Is hypernatremia a risk factor to expansive hematomas among traumatic brain injured patients in a tertiary Sub-Saharan hospital?

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Abstract

Background: Hypernatremia is a common electrolyte imbalance observed in patients with traumatic brain injury (TBI) and it commonly leads to poor outcome. However, the consequence of hypernatremia on occurrence of expansive hematoma (EH) is not well established, though there is limited information on the burden of EH among TBI patients and associated risk factors. This study therefore assessed the proportion of hypernatremia and its correlation with EH among TBI patients at Mulago National Referral Hospital (MNRH), Kampala, Uganda.

Methods: A prospective cohort study was conducted among TBI patients with intracranial hematoma undergoing surgical evacuation during a period of 16th June 2021 to 17th June 2022. A total of 332 patients were prospectively recruited. Demographic, clinical, laboratory and radiological data were captured using the Research Electronic Data Capture (Redcap) system. Patients were monitored for hematoma enlargement complications. The independent outcome was the sodium level (Na) > 145. The dependent outcomes were hematoma enlargement of over 33% evidence by two CT scans (baseline and follow up). Univariate and multivariate analyses were used to identify variables associated with hematoma enlargement.

Results: 184 participants (55.4%) had expansive hematomas identified on CT scan resulting in a proportion of 0.55 95% CI (0.50 to 0.60). Hypernatremia was detected in 80 patients (25.2 %) within 24 hours of admission. At multivariate analyses, the results showed that only hypernatremia PR =1.56 (95% CI 1.17 to 2.10; P=0.003) was found to be a risk factor for expansive hematomas among patients with TBI.

Conclusion: Hypernatremia is common with a prevalence of 25.2.8% among TBI patients. Patients with hypernatremia have 1.56-times higher risk of developing a EH when compared to patients who had no hypernatremia. These findings imply routine plasma sodium levels monitoring and could form the basis for establishing a blood chemistry control protocol for such patients in remote settings.

Background

Traumatic brain injury (TBI) has continued to be a serious cause of premature death globally and most especially in low development countries like Uganda(1). TBI is projected to have a large burden in Africa, with anywhere between 6 and 14 million additional cases by 2050 (1). Traumatic expansive hematomas (TEH) refers to evidence of increased hematoma volume of over 33% or absolute hematoma growth over 6mL from initial scan with varying consequences (2). It is the most dangerous form of brain hematoma that occurs following TBI (3, 4). Currently there is no effective treatment strategy to prevent EH development in patients with TBI. EH frequently causes TBI patients to have poor neurological outcomes (5, 6). The prevalence of TEH occurs in up to 75% of TBI patients (7). Several factors contribute to EH following TBI, previous studies have had varied results (4, 8). Conversely, patients without the predictors may be identified as having a low risk of expanding hematoma. It has been demonstrated that the

transition of fluid from the intracellular to the extracellular compartiment is caused by the development of hypernatremia and, consequently, hyperosmolality. This shift causes brain cell shrinking, which in severe cases might even result in vascular rupture and long-term neurologic impairments (9).

Hypernatremia is common in TBI patients and occurs from a variety of mechanisms, including hyperosmotic fluids, limitation of free water, or diabetes insipidus(10). Sodium has been widely employed as a biomarker for screening, diagnosis, risk stratification, and monitoring in critically sick patients due to its prognostic importance. Additionally, sodium levels can be employed as a surrogate endpoint to direct treatment and for the detection of intracranial expansive hematomas.

The scientific evidence for sodium assessement in intracranial expansive hematomas following TBI is based on the fact that several effects of hypernatremia, from the well-known shrinking of brain cells to decreased glucose utilization, cramping, or reduced left ventricular contraction. The impact of hypernatremia on neurologic function is one of its most well-known adverse effects. The movement of free water from the intracellular to the extracellular space is caused by the development of hypernatremia and, consequently, hyperosmolality. This shift causes brain cell shrinking, which in severe cases might even result in vascular rupture and long-term neurologic impairments (9). Through the methylation of protein phosphatase 2A, hyperosmolality caused proinflammatory cytokine responses in an animal model (11). It has been shown that hypernatremia is indiscriminately linked to a bad prognosis in subarachnoid hemorrhage patients (12). However, whether hypernatremia contributes directly to hematoma enlargement, has not been conclusively determined from previous studies (3, 8, 13) and thus not an appropriate therapeutic target. There is a global dearth of studies on this aspect, and especially in Uganda. In this context, this study assessed the proportion of hypernatremia and its correlation with EH among TBI patients at Mulago National Referral Hospital (MNRH), Kampala, Uganda.

Methods

Study design and setting

This was a prospective cohort study among TBI patients with brain hematoma undergoing surgical evacuation, conducted in Mulago National Referral Hospital (MNRH), Kampala, Uganda, between the 16th of June 2021 and the 17th of June 2022.

Participants

Patients were recruited from their admission at the Accident and Emergency Department, followed up in the operative theaters in the neurosurgery ward, and neurosurgical outpatient clinics for up to 6 months for occurrence of complications and neurological outcomes. Participants were TBI patients aged 18 years and above, Glasgow coma scale (GCS)<14, with brain CT evidence of EH (increase in hematoma volume >33% or absolute hematoma growth > 6ml from the initial scan) exclusively, eligible for cranial surgery, enrolled in the study within 24 hours of initial presentation to hospital. A written signed informed consent from the patient or their next of kin was obtained from each participant. Patients with (1) no laboratory

parameters available, (2) no coagulation parameters available, and (3) used anticoagulants, pregnancy, and those with inability to consent before surgical intervention were excluded from the study. Patients were recruited consecutively until the target sample size of 332 patients was attained. The sample size was calculated by using the formula for comparison between two groups (THE and No TEH) with continuous variables with 10% of possible dropout, and was estimated at 332 patients (https://epitools.ausvet.com.au/samplesize).

Procedures

After the initial trauma assessment and resuscitation, a Brain CT scan was obtained. Hematoma CT findings and measurement were obtained from the neuro-radiologists. Follow-up scans were performed based on neurosurgeons' recommendations. Hypernatremia was defined as serum sodium concentration > 145 mEq/L (> 145 mmol/L) (14, 15). For the electrolyte panel, the blood samples were collected in the pre-operative period based on the different timing of surgical evacuation (early and delayed). During the preoperative period peripheral venous blood samples were collected in a 3.2% sodium citrate vacutainer, and were centrifuged within 30 minutes of collection at 2,000g for 10 minutes, and the sodium (Na), chloride (Cl),potassium (K), creatinine; platelet-poor plasma (PPP), obtained were analyzed for PT, INR, and APTT tests at 0 hours on a fully automated coagulation analyzer at a strict storage condition (freezer) at the Mulago National referral hospital laboratory, Kampala, Uganda. The results were categorized into two groups: group 1 comprised results with normal electrolytes and coagulation profile and group 2 comprised results with abnormal electrolytes and coagulation profile. After discovering the hypernatremia, patients got uniform correction based on current guidelines and were monitored for hematoma enlargement complications until surgical evacuation decision making. The date, time and results of initial and all subsequent scans were recorded.

Variables: Independent variables were the sodium (Na), chloride (Cl), potassium (K), creatinine; international normalized ratio (INR), a platelet count, an activated partial thromboplastin time (APTT). The outcome variables were: hematoma enlargement of over 33% evidence by two CT scans (baseline and follow up), the types of traumatic EH, location, size, diameter (16). Other secondary outcomes control variables are the sociodemographic, cause/etiology of injury, associated injuries.

Statistical analysis

Collected data were entered into MS excel then exported to Statistical Package for Social Sciences (SPSS) version 28.0. Descriptive analyses were summarized as frequency and percentages for categorical variables and the mean and standard deviation (SD) or median and interquartile range (IQR) depending on the distribution and scale of measurement for continuous variables. The prevalence risk (RR) with a 95% confidence interval (CI) was calculated for each variable factor. First, variables from the univariate analysis with P 0.02 were selected for inclusion in the multivariate model. Then variables that are independently contributing to the hematoma enlargement were selected and examined. P value was set at 0.05 for significance

Ethical consideration

Approval for this study was obtained from the Makerere University School of Medicine Research Ethics Committee (SOMREC), registered as Mak_SOMREC-2020-38. Informed consent was obtained from all patients or patients' Next-of-kin/attendants by signing or thumb printing on the consent forms.

Results

Sociodemographic characteristics of patients with expansive hematomas.

A total of 332 patients with traumatic brain injury (TBI) attending Accident and Emergency Unit at Mulago National Referral Hospital (MNRH) were enrolled into the study between June 2021 to June 2022. Of these, 184 (55.4%) had expansive hematomas identified on a second CT scan resulting in a proportion of 0.55 95% CI (0.50 to 0.60). The mean age (± standard deviation [SD]) of the study cohort was 37.5 (± 17.4) years of patients overall and the mean age (±SD) of patients who had EH was statistically different from patients who did not have EH (42.3±17.9 vs. 30.5±14.0 years, p = 0.000) (Table 1). The male/female ratio was 4.1:1 (Table 1).

Table 1: Baseline characteristics of patients with expansive hematomas

Variable	No Expansive hematoma (no.)	Percentage (%)	Expansive hematoma (no.)	Percentage (%)	Overall No. (%)
Gender (324)					
Male	128	47.6	141	52.4	269 (83.0)
Female	17	30.9	38	69.1	55 (17.0)
Age (315)					
18 – 28	63	44.1	80	55.9	143 (45.4)
29 - 38	19	38.8	30	61.2	49 (15.6)
39 - 48	19	54.3	16	45.7	35 (11.1)
>48	37	42.0	88	58.0	88 (27.9)
Mechanism of injury (223)					
Pedestrian/bicycle (23)	17	73.9	6	26.1	23 (10.3)
Motorcycle (131)	62	47.3	69	52.7	131 (58.7)
Vehicle (18)	6	33.3	12	66.7	18 (8.1)
Assault (51)	24	88.9	27	11.1	51 (22.9)
Occupation (307)					
Others	54	35.5	98	64.5	152 (49.5)
Business	21	38.9	33	61.1	54 (17.6)
Employed	13	59.1	9	40.9	22 (7.2)
Bodaboda	25	59.5	17	40.5	42 (13.6)
Farming	20	54.1	17	45.9	37 (12.1)

Residence (317)					
Rural	74	41.8	103	58.2	177 (55.8)
Urban	65	46.4	75	53.6	140 (44.2)
Marital status (320)					
Married	83	43.0	110	57.0	193 (60.3)
Unmarried	59	46.5	68	53.5	127 (39.7)

Risk factors leading to expansive brain hematoma development following TBI.

At bivariate analysis, all variables with a P-value less than 0.2 were included in the multivariate analysis. Gender, occupation, mechanism of injury, ALT, Na, creatinine, HB and INR had levels of significance of less than 0.2. These were considered to have independent associations with expansive hematomas and were therefore included in the multivariate analysis (Table 2).

Table 2 : Bivariate analysis of sociodemographic characteristics of patients with brain hematomas

Variable	PR	95% CI	P-value
***Gender (324)**			
Male (269)	**ref**		
Female (55)	**1.32**	**1.07 to 1.63**	**0.010**
Age (315)			
18 – 28 (143)	***ref***		
29 – 38 (49)	1.14	0.88 to 1.48	0.316
39 – 48 (35)	0.92	0.64 to 1.31	0.643
>48 (88)	1.06	0.83 to 1.34	0.652
***Mechanism of injury (223)**			
Pedestrian/bicycle (23)	***ref***		
Motorcycle (131)	2.02	0.99 to 4.10	0.052
Vehicle (18)	**2.56**	**1.19 to 5.48**	**0.016**
Assault (51)	2.03	0.99 to 4.24	0.060
***Occupation (307)**			
Farming (37)	***ref***		
Bussiness (54)	1.33	0.88 to 1.64	0.173
Employed (22)	0.89	0.48 to 1.64	0.710
Bodaboda (42)	0.88	0.53 to 1.46	0.624
Others (152)	**1.40**	**0.97 to 2.03**	**0.072**
Residence (317)			
Rural (177)	***ref***		
Urban (140)	1.09	0.89 to 1.33	0.415
Marital status (320)			
Married (193)	***ref***		
Unmarried (127)	1.06	0.87 to 1.30	0.547

able 3: Bivariate analysis of Clinical and laboratory characteristics of patients with expansive hematomas

At bivariate, only hypernatremia PR =1.56 (95% CI 1.17 to 2.10; P=0.003), ALT>30 PR =1.26 (95% CI 1.02 to 1.55; P=0.003) were found to be a risk factor for expansive hematomas among patients with traumatic brain injury (Table 3).

Variable	PR	95% CI	P-value
Comorbidities (332)			
No (278)	***ref***		
Yes (54)	1.00	0.77 to 1.30	0.983
Consume alcohol (310)			
No (252)	***ref***		
Yes (58)	1.05	0.82 to 1.34	0.707
Hyperglycemia (314)			
No (280)	***ref***		
Yes (34)	1.00	0.73 to 1.37	0.993
HB <11.5g/dl (321)			
No (277)	***ref***		
Yes (44)	1.23	0.96 to 1.56	0.096
***Na >145 (317)**			
No (237)	***ref***		
Yes (80)	**1.56**	**1.17 to 2.10**	**0.003**
Creatinine >1.2 (311)			
No (156)	***ref***		
Yes (155)	1.17	0.96 to 1.43	0.124
***ALT >30 (303)**			
No (171)	***ref***		
Yes (132)	**1.26**	**1.02 to 1.55**	**0.031**
INR >1.2 (310)			
No (142)	***ref***		
Yes (168)	0.87	0.71 to 1.06	0.160
Platelets <100 (320)			
No (292)	***ref***		
Yes (28)	0.96	0.67 to 1.38	0.823
MAP >100mmHg (321)			

No (213)	*ref*		
Yes (108)	0.93	0.75 to 1.15	0.500

Table 4: Multivariate analysis of sociodemographic and clinical characteristics of patients with expansive hematomas

At multivariate, only hypernatremia PR =1.56 (95% CI 1.17 to 2.10; P=0.003) was found to be a risk factor for expansive hematomas among patients with traumatic brain injury (Table 4).

Variable	PR	95% CI	P-value
Na >145 (317)			
No (237)	*ref*		
Yes (80)	1.56	1.17 to 2.10	0.003

Discussions

This study assessed the proportion of hypernatremia and its correlation with expansive hematoma among TBI patients at Mulago National Referral Hospital (MNRH), Kampala, Uganda. Through prospective study, using well trained research assistants and a designed tool, the information on the proportion of hypernatremia among TBI patients and those with expansive hematoma (EH) was captured and the information on the contributing factors to EH following TBI was documented. The prevalence of expansive hematoma was noted in 55.4% of TBI patients undergoing surgical evacuation. Hypernatremia was noted in 25.2% of TBI patients with expansive intracranial hematoma. According to this study, TBI patients with hypernatremia were 1.56 times more likely to be at risk for expansive hematoma (EH) than their counterparts.

Using 33% of volume progression within an average of 24 hours between the baseline and follow-up CT as the cut off, the proportion of expansive hematoma following TBI at MNRH was 55.4%. This result correlates with reports from several series, in which it was demonstrated that the rate of EH after TBI ranging from 38 to 59% of intracranial hemorrhages (3, 17–20), but lower compared with a study conducted by Adatia and colleagues (75%)(7). These differences, in part, may have been due to a lack of standardized definition of EH across the literature(21–23). On the other hand, different methods of hematoma volume assessment, study inclusion criteria and timing between baseline and follow up scans may explain this discrepancy in proportion across studies(7).

In the univariate model, 45.4% of the participants were between 18 and 28 years. This finding concurs with a study conducted by Maas et al. which revealed that TBI affects the more productive age groups which put additional pressure on the existing economic and health care burden(24). In addition, 55.8% of

TBI occurred in rural areas in Uganda. This result is consistent with a study conducted by LaGrone et al which showed that the high incidence of TBI in developing regions may be due partly because of an increased number of individuals with unlimited demand of movement in unsafe ways and partly due to poor infrastructure. Other contributing factors include inadequate enforcement of traffic laws, alcohol abuse, and inefficient response from an already weak health care system (25).

Previous reports and observations have reported a number of factors contributing to EH following TBI including old age, mechanism of trauma, hypoxia, prehospital systolic blood pressure, platelet medication use, low platelet count, etc (18, 26–28). However, this study revealed that TBI patients with hypernatremia have a 1.56-times higher risk of developing a EH when compared to patients who had no hypernatremia (95% CI 1.17 to 2.10; P = 0.003). This result was supported by a study of David B. et al. which revealed that hypernatremia can contribute to intracranial hematoma enlargement. The proposed mechanism for this effect is that an acute hypernatremia can cause abrupt shrinking of brain cells, which can cause cortical veins to break, causing parenchymal or subarachnoid hemorrhage and subdural hematoma (29). This result however, is inconsistent with research conducted by Carcel C et al., where hypernatremia was not related with expansive hematoma(30). Boland et al raise the possibility that hypernatremia after hospital release may have a detrimental effect on the expansive hematoma outcomes (31). In critically sick patients, hypernatremia has negative effects on physiological courses and may be associated with increased mortality rate (9, 31). Patients with hypernatremia may experience any intracranial hemorrhage such as subarachnoid hemorrhage (4). The current study raises concerns regarding the harmful implications of hypernatremia on expansive hematoma development. Therefore, it is important to balance the possible morbidity of hypernatremia against the advantages of hyperosmolar treatment in managing cerebral edema.

Common monitoring of serum sodium levels is vital and may avoid a rapid and substantial increase in sodium throughout hyperosmolar treatment among traumatic brain injury patients.

The limitations of this study may be summarized as there is not established protocol for correction of hypernatremia and acquisition of serial CT scans in our institution. In addition, hypernatremia must come before the expansion of hematoma. That is critical in assessing causal relationships. It could be better to also assess the effect of hypernatremia correction. However, many TBI patients with EH die before interventions are instituted or during the course of intervention due to inadequate healthcare facilities, cost of repeat electrolyte panel, imaging and surgical utilities, limited theater access, few neurosurgeons, few anesthetists, delayed decision making and lack of scientific up-to-date information and evidence (protocols) on the management of such patients in Uganda and many other developing nations worldwide. It has been difficult to analyze and provide additional insights about the source of hypernatremia, the impact of hypernatremia correction on hematoma development due to lack of medication data. Therefore, authors assessed only the proportion of hypernatremia and its correlation with expansive hematoma among TBI patients at Mulago National Referral Hospital (MNRH). All the potential confounders including normalized ratio (INR) > 1.20, mean arterial pressure (MAP), age, sex etc. have been controlled by using multivariate analysis. Global, in spite of these restrictions, this study

reveals that TBI patients with hypernatremia have a 1.56-times higher risk of developing a EH when compared to patients who had no hypernatremia.

Conclusion

This study has revealed that the prevalence of expansive hematoma among TBI patients is 55.4%. The direct associated risk factor of EH following TBI is hypernatremia > 145 mEq/L. Future clinical trials must elucidate the effect of hypernatremia on occurrence of expansive hematomas among TBI patients. Targeting sodium levels after Intracranial hematoma may be the direction to move in, thus reducing hematoma expansion and its effects on outcome by increasing clot stabilization and preventing further growth.

Recommendations

To assess the effect of hypernatremia correction on a patient's outcomes.

To compare trends in sodium levels with whether hematoma will expand or not

To balance the possible morbidity of hypernatremia against the advantages of hyperosmolar treatment in managing cerebral edema.

Abbreviations

Na: sodium, APTT: activated partial thromboplastin time, DC: decompressive craniotomy, GCS: Glasgow coma scale, GOS: Glasgow outcome scale, HIC: high income countries, ICP: Intracranial pressure; INR: international normalized ratio; LMIC: low middle-income countries, MIS: minimally invasive surgery, MNRH: Mulago National Referral Hospital; PPP : platelet-poor plasma; PHE: perihematomal edema; PT: prothrombin time; PTS: PR: prevalence ratio, CT: randomized clinical trials, TBI: Traumatic Brain Injury; TEH: Traumatic expansive hematoma, TIC: Trauma-induced coagulopathy,

Declarations

Ethical approval and consent to participate

Approval for this study was obtained from the Makerere University School of Medicine Research Ethics Committee (SOMREC), registered as Mak_SOMREC-2020-38. All study procedures were done in accordance with the Declaration of Helsinki, Good Clinical Practice and the Ugandan laws and regulation.

Informed consent

A written signed informed consent from the patient or their next of kin was obtained from each participant.

Consent for publication

Not applicable.

Competing interests

All authors have declared no conflict of interest.

Availability of data and material

Datasets used in the current study are available from the corresponding author on reasonable request.

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Authors' contributions

Larrey Kasereka Kamabu was involved in study design and conception of the first manuscript. Louange Maha Kataka did data acquisition and Irene Najiingo did statistical analysis and data interpretation, Godfrey S. Bbosa, Herve Monka Lekuya, Bives Mutume Nzanzu Vivalya, Juliet Nalwanga Sekabunga, Doomwin Oscar Deogratius Obiga, Joel Kiryabwire and Moses Galukande involved in critical review of the manuscript. All authors agreed on the final manuscript.

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References

1. Wong J, Linn K, Shinohara R, Mateen F. Traumatic brain injury in Africa in 2050: a modeling study. European journal of neurology. 2016;23(2):382-6.
2. Hannah TC, Kellner R, Kellner CP. Minimally Invasive Intracerebral Hemorrhage Evacuation Techniques: A Review. Diagnostics. 2021;11(3):576.
3. Narayan RK, Maas AI, Servadei F, Skolnick BE, Tillinger MN, Marshall LF, et al. Progression of traumatic intracerebral hemorrhage: a prospective observational study. Journal of neurotrauma. 2008;25(6):629-39.
4. Qureshi AI, Malik AA, Adil MM, Defillo A, Sherr GT, Suri MFK. Hematoma enlargement among patients with traumatic brain injury: analysis of a prospective multicenter clinical trial. Journal of Vascular and Interventional Neurology. 2015;8(3):42.

5. Jiang Y, Sun X, Gui L, Tang W, Zhen L, Gu Y, et al. Lack of association between apolipoprotein E promoters in 4 carriers and worsening on computed tomography in early stage of traumatic brain injury. Cerebral Hemorrhage: Springer; 2008. p. 233-6.
6. Moriya T, Tagami R, Furukawa M, Sakurai A, Kinoshita K, Tanjoh K. A case of traumatic hematoma in the basal ganglia that showed deterioration after arrival at the hospital. Brain Edema XV: Springer; 2013. p. 147-9.
7. Adatia K, Newcombe VF, Menon DK. Contusion progression following traumatic brain injury: a review of clinical and radiological predictors, and influence on outcome. Neurocritical care. 2021;34(1):312-24.
8. Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. Journal of neurosurgery. 2002;96(1):109-16.
9. Lindner G, Funk G-C. Hypernatremia in critically ill patients. Journal of critical care. 2013;28(2):216. e11-. e20.
10. Kolmodin L, Sekhon MS, Henderson WR, Turgeon AF, Griesdale DE. Hypernatremia in patients with severe traumatic brain injury: a systematic review. Annals of intensive care. 2013;3(1):1-7.
11. Abolhassani M, Wertz X, Pooya M, Chaumet-Riffaud P, Guais A, Schwartz L. Hyperosmolarity causes inflammation through the methylation of protein phosphatase 2A. Inflammation Research. 2008;57(9):419-29.
12. Loggini A, El Ammar F, Mansour A, Kramer CL, Goldenberg FD, Lazaridis C. Association between electrolyte levels at presentation and hematoma expansion and outcome in spontaneous intracerebral hemorrhage: a systematic review. Journal of critical care. 2021;61:177-85.
13. Ding J, Yuan F, Guo Y, Chen S-W, Gao W-W, Wang G, et al. A prospective clinical study of routine repeat computed tomography (CT) after traumatic brain injury (TBI). Brain injury. 2012;26(10):1211-6.
14. Mendelow AD, Gregson BA, Mitchell PM, Murray GD, Rowan EN, Gholkar AR. Surgical trial in lobar intracerebral haemorrhage (STICH II) protocol. Trials. 2011;12(1):1-9.
15. van Gent JA, van Essen TA, Bos MH, Cannegieter SC, van Dijck JT, Peul WC. Coagulopathy after hemorrhagic traumatic brain injury, an observational study of the incidence and prognosis. Acta neurochirurgica. 2020;162(2):329-36.
16. Wilson L, Marsden-Loftus I, Koskinen S, Bakx W, Bullinger M, Formisano R, et al. Interpreting quality of life after brain injury scores: cross-walk with the short form-36. Journal of neurotrauma. 2017;34(1):59-65.
17. Servadei F, Nanni A, Nasi MT, Zappi D, Vergoni G, Giuliani G, et al. Evolving brain lesions in the first 12 hours after head injury: analysis of 37 comatose patients. Neurosurgery. 1995;37(5):899-906; discussion
18. Cepeda S, Gómez PA, Castaño-Leon AM, Martínez-Pérez R, Munarriz PM, Lagares A. Traumatic intracerebral hemorrhage: risk factors associated with progression. Journal of neurotrauma.

2015;32(16):1246-53.
19. Nasi D, Di Somma L, Gladi M, Moriconi E, Scerrati M, Iacoangeli M, et al. New or blossoming hemorrhagic contusions after decompressive craniectomy in traumatic brain injury: analysis of risk factors. Frontiers in Neurology. 2019;9:1186.
20. Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. The Lancet Neurology. 2006;5(1):53-63.
21. Juratli TA, Zang B, Litz RJ, Sitoci K-H, Aschenbrenner U, Gottschlich B, et al. Early hemorrhagic progression of traumatic brain contusions: frequency, correlation with coagulation disorders, and patient outcome: a prospective study. Journal of neurotrauma. 2014;31(17):1521-7.
22. Allison RZ, Nakagawa K, Hayashi M, Donovan DJ, Koenig MA. Derivation of a predictive score for hemorrhagic progression of cerebral contusions in moderate and severe traumatic brain injury. Neurocritical care. 2017;26(1):80-6.
23. Cepeda S, Gómez PA, Castaño-Leon AM, Munarriz PM, Paredes I, Lagares A. Contrecoup traumatic intracerebral hemorrhage: a geometric study of the impact site and association with hemorrhagic progression. Journal of neurotrauma. 2016;33(11):1034-46.
24. Maas AI, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. The Lancet Neurology. 2022.
25. LaGrone L, Riggle K, Joshipura M, Quansah R, Reynolds T, Sherr K, et al. Uptake of the World Health Organization's trauma care guidelines: a systematic review. Bulletin of the World Health Organization. 2016;94(8):585.
26. Yatsushige H. Surgical Management of a Post-traumatic Intracranial Hematoma. No Shinkei geka Neurological Surgery. 2021;49(5):977-85.
27. Homnick A, Sifri Z, Yonclas P, Mohr A, Livingston D. The temporal course of intracranial haemorrhage progression: how long is observation necessary? Injury. 2012;43(12):2122-5.
28. Rodriguez-Luna D, Rodriguez-Villatoro N, Juega JM, Boned S, Muchada M, Sanjuan E, et al. Prehospital systolic blood pressure is related to intracerebral hemorrhage volume on admission. Stroke. 2018;49(1):204-6.
29. David B. Fluid and electrolyte disturbances, Hyperkalemia; Dennis LK, Anthony SF, Stephen LH, Dan LL, Larry JJ, Joseph L. Harrison's Principles of internal Medicine19 th edition. 2015;1:308-10.
30. Carcel C, Sato S, Zheng D, Heeley E, Arima H, Yang J, et al. Prognostic significance of hyponatremia in acute intracerebral hemorrhage: pooled analysis of the intensive blood pressure reduction in acute cerebral hemorrhage trial studies. Critical Care Medicine. 2016;44(7):1388-94.
31. Boland T, Henderson GV, Gibbons FK, Brouwers HB, Greenberg SM, Raffeld M, et al. Hypernatremia at hospital discharge and out of hospital mortality following primary intracerebral hemorrhage. Neurocritical care. 2016;25(1):110-6.