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Abnormal Body Temperature in Patients with Severe Traumatic Brain Injury - A Predictor of Unfavourable Outcome

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Abstract

Background: Traumatic brain injury (TBI) is a global cause of disability and mortality. Clinical research on the epidemiological profile of TBI is suboptimal in low resource settings. Early identification of the predictors of outcome may be crucial in the triage and management of these patients. This study sought the predictors of outcome among demographic, clinical and computerized tomography (CT) scan variables in a tertiary centre in Nigeria.

Patients and Methods: The study population consisted 97 patients after the exclusion of 27 poly-traumatized patients from an initial 124 with severe TBI (post-resuscitation GCS of 3 - 8) admitted to neurosurgical care from June 2009 to May 2011 at our teaching hospital. Data were obtained from a computerized log of all TBI patients, case files and intensive care unit records, and analysed using STATA software version 12.

Results: Age was not associated with the binary outcome of this study. Delay in arrival to the emergency room (ER) > 6 hours, lower GCS, systolic hypotension (< 90mmHg) and hypertension (> 140 mmHg), increasing respiratory rate (RR) > 30 cycles/min, non-reactive pupils, abnormal body temperature (< 36 and > 37.9 degree Celsius), endotracheal intubation (ETT) and mechanical ventilation were significantly associated with greater odds of an unfavourable outcome on univariate regression analysis. Abnormal body temperature was the most significant independent predictor of unfavourable outcome after multivariate regression analysis. The odds for unfavourable outcome in patients < 36.0 and > 37.9 degrees Celsius were 21.18 times (95% CI 3.45-130.09, p = 0.001) and 23.83 times (95%CI 5.47-103.86, p < 0.001), respectively, the odds in patients with normal body temperature respectively in a model of five covariates (See table 4). The presence of intracranial haematoma seemed associated with unfavourable outcome but did not attain statistical significance, while cerebral oedema (in the abscess of haematoma) was in the opposite direction predicting a favourable outcome after administration of intravenous mannitol as a standard protocol.

Conclusion: Abnormal body temperature could be a more sensitive pointer of an acute hypothalamic injury relative to abnormal pupillary reactivity. Hence, close body temperature monitoring could help early identification of the onset of secondary brain injury in rapidly deteriorating patients with severe TBI. This could facilitate early triage to ICU or neurosurgical intervention in low resource settings.

Keywords: *Severe Traumatic Brain Injury (TBI); Predictors of Outcome; Abnormal Body Temperature; Most Significant Independent Predictor of Outcome; Acute Hypothalamic Injury*

Introduction

Traumatic brain injury (TBI) is a major cause of disability and mortality. The global incidence rate is 200 per 100 000 people per year [1], but this is underestimated due to poor reporting systems and discrepancies in defining TBI across countries [2].

The Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS - see table 1) are universally accepted clinical scales used in accessing the neurological state of patients at accident scenes or emergency rooms (ER) in facilitating admission triage and planning for reha-

bilitation at discharge respectively [3,4]. These scales are used to prognosticate survival or disability, but research on the epidemiological profile of TBI is suboptimal in low and middle-income countries [5].

The mechanism of causation of fever, following acute brain injury, is composite[6]. Central to several other factors is a dysfunctional hypothalamic temperature regulation; others include disorders of cellular metabolism, anaerobiosis, reperfusion injury, the presence of blood and its degradation products and increased cerebral production of cytokines [6].

An earlier publication sought the time-related outcomes in patients with TBI in our tertiary centre with specialist neurosurgical care [7]. This paper sought the demographic, clinical and computerized tomography (CT) scan variables that are associated with outcome and the predictors of outcome in a setting of a low-income country.

Patients and Methods

A retrospective study of all consecutive patients with TBI admitted through the ER at the University of Benin Teaching Hospital (UBTH) from 2009 to 2011. They arrived from the scene of the accident or through referrals from primary and secondary health centres. Resuscitation on arrival was instituted by the emergency unit and trauma team, followed by the neurosurgical referral. Admission protocol included detailed neurosurgical evaluation as well as radiological and laboratory investigations. The radiological assessment included cranial CT scan and cervical spine radiographs to determine the type and extent of brain injury and to rule out cervical spine injury, respectively. Relevant laboratory investigation included complete blood counts, serum electrolyte, urea, creatinine, and blood sugar estimation; which were potential indicators for the presence of risk of secondary brain injury [8].

Selection of study population

Three hundred and eighty-five (385) of 483 patients with TBI had complete data; 157 patients had pre-resuscitation GCS 3 - 8 (severe TBI) as documented by the emergency room (ER) physician. One hundred and twenty-four (124) patients had post-resuscitation GCS 3 - 8 as documented by a neurosurgical residents; 27 had poly-trauma and were excluded from the study.

The study population of 97 patients essentially had routine full blood count parameters ruling-out sepsis at admission.

Statistical analysis

Data were analysed using STATA software version 12. The outcome (dependent) variable was dichotomized into favourable and unfavourable groups [9] (Table 1) based on the GOS for each patient at 3 months post-injury. Independent continuous variables expressed in means (± SD) were tested using Student's t-test for the difference between group means for the binary outcome. Also, independent categorical variables were compared using the Chi-square test or Fisher's exact (test if any cell in a category was < 5). P-value < 0.05 was considered statistically significant (See table 2).

Nine independent variables associated with the binary outcome were assessed by univariate logistic regression analysis to determine the crude odds ratio, and then a multivariate model was fitted with these covariates to study the relation (See table 3). A second multivariate regression model was fitted with five of the most consistent predictors of outcome (-available in the dataset) and their effects assessed in the data set (See table 4). Goodness-of-fit of multivariate models were assessed by the likelihood ratio chi-square and associated p-value (good fit $p < 0.05$), the Hosmer-Lemeshow Chi-square [9] and associated p-value (good fit $p > 0.05$) and finally sensitivity and specificity of the models in predicting the outcome (See table 3 and 4).

Score	Outcome	Binary outcome
1	Dead	Unfavourable
2	Persistent vegetative state	"
3	Severe disability	"
4	Moderate disability	Favourable
5	Good recovery	"

Table 1: *Glasgow Outcome Scale*

		Outcome		
Variables	**n (%) Total = 97**	**Favourable n = 56 (57.74%)**	**Unfavourable n = 41 (42.27%)**	**P-value**
Age, mean (SD)	97 (100)	28.04 (15.98)	32.80 (16.86)	0.1592µ
Age, < 40 years ≥40 years	74 (76.29) 23 (23.71)	43 13	31 10	0.893*
Gender, Female Male	18 (18.56) 79 (81.44)	10 46	8 33	0.836*
Cause, Fall RTA Civil violence Others	8 (8.25) 79 (81.44) 6 (6.19) 4 (4.12)	5 46 1 4	3 33 5 0	0.069^
Time to ER, < 6 hours 6 -12 hours > 12 -24hours > 24 hours	 26 (26.80) 12 (12.37) 24 (24.74) 35 (36.08)	 19 3 17 17	 7 9 7 18	0.014^
GCS, 7-8 5-6 3-4	64 (65.98) 25 (25.77) 8 (8.25)	43 9 4	21 16 4	0.026^
Bilateral reactive pupil Reactive Non-reactive	 56 (57.73) 41 (42.27)	 42 14	 14 27	< 0.001*
Systolic blood pressure 90 - 140 mmHg < 90 mmHg > 140 mmHg	 60 (61.86) 8 (8.25) 29 (29.90)	 41 2 13	 19 6 16	0.015^
Pulse rate (beat/min) 60 - 100 < 60 > 100	 38 (39.18) 14 (14.43) 45 (46.39)	 24 6 26	 14 8 19	0.421*

Respiratory rate				
15 - 20	13 (13.40)	10	3	0.006^
21 - 30	54 (55.67)	36	18	
> 30	28 (28.87)	9	19	
Cheyne Stokes	2 (2.06)	1	1	
Temperature (Celsius)				
Normal	43 (44.33)	40	3	< 0.001^
< 36	14 (14.43)	5	9	
> 37.9	40 (41.24)	11	29	
Haematoma				
No	31 (31.96)	20	11	0.354*
Yes	66 (68.04)	36	30	
Cerebral Oedema				
No	34(35.05)	10	24	< 0.001*
Yes	63(64.95)	46	17	
ETT and Ventilation				
No	63 (64.95)	48	15	< 0.001*
Yes	34 (35.05)	8	26	
Admission duration (SD)		16.46 (10.57)	12.54 (18.11)	0.1828µ

Table 2: *Binary outcome by demographic, clinical and computerized tomography scan variables.*

*SD: Standard Deviation; µ; Student's t-test between group means; * Chi-square test; ^ Fisher's exact test; RTA: Road Traffic Accident; ER: Emergency Room; GCS: Glasgow Coma Scale; ETT: Endotracheal Tube and Mechanical Ventilation.*

Factors* (baseline)	Crude OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
Time to ER (< 6 hours)				
6-12 hours	8.14 (1.70-39.06)	0.009	4.97 (0.49-50.08)	0.174
12-24 hours	1.12 (0.32-3.84)	0.860	0.37 (0.04-3.35)	0.379
> 24 hours	2.87 (0.97-8.56)	0.058	0.88 (0.15-5.12)	0.885
GCS (7-8)				
5-6	3.64 (1.38-9.59)	0.009	2.55 (0.47-14.01)	0.281
3-4	2.05 (0.47-9.00)	0.343	0.43 (0.04-4.04)	0.457
SBP (90-140 mmHg)				
< 90mmHg	6.47 (1.19-35.09)	0.030	2.14 (0.11-41.89)	0.617
> 140mmHg	2.66 (1.07-6.61)	0.036	0.89 (0.18-4.35)	0.889
RR (15-20 cycles/min)				
21-30	1.67 (0.41-6.82)	0.480	0.86 (0.06-11.87)	0.908
> 30	7.04 (1.54-32.00)	0.012	1.25 (0.09-17.73)	0.871
Cheyne Stokes	3.33 (0.16-70.91)	0.440	0.30 (5.7^-5-1.6^3)	0.782
Pupil (Reactive)				
Non-reactive	5.79 (2.39-14.01)	< 0.001	2.14 (0.51-9.02)	0.301

Temperature (normal) < 36 Celsius > 37.9 Celsius	 24 (4.83-119.32) 35 (9.00-137.40)	 < 0.001 < 0.001	 15.70 (2.16-114.23) 13.75 (2.43-77.76)	 0.007 0.003
Haematoma (No) Yes	 1.52 (0.63-3.66)	 0.355	 1.23 (0.30-4.95)	 0.774
Cerebral Oedema (No) Yes	 0.15 (0.06-0.39)	 < 0.001	 0.36 (0.08-1.68)	 0.196
ETT & Ventilation (No) Yes	 10.40 (3.90-27.76)	 < 0.001	 2.45 (0.46-13.00)	 0.291

Table 3: *Crude and adjusted odds ratio in predicting unfavourable outcome.*

**All independent variables associated with outcome were included in multivariate logistic regression model; OR: Odds Ratio; CI: Confidence Intervals; ER: Emergency Room; GCS: Glasgow Coma Scale; SBP: Systolic Blood Pressure; RR: Respiratory Rate; ^: x10; ETT: Endotracheal tube and mechanical ventilation. Likelihood Ratio Chi-square (16) = 63.84, and associated P value < 0.001. Hosmer-Lemeshow Chi-square (8) = 13.11 and associated P value 0.1080. Sensitivity of multivariate model is 78.05%, specificity is 82.14% and total correctly classified is 80.41%.*

Factors (Baseline)	Odds Ratio	95% CI	P-Value
GCS (7-8) 5-6 3-4	 1.47 0.26	 0.36-6.02 0.03-2.17	 0.595 0.212
SBP (90-140mmHg) < 90mmHg > 140mmHg	 3.02 0.98	 0.31-29.18 0.24-4.03	 0.339 0.973
Pupil (Reactive) Non-reactive	 2.66	 0.74-9.49	 0.133
Temperature (Normal) < 36 Celsius > 37.9 Celsius	 21.18 23.83	 3.45-130.09 5.47-103.86	 0.001 < 0.001
Cerebral Oedema (No) Yes	 0.29	 0.08-1.08	 0.064

Table 4: *Multivariate logistic regression analysis of relevant factors predicting unfavourable outcome.*

CI: Confidence Intervals; GCS: Glasgow Coma Score; SBP: Systolic Blood Pressure. Likelihood Ratio Chi-square (8) = 57.28, and associated P value < 0.001. Hosmer-Lemeshow Chi-square (7) = 8.61 and associated P value 0.2821. Sensitivity of multivariate model 82.93%, specificity 87.50% and total correctly classified 85.57%.

Results

The association of demographic, clinical and computerized tomography scan variables with the binary outcome (Table 2)

42% of the study population had an unfavourable outcome. 76% were below 40 years old. There was no statistically significant difference (p = 0.1592) in mean age (± SD) for favourable vs unfavourable outcomes (28.04 ± 15.98 vs 32.80 ± 16.86). Age below or above 40

years was not associated with the binary outcome (p = 0.893). The traditional male-female gender distribution was 4:1. Road traffic accidents accounted for 81% of injury, falls 8%, and civil violence 6%. Only 27% of patients presented at the ER within 6 hours of injury while 36% presented after 24 hours. This is due in part to the lack of a functional paramedic-emergency response system and patients were brought in mostly by relatives and friends. 68% had an intracranial haematoma and 64% had features of cerebral oedema (± haematoma).

Time from injury to arrival at ER (p = 0.014), Glasgow coma scale (p = 0.026), bilateral pupil reactivity (p < 0.001), systolic blood pressure (SBP, p = 0.015), respiratory rate (RR, p = 0.006), body temperature (p < 0.001), cerebral oedema (p < 0.001), endotracheal intubation (ETT) and mechanical ventilation (p < 0.001) were significantly associated with the binary outcome, while age, gender, cause of injury, pulse rate, intracranial haematoma, and admission duration were not associated (p > 0.05) with the binary outcome (See table 2).

Univariate model (Table 3)

Variables significantly associated with the binary outcome were further assessed by univariate logistic regression analysis to identify initial prognostic significance.

Time to ER: Delayed arrival to ER after 6 hours post-injury in all-time categories had a higher crude odds ratio for an unfavourable outcome. The odds of unfavourable outcomes in patients in 6 - 12 hour and > 24-hour categories were 8.14 times (p = 0.009) and 2.87 times (p = 0.058, marginally significant) the odds of patients in < 6-hour category respectively.

GCS: Even among patients with severe TBI, lower GCS seemed to be more linked with high odds of an unfavourable outcome. The odds for unfavourable outcomes in patients with GCS 5 - 6 and 3 - 4 were 3.64 times (p = 0.009) and 2.87 times (p = 0.343) the odds of patients with GCS 7 - 8 respectively. Only 8 patients were in the 3 - 4-category with 4 patients having both binary outcomes each. This could have explained the non-significant p-value observed.

SBP: The odds for unfavourable outcomes in patients with systolic hypotension (< 90mmHg) and hypertension (> 140mmHg) were 6.47 times (p = 0.030) and 2.66 times (p = 0.036) the odds of patients with SBP 90-140mmHg respectively.

RR: Higher respiratory rate above 20 cycles per minute seemed linked with higher odds of an unfavourable outcome. Notably, the odds for unfavourable outcome in patients with respiratory rate > 30 cycles per minute was 7.04 times (p = 0.012) the odds of patients with 15 - 20 cycles per minute.

Bilateral pupillary reactivity: The odds for unfavourable outcome in patients with bilaterally non-reactive pupils was 5.79 times (p < 0.001) the odds of patients with bilaterally reactive pupils.

Body temperature: The odds for unfavourable outcome in patients < 36 Celsius and > 37.9 were 24 times (p < 0.001) and 35 times (p < 0.001) the odds of patients with normal body temperature respectively.

Intracranial hematoma and cerebral oedema: The risk for unfavourable outcome was reduced by 85% (p < 0.001) in patients with features of cerebral oedema. This could have resulted from the fact that all patients had a single brain CT scan at admission and those having features of cerebral oedema without hematoma had intravenous mannitol which might have quickly resolved cerebral oedema and improve the tendency for a favourable outcome.

ETT and mechanical ventilation: The patients with seemingly bad prognosis and respiratory difficulty were mostly admitted in the intensive care unit with 4 limited bed spaces. These were patients that were likely intubated and mechanically ventilated. The odds of unfavourable outcome in these patients was 10.4 times ($p < 0.001$) the odds of patients who were not intubated.

Multivariate models

Two multivariate models were fitted to the data. The first model (Table 3) included 9 independent variables associated with binary outcome noted from the tests of association and univariate analysis. After adjusting for the effect of time to ER, GCS, SBP, RR, pupillary reactivity, intracranial hematoma, cerebral oedema, ETT and ventilation, only body temperature remained the most significant independent predictor of outcome. The odds for unfavourable outcome in patients < 36 Celsius and > 37.9 were 15.7 times ($p = 0.007$) and 13.75 times ($p = 0.003$) the odds of patients with normal body temperature respectively. Model checked by Likelihood Ratio Chi-square (16 degrees of freedom) = 63.84 and associated P-value < 0.001. Hosmer-Lemeshow Chi- square (8 degrees of freedom) = 13.11 and associated P-value 0.1080. The sensitivity of the multivariate model 78.05%, specificity 82.14%, and total correctly classified 80.41% (Table 3).

The second multivariate model (Table 4) included 5 independent variables judge the most relevant predictors of outcome from the literature and concurrent analysis of the data set. Similarly, after adjusting for the effect of GCS, SBP, bilateral pupillary reactivity, and cerebral oedema, only body temperature remained the significant independent predictor of outcome. The odds for unfavourable outcome in patients < 36 Celsius and > 37.9 were 21.18 times ($p = 0.001$) and 23.83 times ($p < 0.001$) the odds in patients with normal body temperature respectively. Model checked by Likelihood Ratio Chi-square (8 degrees of freedom) = 57.28 and associated P-value < 0.001. Hosmer-Lemeshow Chi-square (7 degrees of freedom) = 8.61 and associated P-value 0.2821. The sensitivity of the multivariate model 82.93%, specificity 87.50% and total correctly classified 85.57% (See table 4).

Discussion

The International Mission on Prognosis and Analysis of Clinical Trials in TBI (IMPACT) [10] and Medical Research Council Corticosteroid Randomization after Significant Head Injury (MRC CRASH) [11] trials databases have provided robust risk prediction models for TBI patients in high and middle-low income countries which have been cross-validated, but limitations persist in their use to prognosticate outcomes for patients across different clinical settings/health systems due to injury heterogeneity, variation in clinical practice or case-mix in the databases used in creating these predictive models [8,12]. Further validation of the CRASH trial noted patients in low-middle income countries had over twice the odds of dying following severe TBI compared to high-income countries, but no such difference was observed for mild and moderate TBI [13].

The practice of neurological surgery in limited-resource settings are associated with unique challenges that may influence the outcome in patients with severe TBI; due to a low number of intensive care unit (ICU) beds, inadequate staffing and limited invasive monitoring of real-time intracranial parameters (intracranial pressure and cerebral perfusion pressure), the majority of patients with severe TBI are managed in ER and neurosurgical wards, the ICU being reserved for just few of the most critically ill patients [14].

Age was not associated with outcome in this study; this was in keeping with the CRASH study that showed no association between age and the log odds of death within 14 days until the age of 40 and then a linear increase afterwards [13]. Delay in arrival to ER (> 6 hours), lower GCS, systolic hypotension (< 90 mmHg) and hypertension (> 140mmHg), increasing RR > 30 cycles/min, non-reactive pupils, abnormal body temperature (< 36 and > 37.9 degree Celsius), ETT and mechanical ventilation were significantly associated with greater

odds of an unfavourable outcome on univariate regression analysis. Abnormal body temperature was the most significant independent predictor of unfavourable outcome after multivariate regression analysis (See table 3 and 4). The presence of intracranial haematoma seemed associated with unfavourable outcome, but did not attain statistical significance, while the presence of cerebral oedema predicted a favourable outcome. This was probably due to the administration of intravenous mannitol to all patients who had features of cerebral oedema (without hematoma) facilitating a favourable outcome.

The effect of abnormal body temperature as the most significant predictor of outcome in this study probably resulted from late presentation to specialised care and, consequently, onset of secondary brain injury in the majority of the study population - only 38 patients (39.17%) arrived within 12 hours of injury. The study also emphasises abnormal body temperature as a more sensitive indicator of post-traumatic hypothalamic dysfunction, and, hence, poor outcome, in comparison to abnormal pupillary reactivity. Thus, an abnormal initial body temperature measurement at admission would seem to be an early, but strong indicator of poor outcome which also facilitates early triage to ICU or neurosurgical intervention in low resource settings.

In patients with TBI, brain temperature has been noted to be higher than body or rectal temperatures [15]. Its significance in predicting the outcome is uncertain, but relevant if therapeutic hypothermia is considered for patients with TBI and this is due to the wide differentials that can occur during rapid cooling [16-18].

The finding of spontaneous hyperthermia or hypothermia has been linked with secondary brain injury, hypothalamic dysregulation and/or injury and unfavourable outcomes; this underscores the importance of close monitoring of brain/body temperature and achieving normothermia, especially in patients on targeted temperature management [16,19-23].

Literature is replete on specific organ dysfunction from hyperthermia-induced disruption of the blood - brain barrier and, consequently, increased content of brain water, sodium, potassium and chloride ions, caused by many conditions [6,24]. Comparatively, there is paucity of data on abnormal temperatures, lower or higher than normal, immediately following severe brain trauma and its sequel on eventual outcome as foregrounded in this study.

About two-fifths of case fatalities from traumatic brain injury array hypothalamic lesions which may be ischaemic or micro-haemorrhages (or both) [25]. The former occur arbitrarily in the anterior hypothalamus while the latter are found in definite regions such as the paraventricular nuclei, the median fore-brain bundle, supraoptic nuclei and the median eminence; moreover, the patients were almost unvaryingly comatose throughout the period of hospitalisation [25]. Thus, dysfunctional temperature regulation, which underscores post-traumatic hypothalamic injury, presages poor outcomes in persons with severe TBI.

Conclusion

Abnormal body temperature could be a more sensitive pointer of an acute hypothalamic injury relative to abnormal pupillary reactivity. Hence, close body temperature monitoring could help early identification of the onset of secondary brain injury in rapidly deteriorating patients with severe TBI. This could facilitate early triage to ICU or neurosurgical intervention in low resource settings.

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