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REPORTS OF ORIGINAL INVESTIGATIONS

Intensity of care and withdrawal of life-sustaining therapies in severe traumatic brain injury patients: a post-hoc analysis of a multicentre retrospective cohort study

Intensité de soins et retrait de maintien des fonctions vitales chez des patients ayant subi un traumatisme craniocérébral grave : une analyse post-hoc d'une étude de cohorte multicentrique rétrospective

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Abstract

Purpose *The intensity of care provided to critically ill patients has been shown to be associated with mortality. In patients with traumatic brain injury (TBI), specialized neurocritical care is often required, but whether it affects clinically significant outcomes is unknown. We aimed to determine the association of the intensity of care on mortality and the incidence of withdrawal of life-sustaining therapies in critically ill patients with severe TBI.*

Methods *We conducted a post hoc analysis of a multicentre retrospective cohort study of critically ill adult patients with severe TBI. We defined the intensity of care as a daily cumulative sum of interventions during the intensive care unit stay. Our outcome measures were all-cause hospital mortality and the incidence of withdrawal of life-sustaining therapies.*

Results *Seven hundred sixteen severe TBI patients were included in our study. Most were male (77%) with a mean (standard deviation) age of 42 (20.5) yr and a median [interquartile range] Glasgow Coma Scale score of 3 [3-6]. Our results showed an association between the intensity of care and mortality (hazard ratio [HR], 0.69; 95% confidence*

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interval [CI], 0.63 to 0.74) and the incidence of withdrawal of life-sustaining therapy (HR, 0.73; 95% CI, 0.67 to 0.79).

Conclusion *In general, more intense care was associated with fewer deaths and a lower incidence of withdrawal of life-sustaining therapies in critically ill patients with severe TBI.*

Résumé

Objectif *L'intensité des soins fournis à des patients dans un état critique est associée à la mortalité. Chez des patients ayant subi un traumatisme craniocérébral (TCC), des soins intensifs neurologiques spécialisés sont souvent nécessaires, mais on ignore s'ils ont un impact cliniquement significatif sur le devenir de ces patients. Nous avons cherché à déterminer l'association entre, d'une part, l'intensité des soins et, d'autre part, la mortalité et l'incidence du retrait des thérapies de maintien des fonctions vitales chez des patients dans un état critique suivant un TCC.*

Méthodes *Nous avons réalisé une analyse post hoc d'une étude de cohorte multicentrique rétrospective chez des patients dans un état critique suivant un TCC grave. Nous avons défini l'intensité des soins par la somme cumulée journalière des interventions au cours du séjour en unité de soins intensifs. Nos intensifs d'évaluation étaient la mortalité hospitalière, toutes causes confondues, et l'incidence du retrait des thérapies de maintien des fonctions vitales.*

Résultats *Sept cent seize patients atteints de TCC grave ont été inclus dans notre étude. La plupart étaient des hommes (77 %) d'un âge moyen (écart-type) de 42 (20,5) ans et ayant un score de Glasgow pour le coma (Glasgow coma scale) médian [écarts interquartiles] de 3 [3 à 6]. Nos résultats ont montré une association entre l'intensité des soins et la mortalité (rapport de risque [RR] : 0,69; intervalle de confiance [IC] à 95 % : 0,63 à 0,74) et l'incidence du retrait des thérapies de maintien des fonctions vitales (RR : 0,73; IC à 95 % : 0,67 à 0,79).*

Conclusion *D'une manière générale, des soins plus intenses ont été associés à moins de décès et à une plus faible incidence du retrait des thérapies de maintien des fonctions vitales chez des patients dans un état critique suivant un TCC grave.*

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Traumatic brain injury (TBI) is a major global health problem. An average of 1.4 million cases of TBI occur every year in the United States with 50,000 associated deaths.[1] In Canada, serious brain injuries occur to 165,000 persons each year.[2] The care provided to patients with TBI can be defined in terms of quality as well as quantity, also known as intensity of care. The incidence of mortality and unfavorable outcomes associated with severe TBIs remains high[3] with limited improvement in recent decades[4-11] despite concurrent improvements in quality of care in the intensive care unit (ICU). This raises a question regarding the potential of other aspects of care, such as intensity, to affect clinical outcomes.

Intensity of care has been shown to be associated with lower mortality in the general ICU population and specifically in non-surgical and neurocritically ill populations.[12,13] Very few studies to date have quantified intensity of care for patients with severe TBI.[14] Nevertheless, a systematic review recently suggested that trauma centres providing aggressive treatment and monitoring of severe TBI patients had improved neurologic outcomes and reduced mortality.[15] A cohort study showed that mortality and decisions to withdraw life-sustaining therapies in patients with severe traumatic brain injury varied significantly across Canadian trauma centres.[16] These findings may suggest a potential association between intensity of care and decisions to withdraw life-sustaining therapies in patients with severe TBI.

We aimed to evaluate the association of the intensity of care with the withdrawal of life-sustaining therapies and mortality in critically ill patients with severe TBI. Our hypothesis was that intensity of care was associated with decreased incidence of withdrawal of life-sustaining therapies and mortality.

Methods

We conducted a *post hoc* analysis of a large multicentre retrospective cohort study of critically ill patients with severe TBI.[16,17] The multicentre cohort study was conducted in six level I trauma centres from three Canadian provinces (Québec, Ontario, Alberta) over a 24-month period (n = 720) (16, 17). Patients were identified at all centres using the *International Statistical Classification of Diseases and Related Health Problems*, tenth revision (codes for traumatic brain injury: S06.0–S06.9). We included 720 patients who were 1) $\geq$ 16 yr old, 2) mechanically ventilated for $\geq$ 48 hr, and 3) admitted to an ICU following a blunt severe TBI with a Glasgow Coma Scale (GCS) score $\leq$ 8. We randomly selected 120 patients

Table 1 Components of intensity of care and interventions

Interventions	Medical	Surgical	Diagnostic
Specific to TBI	• Mannitol	• ICP monitoring	• Head CT scan
	• Hypertonic saline	• Craniotomy/craniectomy	• Brain magnetic resonance imaging
	• Induced hypothermia		• Electroencephalogram
	• Phenytoin		• SSEP
	• Barbiturates		
	• SjO_2 monitoring		
Non-specific to TBI	• Mechanical ventilation	• PEG tube insertion and tracheostomy	
	• Vasopressors	• Other surgical procedures	
	• Propofol		
	• Muscle-paralyzing agents		
	• Intravenous insulin infusion		
	• Heparin		
	• Opioids		
	• Benzodiazepines		

CT = computed tomography; ICP = intracranial pressure monitoring; PEG = percutaneous endoscopic gastrostomy; SjO_2 = jugular venous saturation; SSEP = somatosensory evoked potentials; TBI = traumatic brain injury

from the trauma registries and/or discharge databases at each centre. We excluded patients with penetrating brain injuries and those with no record of ICU stay. Trained research assistants reviewed the charts and retrieved data at each centre using a standardized case report form. Research Ethics Board approval was obtained from all participating institutions.

Intensity of care

We defined intensity of care based on the number and type of interventions performed during the ICU stay. We divided these interventions into two main categories: 1) specific to TBI and 2) interventions not specific to TBI. Additionally, we classified each of these interventions into three mutually exclusive categories: 1) medical, 2) surgical, and 3) diagnostic interventions (Table 1). Interventions were measured for a maximum of 14 days following admission to the ICU or for fewer days if the patient died or was discharged from the ICU before day 14. The intensity of care referred to a score that is the cumulative sum of interventions performed on each day during the ICU stay for each patient. This daily "intensity" may range from 0 to a maximum of 22.

Outcome measures

Our outcome measures were all-cause hospital mortality and withdrawal of life-sustaining therapies. Withdrawal of life-sustaining therapy was coded when therapies such as mechanical ventilation, inotropes, vasopressors, or renal replacement therapy were withdrawn without the expectation of survival.

Data collection

At each centre, qualified and trained research personnel with nursing or medical backgrounds retrieved the data. We extracted the following patient characteristics at the time of admission: age, sex, GCS motor score, pupillary reactivity, cause of trauma, injury severity score, and other associated traumatic injuries (Table 2) as well as the types of interventions used throughout the ICU stay (Table 3).

Statistical analysis

We evaluated the association of the intensity of care with mortality and the withdrawal of life-sustaining therapies using a Cox shared frailty model[18,19] to take account of between-cluster heterogeneity. We used the extended Cox model to allow the number of interventions (and other covariables) to vary over time. We used counting process methodology based on Anderson-Gill data structure.[20-22] Allowing the number of interventions to vary over time allowed us to avoid survivor treatment bias and violations in proportional-hazards assumptions.[23]

Intensity of care was operationalized by creating a composite measure aggregating the contributing interventions (Table 1) over the first 14 days in the ICU. The use of each contributing intervention was assessed on a daily basis (1 point if present; maximum 22 points per day for total intensity). Models were adjusted for sex and three

Table 2 Patient characteristics

Characteristics *n* (%)	Overall			Non-survivors	
	Total (*n* = 716)	Survivors (*n* = 488)	Non-survivors (*n* = 228)	WLST (*n* = 160)	No WLST (*n* = 68)
Demographics					
Age (mean [SD])	42 (20)	39 (19)	51 (22)	54 (21)	43 (21)
Age > 55 yr	213 (29)	102 (21)	111 (48)	88 (55)	23 (34)
Male sex	551 (77)	391 (80)	160 (70)	110 (69)	50 (74)
Cause of trauma					
Motor vehicle collision	399 (56)	292 (60)	107 (47)	67 (42)	40 (59)
Assault (stuck by/against)	54 (7)	42 (8)	12 (5)	5 (3)	7 (10)
Fall	214 (30)	120 (25)	94 (41)	74 (46)	20 (29)
Other	31 (4)	20 (4)	11 (5)	10 (6)	1 (2)
Unknown	18 (3)	14 (3)	4 (2)	4 (3)	0 (0)
Non-reactive pupils	155 (22)	25 (5)	130 (57)	84 (53)	46 (68)
Injury severity score (median [IQR])	30 [25-41]	29 [25-41]	34 [25-43]	29 [25-41]	36 [26-45]
Abbreviated injury scale head					
Missing or 9	288 (40)	172 (35)	116 (51)	89 (56)	27 (40)
1 or 2	16 (2)	14 (3)	2 (1)	1 (1)	1 (2)
3	26 (4)	22 (5)	4 (2)	4 (2)	0 (0)
4	113 (16)	99 (20)	14 (6)	7 (4)	7 (10)
5 or 6	273 (38)	181 (37)	92 (40)	59 (37)	33 (48)
GCS total score (median [IQR])	3 [3-6]	6 [3-7]	3 [3-4]	3 [3-4]	3 [3-3]
GCS motor score					
1	352 (49)	187 (38)	165 (72)	107 (67)	58 (85)
2 or 3	67 (9)	42 (9)	25 (11)	21 (13)	4 (6)
4, 5, or 6	285 (40)	250 (51)	35 (16)	29 (18)	6 (9)
Unknown	12 (2)	9 (2)	3 (1)	3 (2)	0 (0)
Median [IQR]	2 [1-4]	4 [1-5]	1 [1-2]	1 [1-3]	1 [1-1]

IQR = interquartile range; GCS = Glasgow Coma Scale; SD = standard deviation; WLST = withdrawal of life-sustaining therapy

baseline confounding factors, which are known to be associated with prognosis of severe traumatic brain injury: age (dichotomized at 55 yr),[24-28] absence of pupillary reactivity,[8,29-32] and motor score on the GCS on ICU admission.[8,30-34] Motor GCS score[35,36] was categorized as follows: 1, 2-3, 4-6.[17,37]

We reported associations with hazard ratios (HR) and corresponding 95% confidence intervals (CI). The HR was interpreted as an average effect of the time-varying factor "intensity of care" over the period of observation.

We conducted sensitivity analyses to assess whether results vary according to ICU length of stay (three day, seven day, discharge) or type of intervention. Analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

Sample size

We randomly selected 120 patients (60 patients per year) from the trauma registries and/or discharge databases of each of the six centres using the *International Statistical Classification of Diseases and Related Health Problems*, tenth revision (codes for traumatic brain injury: S06.0–S06.9). This sample size was calculated to generate 95% confidence intervals (CI) with ± 10% precision for proportion of death associated with withdrawal of life-sustaining therapy.

Results

We excluded four patients because of missing ICU discharge time. A total of 716 severe TBI patients were included in our analyses. Most patients were male (77%) with a mean [standard deviation (SD)] age of 42.4 (20.5) yr and a median (interquartile range [IQR]) GCS score of [3-6] on admission (Table 2). Hospital mortality was 32 % (*n* = 228) with most deaths (70%) associated with decisions to withdraw life-sustaining therapies. Interventions by

Table 3 Interventions used to determine the intensity of care

Interventions	Overall			Non-survivors	
	Total (n = 716)	Survivors (n = 488)	Non-survivors (n = 228)	WLST (n = 160)	No WLST (n = 68)
Medical					
Mechanical ventilation	710 (99)	482 (99)	228 (100)	160 (100)	68 (100)
SjO_2 monitoring	29 (4)	20 (4)	9 (4)	5(3)	4 (6)
Vasopressor infusion	268 (38)	126 (26)	142 (62)	91 (57)	51 (75)
Propofol	485 (68)	373 (76)	112 (49)	82 (51)	30 (44)
Barbiturates	10 (1)	3 (1)	7 (3)	5 (3)	2 (3)
Opioids	409 (57)	304 (62)	105 (46)	81 (51)	24 (35)
Benzodiazepine	363 (51)	289 (59)	74 (33)	56 (35)	18 (27)
Mannitol	216 (30)	113 (23)	103 (45)	76 (48)	27 (40)
Hypertonic saline	112 (16)	64 (13)	48 (21)	33 (21)	15 (22)
Muscle-paralyzing agents	86 (12)	54 (11)	32 (14)	19 (12)	13 (19)
Phenytoin	420 (59)	303 (62)	117 (51)	88 (55)	29 (43)
Insulin intravenous infusion	412 (58)	266 (55)	146 (64)	113 (71)	33 (49)
DVT prophylaxis	249 (35)	224 (46)	25 (11)	17 (11)	8 (12)
Induced hypothermia	69 (10)	36 (7)	33 (15)	24 (15)	9 (13)
Surgical					
Intracranial pressure monitoring	214 (30)	135 (28)	79 (35)	58 (36)	21 (31)
Craniotomy/craniectomy	166 (23)	108 (22)	58 (25)	44 (28)	14 (21)
Tracheotomy/tracheostomy OR PEG tube insertion	158 (22)	150 (31)	8 (4)	6 (4)	2 (3)
Other surgical procedures	247 (35)	205 (42)	42 (18)	26 (16)	16 (24)
Surgical procedure within the first 48 hr	328 (46)	225 (46)	103 (45)	75 (47)	28 (41)
Diagnostic					
Head CT scan	538 (75)	425 (87)	113 (47)	84 (53)	29 (43)
Brain magnetic resonance imaging	93 (13)	78 (16)	15 (7)	12 (8)	3 (4)
Electroencephalogram	86 (12.0)	65 (13.3)	21 (9.2)	16 (10.0)	5 (7.4)
Somatosensory evoked potentials	15 (2.1)	8 (1.6)	7 (3.1)	5 (3.1)	2 (2.9)

Numbers in parentheses are percentages

CT = computed tomography; DVT = deep venous thrombosis; GCS = Glasgow Coma Scale; OR = operating room; PEG = percutaneous endoscopic gastrostomy; SjO_2 = central jugular venous saturation monitoring; WLST = withdrawal of life-sustaining therapy

mortality and withdrawal of life-sustaining therapies are presented in Table 3.

Adjusted mortality

In the overall analysis, an HR of 0.69 (95% CI, 0.63 to 0.74) suggested that the hazard of mortality decreased by an average of 31% for each additional intervention, if all other covariates were held fixed. In the same manner, an association with decreased mortality was observed with TBI-related interventions (HR, 0.71; 95% CI, 0.60 to 0.85) and interventions not specifically related to TBI (HR, 0.67; 95% CI, 0.60 to 0.75). When analyzed by type of intervention, medical interventions (HR, 0.69; 95% CI, 0.63 to 0.76) and diagnostic testing (HR, 0.57; 95% CI, 0.40 to 0.83) were significantly associated with a reduction of mortality hazards, whereas the association was not statistically significant with surgical interventions (HR, 0.76; 95% CI, 0.57 to 1.01) (Table 4). Similar associations were observed regardless of the timing of outcome assessment (eTable 1, available as Electronic Supplementary Material [ESM]).

Withdrawal of life-sustaining therapies

Adjusted Cox proportional hazard analyses showed a significant decrease in the hazards of withdrawing life-sustaining therapies in the overall cohort with increasing overall intensity of care (HR, 0.73; 95% CI, 0.67 to 0.79). This reduction in the hazard of withdrawing life-sustaining therapies was observed for both the intensity of traumatic brain injury-related interventions (HR, 0.75; 95% CI, 0.62 to 0.92) and interventions not specifically related to TBI (HR 0.71; 95% CI, 0.63 to 0.81). When analyzed by type of

Table 4 Adjusted hazard ratios of the intensity of care on mortality

Intensity of Care	HR*	95% CI	
Overall	0.69	0.64	0.74
Type of Intervention			
TBI-specific	0.71	0.60	0.85
Non TBI-specific	0.67	0.60	0.75
Medical	0.69	0.63	0.76
Surgical	0.76	0.57	1.01
Diagnostic	0.57	0.40	0.83

*Adjusted for sex, age, pupillary reactivity, and score on the Glasgow Coma motor scale. The HR is interpreted as an average effect of the time-varying factor "intensity of care" over the period of observation; CI = confidence interval of hazard ratio; HR = hazard ratio; TBI = traumatic brain injury

Table 5 Adjusted hazard ratios of the intensity of care on the incidence of withdrawal of life-sustaining therapies

Intensity of Care	HR*	95% CI	
Overall	0.73	0.67	0.79
Type of Intervention			
TBI-specific	0.75	0.62	0.92
Non TBI-specific	0.71	0.63	0.81
Medical	0.74	0.67	0.82
Surgical	0.73	0.50	1.06
Diagnostic	0.58	0.37	0.90

*Adjusted for sex, age, pupillary reactivity and score on the Glasgow Coma motor scale. The HR was interpreted as an average effect of the time-varying factor "intensity of care" over the period of observation; CI = confidence interval of hazard ratio; HR = hazard ratio; TBI = traumatic brain injury

intervention, intensity of medical interventions (HR 0.74; 95% CI, 0.67 to 0.82) and diagnostic testing (HR 0.58; 95% CI, 0.37 to 0.90) were significantly associated with a reduced hazard of withdrawal of life-sustaining therapies, whereas the association was not significant with surgical interventions (HR 0.73; 95% CI, 0.50 to 1.06) (Table 5 and subgroup analysis in eTable 2 [available as ESM]). When looking at withdrawal of life-sustaining therapies in non-survivors only, similar findings were observed, as well as for the sensitivity and subgroup analyses (eTable 3 and eTable 4; available as ESM).

Discussion

In our study, we observed that increasing intensity of care provided to severe TBI patients is associated with lower mortality and lower incidence of withdrawal of life-sustaining therapies, even after adjusting for severity of illness, age, and pupillary reactivity. These associations were observed even if intensity of care was assessed based on TBI-related interventions or interventions not specifically related to traumatic brain injury, and specifically for medical interventions and diagnostic testing. In sensitivity analyses, the association of intensity of care with outcome was maintained throughout the ICU stay, regardless of the timing of assessment.

Context with previous literature

No previous study has specifically addressed the impact of intensity of care in the TBI population across centres at a patient level. One previously published study evaluated the effect of intensity of care on mortality following severe TBI. The results of this study suggested that a decreased intensity of care in the elderly patients was a possible cause for the increased mortality observed in this population.[38] In our study, we controlled and adjusted for age and observed that this inverse relationship between intensity of care and mortality was not restricted to the elderly but present in the whole population. A systematic review with meta-analyses of cohort studies examined the effect of aggressive monitoring (mainly intracranial pressure monitoring) on mortality in patients with severe TBI.[14] Centres considered to be using aggressive monitoring had lower mortality. This finding has been observed in a previous study.[15] In our study, all centres were using intracranial pressure monitoring as part of the standard of care, which enabled us to address the question at a patient level by adjusting for a potential centre effect using hierarchical modelling.[18] Our study was also designed to quantify intensity of care as a continuous, time-varying variable. Interestingly, we did not observe an association between surgical intensity, including intracranial pressure monitoring, and mortality or the incidence of life-sustaining therapies.

Strengths and limitations

One important limitation of our study is the absence of long-term functional outcome measures, which are considered standard of care to evaluate patients with traumatic brain injury. Nonetheless, the evaluation of the short-term association of intensity of care with mortality and the incidence of withdrawal of life-sustaining therapies is clinically relevant considering that these events occur early in the care of patients with severe traumatic brain injury. Second, we used data from a previous study that was not designed to evaluate the impact of intensity of care on outcome measures and in which data collection regarding intensity of care was limited to the first 14 days in the ICU. This may be an adequate data collection period, since the most active phase of care is in the first week after injury and most deaths and decisions to

withdraw life-sustaining therapies occur within this two-week period.[16] Third, we quantified intensity of care by assigning an equal weight to the different interventions. We aimed to evaluate the relative association of these interventions, defined by the overall cumulative sum of the intensity of care in patients with severe TBI, with mortality and the incidence of withdrawal of life-sustaining therapies. Notwithstanding, some interventions may play a greater role in the observed associations than others, as addressed in part by our subgroup analyses for type of intervention. Fourth, the most important limitation of our study is likely the fact that we only adjusted for four confounders. Nevertheless, the strength of the confounders we adjusted for with our outcome is the most important among all potential known confounders. Nonetheless, the probability of residual confounding is quite high, and this may explain, in part, the associations observed between intensity of care and mortality and the incidence of withdrawal of life-sustaining therapies. Despite having adjusted for the most important prognostic indicators, we cannot exclude the possibility of bias by indication. Indeed, the clinician's decision to use more aggressive care may be related to unmeasured risk factors. A Pygmalion effect (self-fulfilling prophecy) may thus explain our findings, physicians being more aggressive with patients they believe have a chance to survive or have a more favorable prognosis. Contrarily, since most deaths are associated with a decision to withdraw life-sustaining therapies in this population and physicians are involved in this shared-decision making process, a lower intensity of care may be provided to the patients and explain the findings.

Our study has several strengths. First, our study used data collected from six trauma centres across Canada offering a broad representation of potential current practice variation. Second, we used hierarchical modelling to partition variance between centres and patients. Third, we modelled intensity of care as a time-varying variable and stratified by window of exposure. Failure to appropriately account for changes in treatment intensity over time could lead to survivor treatment bias and overestimates of potential benefits of interventions. Finally, we also took into consideration the incidence of withdrawal of life-sustaining therapies in our analysis, as many deaths in severe TBI patients are associated with these decisions.[16]

Conclusion

We observed a significant association between the overall intensity of care and the incidence of both mortality and withdrawal of life-sustaining therapies in critically ill patients with severe TBI. Nevertheless, we cannot exclude the possibility of important residual confounding, such as a bias by indication, considering that patients with a less favorable prognosis may not benefit from the same interventions during the acute phase of care (self-fulfilling prophecy). Future research should aim to understand how clinicians make decisions regarding intensity of care for patients with severe TBI and clarify the impact of decision-making on outcomes and resource allocation.

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