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ORIGINAL ARTICLE

The use of tier three therapies in acute brain injured patients

Insight from the Extubation strategies in Neuro-Intensive care unit patients and associations with Outcomes observational study

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BACKGROUND In patients with acute brain injury (ABI) and refractory intracranial hypertension, the so-called 'tier three therapies' (TTT) (hypothermia, metabolic suppression with barbiturates, and decompressive craniectomy) may be used.

OBJECTIVE We aimed to describe the incidence of use of TTT, and to assess their effect on outcome.

DESIGN A secondary analysis of the ENIO observational study.

SETTING Seventy-three intensive care units (ICUs) in 18 countries worldwide between June 2018 and November 2020.

PATIENTS One thousand five hundred and twelve adult patients admitted to an intensive care unit (ICU) with ABI were included and categorised according to use or not of one or more TTT.

RESULTS Three hundred and ninety-six patients (26.2%) received at least one TTT during the ICU stay. Five patients (0.3%) received all three TTT. TTT patients were younger ($P < 0.0001$), less likely to have a preinjury history of hypertension ($P = 0.0008$), and less frequently anisocoric within 24 h from ICU admission ($P < 0.0001$) than those with no tier three therapy. TTT were used less frequently in high-income countries than in upper income and lower middle-income countries (no TTT in 78% of patients in high-income countries, in 60.6% of patients in upper middle-income countries, and in 56.6% of patients in lower middle-income countries; $P < 0.0001$). TTT were more frequent in patients with traumatic brain injury (TBI) compared with other types of ABI and in patients with invasive intracranial pressure (ICP) monitoring ($P < 0.0001$). TTT use was associated with a higher incidence of ventilator-associated pneumonia ($P < 0.0001$), need for tracheostomy ($P = 0.0194$), and prolonged ICU length of stay (LOS; $P < 0.0001$) but not with increased ICU or hospital mortality ($P = 0.999$).

CONCLUSION Patients with ABI are frequently managed using at least one TTT. Their use varies according to a country's economic resources, the type of ABI, and ICP monitoring and is associated with a higher risk of complications but not with ICU or hospital mortality.

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KEY POINTS

- Tier three therapies for ICP control are frequently used in patients with ABI, with differences according to the type of brain injury, the use or not of an invasive ICP monitoring system, and across countries.
- Their use is associated with an increased risk of ventilator pneumonia and need for tracheostomy, as well as prolonged mechanical ventilation and length of stay.
- Use of a TTT is not associated with an increased risk of ARDS or with ICU or hospital death.

Introduction

In patients with acute brain injury (ABI), one of the most common management problems is raised intracranial pressure (ICP),[1] which is independently associated with worse clinical outcomes by causing additional secondary brain damage.[2,3] There is still uncertainty regarding the optimal treatment of intracranial hypertension (hICP), especially in refractory cases.[4] In a recent expert consensus meeting, the available therapies for ICP management were grouped into three tiers, with the intensity of each intervention classified according to the 'therapy intensity level' score.[5] A stepwise approach acknowledging the increased risks intrinsic to more aggressive strategies[6,7] was developed, the Seattle algorithm.[8] Higher tier therapies, the 'tier three therapies' (TTT), include hypothermia, metabolic suppression with barbiturates and decompressive craniectomy. These strategies are considered as a final resort when less invasive clinical management interventions (such as sedation, osmotic therapy and neuromuscular blockade) have failed to control ICP. Currently, the different treatments within a tier are not used uniformly, and there is no consensus about which should have priority. As higher tier treatments have more adverse effects, clinicians must weigh the balance between potential risks and benefits of each as effects on neurologic outcomes and mortality. No definitive data exist about the superiority of one strategy over another, and differences across countries have never been explored in detail. In addition, most clinical practice guidelines are primarily based on cohorts of patients with traumatic brain injury (TBI), with no information on groups of patients with other forms of ABI and no clear indications regarding the need for invasive ICP monitoring as a guide to treatment escalation.

We performed a sub-analysis of the 'Extubation strategies in Neuro-Intensive care unit patients and associations with Outcomes' (ENIO) study[9] to explore current practice regarding use of TTT, as defined in the Seattle algorithm,[8] across different countries and the impact of use of a TTT on patient outcomes.

Methods

Study population

The ENIO study (registered at clinicaltrials.gov NCT03400904) has been a multicentre, international, observational study supported by the European Society of Intensive Care Medicine (ESICM).[9] It prospectively collected data from patients with ABI admitted to 73 intensive care units (ICUs) in 18 countries worldwide between June 2018 and November 2020. Its inclusion criteria were: adult patients (>18 years) admitted to an ICU with ABI [traumatic brain injury (TBI), aneurysmal subarachnoid haemorrhage (aSAH), intracranial haemorrhage (ICH), ischaemic stroke, central nervous system (CNS) infection, brain tumour]; an initial Glasgow Coma Scale (GCS) score 12 or less and an abnormal brain computed tomography (CT) scan; and duration of invasive mechanical ventilation (IMV) at least 24 h at ICU admission. Exclusion criteria were: age less than 18 years; pregnancy; spinal cord injury above the T_4 level; patients resuscitated from cardiac arrest and patients in whom life-sustaining treatment was withdrawn in the first 24 h post admission.

The present study is a secondary analysis of the ENIO study, focusing on the use of TTT for ICP management. The project proposal was submitted to the Steering committee, approved, and then conducted according to the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement,[10] available at the end of the manuscript. All patients from the ENIO study with data available on the use of TTT were considered eligible for inclusion. According to local regulations, the Medical Ethics Committees approved the ENIO study in all participating centres, and informed consent was obtained, when possible, from all individual participants or from their next of kin. No further ethical approval was necessary for this subanalysis.

Data collection and definitions

Local ENIO investigators transcribed all collected data into an internet-based electronic Case Report Form (eCRF). All patient data were anonymised, and patients were associated with a randomly allocated GUPI (Global Unique Patient Identifier), which was only linked locally to hospital records. Data were collected on pre-injury factors and patient characteristics, type of injury, Glasgow Coma Scale (GCS) score at admission and episode of anisocoria of neurological origin in the first 24 h from ICU admission. Data on TTT used for the management of intracranial hypertension were defined according to the Seattle algorithm[8] (therapeutic hypothermia 35 to 36 °C, barbiturate coma of ≥24 h duration, secondary decompressive craniectomy). In the database, these strategies were depicted specifically according to the management

of intracranial hypertension; for instance, secondary decompressive craniectomy was clearly separated from primary decompressive craniectomy. The use of other strategies for the management of intracranial hypertension, neurocritical care details, such as the positioning of an intracranial probe or an external ventricular drain (EVD) for invasive ICP monitoring, as well as sedation and specific ventilatory care information, including ventilator settings, were also collected.[9] Additional data regarding postacute care, ICU complications, such as ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS), need for tracheostomy, and clinical outcomes, that is, hospital and ICU mortality, ICU length of stay (LOS) and duration of IMV, were also noted. VAP was defined according to the latest international guidelines[11] as a nosocomial pneumonia that develops in ICU patients who have been mechanically ventilated for at least 48 h. ARDS was defined according to the Berlin criteria,[12] with a threshold of arterial partial pressure of oxygen to inhaled oxygen fraction (PaO_2/FiO_2) ratio set at greater than 300 mmHg to dichotomise ARDS vs. non-ARDS patients. Countries were categorised according to their Gross National Income (GNI) per capita into high-income, upper middle income and lower middle income as defined using the Atlas Method.[13]

Endpoints

The primary endpoint of this subanalysis was to assess the frequency and types of TTT used in patients with ABI. Secondary outcomes included:

(1) differences in TTT according to patients' characteristics, admission pathology, country of origin, and use of an intracranial ICP monitoring;
(2) effects of use of a TTT on development of ICU complications, such as VAP, ARDS occurrence, need for tracheostomy, and clinical outcomes, that is, ICU and hospital mortality, ICU LOS, and duration of IMV.

Statistical analysis

Continuous variables are shown as means with standard deviations (SD), and categorical variables as the number of individuals and percentage values. The occurrence of VAP, tracheostomy, or ARDS, hospital mortality, ICU mortality and duration of ICU LOS and IMV were considered as clinical outcomes. The clinical and demographic baseline differences according to use of TTT were tested using the Student's t test (ANOVA whenever appropriate) or Pearson's χ^2 test (Fisher's exact wherever appropriate) for continuous and categorical variables, respectively. Univariate logistic and negative binomial regression models were performed to screen the effect of the demographic and clinical variables on the dichotomic and count outcomes, accordingly. We then selected all covariates with a P value less than 0.05 for the multivariate analysis; VAP, tracheostomy, ARDS, ICU and hospital mortality, ICU discharge and duration of IMV were chosen as dependent variables. The multivariate analysis was also performed using a logistic and negative binomial regression model for dichotomic and count outcomes. The odds ratios and exponential regression coefficient associated with each outcome were calculated with 95% confidence intervals for each factor. The model selection was made according to the backward elimination with the Akaike Information Criterion (AIC),[14] and all univariate and multivariate regression models were corrected for the admission GCS-total score, age, and anisocoria episode within 24 h of admission. Sensitivity analyses excluding patients subjected to the withdrawal of life-sustaining treatment were also run. The likelihood ratio test was used as the statistical significance test, and the estimated P values were adjusted for multiple comparisons using the Holm correction method. Differences with a P value less than 0.05 were selected as significant, and data were acquired and analysed using the R v4.2.0 software.[15]

Results

Study population and use of tier three therapies

A total of 1512 patients were included. Demographic and clinical characteristics, as well as outcomes are summarised in Table 1. The mean age was 52 ± 18.2 years and 514 patients (34%) were women. Seven hundred and twenty-five patients (47.9%) were admitted to the ICU for TBI, 269 (17.8%) for aSAH, 521 (34.5%) for intracranial haemorrhage, 141 (9.3%) for ischaemic stroke, 74 (4.9%) for CNS infection and 72 (4.8%) with a diagnosis of CNS tumour.

Most patients ($n = 1170$, 77.4%) were from high-income countries, with 259 (17.1%) and 83 (5.5%) from upper income and lower middle-income countries, respectively. Of the 1512 patients, 396 (26.2%) received at least one TTT during the study period [38 patients (2.5%) received only hypothermia, 55 (3.6%) only barbiturate therapy, and 264 (17.5%) underwent only decompressive craniectomy]. Five patients (0.3%) received all three treatments during their ICU stay (Table 1).

Tier three therapy according to different subgroups

A TTT was more frequently used in patients 60 years old or less than in older patients; this applied for all three therapies and for each treatment separately (ranges: 57.9 to 78.2% vs. 21.8% to 42.1%, $P < 0.0001$) [Supplemental digital content (SDC) 1: Table E1, http://links.lww.com/EJAIC/A61]. TTT were more often used in patients with no pre-injury history of hypertension ($P = 0.0008$) and in patients who did not have anisocoria at ICU admission ($P < 0.0001$) than in other patients.

Overall, TTT were used less frequently in high-income countries than in middle-income countries (SDC 1: Tables E1 and E2, http://links.lww.com/EJAIC/A61; $P < 0.0001$; no TTT in 78% of patients in high-income countries, in 60.6% of patients in upper middle-income countries and in 56.6% of patients in lower middle

Table 1 **Demographic and clinical characteristics of Extubation strategies in Neuro-Intensive care unit patients and associations with Outcomes study participants ($n = 1512$)**

Characteristic	Overall	Missing data
Women	514 (34%)	
Age (years)	52 ± 18	12 (0.8%)
BMI (kg m^{-2})	26.3 ± 5.1	46 (3.0%)
Country income		
High income	1170 (77.4%)	0 (0%)
Upper middle income	259 (17.1%)	0 (0%)
Lower middle income	83 (5.5%)	0 (0%)
Comorbidities		
Pulmonary disease	51 (3.34%)	1 (0.07%)
Heart failure	44 (2.9%)	1 (0.07%)
Hypertension	451 (29.8%)	1 (0.07%)
Malignancy	68 (4.5%)	1 (0.07%)
Type of ABI		
TBI	725 (48.0%)	1 (0.8%)
aSAH	269 (17.8%)	4 (0.3%)
ICH	521 (34.5%)	1 (0.1%)
Ischaemic stroke	141 (9.3%)	4 (0.3%)
CNS infection	74 (4.9%)	4 (0.3%)
Brain tumour	72 (4.8%)	6 (0.4%)
Admission GCS-total score	6.9 (2.6)	0 (0%)
Moderate (GCS 9 to 13)	388 (25.7%)	
Severe (GCS 3 to 8)	1124 (74.3%)	
Anisocoria episode within 24 h from admission	412 (27.3%)	4 (0.3%)
PaO_2/FiO_2 ratio (mmHg)	331 (150.3)	38 (2.5%)
Invasive ICP monitoring	1083 (71.6%)	2 (0.1%)
Intraparenchymal probe	642 (42.5%)	
EVD	441 (29.1%)	
Tier three therapy	396 (26.2%)	1 (0.8%)
Therapeutic hypothermia	38 (2.5%)	
Decompressive craniectomy	264 (17.5%)	
Barbiturate therapy	55 (3.6%)	
Barbiturate therapy + decompressive craniectomy	15 (1.0%)	
Therapeutic hypothermia + decompressive craniectomy	7 (0.5%)	
Therapeutic hypothermia + barbiturate therapy	11 (0.7%)	
Therapeutic hypothermia + decompressive craniectomy + barbiturate therapy	5 (0.3%)	
Outcomes		
ARDS during ICU stay	137 (9.1%)	19 (1.3%)
VAP during ICU stay	597 (39.5%)	17 (1.1%)
Need for tracheostomy	417 (27.6%)	16 (1.1%)
ICU mortality	95 (6.3%)	35 (2.3%)
Hospital mortality	168 (11.1%)	58 (3.8%)
ICU LOS (days)	18.1 (15.7)	72 (4.8%)
IMV (days)	11.9 (15.2)	87 (5.8%)

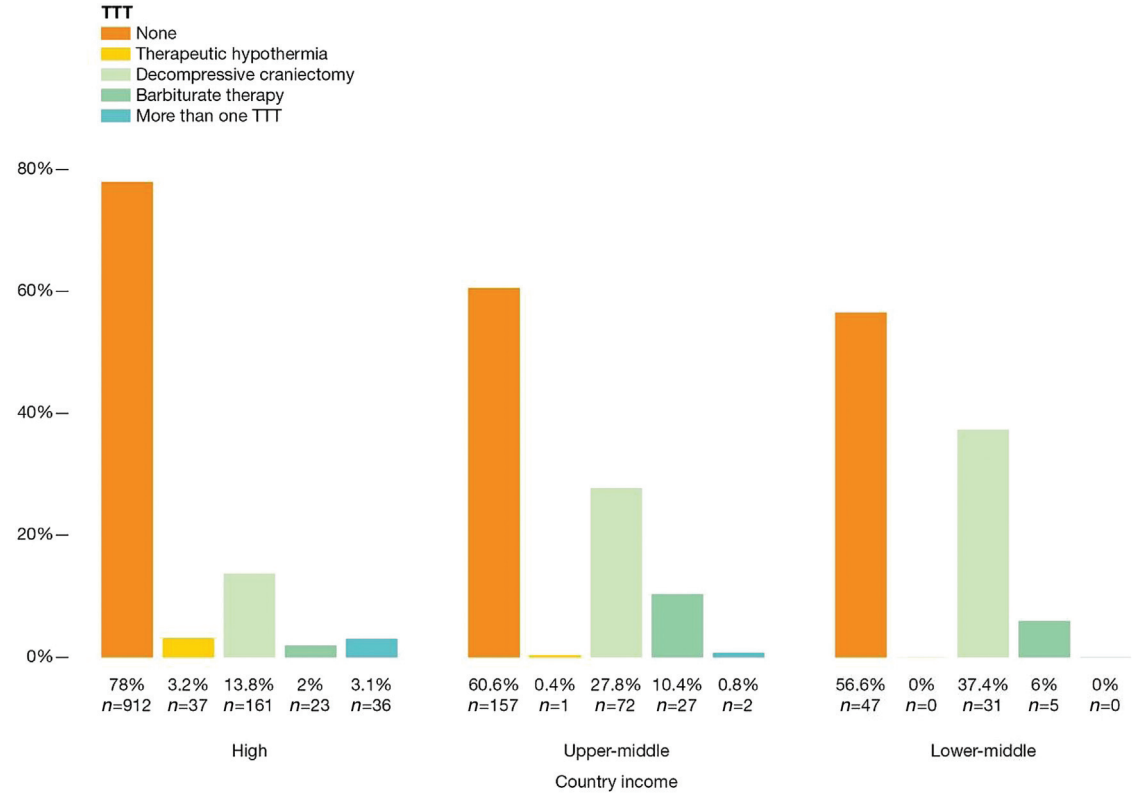
Data are given as number (%), mean ± SD or mean (CI). ABI, acute brain injury; ARDS. acute respiratory distress syndrome; aSAH, acute subarachnoid hemorrhage; CI, confidence interval; CNS, central nervous system; EVD, external ventricular drain; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; ICP, intracranial pressure; IMV, invasive mechanical ventilation; LOS, length of stay; *n*, number; PaO_2/FiO_2 ratio, arterial partial pressure of oxygen over inhaled oxygen fraction; SD, standard deviation; TBI, traumatic brain injury; VAP, ventilator-associated pneumonia.

income countries; $P < 0.0001$). More specifically, therapeutic hypothermia was more frequently used in high income than in upper middle or lower middle-income countries (3.2 vs. 0.4 and 0%, respectively), whereas decompressive craniectomy and barbiturate therapies were more frequently used in lower income countries (Fig. 1 and SDC 1: Table E2, http://links.lww.com/EJAIC/A61). ICP monitoring was also more frequently used in high-income countries than in upper middle-income and lower middle-income countries (66.1 vs. 17.4%, and 19.3%, respectively) (SDC 1: Figure E1, Table E2, http://links.lww.com/EJAIC/A61). Descriptive statistics of the use of tier three strategies according to ICP monitoring and country income are shown in SDC 1: Figure E2, http://links.lww.com/EJAIC/A61.

TTT were more frequently used in patients who had ICP monitoring (27.2%) than in those who did not (24.8%; $P < 0.0001$; Fig. 2 and SDC 1: Table E1, http://links.lww.com/EJAIC/A61). More specifically, hypothermia was more commonly used in ICP-monitored patients (4.3%) than in those without ICP monitoring (0.3%), whereas barbiturates (4.7 vs. 2.8%) and decompressive craniectomy (19.1 vs. 16.2%) were more often used in the absence of ICP monitoring. A combination of more than one tier three treatments was more frequent in ICP-monitored patients than in those without ICP monitoring (4 vs. 0.7%).

Overall, use of TTT was more frequent in patients with TBI than in those with aSAH or acute ischaemic stroke

Fig. 1 Use of tier three therapies according to country income. *n*, number.



(SDC 1: Figure E3, http://links.lww.com/EJAIC/A61). Among patients who received hypothermia, 39.5, 36.8 and 5.3% had a diagnosis of TBI, aSAH or ischaemic stroke, respectively. Decompressive craniectomy was more frequent in patients with ischaemic stroke (34%) than in those with TBI (19.3%) or aSAH (10.4%); whereas barbiturate therapy showed a more frequent use in TBI (5.4%) than in aSAH or ischaemic stroke (2.6 and 1.4%, respectively). Patients with TBI more frequently received more than one TTT than did patients with aSAH or stroke (3.7, 1.5, and 2.1%, respectively).

Effect of tier three therapy use on complications and clinical outcomes

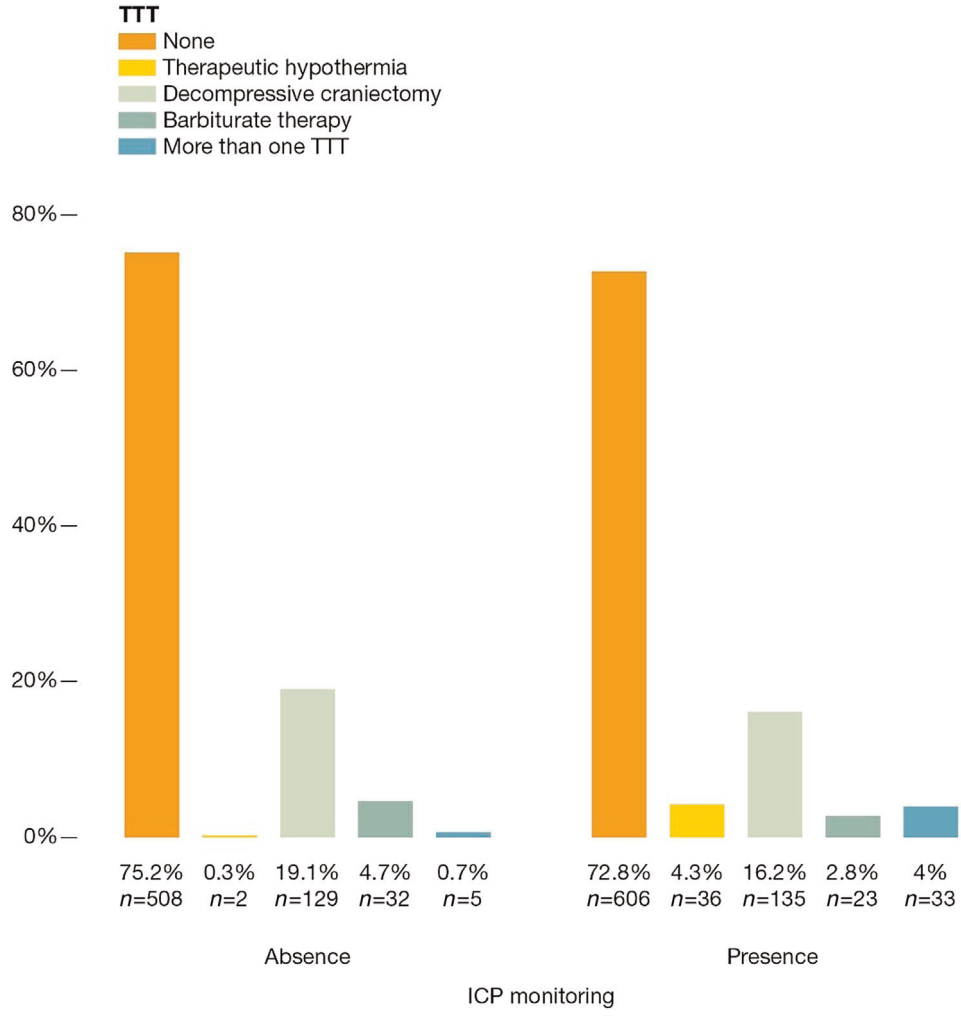
Intensive care unit complications

VAP was observed in 597 out of 1512 patients (39.5%) and in 179 out of 389 patients who received almost one TTT. Use of at least one TTT was associated with VAP occurrence in logistic regression analysis ($P < 0.0001$; Table 2 and SDC 1: Table E3, http://links.lww.com/EJAIC/A61). In particular, patients who received therapeutic hypothermia or more than one TTT were more likely to develop VAP than those who received no TTT, OR (95% confidence interval) = 2.4 (1.2 to 5.1) and 3.8 (1.8 to 8.9), respectively. Tracheostomy was required in 417 out of 1512 patients (27.6%) and in 149 out of 388 patients who received one TTT; use of a TTT was significantly associated ($P = 0.0194$) with the need for tracheostomy (Table 3 and SDC 1: Table E4, http://links.lww.com/EJAIC/A61). Patients receiving more than one TTT were 3.1 times more likely to undergo a tracheostomy than those who received no TTT, OR (95% CI) 3.1 (1.3 to 6.7). Finally, 137 (9.1%) patients in the ENIO cohort developed ARDS during the ICU LOS (Table 1), and use of TTT was not associated with its development (SDC 1: Tables E5 and E6, http://links.lww.com/EJAIC/A61).

Clinical outcomes

Overall ICU and hospital mortality rates were 6.3 and 11% (95 and 168 out of 1512 patients), respectively. Moreover, overall ICU and hospital mortality events were, respectively, observed in 28 out of 381 and 47 out of 376 patients who received almost one TTT. The chances of ICU or hospital death were about six times higher in lower middle income countries than in high-income countries (Tables 4 and 5); ORs (95% CI) = 6.0 (3.1 to 11.5) and 5.5 (3.0 to 10.0), respectively; *P* less than 0.0001. Use of a TTT was not associated with ICU or hospital mortality (SDC 1: Tables E7 and E8, http://links.lww.com/EJAIC/A61; $P = 0.9999$). In patients with an intracranial probe, the chances of ICU and hospital death were, respectively, reduced by 60 and 50% compared with those of patients without an

Fig. 2 Tier three therapy use according to presence or absence of intracranial pressure monitoring.



ICP, intracranial pressure; *n*, number; TTT, tier three therapy.

intracranial probe (Tables 4 and 5); ORs (95% CI): 0.4 (0.2 to 0.7), $P = 0.0002$ and 0.5 (0.3 to 0.8), $P = 0.0006$, respectively.

The mean duration of ICU stay was 18.1 days, and the mean duration of IMV was 11.9 days. The use of a TTT was independently associated with the ICU LOS and duration of IMV (SDC 1: Tables E9, E10, E11, E12, http://links.lww.com/EJAIC/A61; $P < 0.0001$). Specifically, the ICU LOS in patients undergoing decompressive craniectomy or receiving more than one TTT was 30 and 60% longer, respectively, than in patients who did not receive a TTT, ORs (95% CI) = 1.3 (1.2 to 1.5) and 1.6 (1.2 to 2.0), respectively.

Similarly, the use of a TTT (therapeutic hypothermia, decompressive craniectomy, barbiturate therapy, and more than one TTT) was associated with an increase in the duration of IMV by 50, 20, 30, and 60%; ORs (95% CI)= 1.5 (1.1 to 2.0), 1.2 (1.1 to 1.4), 1.3 (1.0 to 1.6) and 1.6 (1.2 to 2.1), respectively (SDC 1: Table E12, http://links.lww.com/EJAIC/A61; $P < 0.0001$).

Sensitivity analysis

Regarding hospital mortality, TBI was the only factor that was not confirmed in our sensitivity analysis. Instead, the others SA analysis gave very similar results (data not shown for clarity).

Discussion

In this sub-analysis of the ENIO study,[9] we found that: TTT were frequently used to manage intracranial hypertension, with a preference for decompressive craniectomy; patients receiving TTT were younger and with fewer comorbidities; decompressive craniectomy and barbiturates or a combination of TTT were more frequently used in TBI and with ICP monitoring; TTT were less frequent in high income than in upper and lower middle-income countries; and TTT use increased

Table 2 Multivariate analysis of occurrence of ventilator-associated pneumonia corrected for Glasgow Coma Scale score at admission, age and episode of anisocoria within 24 h of Intensive Care Unit admission ($n = 1473$; $n = 1374$ for SA)

Characteristic	OR (95%CI)	*P* value	SA *P* value
Tier three therapy (TTT)		<0.0001	<0.0001
None	1		
Therapeutic hypothermia	2.4 (1.2 to 5.1)		
Decompressive craniectomy	1.2 (0.9 to 1.5)		
Barbiturate therapy	0.9 (0.5 to 1.6)		
More than one TTT	3.8 (1.8 to 8.9)		
CNS infection		0.0003	0.0006
Absence	1		
Presence	0.4 (0.2 to 0.7)		
Intracranial probe		<0.0001	<0.0001
No	1		
Yes	2.1 (1.7 to 2.6)		
EVD		0.0092	0.0213
No	1		
Yes	1.4 (1.1 to 1.8)		
Age (years)		0.7025	0.5680
≤60	1		
>60	1.0 (0.8 to 1.3)		
Admission GCS-total score		0.4127	0.3416
Moderate (GCS 9 to 13)	1		
Severe (GCS 3 to 8)	1.0 (0.8 to 1.3)		
Anisocoria episode		0.1702	0.3828
Absence	1		
Presence	1.0 (0.8 to 1.3)		

CNS, central nervous system; EVD, external ventricular drain; GCS, Glasgow Coma Scale; *n*, number; OR (95% CI), odds ratio with 95% confidence interval; *P* value, likelihood ratio *P* value; SA, sensitivity analysis; TTT, tier three therapy.

the risk of ICU complications and LOS but did not affect mortality.

To our knowledge, this is the most extensive prospective observational study describing the use of TTT, defined according to the Seattle algorithm,[8] for management of intracranial hypertension in patients with ABI during the ICU stay, and assessing the effects of use of these therapies on outcome. The study included 1512 patients from 73 centres and 18 countries, thus providing a good representation of the current clinical practice in neurocritical care around the world.

Management of intracranial hypertension is fundamental in the treatment of patients with ABI,[1,3,16–20] and includes measures ranked in increasing tiers of severity.[21]

Table 3 Multivariate analysis on the need for tracheostomy corrected for Glasgow Coma Scale score at admission, age and episode of anisocoria within 24 h of intensive care unit admission ($n = 1475$; $n = 1376$ for SA)

Characteristic	OR (95% CI)	*P* value	SA *P* value
Tier three therapy		0.0194	0.0169
None	1		
Therapeutic hypothermia	1.7 (0.6 to 3.9)		
Decompressive craniectomy	1.3 (0.8 to 2.1)		
Barbiturate therapy	1.5 (0.6 to 3.5)		
More than one TTT	3.1 (1.3 to 6.7)		
ICH		0.0003	0.0008
Absence	1		
Presence	0.5 (0.3 to 0.7)		
Intracranial probe		0.0002	<0.0001
No	1		
Yes	2.1 (1.4 to 3.0)		
Age (years)		0.6617	0.6346
≤60	1		
>60	1.1 (0.8 to 1.6)		
Admission GCS-total score		0.7686	0.5760
Moderate (GCS 9 to 13)	1		
Severe (GCS 3 to 8)	0.9 (0.6 to 1.5)		
Anisocoria episode		0.0589	0.1445
Absence	1		
Presence	1.2 (0.8 to 1.8)		

GCS, Glasgow Coma scale; *n*, number; OR (95% CI), odds ratio with 95% confidence interval; *P* value, likelihood ratio *P* value; SA, sensitivity analysis; TTT, tier three therapy.

Table 4 Multivariate analysis of intensive care unit mortality corrected for Glasgow Coma Scale score at admission, age and episode of anisocoria within 24 h of intensive care unit admission ($n = 1460$; $n = 1370$ for SA)

Characteristic	OR (95% CI)	*P* value	SA *P* value
Country income		<0.0001	<0.0001
High income	1		
Upper middle income	0.5 (0.2 to 1.1)		
Lower middle income	6.0 (3.1 to 11.5)		
Intracranial probe		0.0002	<0.0001
No	1		
Yes	0.4 (0.2 to 0.7)		
Age (years)		0.0004	0.2284
≤60	1		
>60	2.3 (1.5 to 3.8)		
Admission GCS total score		0.4643	0.5884
Moderate (GCS 9 to 13)	1		
Severe (GCS 3 to 8)	1.3 (0.8 to 2.2)		
Anisocoria episode		0.9292	0.3228
Absence	1		
Presence	1.3 (0.8 to 2.1)		

GCS, Glasgow Coma Scale score; *n*, number; OR (95% CI), odds ratio with 95% confidence interval; *P* value, likelihood ratio *P* value; SA, sensitivity analysis.

The impact of these invasive measures on the patients' homeostasis represents an issue itself, yielding an effect on outcomes.[20,22] The stepwise approach[3] begins with standard measures such as head elevation and respiratory optimisation that cause little to no harm and ends with TTT including mild hypothermia (35 to 36°C),[23] barbiturate therapy,[24] and the performance of decompressive craniectomy,[25] when feasible.[21]

These treatments, including hypothermia,[26] all carry risks; therefore, the decision to use a TTT should take into account the adverse effects of each therapy. A decompressive craniectomy chosen as a last resort after escalating medical treatment can decrease mortality but still increase the incidence of poor neurological outcomes.[27] Unfortunately, there is no indication yet in the literature regarding the priority treatments in the same tier should be given, and whether it is possible to skip one or more tiers in some clinical circumstances.[19]

Few randomised controlled clinical trials have compared one strategy with another or all TTT. Thus, the selection of the most appropriate treatment is made on a case by case basis using clinical judgment and balancing patient criteria and environmental factors, such as local protocols and standards, which rely, in part, on economic resources.

A prolonged increase in ICP represents such a crucial issue in neuro-ICU patients that the use of aggressive

Table 5 Multivariate analysis of hospital mortality corrected for Glasgow Coma Scale score at admission, age, and episode of anisocoria within 24 h of intensive care unit admission ($n = 1438$; $n = 1350$ for SA)

Characteristic	OR (95%CI)	*P* value	SA *P*-value
Country income		<0.0001	<0.0001
High income	1		
Upper middle income	0.6 (0.3 to 1.1)		
Lower middle income	5.5 (3.0 to 10.0)		
Heart failure		0.0006	0.0005
Absence	1		
Presence	3.2 (1.6 to 6.2)		
TBI		0.0024	
Absence	1		
Presence	0.6 (0.4 to 0.9)		
Intracranial probe		0.0006	<0.0001
No	1		
Yes	0.5 (0.3 to 0.8)		
Age (years)		<0.0001	<0.0001
≤60	1		
>60	2.9 (2.0 to 4.3)		
Admission GCS total score		0.0881	0.4023
Moderate (GCS 9 to 13)	1		
Severe (GCS 3 to 8)	1.6 (1.1 to 2.4)		
Anisocoria episode		0.4420	0.2356
Absence	1		
Presence	1.4 (1.0 to 2.1)		

The sensitivity analysis was performed only for the items included in the multivariate analysis. GCS, Glasgow Coma Scale; *n*, number; OR (95% CI), odds ratio with 95% confidence interval; *P* value, likelihood ratio *P* value; SA, sensitivity analysis; TBI, traumatic brain injury.

TTT is often considered necessary despite the known associated risks. In our cohort, a significant number of patients received a tier three treatment, in line with the results from a recent article by Huijben *et al.*,[28] with higher use of decompressive craniectomy than of the other strategies, possibly because of the beneficial effect on mortality demonstrated in a large trial.[27]

Patients receiving TTT were younger (≤60 years), with fewer cardiovascular comorbidities, and were less likely to have had an episode of anisocoria. These findings suggest that physicians should consider these strategies when the benefits outweigh the risks, based on the single centre's judgment. Local practices and resources also influence treatment approaches. Upper middle-income countries used aggressive treatments less frequently than high-income countries. Lower middle-income countries preferred metabolic suppression or decompressive craniectomy over therapeutic hypothermia. In high-income countries, ICP monitoring was more common, indicating its role in clinical decision-making and as a trigger for TTT. The differences between countries may be because of budget constraints and tool availability. Metabolic suppression and decompressive craniectomy are more cost effective than hypothermia, which requires expensive technology and may be less accessible. In the absence of ICP monitoring, clinical decisions rely on clinical data or imaging,[29] potentially leading to overly aggressive approaches. Notably, the Seattle consensus was created presuming that ICP monitoring would be used, without providing any guidance on what to do when ICP measuring tools are unavailable.

When stratifying for pathology, TTT were used more often in patients with TBI than in those with nontraumatic pathologies, such as aSAH and stroke, especially when considering decompressive craniectomy and barbiturates or a combination of more than one tier three treatment. However, TTT were still used in a consistent number of non-TBI patients, probably because, despite guidelines mainly referring to TBI patients, clinicians tend to extrapolate the indications for TBI and apply them to other ABI pathologies when there is intracranial hypertension. Combining all previous considerations, we would also like to point out that the regional differences observed in the ENIO study, particularly regarding the utilisation of decompressive craniectomy for TBI, can be influenced by various factors. The age distribution of the study samples, with a mean age of 52 years and younger individuals being more prone to TBI and eligible for decompressive craniectomy, plays a significant role. Moreover, a country's economy acts as a potential confounding factor, impacting the availability, accessibility and utilisation of advanced medical interventions.

Finally, use of a TTT can lead to a higher rate of VAP and to more patients needing tracheostomy. In turn, a higher rate of complications leads to prolonged IMV and LOS. Interestingly, however, TTT use did not directly increase ICU or hospital mortality rates, which were higher in lower middle-income countries, and lower in patients with ICP monitoring.

Our data highlight the need to carefully select patients who can benefit from use of a TTT. TTT are aggressive but necessary measures when there is severe intracranial hypertension[30] and patients are refractory to lower tier therapies. Moreover, our results suggest that even if TTT can lead to complications mortality is not increased.

Limitations

This study has several limitations that need to be addressed. Firstly, being an observational study, it cannot establish causal relationships. However, the findings can guide future randomised controlled trials. Secondly, despite this being a preplanned analysis, some data were lacking, such as information on TTT progression over time, duration of metabolic suppression and specific cooling methods used. Therefore, the order of TTT utilisation in individual patients could not be determined. Thirdly, the database limitations prevented investigation of other outcomes like the 6-months Glasgow Outcome Scale Extended (GOSE)[20] or any quality of life or patient and family satisfaction score. Lastly, more detailed data on ICP monitoring thresholds would have provided insight into treatment escalation decisions made by clinicians.

Conclusion

TTTs for ICP control are frequently used in patients with ABI, with differences according to the type of brain injury, to the use or not of an invasive ICP monitoring system, and across countries. The use of a TTT is associated with an increased risk of VAP and need for tracheostomy, as well as with prolonged IMV and LOS. However, use of a TTT is not associated with an increased risk of ARDS or with ICU or hospital death. Considering the limitations and the design of our study, these results should be considered as a prelude of a specifically designed study and in particular randomised controlled trials exploring the effect on mortality of TTT in acute brain injured patients.

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