Comparative effectiveness of surgery for traumatic acute subdural hematoma

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Chapter 12

Comparative effectiveness of decompressive craniectomy versus craniotomy for traumatic acute subdural hematoma: a CENTER-TBI study

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Under review

KEY POINTS

Question: Does primary decompressive craniectomy (DC) yield better outcome than craniotomy in patients surgically treated for a traumatic acute subdural hematoma (ASDH)?

Findings: In this international observational study of 336 ASDH patients from 65 centers, we found substantial practice variation in the employment of DC over craniotomy for ASDH. In an instrumental variable analysis, this variation in treatment strategy did not result in a difference in functional outcome on the Glasgow Outcome Scale-Extended scale at six months (primary outcome). However, primary DC was associated with higher in-hospital mortality, more follow-on surgeries, and more complications.

Meaning: Surgical ASDH evacuation by primary DC as opposed to craniotomy is unlikely to result in better outcomes.

ABSTRACT

Importance: Limited evidence exists on the comparative effectiveness of decompressive craniectomy (DC) versus craniotomy for evacuation of traumatic acute subdural hematoma (ASDH).

Objectives: To compare outcomes of primary DC versus craniotomy.

Design: Instrumental variable analysis of center treatment preference within the prospective observational Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury and Neurotraumatology Quality Registry studies, which enrolled patients throughout Europe and Israel (2014 to 2020).

Setting: International; multicenter.

Participants: Patients with a clinical and radiological ASDH and acute neurosurgery. Patients with severe pre-existing neurological disorders were excluded.

Exposures: Surgical ASDH evacuation with DC versus craniotomy.

Main outcomes: Functional outcome measured by the Glasgow Outcome Scale-Extended (GOSE) at 6 months. Analyses included random-effects ordinal regression with the adjusted center probability of DC as the instrumental variable.

Results: In 65 centers of 336 included patients, 91 (27%) underwent DC and 245 (63%) craniotomy for ASDH evacuation. The proportion of primary DC within total acute surgery cases ranged from 6-67% with an interquartile range (IQR) of 12-26% among 46 centers; odds of receiving a DC for prognostically similar patients in one center versus another randomly selected center were trebled (adjusted median odds ratio 2.7, $p < 0.0001$). Higher center preference for DC over craniotomy was not associated with better functional outcome (adjusted common odds ratio (OR) per 14% [IQR increase] more DC in a center = 0.9 [95% CI 0.7-1.1], n = 200). Primary DC was associated with more clinical complications (eg, higher rate of follow-on surgeries and complications [secondary cranial surgery 27% vs. 18%; shunts 11 vs. 5%]; and higher odds of in-hospital mortality (adjusted OR per 14% IQR more primary DC 1.3 [95% CI (1.0 – 3.5), n = 200].

Conclusions and relevance: In traumatic ASDH, surgical hematoma evacuation by primary DC is unlikely to result in better functional outcome at 6 months than craniotomy. Given greater risk of complications, primary DC should be restricted to salvageable patients in whom immediate replacement of the bone flap is not possible due to severe swelling.

INTRODUCTION

Acute subdural hematomas (ASDH) present in approximately one-third of patients with severe traumatic brain injury (TBI).[1,2] This space-occupying hematoma, can severely reduce blood flow to the brain, and elevate intracranial pressure (ICP), causing brain herniation, poor functional outcome, and death.[3] The decision to treat a patient surgically or conservatively in the acute phase turns on their neurological status, the size of the hematoma, and the degree of mass effect.[4]

Surgical procedure to evacuate ASDH follows one of two approaches: craniotomy with reconstruction of the skull with the bone flap replaced, or decompressive craniectomy (DC), in which the bone flap is not immediately rebuilt to mitigate (future) ICP increase. Several clinical scenarios guide the surgical decision. Primary DC is performed if, after ASDH evacuation, the brain swells beyond the skull intraoperatively, preventing safe replacement of the flap without pathological ICP rise. Another scenario is preventive, if there is concern that the brain may swell post-operatively.[5] Secondary DC is performed later in the clinical course, as a last-resort after exhaustion of neurocritical care measures, with clear benefits to functional outcomes.[6]

DC is considered more invasive than craniotomy, as it leads to a temporary bone defect, requires later skull reconstruction, and is associated with greater occurrence of post-traumatic hydrocephalus, bone flap reabsorption, and post-cranioplasty infection.[7] The Brain Trauma Foundation guideline for surgical treatment of ASDH provides no clear indication for selection of approach.[8]

Literature analyzing selection of technique has methodologic limitations, and comes largely from retrospective cohort studies.[1,4,9,10] This lack of high-quality evidence may lead to practice variation comparing neurosurgical centers, which may further confound results.[11,12] Comparative-effectiveness research (CER) can exploit this variation to determine optimal management.[13] In this observational study we compared primary DC versus craniotomy for ASDH, assessing functional outcome at 6 months, to test the hypothesis that primary DC yields better outcomes. This hypothesis is based on the most rigorous of the current evidence, which suggests better outcomes for primary DC.[14,15]

METHODS

The study and predefined protocol follow the Strengthening the Reporting of Observational Studies in Epidemiology statement with instrumental variable (IV) analyses recommendations, and corresponds to stage 3 in the IDEAL framework.[16,17]

Design

This is a prospective, observational, cohort study within the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI), which enrolled patients between 2014 and 2017 in 65 centers across Europe and Israel.[1] [18,19] Parent studies were conducted in accordance with Good Clinical Practice (CPMP/ICH/135/95). Informed written or oral consent by patients or legal representatives was obtained according to local regulation.

Study population/data management

The CENTER-TBI cohort included patients with TBI and no pre-existing severe neurological disorders that could affect outcome assessment, who presented within 24 hours of trauma, and who had a brain CT ordered as part of clinical care. For the current study, we selected patients from the CENTER-TBI cohort with an ASDH confirmed on admission CT who received acute surgery.[2] We excluded patients who received a craniotomy for other types of injury, those that were brain dead, and those considered by the treating doctor to have an unsurvivable injury, for whom active treatment was futile. Data were collected by trained personnel using online case-report forms (QuesGen Systems, Burlingame, CA, USA), coded with the NIH-NINDS Common Data Elements.[18]

Center characteristics

Center characteristics have been previously reported.[11] Questions included center policy regarding the threshold for primary DC, which was used in sensitivity analyses. Other treatment decisions possibly related to surgical threshold (eg, prehospital care) could affect the internal validity of the study. We therefore did a cluster analysis, showing that center surgical treatment preferences were unrelated to other treatment preferences.[20]

Interventions

Acute hematoma evacuation was performed via craniotomy or primary DC, at the discretion of the treating neurosurgeon. Treatment groups were classified according to first (presenting) CT. Per study protocol, neurosurgeons were queried as to reason(s) surgery was indicated, surgical approach, and confirmed according to operating room disposition and by intervention codes or description. Techniques for durotomy and potential duroplasty were not routinely collected. Other emergency

1 The CENTER-TBI patients enrolled in The Netherlands were co-enrolled in the Neurotraumatology Quality Registry (Net-QuRe), which enrolled patients between 2015 and 2020 in 7 centers across the Netherlands. Net-QuRe had identical eligibility criteria but included patients with a Glasgow Coma Scale (GCS) score < 13.

and post-surgical care followed local protocols (ICU management, ICP monitoring, and/or follow-on surgery).

Outcomes

The primary outcome was functional outcome at 6 months on the Glasgow Outcome Scale-Extended (GOSE).[21] Secondary outcomes were in-hospital mortality, ICP, frequency and type of neurosurgical interventions, medical and surgical complications, 'treatment failure' (subsequent craniotomy or DC), ICU and hospital length of stay (days), dichotomized 6-month GOSE score across multiple thresholds, and quality of life at 6-months postinjury, measured with the Quality of Life after Brain Injury instrument (QOLIBRI).[22]

Statistical analysis

Baseline characteristics are presented using descriptive statistics, including standardized mean differences across the instrument and between groups. The CRASH-CT head injury model was used to calculate predicted probabilities of unfavorable outcome.[23] We calculated the median odds ratio (MOR) to compare between-center differences in surgery. The MOR quantifies treatment variation between centers that is not attributable to chance and not explained by other (case-mix) factors.

Outcomes were analyzed with respect to center treatment strategy (and not actual treatment) using instrumental variable (IV) analyses. In this natural experiment the IV "allocates" patients to either the DC or craniotomy treatment strategy based on the treating center, and reduces (unmeasured) confounding (eMethods).

The common odds ratio (OR) was estimated with a random-effects multivariable proportional odds logistic regression model with the ordinal GOSE as outcome variable, the case-mix adjusted center-specific treatment probability of DC as the independent variable (the IV), and a random intercept for treating center (unexplained residual between-center differences). The OR summarizes the shift in the direction of a better score on the GOSE. Adjustment was made for age, GCS, pupillary reactivity, midline shift, concomitant contusion, and hematoma size as potential confounders. The resulting adjusted common OR was presented as an increase from the first to the fourth quartile (IQR) of the (continuous) instrumental variable (the adjusted probabilities for undergoing DC) and can be interpreted as the odds of a more favorable outcome when comparing centers favoring a strategy of primary DC versus those favoring craniotomy. Only centers with □ 10 patients were included in analyses.

Sensitivity analysis included IV analysis using center-preference for primary DC as the instrumental variable, per prior published provider profile.[11] Sensitivity IV analysis

was also performed excluding centers with < 15 patients. Last, the IV association of surgical preference with outcome was also estimated by linear regression with the case-mix adjusted probability of DC (treatment preference) as the independent variable, mean GOSE by center as the dependent variable, and similar adjustment.
We performed unadjusted and multivariable regression and propensity score matching (PSM) as sensitivity analyses with actual DC received as treatment variable (yes/no; not center DC preference) and GOSE as ordinal outcome variable. We determined adjusted ORs (aOR) for multiple cutoff values on the GOSE to assess consistency of effect estimates. Further details are supplemented (eMethods). Analyses were conducted using R-software 4.1.0, RStudio 1.1.463. Missing data were multiply imputed ('mice' package, m=5), assuming data to be missing-at-random. The 95% CIs for the ORs were obtained from 2.5 and 97.5 percentiles among the bootstrap replications.

RESULTS

Of 4509 patients in CENTER-TBI, 336 patients underwent acute surgery for an ASDH, of whom 91 (27%) received a primary DC and 245 (73%) received a craniotomy (Figure 1). Median time from injury to start of surgery was 3.5 hours for primary DC (IQR 2.2–5.1) and 4.1 hours for craniotomy (IQR 2.8-7.0). Patients undergoing primary DC were younger (median age 49 vs. 59 years), less often on anticoagulants and/or platelet aggregation inhibitors (14 vs. 25%), with more major extracranial injuries (53 vs. 36%), worse presenting GCS scores (median 4 vs. 7), larger ASDH volumes (median 64 vs. 49 cm^3), and more frequent contusions and subarachnoid hemorrhages (66% vs. 55%, and 75% vs. 62% respectively; eTable 1).
These baseline characteristics did not translate into different predicted 6-month unfavorable outcomes calculated according to the CRASH-CT for primary DC compared to craniotomy (respectively, 71 vs. 74 %). The most frequently cited rationale for selecting a DC was a 'pre-emptive approach to treatment of (suspected) raised ICP (not last resort)' in 31% of DC cases (eTable 2).
Secondary DC or craniotomy for contusions or hematomas was performed in 25 (27%) patients initially treated with primary DC and in 43 (18%) patients initially treated with craniotomy. Patients undergoing primary DC vs. craniotomy had longer hospital stays (median 38 vs. 18 days), more frequently required shunts (11 vs. 5%), and had more intracranial complications (delayed intracranial hematoma/seroma, 23 vs. 16%). Cranioplasty during primary admission was performed in 23 (25%) patients in the primary DC group and in 12 (5%) in the craniotomy group (after secondary DC) (eTable 3).

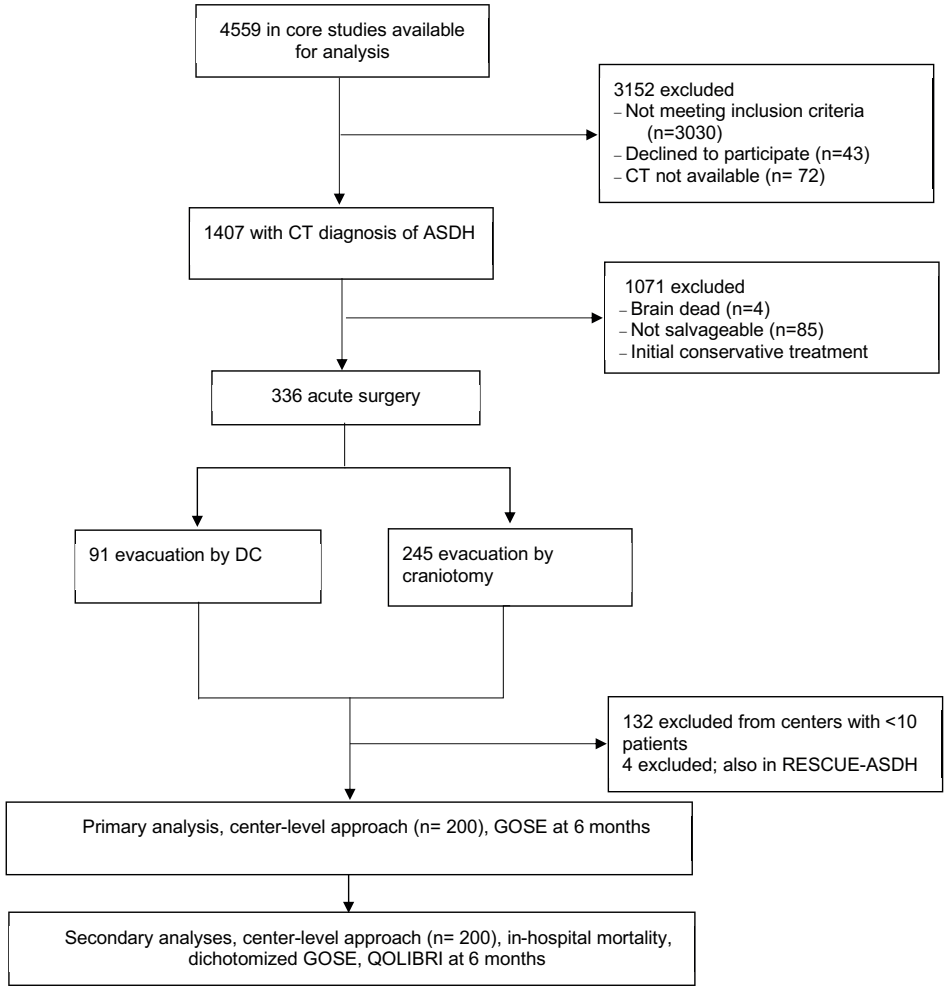

Figure 1. Flow diagram of study population and data analyses

DC: decompressive craniectomy, GOSE: Glasgow Outcome Scale Extended, QOLIBRI, Quality of Life after Brain Injury Questionnaire.

The proportion of primary DC relative to all acute surgeries ranged from 6% to 67% across 46 centers (IQR = 12-26%; Figure 2A), with a MOR of 2.7 ($p < 0.0001$) (Figure 2B and 2C), representing an almost 3-fold higher odds of receiving DC for clinically similar patients, when randomly comparing 2 centers. Moreover, baseline prognosis (predicted 6-month unfavorable outcome of the CRASH-CT score) for surgical patients across regions defined by primary DC treatment rates were similar (Table 1). The testable assumptions for IV analyses were met (eResults).

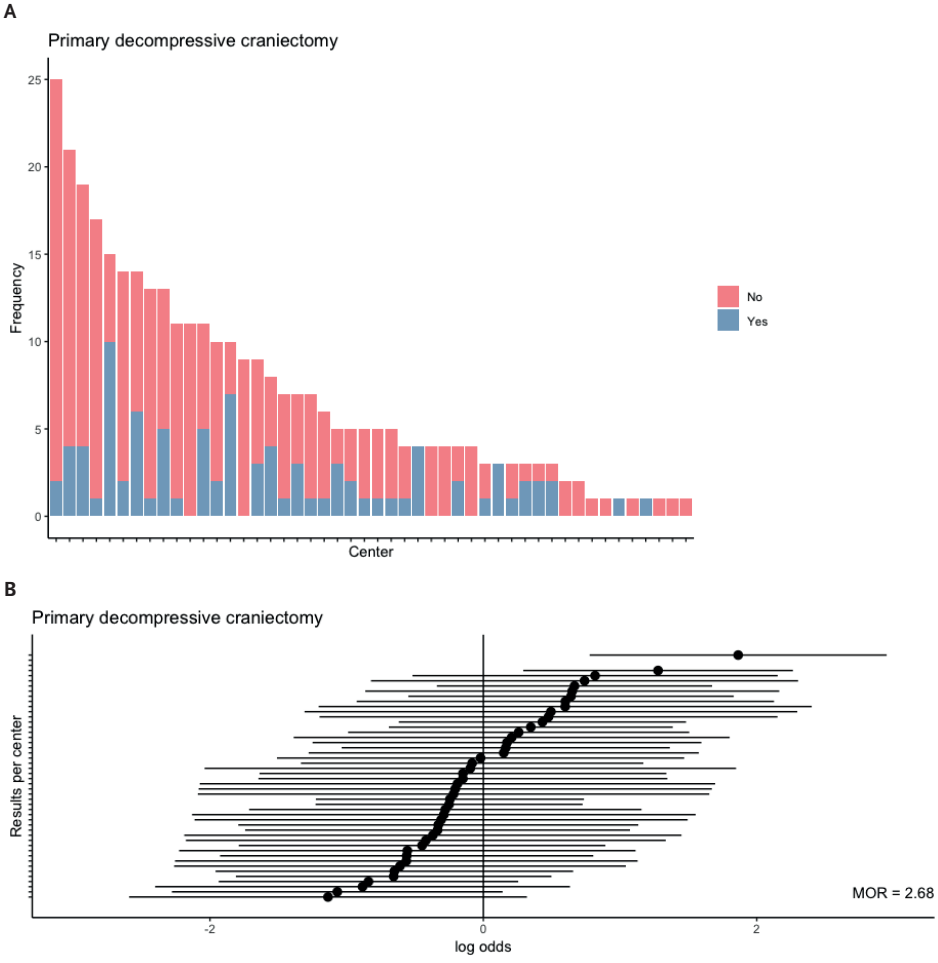

Figure 2. Between-center and between-country differences in primary decompressive craniectomy

Figure 2A shows the observed frequencies of primary decompressive craniectomy of surgical ASDH patients per center. Figure 2B shows the case-mix adjusted log odds ratio for primary decompressive craniectomy per center (A). The median odds ratio (MOR) reflects the between-center variation; a MOR equal to 1 represents no variation, the larger the MOR, the larger the variation. The MOR is 2.7 (p value < 0.0001).

C

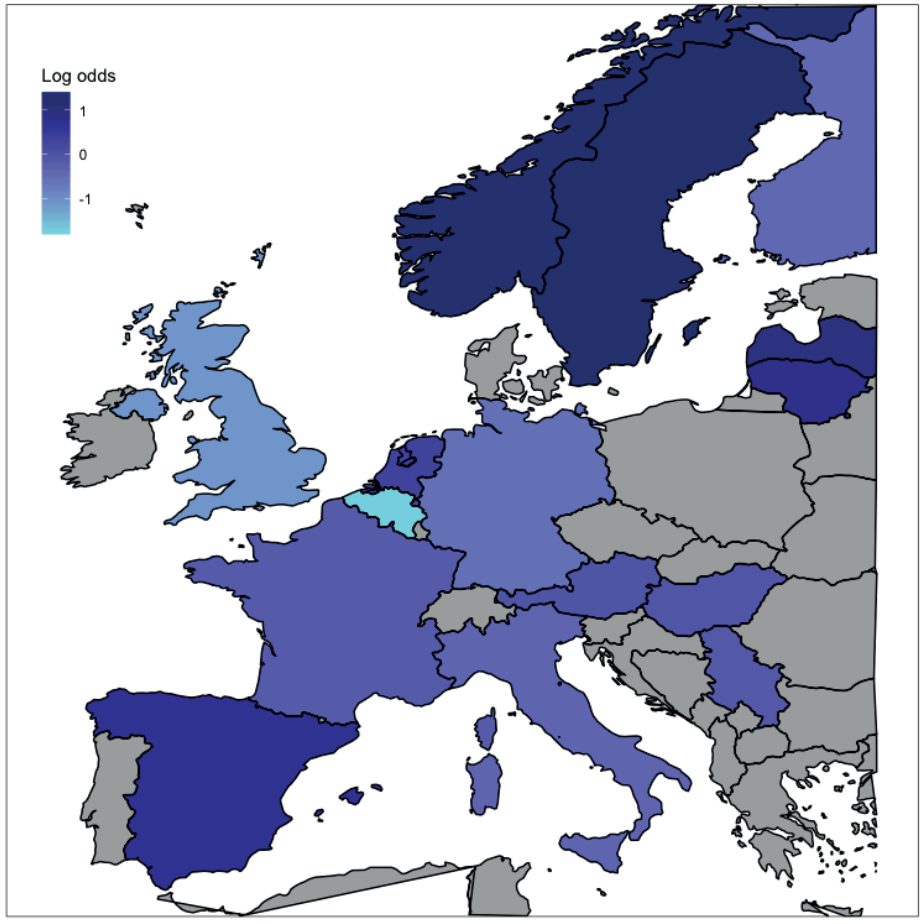

Figure 2. Between-center and between-country differences in primary decompressive craniectomy *(continued)*

Figure 2C represents the log odds ratio for primary decompressive craniectomy as compared to craniotomy per country compared with the overall average, also case-mix adjusted.

Table 1. Selected baseline characteristics and prognosis across centers with different preferences for primary decompressive craniectomy

	Treatment preference (observed primary DC rates per centre) [a]				
	Quartile 1 (6 - 12%)	Quartile 2 (12 – 19%)	Quartile 3 (19 – 26%)	Quartile 4 (26 - 67%)	SMD
n	53	48	51	48	
Age (median [IQR])	63 [56, 69]	56 [43, 66]	56 [38, 68]	53 [34, 64]	0.26
ASAPS (%)					0.44
Healthy	28 (53)	17 (35)	28 (55)	23 (48)	
Mild systemic disease	21 (40)	16 (33)	14 (27)	15 (31)	
Severe systemic disease	4 (8)	11 (23)	7 (14)	7 (15)	
Threat to life	0 (0)	0 (0)	1 (2)	0 (0)	
Unknown	0 (0)	4 (8)	1 (2)	3 (6)	
Hypoxia (%) [b]					0.49
No	41 (77)	42 (88)	44 (86)	37 (77)	
Definite	1 (2)	1 (2)	5 (10)	6 (12)	
Suspect	2 (4)	4 (8)	1 (2)	2 (4)	
Unknown	9 (17)	1 (2)	1 (2)	3 (6)	
Hypotension (%) [c]					0.44
No	41 (77)	46 (96)	46 (90)	39 (81)	
Definite	2 (4)	1 (2)	3 (6)	2 (4)	
Suspect	1 (2)	0 (0)	1 (2)	3 (6)	
Unknown	9 (17)	1 (2)	1 (2)	4 (8)	
Any major extracranial injury (%) [d]	23 (43)	15 (31)	28 (55)	25 (52)	0.27
GCS baseline (median [IQR])	9 [4, 13]	7 [3, 11]	5 [3, 9]	6 [3, 11]	0.30
GCS motor baseline (median [IQR])	5 [2, 6]	4 [1, 5]	1 [1, 4]	2 [1, 5]	0.43

Table 1. Selected baseline characteristics and prognosis across centers with different preferences for primary decompressive craniectomy (*continued*)

	Treatment preference (observed primary DC rates per centre) [a]				
	Quartile 1 (6 - 12%)	**Quartile 2 (12 – 19%)**	**Quartile 3 (19 – 26%)**	**Quartile 4 (26 - 67%)**	**SMD**
Pupils (%)					0.32
Both reacting	36 (68)	35 (73)	32 (63)	28 (58)	
One reacting	3 (6)	7 (15)	9 (18)	10 (21)	
Both unreacting	14 (26)	6 (12)	10 (20)	10 (21)	
Total volume of ASDH (cm3, median [IQR])	58 [31, 97]	70 [40, 114]	70 [32, 103]	50 [18, 79]	0.24
CT large ASDH (%) [e]	35 (66)	37 (77)	42 (82)	31 (65)	0.25
CT midline shift (%) [f]	42 (79)	38 (79)	48 (94)	44 (92)	0.29
CT contusion (%)					0.40
No	19 (36)	25 (52)	21 (41)	23 (48)	
Small	24 (45)	19 (40)	23 (45)	13 (27)	
Large	10 (19)	3 (6)	6 (12)	11 (23)	
Unknown	0 (0)	1 (2)	1 (2)	1 (2)	
CT subarachnoid haemorrhage (%)					0.37
No	18 (34)	21 (44)	12 (24)	21 (44)	
Basal	5 (9)	2 (4)	6 (12)	2 (4)	
Cortical	22 (42)	15 (31)	27 (53)	16 (33)	
Basal and cortical	8 (15)	10 (21)	6 (12)	9 (19)	
CT basal cisterns absent/compressed (%)	20 (38)	19 (40)	25 (49)	21 (44)	0.13
Mean predicted 6-month unfavourable outcome (GOS score ≤ 3, %, median [IQR]) [g]	74 [52, 86]	73 [53, 87]	80 [67, 91]	69 [51, 84]	0.22
Center characteristics					
Academic hospital (vs. non- academic, %)	0 (0)	0 (0)	0 (0)	14 (29)	0.45

Table 1. Selected baseline characteristics and prognosis across centers with different preferences for primary decompressive craniectomy (*continued*)

	Treatment preference (observed primary DC rates per centre) [a]				
	Quartile 1 (6 - 12%)	**Quartile 2 (12 – 19%)**	**Quartile 3 (19 – 26%)**	**Quartile 4 (26 - 67%)**	**SMD**
Number of beds (median [IQR])	655 [600, 850]	1083 [1018, 1148]	1170 [936, 1292]	780 [652, 831]	0.80
Residency program neurosurgery (%)	53 (100)	48 (100)	51 (100)	48 (100)	<0.01
Level I trauma center designation (%)	42 (100)	48 (100)	51 (100)	35 (100)	<0.01
Urban location (vs. suburban and rural location, %)	53 (100)	48 (100)	51 (100)	48 (100)	<0.01
Neurosurgeon staffing (FTE, median [IQR])	11 [8, 19]	11 [10, 12]	10 [6, 12]	8 [8, 11]	0.50
Number of surgeries for ASDH in 2013 (median [IQR])	28 [10, 30]	18 [16, 20]	62 [20, 102]	25 [22, 25]	0.82
Number of surgeries for contusion in 2013 (median [IQR])	7 [5, 8]	10 [7, 14]	15 [4, 236]	10 [8, 14]	0.37
Low threshold policy for primary DC in ASDH (%) [h]	0 (0)	0 (0)	0 (0)	24 (50)	0.71

Abbreviation: AIS, Abbreviated Injury Scale; ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; DC, decompressive craniectomy; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale (5-point); IQR, interquartile range; IV, instrumental variable; SMD, standardized mean difference.

[a] Treatment preference as defined by the case-mix adjusted probability of undergoing primary DC (as opposed to craniotomy) based on the observed primary DC rates per centre. This corresponds to the IV status and presented in quartiles of the range of adjusted regional primary DC rates. The first category is less aggressive than the second and the second is less aggressive than the third and so forth. Importantly, the IV analysis used adjusted primary DC rates as continuous preference, the quartiles are presented for purposes of interpretability of baseline comparability.

[b] Second insult during the pre-hospital or ER phase, defined as $PaO_2 < 8$ kPa (60 mmHg)/$SaO_2 < 90\%$. 'Suspected' was scored if the patient did not have documented hypoxia by PaO_2 or SaO_2, but there was a clinical suspicion, as evidenced by for example cyanosis, apnoea or respiratory distress.

[c] Second insult during the pre-hospital or ER phase, defined as systolic BP < 90 mmHg. 'Suspected' was scored if the patient did not have a documented blood pressure, but was reported to be in shock or have an absent brachial pulse (not related to injury of the extremity)

[d] AIS □ 3

[e] Large is defined qualitatively by the treating neurosurgeon and corresponded to a size larger than 25 cm^3.

[f] Midline shift present is classified as being more than 5 mm.

[g] TBI severity as summarized in predicted unfavorable outcome, proportion with a Glasgow Outcome Scale ≤ 3, based on CRASH-CT variables age, GCS score, pupillary reactivity to light, major extracranial injury, and CT characteristics (midline shift >5mm, traumatic subarachnoid hemorrhage, and obliteration of the basal cisterns).

[h] Before patient inclusion in CENTER-TBI, treatment policies per center were captured by provider profile surveys, including the policy towards primary DC. The resulting threshold for primary DC is dichotomized based on this distinction: Yes', primary DC routinely/pre-emptively versus 'No', no primary DC routinely/pre-emptively.

Table 2. Primary and secondary outcomes and treatment associations for primary decompressive craniectomy

Outcome	Adjusted center-level analyses					
	Treatment preference (observed primary DC rates per centre)				Effect variable	Adjusted value (95% CI) [a]
	Quartile 1 (6 - 12%, n = 53)	Quartile 2 (12 – 19%, n = 48)	Quartile 3 (19 – 26%, n = 51)	Quartile 4 (26 - 67%, n = 48)		
Primary outcome: GOSE at 6 months (median [IQR])	3 [1 to 7]	3 [1 to 6]	3 [1 to 6]	3 [1 to 6]	Common odds ratio	0.9 (0.7 – 1.1)
Secondary outcomes						
In-hospital mortality	12 (23)	11 (23)	21 (41)	18 (38)	Odds ratio	1.3 (1.0 – 3.4)
GOSE of 7 or 8 (%)	13 (25)	10 (21)	7 (14)	8 (17)	Odds ratio	0.9 (0.7 – 1.2)
GOSE of 5-8 (%)	17 (32)	20 (42)	16 (31)	17 (35)	Odds ratio	1.0 (0.8 – 1.2)
GOSE of 4-8 (%)	20 (38)	21 (44)	19 (37)	22 (46)	Odds ratio	1.0 (0.8 – 1.2)
QOLIBRI (median [IQR]) at 6 months [b]	Na [c]					

Abbreviation: CI, confidence interval; DC, decompressive craniectomy; GOSE, Glasgow Outcome Scale Extended; IQR, interquartile range; Na, not available; QOLIBRI, Quality of Life after Brain Injury Scale.

[a] Estimates from random-effect multivariable ordinal/logistic regression with the instrument, adjusted probability of undergoing primary DC as treatment variable. Confounding was furthermore addressed by adjusting for the a-priori defined variables age, GCS, pupil reactivity, hematoma size, contusion presence and midline shift. The adjusted common OR indicates the odds of a higher GOSE score (primary outcome) or experiencing the secondary outcomes, for an increase from the 25th percentile to the 75th percentile of the range in exposure to the center intervention preferences.

[b] QOLIBRI is a standardized health specific quality of life measure specifically designed for and validated in outcome assesment in patients with brain injury. It is a numerical scale with scores ranging from 0 to 100, with higher scores indicating a better quality of life. The score was available for 19 patients of the primary DC group and 111 of the craniotomy group.

[c] The association could not be estimated due to low numbers (no centers with □ 10 patients in the subcohort).

After excluding patients from centers with < 10 patients (n = 132), 200 patients were available for primary IV analysis (Table 1). Center preference for DC over craniotomy was not associated with better functional outcome (adjusted common OR 0.9, 95% CI 0.7 – 1.1 in favor of craniotomy, Table 2, eFigure 2). The aORs were consistent across GOSE cutoffs (Table 2). In-hospital mortality was associated with a higher center preference for primary DC (aOR per 14% IQR more primary DC 1.3 [95% CI (1.0 – 3.4), Table 2). The association between surgical strategy and quality of life could not be estimated due to low numbers (no centers with □ 10 patients in the QOLIBRI subgroup).

Patients from centers with the highest case-mix adjusted probability (ie, preference for) DC more often had a period of neuroworsening and a higher Therapy Intensity Level (TIL). Otherwise, secondary outcomes did not differ between surgical preference groups (eTable 5).

Primary DC was associated with worse outcomes in unadjusted patient-level analysis (eg, GOSE: common OR 0.4, 95% CI 0.3 – 0.6; eTable 6, eTable 7). Covariable adjustment in multivariable regression and PSM (at patient-level) resulted in GOSE-association estimates favoring a craniotomy (adjusted common OR 0.4, 95% CI 0.2 – 0.6 and adjusted common OR 0.4, 95% CI 0.3 – 0.8, respectively; eFigure 1, eTable 6, eTable 8). In sensitivity IV analyses, the primary association estimate remained consistent when excluding centers with < 15 patients (n = 97; adjusted common OR 0.9 [95% CI 0.5 – 1.5], eTable 6, 9, 10 and 11), and when using *a priori* defined IV (adjusted common OR 0.9, 95% CI 0.4 – 2.2; eTable 6). In-hospital mortality did not differ across centers with primary DC preference in sensitivity IV analysis excluding centers with < 15 patients (eTable 10).

DISCUSSION

This prospective observational study demonstrates large treatment variation across European and Israeli centers in the selection of DC versus craniotomy in surgical evacuation of traumatic ASDH. It is the first to exploit this variation using IV analyses, finding that primary DC compared to craniotomy was unlikely to be associated with better functional outcome. These findings held in predefined IV sensitivity analyses. Patient-level analysis with multivariable regression and PSM revealed poorer outcomes for primary DC, although as described below, residual confounding may have been present. Further, primary DC was associated with more complications, more follow-on surgeries and higher in-hospital mortality.

Election of primary DC is well established in cases of ASDH with acutely severe swelling preventing replacement of the bone flap. A recent consensus states that if the brain is bulging beyond the inner table of the skull intra-operatively, the bone

flap should not be replaced.[8,24] The advantage of a DC is more effective control of ICP elevation, potentially preventing secondary brain injury and poor clinical outcome. However, DC necessitates additional reconstructive surgery (cranioplasty) and carries risks related to the bone defect, infections, and bone-flap reabsorption.[7] Further, DC is known to alter cerebrospinal fluid flow dynamics, and cerebral blood flow dynamics, both of which improve with replacement of the bone flap.[25-28] Clinically relevant evidence is weak for primary DC in ASDH; large treatment variations exist,[11,29,30] and support for claims of effectiveness are inconsistent. Most of these observational studies suggest worse outcomes for primary DC.[1,4,9,10,15,31,32] When comparing the preoperative and baseline characteristic of DC versus craniotomy cohorts, all studies show that patients selected to undergo DC are more likely to have lower GCS, more concomitant hematomas and therefore, and have a poorer prognosis at baseline. Neurosurgeons are therefore more likely to select DC for the more severely impaired patients in anticipation of potential cerebral swelling that is difficult to manage medically. The higher number of patients with poor prognosis undergoing DC suggests strong confounding within these observational studies and that interpretation of worse outcomes resulting from primary DC, rather than from worse baseline status, may be incorrect.[5,13] The methodologically best – albeit small - study evaluating this treatment variation through comparison of two neurosurgical centers found postoperative ICP to be better controlled and outcomes improved in the centers with greater utilization of primary DC in TBI.[14] However, these results included patients undergoing emergent DC or craniotomy for any mass or diffuse lesion, not specifically ASDH, which represented only 15 of 52 participants.

Our findings confirm these previously reported treatment variations and the inconsistency displayed by neurosurgeons as to selection of primary DC versus craniotomy in the absence of massive swelling. Patients in our cohort who underwent primary DC were also more severely injured, despite scoring similar prognoses on CRASH-CT, and required more interventions to lower ICP (ie, greater TIL). Although many patients who received primary DC attained similar 6-month GOSE outcomes as patients who received craniotomy, as noted, they experienced a worse clinical course. We maintain that the chance of a favorable outcome after primary DC was less likely when viewed in the context of the IV analyses, which showed an absence of clear benefit, and the patient-level analyses that clearly suggested harm.

Comparative effectiveness research with IV analysis, utilizing heterogeneity in practices across centers to compare their effectiveness of interventions that may be standard practice in some centers, but not in others, offers complementary evidence to the gold standard of RCTs.[33,13,34] Compared with conventional, patient-level analysis, IV CER is less prone to confounding. The validity, however, relies on whether the center treatment rate is an appropriate instrumental variable. Our instrument was

strongly associated with primary DC and did not associate with baseline prognosis: the widely differing surgical strategies are practiced in centers that on average treat similar patients. The balanced confounding between centers suggests a reasonable balance in the distribution of unmeasured confounding.[13] Nonetheless, the observed practice variation might still partly result from prognostic differences. Therefore, we surveyed providers to evaluate whether the between-center variation actually arose from provider preferences.[11] The *a priori* reported center policy for primary DC strongly predicted actual primary DC use (ie, stronger than any single patient characteristic). To further extricate the effect of the ASDH surgical strategy in a center from other between-center care variations associated with outcome, we adjusted with a random-effects for center.

The totality of our analyses suggests that the chance of a favorable outcome after primary DC is less likely when viewed in the context of the IV analyses, which showed an absence of clear benefit, and the patient-level analyses that clearly suggested harm. Given the higher risk of a complicated clinical course, we maintain that the selection of primary DC should be restricted to salvageable patients with brain swelling precluding flap repositioning. Our results apply to patients for whom the neurosurgeon may be in equipoise, because, an identical patient may receive a DC in one center and a craniotomy in another, it naturally follows that there is more than one valid treatment option. And since equipoise differs per center, we cannot readily identify the relative contribution of each subgroup.[35-37]

We acknowledge several limitations. First, possible residual confounding remains due to other local practice variations associated with surgical preference, despite IV analysis, rigorous statistical adjustment (ie, a random-effects term) and multiple sensitivity analyses, particularly the IV analysis with the *a priori* center policy for approach as a different, strong IV, strongly correlated to the actual DC employment, confirming consistent neurosurgeon's preferences. To further account for center-level confounding we performed a separate cluster analysis, with a broader medical domain view than neurosurgical treatment alone, to explore if the assumption of the absence of correlation between treatment choices is tenable. The main conclusion was that specific treatment policies within domains (ICP monitoring, coagulation and transfusion, neurosurgery, prophylactic antibiotics, and more general ICU treatment policies) do not correlate with other treatment policies. Importantly, the absence of correlation between domains was most pronounced for surgical treatment. Another limitation is that participating institutions of CENTER-TBI were mainly tertiary referral centers. Results may not be generalizable to other hospital settings and every patient. Last, the interpretation of the effect of primary DC is hampered by the relatively small sample size, resulting in a wide confidence interval that may obscure

a small, clinically relevant effect. Although this cohort is the largest to date, subgroup analyses were considered infeasible.

CONCLUSION

In patients with a traumatic ASDH, surgical evacuation by primary DC as compared to craniotomy is unlikely to be of benefit, measured in terms of functional outcome at 6 months, and the higher risk of complications. Our study underscores the necessity of collecting granular data on interventions and their sequelae to more accurately delineate the clinical course. The pragmatic RESCUE-ASDH RCT will provide further evidence on the efficacy of primary DC for ASDH.[38] Strong consideration should be given to revising guidelines to restrict selection of primary DC to patients whose severe swelling precludes replacement of the bone flap. Such direction could bring needed evidence-based consistency to current practice and result in better overall outcomes for patients.

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