Comparative Effectiveness of Mannitol versus Hypertonic Saline in Traumatic Brain Injury patients: a CENTER-TBI study

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ABSTRACT

Introduction: Increased intracranial pressure (ICP) is one of the most important modifiable and immediate threats to critically ill patients suffering from traumatic brain injury (TBI). Two hyperosmolar agents (HOA), mannitol and hypertonic saline (HTS) are routinely used in clinical practice to treat increased ICP. We aimed to assess whether a preference for mannitol, HTS or their combined use translated into differences in (functional) outcome.

Methods: The CENTER-TBI Study is a prospective multicenter cohort study. For this study, patients with TBI, admitted to the ICU, treated with mannitol and/or HTS, aged ≥16, were included. Patients and centers were differentiated based on treatment preference with mannitol and/or HTS based on structured, data-driven criteria such as first administered HOA at the ICU. We assessed influence of center and patient characteristics in the choice of agent using adjusted multivariate models. Furthermore, we assessed the influence of HOA preference on (functional) outcome using adjusted ordinal and logistic regression models, and instrumental variable analyses.

Results: In total, 2056 patients were assessed. Of these, 502 (24%) patients received mannitol and/or HTS on the ICU. The first bolus of a HOA was HTS for 287 (57%) patients, mannitol for 149 (30%) patients, and both for 66 (13%) patients. Two unreactive pupils were more common for patients receiving both (13, 21%), compared to patients receiving HTS (40, 14%), or mannitol (22, 16%). Center, rather than patient characteristics, was independently associated with the preferred choice of HOA (p-value < 0.05). ICU mortality and 6-month functional outcome were similar between patients preferably treated with mannitol compared to HTS (OR = 0.8, CI = 0.4 – 1.7; OR = 1.1, CI = 0.7 – 1.8 respectively). Patients who received both also had a similar ICU mortality and 6-month functional outcome compared to patients receiving HTS (OR = 1.9, CI = 0.7 - 4.9; OR = 0.7, CI = 0.3 – 1.6 respectively).

Conclusion: We found between center variability regarding HOA preference. Moreover, we found that center is a more important driver of the choice of HOA than patient characteristics. However, our study indicates that this variability is an acceptable practice given absence of differences in outcomes associated with a specific HOA.

Keywords: Traumatic brain injury, critical care, intensive care unit, osmolar therapy

INTRODUCTION

Intracranial hypertension (IH), or elevated intracranial pressure (ICP > 20-25mmHg),[1] is one of the most important immediate threats to critically ill patients with traumatic brain injury (TBI). IH contributes to secondary brain injury but is modifiable with various treatments, including hyperosmolar agents (HOAs).[2] Two HOAs, mannitol and hypertonic saline (HTS), are routinely used in clinical practice to decrease ICP.[1-6]

Consensus guidelines have not stated a clear preference for one of the HOAs,[1, 2, 5, 6] since systematic reviews and meta-analyses were inconclusive or yielded contradictory findings both in effects on ICP and clinical outcomes, and since there is a dearth of adequately powered randomized clinical trials.[7-16] Therefore, it is likely that centers and clinicians balance potential benefits and risks based on their personal experiences with HOA,[17] but it is unclear whether such variability ultimately results in differences in outcome.[18]

When randomized controlled trials (RCTs) of sufficient size and quality are unfeasible or unavailable, between center differences in policies can be leveraged to study policy-outcome relations in observational data using comparative effectiveness research. Therefore, we aimed to assess the use of and effect on outcome of mannitol versus HTS by: 1) studying the influence of baseline characteristics versus center-effect on the choice of HOA, and: 2) assessing whether a preference for mannitol, HTS or their combined use translated into differences in outcome.

METHODS

Study population

The Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI, registered at clinicaltrials.gov NCT02210221) study is a prospective cohort study conducted in 63 centers from 18 countries across Europe and Israel between 2014 and 2017. Patients were included if they arrived at the hospital within 24 hours after injury with a clinical diagnosis of TBI and had an indication for a head computed tomography (CT) scan. Patients were excluded if they had a severe pre-existing neurological disorder that would confound outcome assessment. Ethics approval was acquired for each center and consent for participation obtained from all patients or their proxies. For more information on the CENTER-TBI study, see previous publications.[19, 20] For this study, we selected patients aged 16 or older who were admitted to the ICU. For further analyses of HOA, we only included patients who were treated with mannitol and/or HTS during their ICU stay, and we extracted data on demographics, country, center, injury, admission, imaging, monitoring, treatment, and outcome characteristics. Moreover, we used data of the CENTER-TBI study on reported practices regarding HOA use. In an earlier publication from Cnossen et al.,[21] detailed information about the development, administration, and content of these provider profilings is available.[21]

Outcomes

First, we aimed to assess the influence of center on HOA preference: mannitol, HTS, or both.

Second, we aimed to assess the association between the preference for a HOA on outcomes, defined as ICU mortality and the Glasgow Outcome Scale-Extended (GOSE), assessed at 6 months after injury. GOSE is an eight-point outcome scale that captures functional outcome. Category 2 and 3 were combined, resulting in a seven-point ordinal scale.

Data collection

Definitions of preferences for mannitol, HTS or the use of both

In the electronic case report form (e-CRF), administration of mannitol, HTS, neither, or both HOAs was scored on a daily level (received: yes/no). To overcome the lack of data on dosages of mannitol and

HTS in the e-CRF, the preference for mannitol, HTS, or both was captured in five post-hoc constructed variables, namely:

1. Preference on *patient-level*: we designated a patient as a 'HTS-patient' if the patient received HTS as their first HOA on the ICU, even if the patient would receive mannitol on subsequent days. We applied the same rule for mannitol and the patient could also be noted as having received both agents.
2. Preference on *center-level*: if more than two-thirds (>66%) of patients in a center were regarded as 'HTS-patients' on *patient-level*, we designated this center as a 'HTS-center', and patients were considered treated with HTS, even if some received mannitol on other occasions. We applied the same rule for mannitol. To test robustness of this definition, sensitivity analyses were done using 75% instead of 66% as cut-off value. When the proportion was less than two-thirds (and in the sensitivity analyses less than 75%), this unit of analysis was designated as 'center preference for using both HOA'.
3. Preference on *management-level*: investigators in all centers indicated their preferred agent in a previous provider profiling analysis . If the investigators in a center indicated that HTS was their preferred HOA, then all patients in this hospital would be regarded as HTS patients, vice-versa for mannitol, and both.
4. Preference using the *patient-HTS sum score*: this unit for analysis is defined as the number of times a patient received HTS divided by the total number of times a patient received any HOA. When a patient received both mannitol and HTS on one day, this patient would score '2' for this day instead of '1' when only receiving mannitol or HTS.
5. Preference using the *center-HTS sum score*: defined as the total of the sum score of all patients, divided by the number of patients in that center.

Statistical analyses

Baseline characteristics

Baseline characteristics were presented as median values with interquartile ranges (IQRs) for continuous variables and as frequencies and percentages for categorical variables. We compared characteristics

between patients who did not receive a HOA, and patients who did receive a HOA, and between patients who received mannitol, HTS, or both as the first gift at the ICU. To test for differences between these groups, we used the Pearson $\chi 2$ test for categorical variables and the independent t-test or Mann–Whitney U-Test for continuous variables.

Baseline variables

We collapsed category 3 and 4 of the American Society of Anesthesiologists (ASA) Physical Status classification because category 4 had <10 patients. We collapsed category V and VI of the Marshall CT classification as grading V and VI could not be differentiated on central review as the raters were not aware of (intent to) surgery. Last, to compare groups at baseline we calculated the expected probability of mortality and unfavorable outcome using the IMPACT core prediction model.[22]

Association of center with HOA preference

To assess the effect of center on the HOA preference, two multivariate regression models were compared using the likelihood ratio test. We compared two multivariate model with a binary dependent variable (mannitol versus HTS). One model had a random intercept on patient level, whereas the other model had a random intercept on patient *and* center level. Both models were adjusted for baseline characteristics (age, GCS motor score, pupillary reactivity, and major extracranial injury (MEI)).

A significant likelihood ratio test indicates an association of the independent variable that is present in one model, and absent in the other. In this case, a significant likelihood ratio test indicates that the choice to administer mannitol or HTS is not based on baseline characteristics, but on the center to which the patient is admitted, indicating random practice variation.

Association of HOA with outcome

We used ordinal and logistic regression to assess associations between the HOA preference and the outcome. Given the observational nature of the data, we used different approaches to assess the reproducibility and robustness of the association of HOAs with ICU mortality and GOSE. Logistic regression was performed for ICU mortality. Ordinal regression was performed for GOSE. The

statistical analyses were performed separately for every post-hoc variable indicating HOA preference. All models were tested univariably, and multivariably. In the multivariable analyses, we first adjusted for baseline characteristics (age, GCS motor score, pupillary reactivity, and MEI). Subsequently, we adjusted for the baseline characteristics and additional treatment characteristics (mean ICP before receiving a HOA, mean therapy intensity level (TIL) before receiving a HOA, and median daily fluid balance during the whole ICU stay). We included a random intercept for center in all multivariable models.

To overcome unmeasured confounding, instrumental variable (IV) analyses is suggested [23]. We used the following post-hoc variables as our instrument for the IV analyses: *'preference on center-level'*, *'preference on management-level'*, and *'center-HTS sum score'*.

Associations for ICU mortality and GOSE were expressed as Odds Ratios (ORs) with 95% confidence intervals (CIs). An OR above 1 indicates *worse* outcome for ICU mortality, but *better* outcome for GOSE.

All statistical analyses were performed in R studio.[24] Multiple imputation was used to handle missing values, with use of the mice package in R.[25] Data were accessed using a bespoke data management tool, 'Neurobot' (neurobot.incf.org), version 3.0 (data freeze: March 2021).

RESULTS

Baseline characteristics

We assessed 2056 patients aged 16 or older, admitted to the ICU. Of these, 502 patients (24%) received a HOA during ICU stay. Patients receiving HOAs were younger, had more severe brain injury on admission, received more ICP lowering treatments and had longer hospital length of stay and worse outcome (p-values < 0.001). The mean ICP during ICU stay was 13.5 mmHg (IQR = 10.7 – 16.9) for patients receiving HOAs versus 9.7 mmHg (IQR = 7.1 – 12.5) for those without (p-value < 0.001). In total, 110 patients (22%) who received a HOA died at the ICU versus 160 (10.4%) patients who did not receive a HOA (p-value < 0.001) (Additional file 1).

In the HOA group, we found a preference for HTS in 287 (57%) patients, mannitol for 149 (30%) patients, and use of both agents for 66 (13%) patients. An overview of the percentage of patients per center, can be found in Figure 1. The median age in the mannitol group was higher (49 years) than for patients receiving HTS or both (42 and 43 years respectively) (p-value 0.04). In the HTS group, 125 (45%) patients had a GCS motor score of 1, compared to 71 (48%) patients in the mannitol group, and 28 (44%) patients receiving both. Two unreactive pupils were more common for patients receiving both (13, 21%), compared to patients receiving HTS (40, 14%), or mannitol (22, 16%). Similarly, more patients receiving both agents, had a MEI (43, 65%), compared to patients receiving HTS (153, 53%), or mannitol (87, 58%). None of these findings were statistically significant (p-values of 0.255, 0.185 and 0.182 respectively) (Table 1).

The mean ICP during ICU stay was 13.2 mmHg (IQR = 10.2 – 16.2) for the HTS group, 13.3 mmHg (IQR = 10.9 – 16.6) for the mannitol group, and 15.3 mmHg (IQR = 12.5 – 20.7) for patients receiving both (p-value 0.001). The mean ICP before receiving an agent was 13.6 mmHg (IQR = 9.8 – 16.7) for the HTS group, 13.5 mmHg (IQR = 11.1 – 17) for the mannitol group and 16.1 mmHg (IQR = 12.8 – 22.7) for patients receiving both (p-value 0.002). The median of the maximum TIL before receiving an agent was higher for patients receiving both agents (15, IQR = 12.3 – 19), compared to the HTS group (11, IQR = 8 – 14), and the mannitol group (11, IQR = 8 – 15) (p-value < 0.001) (Table 1).

Center effect on HOA preference

We compared one model with center as random intercept to one model without center as random intercept. We adjusted for baseline characteristics. The model with center as random intercept was significant with a p-value of < 0.05.

Association of HOA preference with outcome

In the HTS group, 58 (20%) patients did not survive their ICU stay compared to 28 (19%) patients in the mannitol group, and 24 (36%) patients in the group receiving both HOAs (Table 1). In multivariable analyses, after adjustment for baseline characteristics, there were no differences in probability of mortality between the mannitol and HTS group in the *patient-level* analysis (OR = 0.85, CI = 0.45 – 1.51). After additional adjustment for treatment characteristics, no differences in probability of mortality were found between the mannitol and HTS group in the *patient-level* analysis (OR = 0.82, CI = 0.39 – 1.74). Similar observations were found on all levels (Table 2).

In the HTS group, 154 (61%) patients had an unfavourable outcome after 6 months compared to 82 (62%) patients in the mannitol group, and 48 (77%) patients in the group receiving both HOAs (Table 1). In multivariable analyses, after adjustment for patient and treatment characteristics, there were no differences between the mannitol and the HTS group in the probability of a more unfavourable outcome (OR = 1.08, CI = 0.65 – 1.80). Similar observations were found on all levels (Table 3).

DISCUSSION

In this study, we found that the preference for HOA at ICUs across European trauma centers varied. This variation was driven by center rather than patient characteristics indicating random between center variability, based on local preferences. This circumstance facilitated comparative effectiveness analysis on a patient-level, center-level, and management-level, which showed that the choice for a specific HOA was not associated with higher ICU mortality or worse 6-month functional outcome after extensive statistical adjustments for possible confounding factors.

In a recent comparative effectiveness study, effects of bolus HTS versus mannitol were assessed in a pediatric population and the results of this analysis in 521 children showed similar effects on cerebral perfusion pressure and possibly better effect of HTS compared with mannitol on immediate post bolus ICP. This finding is in line with current practice guidelines in pediatric TBI patients favoring HTS over mannitol and shows the robustness of this type of analyses to underpin clinical practice guidelines.[26] Our analysis was different and focused on clinical outcomes, associated with the preference for one of the HOAs and likewise seems to underpin current practices and guidelines that do not favor one HOA over the other. Contrary to our findings, Anstey et al.[27] found that patients who received mannitol compared to patients who received HTS had a higher Marshall CT score, a higher ISS and had a higher predicted probability of 6-month mortality using the extended IMPACT score.[27] However, when comparing patients who received mannitol or HTS to the patients who received both, we found that patients who received both, had higher ICP during their ICU stay, and had a higher maximum TIL. The worse outcome associated with the higher TIL in univariable analysis can be explained, since clinicians will apply more intense treatment regimens in patients with more severe brain injury. This indicates *confounding by indication*. To overcome confounding by indication, multivariable analyses and instrumental variable (IV) analyses have been suggested,[23] and both were applied in this study. Using these analyses, we could not detect differences in outcome depending on the choice of HOA. We performed IV analyses on center-level and on management-level. The IV analyses on center-level represent the clinical choices of the specific center based on prospective clinical data. However, the IV analyses on center-level can still be clouded by case-mix, since the IV was derived from the core data. This is not the case when performing the IV analyses on management-level, since this data was not

derived from the core data, but from previously captured data. The robustness of our results was supported by using different definitions of HOA preference at center, patient, and management level, and various methodological approaches, yielding consistent results after statistical adjustment for possible confounders.

Variable results of comparisons between mannitol and HTS in TBI patients were found in systematic reviews and meta-analyses that were previously published.[7-16, 28] The studies (also) focusing on outcomes, did not previously show any differences.[12, 13, 15, 16] Our findings therefore are in line with previous research and consolidate the notion of lack of superiority of one agent over the other. Future intervention trials, such as the "Sugar or Salt Trial",[29] comparing mannitol and hypertonic saline may shed more light on the risk versus benefit of both agents, especially regarding ease of use and possible side effects.[29]

Given the similar outcomes for mannitol and HTS patients in this and previous studies, the occurrence and the seriousness of adverse events may be important for the choice of a HOA. Previous studies found that high dose mannitol can cause acute renal failure,[30] electrolyte abnormalities,[31, 32] acidosis,[32] hypotension,[31, 33, 34] and congestive heart failure with pulmonary edema.[35] A recent study found that the occurrence of acute kidney injury (AKI) negatively impacts 6-month (functional) outcome. The use of HTS rather than mannitol could represent a modifiable risk factor in the development of AKI during ICU stay after TBI.[36] Following the guidelines of the Neurocritical Care Society, clinicians should monitor intravascular volume status, renal function, and serum osmolarity closely when using mannitol,[6] and, when using HTS, hypernatremia and hyperchloremia, and acid–base balance deserve closer attention.[6]

The CENTER-TBI study is unique for its extensive and prospective data collection in multiple centers, enrolling TBI patients with varying injury severity across a wide range of European centers. However, this study also has limitations which should be considered when interpreting the results. First, all centers participating in CENTER-TBI are characterized by their commitment to TBI research. They might represent a selected sample of the neurotrauma centers in Europe limiting generalizability. Second, receiving mannitol and/or HTS was indicated once per day and as either present or absent, limiting assessment of dose-response relations. Last, due to the limitations in the granularity of the

dataset, we were not able to investigate safety profiles for mannitol and/or HTS.

Future studies, preferably a large RCT such as the "Sugar or Salt Trial",[29] should look more closely at effects of equimolar dosages of mannitol and HTS. If future ongoing RCTs also point to the direction of similar outcomes between mannitol and HTS, safety profiles and cost-effectiveness may become a more important factor in clinicians' preference. Further, efficacy research may be facilitated when patient characteristics can be identified that are associated with either improved effect of a specific agent or less complications and better safety profile to target HOA to specific clinical characteristics which may improve personalized choices.

CONCLUSION

There is a large variation between centers in the use of either mannitol, HTS, or both. Center is a more important driver for the choice of HOA than patient characteristics, indicating random practice variation. We found no differences in clinical outcomes associated with variability in HOA preferences in this comparative effectiveness study. Our results support that the current variation in use of different HOA is an acceptable clinical practice until better evidence will arise on risk versus benefit of using one agent over the other.

ABBREVIATIONS

ASAPS = American Society of Anesthesiologists Physical Status; CT = Computed tomography; DC = decompressive craniectomy; GCS = Glasgow coma scale; GOSE = Glasgow outcome scale extended; HTS = hypertonic saline; ICP = intracranial pressure; ICU = intensive care unit; IQR = interquartile range; ISS = injury severity score; TIL = therapy intensity level

DECLARATIONS

Ethics approval and consent to participate

The Medical Ethics Committees of all participating centers approved the CENTER-TBI study, and informed consent was obtained according to local regulations

Consent for publication

Not applicable

Availability of data and materials

The data supporting the findings in the study are available upon reasonable request from the corresponding Author (EvV) and are stored at https://center-tbi.incf.org/

Conflicts of Interest

GC is Editor-in-Chief of Intensive Care Medicine. GC reports grants, personal fees as Speakers' Bureau Member and Advisory Board Member from Integra and Neuroptics; personal fees from Nestle and UCB Pharma, all outside of the submitted work.

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Authors' contributions

EvV analyzed the data and drafted the manuscript, and the supplementary tables and figures. All coauthors gave feedback on the manuscript. MvdJ supervised the project. All coauthors gave feedback on (and approved) the final version of the manuscript.

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TABLES AND FIGURES

Figure 1. Percentage of patients per group (HTS, mannitol or both)

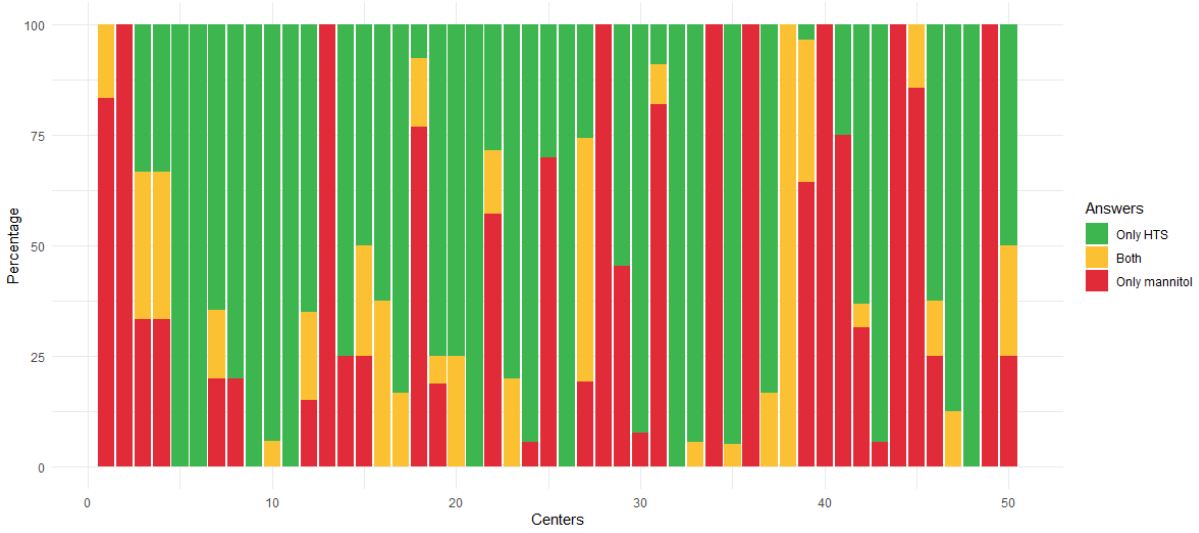


Table 1. Preference for HTS versus mannitol versus both: baseline characteristics					
	HTS	Mannitol	Both	p-value	Missing (%)
n	287	149	66		
Day of first mannitol gift (median [IQR]) *HTS patient may have had mannitol after day 1*	5.00 [3.00, 6.00]	2.00 [1.00, 3.00]	1.00 [1.00, 2.00]	<0.001	48.6
Day of first HTS gift (median [IQR]) *Mannitol patients may have had HTS after day 1*	2.00 [1.00, 3.00]	3.00 [3.00, 6.00]	1.00 [1.00, 2.00]	<0.001	23.1
Patient-HTS sum score	100.00 [100.00, 100.00]	0.00 [0.00, 0.00]	50.00 [50.00, 65.62]	<0.001	0.0
Patient characteristics					
Age (median [IQR])	42.00 [26.00, 57.50]	49.00 [35.00, 67.00]	43.00 [30.00, 61.00]	0.004	0.0
Male (%)	220 (76.7)	112 (75.2)	43 (65.2)	0.151	0.0
ASAPS class (%)				0.535	4.0
1	170 (61.4)	85 (59.9)	36 (57.1)		
2	77 (27.8)	47 (33.1)	22 (34.9)		
3	30 (10.8)	10 (7.0)	5 (7.9)		
Region (%)				<0.001	0.0
Baltic States	14 (4.9)	2 (1.3)	5 (7.6)		
Eastern Europe	1 (0.3)	6 (4.0)	0 (0.0)		
Northern Europe	72 (25.1)	11 (7.4)	3 (4.5)		
Southern Europe	50 (17.4)	41 (27.5)	20 (30.3)		
United Kingdom	68 (23.7)	27 (18.1)	11 (16.7)		
Western Europe	82 (28.6)	62 (41.6)	27 (40.9)		
Baseline characteristics					
GCS motor score at baseline (%)				0.255	2.2
1	125 (44.6)	71 (48.3)	28 (43.8)		
2	11 (3.9)	8 (5.4)	5 (7.8)		
3	27 (9.6)	4 (2.7)	7 (10.9)		
4	24 (8.6)	13 (8.8)	5 (7.8)		
5	61 (21.8)	26 (17.7)	11 (17.2)		
6	32 (11.4)	25 (17.0)	8 (12.5)		
Reactive pupils at baseline (%)				0.185	6.6
Both reactive	192 (71.6)	108 (77.1)	44 (72.1)		
One reactive	36 (13.4)	10 (7.1)	4 (6.6)		
Both unreactive	40 (14.9)	22 (15.7)	13 (21.3)		
Total ISS (median [IQR])	33.00 [25.00, 43.00]	34.00 [25.00, 45.00]	34.00 [25.00, 50.00]	0.297	0.0
Major extracranial injury (%)	153 (53.3)	87 (58.4)	43 (65.2)	0.182	0.0
CT characteristics					
Marshall CT Classification (%)				<0.001	11.4
I	6 (2.3)	0 (0.0)	0 (0.0)		
II	77 (30.1)	29 (22.3)	7 (11.9)		
III	34 (13.3)	16 (12.3)	9 (15.3)		
IV	5 (2.0)	1 (0.8)	6 (10.2)		

V/VI	134 (52.3)	84 (64.6)	37 (62.7)		
Visible pathology on first CT (%)	247 (86.1)	129 (86.6)	52 (78.8)	0.279	0.0
ICP and fluid balance					
ICP monitoring (%)	254 (88.5)	123 (82.6)	61 (92.4)	0.084	0.0
Mean ICP during hospital stay (median [IQR])	13.22 [10.16, 16.23]	13.29 [10.89, 16.59]	15.33 [12.52, 20.72]	0.001	14.5
Mean ICP before receiving an agent (median [IQR])	13.68 [9.83, 16.71]	13.51 [11.05, 16.89]	16.11 [12.82, 22.71]	0.002	20.1
Fluid balance during hospital stay	305.50 [-161.50, 843.00]	433.50 [24.25, 1142.75]	595.75 [42.12, 1116.00]	0.058	12.5
ICP lowering therapies before hyperosmolar therapy					
Metabolic suppression using high dose barbiturates or propofol (%)	74 (26.1)	29 (20.1)	20 (30.8)	0.208	1.8
Neuromuscular blockade (paralysis) (%)	73 (25.7)	37 (25.7)	25 (38.5)	0.099	1.8
Intensive hypocapnia for ICP control [PaCO2 < 4.0 kPa (30 mmHg)] (%)	9 (3.2)	3 (2.1)	6 (9.2)	0.031	2.0
Hypothermia below 35°C (%)	14 (4.9)	7 (4.9)	4 (6.2)	0.912	1.8
DC before hyperosmolar therapy (%)	30 (10.6)	32 (22.2)	18 (27.7)	<0.001	1.8
Maximum TIL (median [IQR])	9.00 [6.00, 13.00]	8.00 [6.00, 13.00]	14.00 [9.00, 18.00]	<0.001	0.0
ICP lowering therapies during the whole ICU stay					
Metabolic suppression using high dose barbiturates or propofol (%)	96 (33.4)	48 (32.2)	23 (34.8)	0.926	0.0
Neuromuscular blockade (paralysis) (%)	105 (36.6)	47 (31.5)	28 (42.4)	0.285	0.0
Intensive hypocapnia for ICP control [PaCO2 < 4.0 kPa (30 mmHg)] (%)	17 (5.9)	4 (2.7)	8 (12.1)	0.024	0.2
Hypothermia below 35°C (%)	22 (7.7)	13 (8.7)	7 (10.6)	0.726	0.0
DC (%)	47 (16.4)	41 (27.5)	20 (30.3)	0.005	0.0
Maximum TIL (median [IQR])	11.00 [8.00, 14.00]	11.00 [8.00, 15.00]	15.00 [12.25, 19.00]	<0.001	0.0
Outcomes					
Probability of mortality (median [IQR])	0.29 [0.19, 0.48]	0.35 [0.19, 0.55]	0.29 [0.19, 0.55]	0.361	8.4
Probability of unfavourable outcome (median [IQR])	0.54 [0.40, 0.74]	0.62 [0.40, 0.80]	0.54 [0.40, 0.80]	0.361	8.4
ICU mortality (%)	58 (20.2)	28 (19.3)	24 (36.4)	0.011	0.8
GOSE after 6 months (%)				0.092	10.6
Dead	74 (29.1)	43 (32.3)	29 (46.8)		
Vegetative state/ Lower severe disability	54 (21.3)	30 (22.6)	14 (22.6)		
Upper severe disability	26 (10.2)	9 (6.8)	5 (8.1)		
Lower moderate disability	41 (16.1)	13 (9.8)	3 (4.8)		
Upper moderate disability – some disability but can potentially return to some form of employment	25 (9.8)	12 (9.0)	3 (4.8)		
Lower good recovery – minor physical or mental defect	17 (6.7)	17 (12.8)	3 (4.8)		
Upper good recovery – full recovery	17 (6.7)	9 (6.8)	5 (8.1)		

Abbreviations: ASAPS = American Society of Anesthesiologists Physical Status; CT = Computed tomography; DC = decompressive craniectomy; GCS = Glasgow coma scale; GOSE = Glasgow outcome scale extended; HTS = hypertonic saline; ICP = intracranial pressure; ICU = intensive care unit; IQR = interquartile range; ISS = injury severity score; TIL = therapy intensity level

Table 2. Unadjusted and adjusted OR and CI for ICU mortality						
Variables	**Unadjusted OR**	**CI**	**Adjusted OR for baseline characteristics**	**CI**	**Adjusted OR for baseline and treatment characteristics**	**CI**
Patient-level						
HTS (ref)	1		1		1	
Mannitol	0.94	0.57 – 1.56	0.85	0.48 – 1.51	0.82	0.39 – 1.74
Both	2.26	1.26 – 4.03	2.35	1.19 – 4.66	1.89	0.73 – 4.86
Center-level (cut-off at 66%)						
HTS (ref)	1		1		1	
Mannitol	1.19	0.64 – 2.23	1.07	0.53 – 2.17	0.61	0.23 – 1.62
Both	1.77	1.11 – 2.84	1.59	0.92 – 2.74	1.23	0.60 – 2.50
Center-level (cut-off at 75%)						
HTS (ref)	1		1		1	
Mannitol	1.19	0.64 – 2.23	1.07	0.53 – 2.17	0.61	0.23 – 1.62
Both	1.77	1.11 – 2.84	1.59	0.92 – 2.74	1.23	0.60 – 2.50
Management-level						
HTS (ref)	1		1		1	
Mannitol	1.76	0.85 – 3.63	1.67	0.72 – 3.87	1.30	0.42 – 4.05
Both	2.14	1.27 – 3.62	1.82	1.00 – 3.33	1.62	0.72 – 3.66
Patient-HTS sum score[1]						
Sum HTS, patient-level	0.999	0.994 – 1.004	1.000	0.994 – 1.006	1.000	0.992 – 1.008
Center-HTS sum score[2]						
Sum HTS, center-level	0.999	0.993 – 1.006	1.001	0.993 – 1.009	1.005	0.994 – 1.015

Odds ratios above 1 indicate **worse** outcome

*Baseline characteristics: age, GCS motor score, pupillary reactivity, and MEI

**Treatment characteristics: mean ICP before receiving a HOA, mean TIL before receiving a HOA, and median daily fluid balance during the whole ICU stay

Abbreviations: CI = confidence interval; GCS = glasgow coma scale; HOA = hyperosmolar agent; HTS = hypertonic saline; ICU = intensive care unit; MEI = major extracranial injury; OR = odds ratio; ref = reference; TIL = therapy intensity level

[1] For example, if a patient received only HTS for 5 days, only mannitol for 3 days, and mannitol and HTS (both) for 2 days, this patient would get a sum score of (5+0+2)/(5+3+4) = 0.6. Or, if a patient received only HTS for 1 day, only mannitol for 9 days, and mannitol and HTS for 0 days, this patient would get a sum score of (1+0+0)/(1+9+0) = 0.1.

[2] For example: a center included 2 patients. One patient has a patient-HTS sum score of 0.7, the other of 0.1. The sum score on center level is calculated as follows: (0.7 + 0.1) / 2 = 0.4. Thus, all patients in that center will have a score of 0.4 for the analyses.

Table 3. Unadjusted and adjusted OR and CI for 6-month GOSE						
Variables	**Unadjusted OR**	**CI**	**Adjusted OR for baseline characteristics***	**CI**	**Adjusted OR for baseline and treatment characteristics****	**CI**
Patient-level						
HTS (ref)	1		1		1	
Mannitol	0.97	0.67 – 1.41	1.11	0.72 – 1.71	1.08	0.65 – 1.80
Both	0.51	0.30 – 0.85	0.57	0.31 – 1.05	0.70	0.31 – 1.59
Center-level (cut-off at 66%)						
HTS (ref)	1		1		1	
Mannitol	0.75	0.47 – 1.18	0.92	0.53 – 1.58	1.45	0.78 – 2.69
Both	0.54	0.37 – 0.78	0.67	0.43 – 1.05	0.76	0.47 – 1.22
Center-level (cut-off at 75%)						
HTS (ref)	1		1		1	
Mannitol	0.75	0.47 – 1.18	0.92	0.53 – 1.58	1.45	0.78 – 2.69
Both	0.54	0.37 – 0.78	0.67	0.43 – 1.05	0.76	0.47 – 1.22
Management-level						
HTS (ref)	1		1		1	
Mannitol	0.73	0.43 – 1.25	0.93	0.50 – 1.74	1.15	0.54 – 2.49
Both	0.49	0.34 – 0.72	0.69	0.43 – 1.12	0.77	0.45 – 1.34
Patient-HTS sum score[1]						
Sum HTS	1.001	0.996 – 1.005	0.999	0.994 – 1.004	0.999	0.993 – 1.004
Center-HTS sum score[2]						
Sum HTS	1.001	0.996 – 1.007	0.999	0.992 – 1.006	0.996	0.988 – 1.003

Odds ratios above 1 indicate **better** outcome

*Baseline characteristics: age, GCS motor score, pupillary reactivity, and MEI

**Treatment characteristics: mean ICP before receiving a HOA, mean TIL before receiving a HOA, and median daily fluid balance during the whole ICU stay

Abbreviations: CI = confidence interval; GCS = glasgow coma scale; HOA = hyperosmolar agent; HTS = hypertonic saline; ICU = intensive care unit; MEI = major extracranial injury; OR = odds ratio; ref = reference; TIL = therapy intensity level

[1] For example, if a patient received only HTS for 5 days, only mannitol for 3 days, and mannitol and HTS (both) for 2 days, this patient would get a sum score of (5+0+2)/(5+3+4) = 0.6. Or, if a patient received only HTS for 1 day, only mannitol for 9 days, and mannitol and HTS for 0 days, this patient would get a sum score of (1+0+0)/(1+9+0) = 0.1.

[2] For example: a center included 2 patients. One patient has a patient-HTS sum score of 0.7, the other of 0.1. The sum score on center level is calculated as follows: (0.7 + 0.1) / 2 = 0.4. Thus, all patients in that center will have a score of 0.4 for the analyses.