Comparative effectiveness of surgery for traumatic acute subdural hematoma

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PART V

GENERAL DISCUSSION

Chapter 13

Summary

SUMMARY

In **Chapter 1**, the knowledge on the surgical management of the acute subdural hematoma (ASDH) in traumatic brain injury (TBI) is summarized. The ASDH is the most prevalent TBI and evacuation of an ASDH is one of the most common acute neurosurgical intervention.[1] Neurosurgeons in favor of evacuation of a subdural estimate that acting too slowly or not at all when there is a large ASDH leads to neurological deterioration or death. Their suspicion is backed by the Brain Trauma Foundation (BTF) guideline, which was devised in 2005 by an international panel of experts and states that every ASDH with a thickness >10mm and a midline shift over 5mm and every ICH larger than 50 cm^3 should be evacuated, irrespective of neurological condition.[2,3] On the other hand, surgeons in favor of a conservative strategy do not want to expose the patient to the risks of a craniotomy or decompressive craniectomy (DC) without a more precise estimation of the chance of neurological deterioration when withholding an operation. It can be argued that the guideline and the evidence so far should not guide treatment, because good quality comparative studies are lacking.

The lack of sound evidence to guide this decision in TBI was the motivation for this PhD project. Subsequently, we postulated the 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 DC versus craniotomy) for ASDH?

Thereafter, we described the datasets of Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) cohort and the Neurotraumatology Quality Registry (Net-QuRe) that we used to answer the questions.

In **PART I** the current evidence is updated. The summary in **Chapter 2** gives an overview of current comparative studies in surgical TBI and opportunities for future research. **Chapter 3** is a systematic review on the effect of surgery in ASDH. We try to improve the current evidence base by using already performed studies. In the first systematic review of the mortality risk in ASDH, we included 102 studies comprising 12,287 patients. The overall mortality in surgically treated ASDH was 48% (95% confidence interval [CI] 44-53%) while mortality was 41% (95% CI 31-51%) in comatose ASDH patients that were surgically treated. The mortality risk associated with the conservative treatment of comatose ASDH patients was 81%

(95% CI 56-98%). In a dramatic effect design, we show that the size of the beneficial effect of surgical evacuation equals 40% mortality reduction.

In **PART II** we describe the current neurosurgical management strategies of TBI. The first study, **Chapter 4**, is a survey in The Netherlands and Belgium on how patients with ASDH are managed. The research question is whether the varying trauma management of ASDH is the result of a variable view among neurosurgeons. Regular day-to-day cases of TBI and an ASDH were presented to them online. Sixty neurosurgeons filled out the questionnaire (response rate 65%). For patients with severe TBI and ASDH (three cases) there was a modest variation in the decision to surgically evacuate the hematoma or not; respectively 88%, 100%, and 77% would perform acute surgery. The variation became more pronounced for patients with a moderate or mild TBI. For example, in a hypothetical case of a 79-year-old male with a mild TBI and a fairly large ASDH, 1 out of 7 (14%) neurosurgeons in one region chose a surgical strategy compared with 9 out of 10 (90%) in another region for the same scenario. However, despite this distinct practice variation, less than half of (the same) neurosurgeons (48%) would leave this decision open for randomization in a study. This practice variation together with the fact that this group, mild or moderate TBI and ASDH, represents the majority of patients with an ASDH, were the impetus for our further research. The variation supports the methodology of the international Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) initiative, and shaped the Dutch Neurotraumatology Quality Registry (Net-QuRe) initiative.[4,5]

This overview of contemporary neurosurgical care in The Netherlands and Belgium is complemented in **Chapter 5**, by a survey aimed to explore differences in neurosurgical strategies for TBI across Europe. The questionnaire consisted of several topics among which the decision when to operate (or not) on traumatic ASDH and ICH, and when to perform a decompressive craniectomy (DC) in raised intracranial pressure (ICP). The survey was completed by 68 centers (100%), mostly by neurosurgeons (78%). All centers provide 24/7 acute neurosurgical coverage, at least within 30 minutes. ASDH represents the highest volume of neurosurgical TBI cases, on average 25 cases per year (per center). Forty percent of responders reported a thickness or volume threshold for evacuation of an ASDH. Most responders (78%) decide on a primary DC in evacuating an ASDH during the operation, when swelling is present. For ICH, 3% would perform an evacuation directly, i.e. on presentation, to prevent secondary deterioration and 66% only in case of clinical deterioration. Treatment strategies varied substantially between regions, specifically for the threshold for ASDH surgery and DC for refractory raised ICP. 31% of centers reported variation within the hospital for inserting an ICP monitor and 43% for evacuating

mass lesions. The results of the questionnaire point out potential substrates for comparative effectiveness research (CER) in CENTER-TBI.

In **PART III** deals with the preparation of designing our study, methodological choices made, to meet our effectiveness objectives. Specifically, it describes two case studies, a review of the literature concerning how to design an observational study to determine the effectiveness of acute intracranial interventions, and the protocol for the main comparative effectiveness studies.
Observational studies constitute the alternative to the gold-standard of a randomized controlled trial (RCT). A key challenge in observational studies of interventions is confounding by indication, a phrase that refers to a situation where patient characteristics, rather than the intervention, are independent predictors of outcome. The objective of the study in **Chapter 6** was to define the circumstances for the validity of methods to adjust for confounding in observational studies of interventions in TBI. Three large TBI datasets were used to perform post-hoc analyses with the interventions intracranial pressure (ICP) monitoring, intracranial operation and primary referral. Multivariable regression, propensity score matching and instrumental variable (IV) analysis were compared. Furthermore, in a simulation study these methods were compared in their ability to correct unmeasured confounding in a hypothetical not further defined intervention. For all three interventions, multivariable regression and propensity score matching resulted in negative estimates of the treatment effect (OR ranging from 0.80 to 0.92), whereas the IV approach indicated that both ICP monitoring and intracranial operation might be beneficial (OR per 10% change 1.17, 95% CI 1.01–1.42 and 1.42, 95% CI 0.95–1.97). In our simulation study, multivariable regression and propensity score matching resulted in an invalid estimate of the treatment effect in case of unmeasured confounders (OR ranging from 0.90 to 1.03). The IV approach provided an estimate in the similar direction as the simulated effect (OR per 10% change 1.04–1.05) but was statistically inefficient. The conclusion is that IV analysis might provide a more valid estimate of the treatment effect compared to conventional analytical methods. However, the findings also suggest that alternative methods should be used simultaneously to strengthen the credibility of effect estimation.[6]
Chapter 7 is a letter to the editor in which we respond to an observational study investigating the effect of surgical evacuation for spontaneous intracerebellar hematoma.[7]We question the validity of the results and we point out our concerns with regards to the study analysis. We suggest that the study should preferably use an IV effect estimation to reliably correct for the unmeasured confounding because the cohort stems from 64 centers with likely differing practice culture. In their response the authors performed this analysis and conclude to have provided similar

results as with their original estimates across the investigated primary and secondary outcomes.[8]

In **Chapter 8**, we work out a proposal for the comparative studies. We designed part of the CENTER-TBI cohort and setup the Net-QuRe with the aim to answer who to surgically treat acutely in ASDH, ICH and when to perform a primary DC. This study uses a comparative effectiveness research (CER) design, a multicenter prospective observational cohort study that exploits variation in neurotrauma care to create and compare parallel study groups. The multicenter design is necessary to ensure the required number of patients with different neurotrauma treatment strategies for ASDH and t-ICH. Patients with an ASDH and/or a t-ICH are eligible for inclusion. Inherent to the observational design of this study the management strategies under investigation proceed according to local emergency and intensive care protocols or surgeon's expertise. Consequently, the resulting variation in management is accepted and analyzed. To gain insight into this variation, detailed information is collected on the reasons for specific interventions or management strategies (see section 'why' questions). The interventions of interest are acute surgery, defined as surgery directly after the first CT at presentation versus late or no surgery and craniotomy versus DC. The primary outcome measure is the Glasgow Outcome Score-Extended at 6 months. Secondary outcome measures include in-hospital mortality, quality of life and neuropsychological tests. In the primary analysis, the effect of treatment preference (i.e. the proportion of patients in which the intervention under study is preferred) per hospital will be analyzed with random effects proportional odds ordinal regression models, adjusted for case mix. Sensitivity analyses will include (conventional) multivariable regression modelling and propensity score matching, with treatment defined on patient level. In CENTER-TBI and Net-QuRe together approximately 1000 patients with ASDH and 750 patients with ICH were expected, recruited from approximately 70 centers. These samples would lead to a power of 80% to detect a difference (assuming a two-sided significance 0.05).

PART IV is focused on the effectiveness of surgery in ASDH. Timely evacuation of an expanding traumatic intracranial hematoma in a patient with deteriorating level of consciousness is lifesaving. Most patients with a traumatic intracranial hematoma, however, present with a moderately decreased or high conscious level. Uncertainty exists, particularly in patients with an ASDH or an ICH on indications, timing of surgery and type of surgery, reflected in large practice variations.

We start with an observational comparative effectiveness study among two trauma regions in The Netherlands in **Chapter 9**. We compared treatment strategies on center level rather than patient level to reduce confounding by indication. These regions are geographically distinct and covered by separate neurosurgical departments. These

regions were chosen for their – a-priori defined – diverging treatment preferences derived from the survey in Chapter 7. Baseline characteristics were comparable between regions. The median age was relatively high at 68 years (interquartile range [IQR], 54–76). Primary evacuation was performed in 84% of patients in region A and in 65% of patients in region B ($p < 0.01$). The strategy favoring surgical evacuation was associated with significantly lower odds of unfavorable outcome (OR 0.53; 95% CI: 0.27–1.02) 3–9 months post-injury. Thus, we concluded that an aggressive surgical management strategy might be associated with better outcome in an elderly population with traumatic ASDHs. However, the important limitation is that other regional differences might account for this finding. The higher incidence of clinical deterioration in one of these regions, for example, may be consequent to the larger number of secondary referrals. Primary presentation to a neurosurgical center has a close relationship with time to surgery and could even improve patient outcome.[9] And although the primary referral and other imbalances are counteracted by other (measured) confounders – after all, the cohorts of both regions have a similar prognosis according to a validated prognostic model - residual confounding is possible. We proposed larger comparative studies with more hospitals to examine this effect of surgery and to explore generalizability (**Chapter 8**).

In **Chapter 10** we analyzed data on 1407 patients with an ASDH and found that the proportion of patients undergoing acute surgery ranged from 6 to 52% (interquartile range [IQR] = 13-35%) between centers. The resulting median odds ratio (MOR) of 1.8 ($p < 0{\cdot}001$) can be interpreted as a twofold higher probability that an identical patient will receive acute surgery in one versus another random center. These large between-center variations enabled exploration of effectiveness of surgery in comparative effectiveness analyses. For acute surgery in ASDH, we found that center preference for an acute surgical strategy over that of an (initial) conservative treatment was not significantly associated with better outcome (odds ratio 0.92 [95% CI 0.77 to 1.09]). Delayed surgery within the conservative group (n=982) occurred in 107 patients (11%) after a median of 19.1 hours (IQR 8.1-84.6). These results should be interpreted in light of the comparative effectiveness design and do not imply no effect of surgery. Because an identical patient may be operated in one center but not in another, it naturally follows that there is more than one valid treatment option. The results apply to those patients for whom the neurosurgeon sees no clear superiority of either treatment. Therefore, the data suggest that acute surgical evacuation of an ASDH in patients for whom equipoise exists on surgical indication may not lead to a better outcome compared to (initial) conservative treatment.
In **Chapter 11** we respond to a letter to the editor in which some aspects of our study in Chapter 10 are questioned.[10]

In **Chapter 12**, we explored the effectiveness of a primary DC as compared to a craniotomy in patients with ASDH, by exploiting the aforementioned practice variation. The type of primary acute surgery for ASDH highly varied between centers: the proportion of patients undergoing primary DC of all acute surgeries, as opposed to craniotomy ranged from 6 to 67 % (IQR = 12-26%) with an adjusted MOR for primary DC of 2.7 ($p < 0 \cdot 001$). Centre preference for primary DC over craniotomy to evacuate the hematoma was not associated with a better outcome (odds ratio per 13% (IQR) more primary DC in a center 1.09 [95% CI 0.53 to 1.53]). Again, these findings apply to those patients for which there is uncertainty in the first place. We conclude that the initial decision for primary DC should be restricted to those salvageable patients for which craniotomy is not a reasonable alternative. The decision for primary craniotomy leads to similar outcome, has less complications and does not need a cranioplasty to achieve this outcome.

The decision whether to operate or not in patients with a traumatic ASDH can, in many cases, be a neurosurgical dilemma. In the current thesis the surgical treatment of TBI was studied and discussed. Current treatment strategies were described, clinical characteristics of the patient domain were studied and the optimal study methodology to answer the effectiveness questions was examined. This thesis contributes to the assessment of surgical interventions in TBI and will influence future research.

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