoma diagnosed within 14 days of TBI.[7]

The etiology distinguishes roughly between high-energy road traffic injuries, which are mostly motorized incidents, and low-energy incidental falls, which are typically

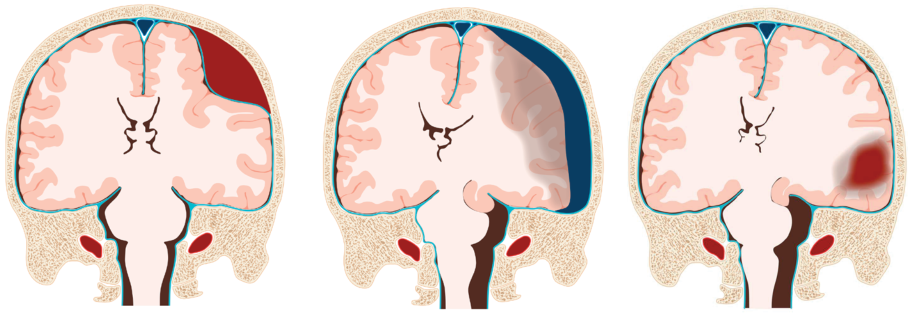

Figure 1. Different types of traumatic intracranial hematoma
(A) Epidural hematoma: a collection of blood between the skull and the outer membrane covering the brain (dura mater). Epidural hematomas are mostly arterial in origin and can thus expand rapidly, causing clinical deterioration and—if untreated—death. Treatment entails prompt surgical removal if symptomatic. (B) Subdural hematoma: a collection of blood located underneath the dura mater, generally associated with bruising of the underlying brain tissue (contusions). (C) Hemorrhagic contusion and intracerebral hematoma: lesions that reflect similar underlying pathologies, ranging from local bruising (contusions) to bleeding into the brain tissue (hematoma). Figure courtesy of Maartje Kunen, Medical Visuals, Arnhem, Netherlands. Reproduced with permission from Maas et al.[11]

ground level falls in the elderly.[9] Incidental falls mostly cause an isolated ASDH that originate from tearing of anchor venes intradurally. High velocity injuries induce several trauma mechanisms upon the brain. Acceleration and deceleration may cause shearing of neurons (diffuse axonal injury) and vessels.[10] Direct impact, whether a blow to the head or a head injury against an object, may result in bruising of the brain (contusion) and fracturing of the skull, sometimes leading to vascular rupturing. Hemorrhagic contusion injuries are frequently associated with ICH, which can progress in time and transform hemorrhagically, leading to a large intraparenchymal hematoma that sometimes also require surgical evacuation.
Thus, a TBI often constitutes of a combination of clinical diagnoses to describe the brain damage. The diverse clinical manifestation with the complicated etiopathophysiology has led to the denotation that TBI is 'the most complex disease in the most complex organ'.[12]

Immediate treatment decisions in acute subdural hematoma

Patients with an ASDH are usually treated non-surgically.[13] The non-surgical treatment strategy is best medical management that includes watchful monitoring on the hospital ward or management on the intensive care unit (ICU) with intracranial pressure (ICP) monitoring. Intensive care management aims to prevent brain ischemia by the initiation of ICP lowering treatments while also maintaining sufficient blood and oxygen supply to the brain. Surgical interventions can complement the ICU treatments to minimize the burden of raised ICP.

Surgical evacuation of an ASDH is commonly employed through a craniotomy or a decompressive craniectomy (DC). A craniotomy entails opening of the skin, removal of a piece of skull, removal of the hematoma clot, replacement of the skull flap and closure of the skin. In a DC the skull flap is left out prior to closing the skin.
The surgical intervention can be targeted causally, by evacuation of a focal hematoma, or symptomatically by opening the skull to reduce the (duration of) brain compression, typically to treat suspected or proven (refractory) raised ICP. By evacuation of the hematoma and, if indicated, performing concurrent DC, the raised ICP is assumed to normalize and outcome is thought to improve (Figure 2).
Whether to treat a patient surgically or conservatively is made on the basis of the neurological status of the patient, the size of the hematoma and the degree of the mass effect. Surgery has risks that have to be weighed against the risks of ensuing brain compression by the hematoma.[14] Primary DC is performed if the brain is bulging beyond the inner table of the skull intraoperatively, preventing the safe replacement of the bone flap without pathological ICP rise. Another reason is preventive; if there is concern that the brain may swell further in the first days after the operation. When the swelling goes down, the patient has another operation to reconstruct their skull, a cranioplasty. The associated risk of a cranioplasty are infection, cerebral edema and bone-flap reabsorption. The advantage of a craniotomy is that the patient will not need a later operation to rebuild the skull. However, this type of operation may fail to control the brain swelling in some patients.

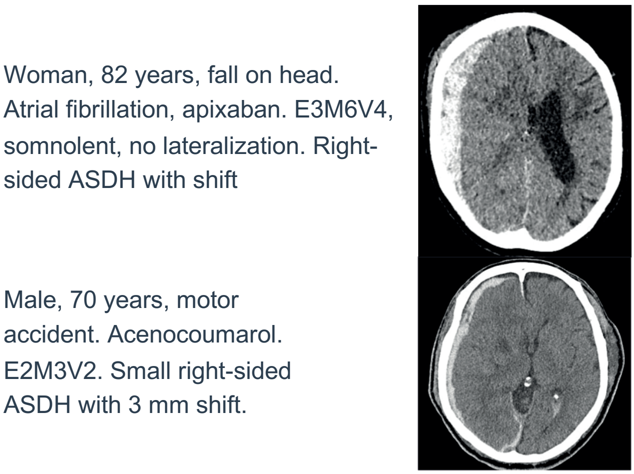

Figure 2. Hypothetical cases to illustrate the question clinicians are faced with in patients with an ASDH; to operate or not
Specifically, the question can broadly be divided into two typical patients: A) whether to evacuate the hematoma acutely or wait and monitor, possibly a delayed burr hole drainage, or B) in case of coma (Glasgow Coma Scale < 9) and a small ASDH, evacuate with (primary) DC or place an ICP sensor and evacuate in case of ICP rise.

The degree of brain compression is inferred from the decrease in consciousness level, expressed by the Glasgow Coma Scale (GCS), and the loss of pupil reactivity, an imminent sign of transtentorial herniation. In clinical practice, patients may present with multiple conditions, such as an ASDH combined with an ICH. The presence of concurrent pathologies affects the choice of treatment. Importantly, the surgical decision has to be made in far from ideal circumstances, in an emergency setting, often with incomplete clinical information and without the option to consult colleagues.

Current evidence

History

Several studies have played a pivotal role in shaping the course of treatment for ASDH throughout history. Although the evolution of the surgical evacuation of traumatic focal lesions starts very early in history (Figure 3), the path to the modern evaluation of the effect of surgery starts in the 20th century. In 1934 Munro shifted the viewpoint for the disease ASDH from 'being exclusively pathological' to 'more (frequently) surgical'.[15] Seelig and colleagues proved in 1981 the strong curative potential of surgery in ASDH by showing the sooner the better in comatose patients.[16] Several observations from fundamental studies of surgery in animals and hyperacute measurements of (human) ASDH perioperatively have, furthermore, elucidated mechanisms through which surgery may reduce damage of ASDH to the brain. Cerebral focal ischemia was shown to be the common denominator that explains the exceptional poor outcome of ASDH.[17] This ischemia can be caused by generalized pressure effects through raised ICP,[18] focal pressure effects from the hematoma,[19] metabolic derailments and local toxic effects,[20] especially in combination with ICH.[21,22] And although these studies show a multifactorial and sometimes contradictory genesis, the underlying translational theme is that the ischemia should be prevented.[23] Accordingly, the therapeutic mechanism of surgery extends beyond the effect of decompressing the brain by reducing the ICP, but it also serves to prevent local (neurotoxic) events that induce ischemia and worsen outcome.[24]

Current evidence

The Brain Trauma Foundation (BTF) has issued surgical guidelines (Figure 4). Surgery should be performed when the hematoma is significantly large irrespective of neurological condition ór in case of progressive neurological deterioration relatable to the lesion. These advices were based on observational studies with selected patients from single centres.[28-32] The guideline was issued in 2006, thus based on studies published before 2006 and there has been no update since then.[33]

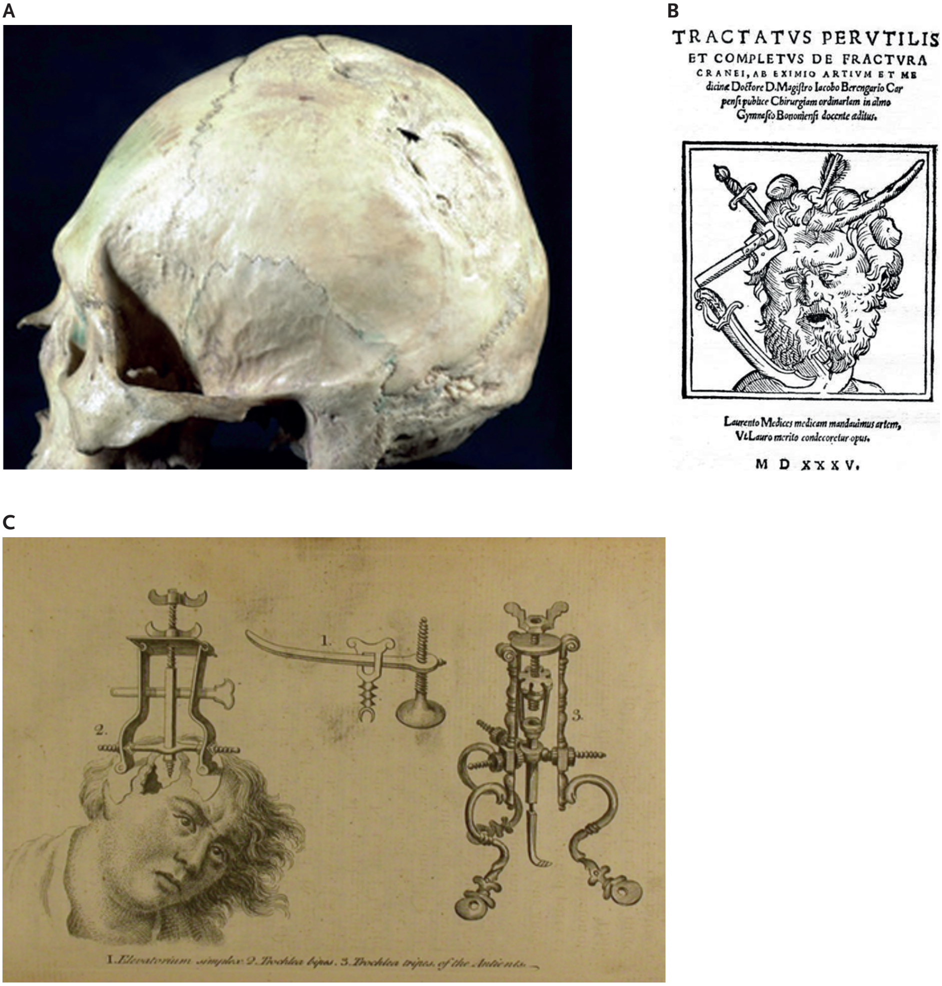

Figure 3. Brief history of the evolution of surgical evacuation in traumatic brain injury

Ancient man already knew that crushing the skull is the most effect method to eliminate an enemy. Concurrently, neurosurgical treatment with trepanation and burr-holes was devised to treat these injuries (mainly skull deformities). It might be the oldest surgical procedure with archaeological evidence dating back to the Neolithic period with anecdotal prove of trephinations for skull injuries already from 12,000 BC (A. The ancient skull has a large left parietal trephination with clear signs of antemortem healing. Adapted from [25]). In the Greco-Roman era, Hippocrates postulated - in line with his *do no harm* principle - that surgery below the dura is too dangerous to perform, restricting trephination for the treatment of skull injuries only, thereby setting the general consensus for surgery of the brain well up into the renaissance. The first systematic description of surgical indications for TBI, guidelines *avant la lettre*, have been written down by Jacopo (Giacomo) Berengario da Carpi (1470–1550) in 'Tractatus de Fractura Calvae sive Cranei' (B. Cover of the third edition of Berengario's Treatise on Skull Fractures, Venice, 1535).[26] He noted "..if the contused brain seems to be deeper than the surgeon's index finger, surgery is indicated" and in effort to introduce some cost-effectiveness considerations he mentions: "..surgery has a price and surgeons with experience in TBI are rare... therefore you must be prepared to pay for surgery... (the amount) equivalent to the price of a small house".

It was not until the 18th century, however, that the English surgeon Percivall Pott (1714–1788) shifted the predominant focus on skull to brain injuries and argued that surgery of the skull should go alongside an appreciation of whether or not it should be accompanied by treatment of accumulated blood under the skull (C. A illustration from Pott's work on head injuries detailing the "tripod" style of trephine that he favored. From Pott P: The Chirurgical Works of Percival Pott. London: Hawke, W. Clarke, R. Collins, 1775). He suggested that the symptoms seen in head injury might be due to direct injury of the brain and not due to just skull injury, and that the distinction should be made between compression and concussion of the brain when evaluating a head injury.[25]

While these historical anecdotes certainly have some medical and surgical merits, surgery in general probably did more harm than good until the 20th century.[27] It was not until the introduction of anesthesia and antisepsis in 1867, by Sir Joseph Lister (1827–1912), that surgeries of the skull were becoming safer.

The BTF acknowledged the lack of high-quality evidence and advised to conduct well-conducted comparative studies on surgery vs conservative treatment in ASDH. Thus, observational studies have provided valuable insights but the effectiveness of surgery remains unclear.

Surgical Management of Acute Subdural Hematomas

RECOMMENDATIONS
(see *Methodology*)

Indications for Surgery

- An acute subdural hematoma (SDH) with a thickness greater than 10 mm *or* a midline shift greater than 5 mm on computed tomographic (CT) scan should be surgically evacuated, regardless of the patient's Glasgow Coma Scale (GCS) score.
- All patients with acute SDH in coma (GCS score less than 9) should undergo intracranial pressure (ICP) monitoring.
- A comatose patient (GCS score less than 9) with an SDH less than 10-mm thick and a midline shift less than 5 mm should undergo surgical evacuation of the lesion if the GCS score decreased between the time of injury and hospital admission by 2 or more points on the GCS and/or the patient presents with asymmetric or fixed and dilated pupils and/or the ICP exceeds 20 mm Hg.

Timing

- In patients with acute SDH and indications for surgery, surgical evacuation should be performed as soon as possible.

Methods

- If surgical evacuation of an acute SDH in a comatose patient (GCS < 9) is indicated, it should be performed using a craniotomy with or without bone flap removal and duraplasty.

KEY WORDS: Coma, Computed tomographic parameters, Craniotomy, Decompressive craniectomy, Head injury, Hematoma, Intracranial pressure monitoring, Salvageability, Subdural, Surgical technique, Timing of surgery, Traumatic brain injury

Figure 4. Brain Trauma Foundation guidelines regarding surgical indications in acute subdural hematoma.[34,35]

Generating new evidence

With well-known limits in time, money and other resources, clinical research should be focused on answering questions that directly result from daily clinical practice, are thus clinically relevant.[36] Although surgical evacuation of an ASDH is the most frequently performed acute surgical intervention within the skull,[37] its effectiveness relies on the lowest category on the evidence hierarchy.[38] Many neurosurgical intervention, especially acute surgery in TBI, have become well established before the methodological principles of evidence-based medicine became common practice. Although this may explain part of the lack of high-quality evidence, there is not a single explanation why a higher evidence level has not been attained since then. A part maybe explained by the fact that TBI surgery is considered common sense. The analogy to the effectiveness of a parachute is made (Figure 5), even by authorities in the field.[37]

Figure 5. In 2002 Smith and Pell published "Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials."

In poking fun at those who demand randomized controlled trial evidence to support therapeutic intervention, they use the parachute as an example of an imperfect intervention for which no randomized controlled trial evidence exists, sensibly enough suggest that no one is likely to volunteer to participate in such a trial. This common sense is applied to many interventions among which one is acute surgery for acute subdural hematoma. This extrapolation attests to the intractable opinion held among neurosurgeons of ASDH being a purely a surgical disease and underestimates the complexity of the disease.

This analogy disregards the complexity of the disease: it is not merely a matter of assuming a lower ICP will lead to a good outcome. Every (new) intervention in health care should be accompanied by a proper assessment of its benefit and harms. RCTs provide the strongest evidence on the effectiveness of medical interventions.[39-41] However, there is an abundance of literature showing the lack of successful RCTs in neurosurgery.[42-45] RCTs in neurosurgery are difficult to conduct due to methodological, pragmatic and sometimes ethical constraints. Investigating surgical interventions involves particular challenges compared to non-surgical medical research because of the complexity of (peri)operative procedures, surgical learning curves, patients' and surgeons' equipoise, blinding issues, and cultural or psychological barriers towards the use of randomization. For the specific challenges posed by surgical research, the IDEAL (Idea, Development, Exploration, Assessment, Long-term) framework guides researchers and clinicians in evaluating surgical interventions.[46] Specific for TBI are the heterogeneity of the population and interventions, the emergency setting of an acutely life-threatening condition, limited patient information in the absence of proxies and the largely unknown pathophysiological mechanisms of brain injury.[47,48] This failure of RCTs goes along a significant waste of clinical data and resources, and stands in stark contrast to the need for updated surgical guidelines and burden incurred by TBI.

The extent to which classical observational studies can inform treatment decision is limited. Observational studies of intervention are prone for bias, i.e. potential differences in outcome between intervention groups could also be explained by other factors than the intervention under study. When using observational studies, careful decisions in data collection and analysis should be made to allow causal interpretation.[49]

Therefore, the second-best study design is a prospective high-quality observational comparative effectiveness study, also referred to as a form of comparative effectiveness research (CER).[50] CER studies have gained popularity over the years.[48] Although principally inferior to RCTs with regard to internal validity, more advanced analysis such as instrumental variable analysis can lead to causal inference closely resembling RCTs (Figure 6).[51] There have been many precedents of these observational studies that directly impacted clinical practice.[52-55] The appealing aspect in TBI to use CER is the fact that there might be large practice variations due to the absence of high-quality evidence, possibly a result of the strong treatment preferences of the neurosurgical mindset. These possible large variations in care and outcome are worthwhile to investigate because recognizing beneficial treatment strategies may far outweigh any benefit that realistically can be expected from a new intervention.[56]

Thus, there is a clear role for conducting high-quality observational studies with sophisticated analyses to inform practice.

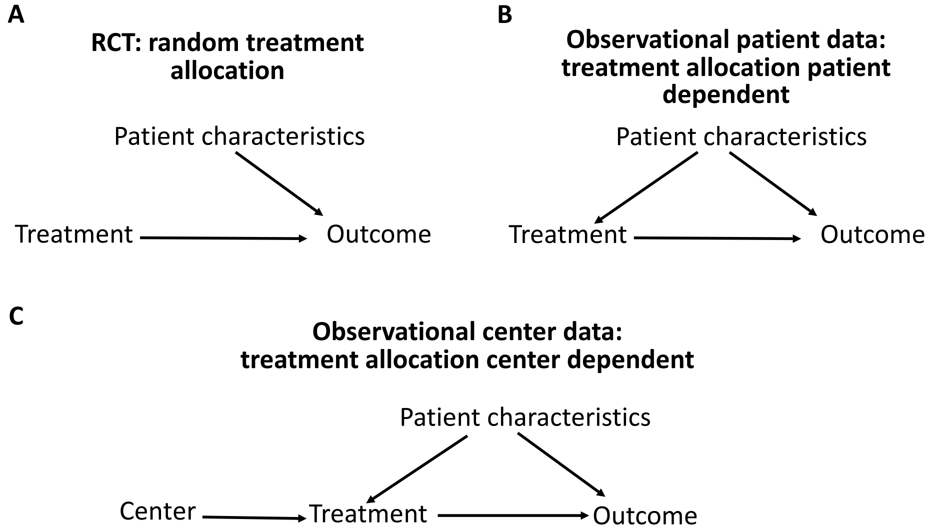

Figure 6. Instrumental variable (IV) analysis to reduce confounding by indication, as compared to randomization in randomized controlled trials (RCTs) and to traditional analysis in observational studies

Randomization separates treatment from patient characteristics and thereby ensures no confounding when estimating the effect of treatment on outcome (A). Effect estimation in observational data relies on statistical correction (f.e. regression modelling or propensity scores) but unmeasured confounding may remain a problem (B). In IV analysis (C), the instrumental variable center 'allocates' patients to be exposed to different likelihoods of receiving treatment. In analyzing treatment as center characteristic instead of a patient characteristic the intervention is again independent from the patient characteristics (no arrow from patient characteristics to center, just like with randomization).

Datasets used in this thesis

CENTER-TBI

The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study was an international observational cohort study in centers across Europe and Israel, including patients between December 19th 2014 and December 17th 2017.

The aims of CENTER-TBI were to provide new, multidimensional insight into TBI characterization and to determine effectiveness of several treatment interventions in TBI.[12,57]

In total 4559 patients from 65 centers were included in the core study, which collected data on demographics, injury, imaging, monitoring, treatment, and outcomes up to 1-year post-injury (Figure 7). Provider profiling questionnaires captured the structures and processes of care of participating centers.

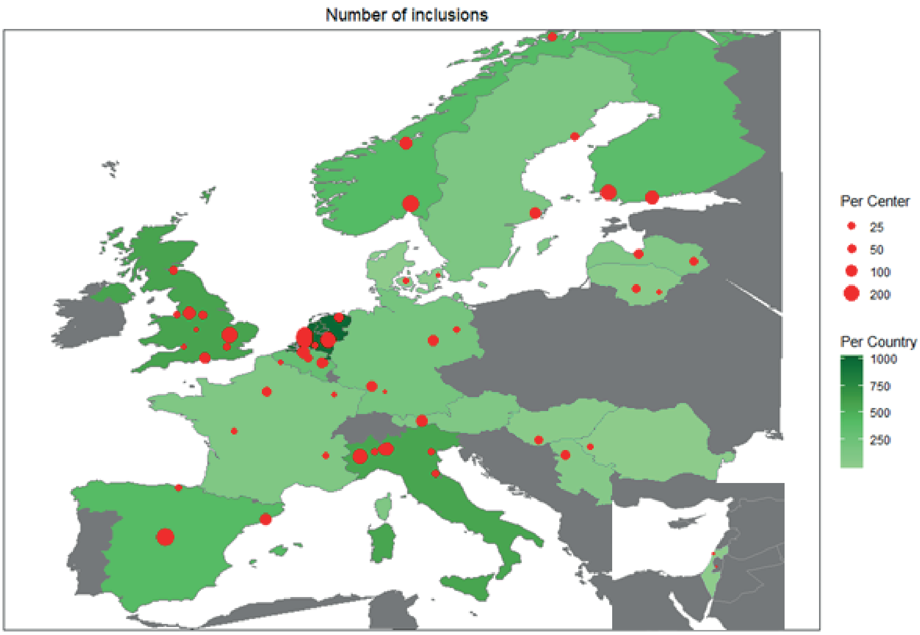

Figure 7. Participation per study center and country in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Core study (n=4509 patients).

Net-QuRe

The Neurotrauma Quality Registry (Net-QuRe) is a multi-center, prospective, observational cohort study designed to form the basis of a quality registry for moderate and severe TBI in The Netherlands.[58,59]

Five level 1 trauma centers and eight rehabilitation facilities in The Netherlands partook in Net-QuRe. All trauma centers serve a regional function for neurosurgical care in geographically distinct areas. One of the trauma centers consists of three separate hospitals, all of which facilitate complex neurocritical care.

Inclusion started in January 1, 2015 along with the commencement of the overarching CENTER-TBI project and continued after its completion until the 1st of January, 2020. 937 patients were included. Next to general demographic measures, process measures were collected. Data were gathered during admission in the hospital and also in the rehabilitation center. Outcome measures are collected at 6, 12 and 24 months after hospital discharge.

In the studies in this thesis, we used the core study and provider profiling of CENTER-TBI, as well as the Net-QuRe dataset.

Objectives

The overall aim of this thesis is to evaluate the comparative effectiveness of treatment approaches for patients with ASDH. This aim led to the following research questions:

I. What is the current evidence on the effectiveness of surgical treatment of ASDH?

II. What is the current practice in treatment of patients with ASDH in Europe?

III. Which study designs and analyses are suited to determine the effectiveness of surgical treatment of ASDH?

IV. What is the effectiveness of different treatment approaches (surgery versus initial conservative treatment and decompressive craniectomy versus craniotomy) for ASDH?

OUTLINE OF THE THESIS

In **Part I** the current evidence base for neurosurgical interventions in TBI is addressed. Chapter 2 provides an overview of recent effectiveness studies on neurosurgical interventions and describes the neurosurgical considerations in the treatment of patients with TBI. Chapter 3 is a systematic review of the available comparative studies on surgery in ASDH

In **Part II** I present the current state of neurosurgical management of TBI in Europe (Chapter 4) with an emphasis on the treatment of ASDH (Chapter 5).

Part III focuses on how to properly design a study aiming to measure the effectiveness of neurosurgical interventions (Chapter 6) with a focus on how to deal with confounding in observational studies on acute neurosurgical decompression in focal lesions (Chapter 7). Chapter 8 presents the study protocol, which discusses the choices made in the design and conduct of the prospective observational studies CENTER-TBI and Net-QuRe to determine the comparative effectiveness of acute surgery vs conservative treatment for ASDH and ICH. The protocol has been published for transparency and accountability, and to inspire subsequent observational effectiveness studies on surgical interventions. The presented study with regard to early surgical intervention in ICH is not part of this thesis.

The studies in **Part IV** aim to compare the effectiveness of surgical treatment approaches in ASDH. First, a retrospective observational study with routinely available data is presented in Chapter 9. The study is conducted in the centers of our survey (Chapter 4) that had the most divergent views on the acute management of ASDH. Chapter 10 describes the results of the observational study with regard to the effectiveness of a strategy of acute neurosurgical decompression in ASDH, in terms of both objective and subjective outcomes. Chapter 11 is a reply to a letter to the editor. This letter is a reaction on the effectiveness study in Chapter 10 and

serves as an example of the response among the neurosurgical community. Chapter 12 presents the study with regard to DC as compared to craniotomy in ASDH.
In **Part V** we summarize the preceding chapters and discuss the relevance, limitations and clinical implications of our findings. We end by providing suggestions for future research.

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