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Original Article

Prevalence, Risk Factors, and Short-term Consequences of Traumatic Brain Injury-associated Hyponatremia

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Hyponatremia, a common electrolyte disorder associated with traumatic brain injuries (TBIs), has high mortality and morbidity rates. The aim of this study was to identify the risk factors for hyponatremia associated with TBI. We retrospectively analyzed the cases of TBI patients who were admitted to the emergency intensive care unit at Okayama University Hospital between October 2011 and September 2014. A total of 82 TBI patients were enrolled. The incidences of hyponatremia (serum sodium level of < 135 mEq/L) and severe hyponatremia (serum sodium level of < 130 mEq/L) within the first 14 days after admission were 51% (n = 42) and 20% (n = 16), respectively. After admission, hyponatremia took a median period of 7 days to develop and lasted for a median of 3 days. Multivariate analysis demonstrated that higher fluid intake from days 1 to 3 and the presence of cranial fractures were risk factors for hyponatremia. The 58 patients with hyponatremia experienced fewer ventilator-free days, longer intensive care unit stays, and less favorable outcomes compared to the 24 patients without hyponatremia; however, these differences were not significant. Further studies are needed to determine the optimal management strategy for TBI-associated hyponatremia in the intensive care unit setting.

Key words: traumatic brain injury, hyponatremia, cranial fracture, fluid intake

The cases of neurocritical care patients such as those who suffer strokes, traumatic brain injuries (TBIs), brain tumors, or infectious diseases are often complicated with hyponatremia, which has high mortality and morbidity rates [1, 2]. Approximately 30–40% of patients in intensive care units (ICUs) experience hyponatremia [3], and up to 50% of neurosurgical patients are affected by it [4–7]. As hyponatremia can result in brain swelling, physical or cognitive impairments, and a prolonged hospital stay, it is important to detect it early and administer appropriate treatment [8, 9].

The syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting syndrome (CSWS) are considered common etiologies of hyponatremia in neurocritical care patients. It is challenging to distinguish between these 2 conditions due to the difficulty of assessing patients' volume status [1, 2, 10].

Clinical guidelines for hyponatremia in neurosurgical patients have been developed, but little is known about the risk factors and optimal management strategy for hyponatremia in TBI patients [11]. As the early recognition and prevention of hyponatremia are important, we investigated the prevalence, risk fac-

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tors, and short-term consequences of TBI-associated hyponatremia.

Materials and Methods

Study population. We retrospectively analyzed the cases of TBI patients who were admitted to the emergency ICU at Okayama University Hospital between October 1, 2011 and September 30, 2014. Patients in whom an intracranial hemorrhage was detected on computed tomography (CT) after a traumatic injury were considered to have suffered a TBI. Patients who were younger than 16 years of age, died within 72 h of admission, required dialysis, or presented with central diabetes insipidus were excluded. This study was approved by the Institutional Review Board at Okayama University.

Management protocol. Ringer's solution was administered as appropriate to prevent secondary brain damage followed by cerebral hypoperfusion during the first few days of the resuscitation phase according to the patient's serum lactate levels and urinary output. Fresh frozen plasma was administered as appropriate in cases of TBI-related coagulopathy. When hyponatremia was detected, sodium supplementation therapy was administered according to the severity of the patient's hyponatremia. At the same time, the patient's urinary sodium excretion was analyzed to determine whether the mineralocorticoid administration had been effective against sodium retention. Hyponatremia was corrected at a rate of ≤ 0.5 mEq/h and ≤ 10 mEq/day to prevent osmotic demyelination syndrome.

Data collection. Information was collected about the following parameters: age, sex, Glasgow Coma Scale (GCS) score, serum lactate level, D-dimer level on arrival, daily serum sodium level, Injury Severity Score (ISS), the presence or absence of cranial and/or skull base fractures, Abbreviated Injury Scale (AIS) score for the head, Traumatic Coma Data Bank (TCDB) CT scan category (diffuse injury-type or evacuated mass lesion-type), Rotterdam CT score, the total amount of fluid intake from days 1 to 3, whether osmotherapy was employed as a treatment for cerebral edema, whether surgical decompression was performed to control intracranial pressure, the number of ventilator-free days during the period from days 1 to 28, the duration of the patient's ICU stay, and the outcome at discharge. A favorable outcome was defined as good recovery or moderate disability according to the Glasgow Outcome Scale (GOS). In the hyponatremic group, the treatment administered for hyponatremia; active sodium supplementation or mineralocorticoid administration, was also recorded.

Definition and management of hyponatremia. Hyponatremia and severe hyponatremia were defined as serum sodium levels of < 135 mEq/L and < 130 mEq/L, respectively, within 14 days of admission. When hyponatremia was detected, active sodium supplementation therapy was performed.

Statistical analysis. Categorical variables are shown as frequencies or percentages, and continuous variables are presented as the mean and standard deviation (SD) values or median and interquartile range values depending on their distributions. Categorical variables were compared using Fisher's exact probability test. Student's *t*-test was used to assess continuous variables with normal distributions, and the Mann-Whitney U-test was used to evaluate variables with non-normal distributions. A multiple logistic regression analysis was performed to identify independent risk factors for hyponatremia in TBI patients. *P*-values < 0.05 were considered significant. All analyses were performed using the software SPSS for Windows (release 22.0).

Results

A total of 82 TBI patients were included in this study (Fig. 1). The patients' demographic data are shown in Table 1; 55 were male (67%) and 27 were female (33%), and the median age was 61 years. The patients' median GCS score on arrival was 9, their median ISS was 31, and their median ICU stay was 21 days. Forty-two (51%) and 16 (20%) patients presented with hyponatremia and severe hyponatremia, respectively, within 14 days of admission.

The overall mortality rate at discharge was 4% (n = 3). After admission, hyponatremia took a median period of 7 days to develop and lasted for a median of 3 days. The baseline characteristics of the hyponatremic and normonatremic groups are shown in Table 2. The daily serum sodium levels of the 2 groups are shown in Fig. 2. There were no significant differences between the ISS of the 2 groups. Although the

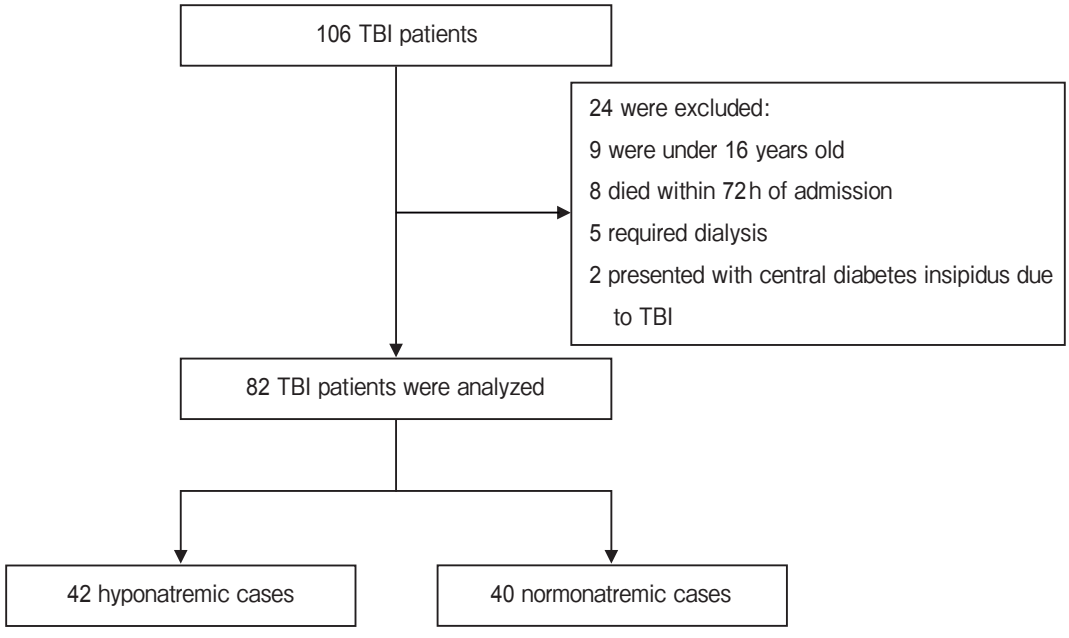

Fig. 1 Patient flow diagram.

Table 1 Traumatic brain injury patients' demographic data (n = 82)

Age (yr), median (IQR)	61 (30, 73)
Males, n (%)	55 (67)
GCS score on arrival, median (IQR)	9 (6, 14)
ISS, mean ± SD	31 ± 10
Hyponatremia (serum sodium level of < 135 mEq/L), n (%)	42 (51)
Severe hyponatremia (serum sodium level of < 130 mEq/L), n (%)	16 (20)
No. of ventilator-free days from days 1 to 28, median (IQR)	22 (13, 28)
Duration of ICU stay (days), median (IQR)	21 (13, 30)
Favorable outcome at discharge, n (%)	42 (51)
Mortality at discharge, n (%)	3 (4)

IQR, interquartile range; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SD, standard deviation; ICU, intensive care unit.

58 patients in the hyponatremic group exhibited more severe AIS scores for the head and a lower frequency of diffuse-type injuries (as defined by the TCDB) than the 24 patients in the normonatremic group, the differences were not significant.

The univariate analysis showed that the risk factors for TBI-associated hyponatremia include a higher D-dimer level on admission, the presence of cranial fractures, and greater fluid intake from days 1 to 3. The hyponatremic group experienced fewer ventilator-free days from days 1 to 28, longer ICU stays, and less favorable outcomes at discharge than the normonatremic group, but the differences were not significant. Among the risk factors for hyponatremia, we examined whether an increased D-dimer level, the presence of cranial fractures, and the total fluid intake from days 1 to 3 are clinically significant.

The multivariate analysis demonstrated that the presence of cranial fractures and greater fluid intake from days 1 to 3 are risk factors for TBI-associated hyponatremia during the first 2 weeks after admission (Table 3). Sixty-two % (n = 26) of the 42 patients with hyponatremia and 94% (n = 15) of the 16 patients with severe hyponatremia were treated with active sodium supplementation or mineralocorticoid administration.

Table 2 Baseline characteristics of the hyponatremic and normonatremic groups

	Hyponatremic group (serum sodium < 135 mEq/L) n = 42	Normonatremic group (serum sodium ≥ 135 mEq/L) n = 40	*P*-value
Age (yr), median (IQR)	65 (42, 71)	48 (23, 76)	0.378
Males, n (%)	30 (71)	25 (63)	0.482
GCS score on arrival, median (IQR)	8 (6, 13)	10 (6, 14)	0.190
Lactate (mmol/L), median (IQR)	3.1 (1.9, 3.9)	2.3 (1.6, 3.8)	0.226
D-dimer level (μg/mL), median (IQR)	26 (14, 57)	14 (7, 45)	0.048
ISS, mean ± SD	32 ± 11	30 ± 10	0.271
Cranial fractures, n (%)	27 (64)	13 (33)	0.005
Cranial and skull base fractures, n (%)	16 (38)	5 (13)	0.011
AIS score for the head of 5, n (%)	25 (60)	17 (43)	0.185
TCDB CT category of 2 to 4 (diffuse type), n (%)	21 (50)	27 (68)	0.122
Rotterdam CT score category, 1 to 5	2 (2, 3)	2 (2, 2)	0.442
Presence of traumatic SAH, n (%)	38 (59)	26 (41)	0.292
Craniotomy or burr hole drainage, n (%)	11 (26)	5 (13)	0.165
Fluid intake from days 1 to 3 (mL), median (IQR)	10,618 (7,527, 15,151)	9,149 (5,913, 11,084)	0.012
Osmotherapy, n (%)	27 (64)	19 (48)	0.182
Infection, n (%)	25 (60)	16 (40)	0.121
No. of ventilator-free days from days 1 to 28, median (IQR)	20 (13, 24)	24 (13, 28)	0.104
Duration of ICU stay (days), median (IQR)	24 (14, 32)	18 (12, 28)	0.071
Favorable outcome at discharge, n (%)	18 (43)	24 (60)	0.130
Mortality at discharge, n (%)	2 (5)	1 (3)	1.000

IQR, interquartile range; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SD, standard deviation; AIS, Abbreviated Injury Scale; TCDB, Traumatic Coma Data Bank; CT, computed tomography; SAH, subarachnoid hemorrhage; ICU, intensive care unit.

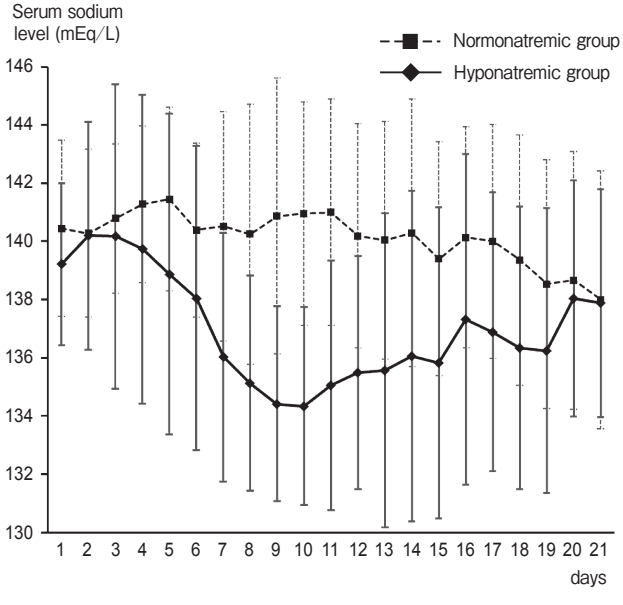

Fig. 2 Daily serum sodium levels of the hyponatremic (n = 42) and normonatremic (n = 40) groups (mean ± SD).

Discussion

Hyponatremia in critically ill patients is associated with a longer duration of mechanical ventilatory support, a longer stay in the ICU, and an increased mortality rate [3, 14, 15]. The prevalence of hyponatremia has been reported to be as high as 30–40% among ICU patients [14], and up to 50% of neurosurgical patients are affected by the condition [4–7]. Previous studies have suggested that 27–41% of TBI patients develop hyponatremia; however, the definition of hyponatremia varied among these studies [2, 8, 16]. In our present study, the incidence of hyponatremia (serum sodium level of < 135 mEq/L) was 51% and that of severe hyponatremia (serum sodium level of < 130 mEq/L), which should be diagnosed and treated promptly, was 20%.

There have not been many studies of the risk factors for hyponatremia in TBI patients. Although hyponatremia has been shown to be associated with the severity of brain injuries, patients with mild to moderate TBI, which are generally defined as those

Table 3 Multivariate analysis of the risk factors for hyponatremia in TBI patients

Variables	Odds ratio (95% CI)	*P*-value
Cranial fractures	3.25 (1.22–8.60)	0.018
D-dimer level (μg/mL)	1.01 (0.99–1.02)	0.427
Fluid intake from days 1 to 3 (L)	1.11 (1.01–1.23)	0.04

CI, confidence interval.

associated with initial GCS scores of 9 to 15, are considered to be at greater risk of hyponatremia than those with severe TBI [2, 17–19]. Thus, it seems that the risk of hyponatremia does not correlate well with the GCS score on arrival, as was seen in the present study.

Regarding the patients' demographics, no meaningful correlations between age or sex and the frequency of hyponatremia were detected in the present study, as reported previously [8, 17]. Conversely, the presence of cranial fractures and greater fluid intake from days 1 to 3 were found to be risk factors for hyponatremia in TBI patients, regardless of the type of TBI or the patient's ISS, which is indicative of the anatomical severity of the injury.

Regarding the type of TBI, Lohani *et al.* reported that increased Rotterdam CT scores are associated with a higher incidence of hyponatremia, but their study did not examine the effects of cranial or skull base fractures [17]. In the present patient series, the presence of cranial fractures proved to be a risk factor for hyponatremia in TBI patients with intracranial hemorrhage, first reported here.

Regarding fluid intake, as lower fluid balance is associated with poor outcomes, adequate fluid resuscitation is necessary to prevent secondary brain damage followed by hypoperfusion in TBI patients [20, 21]. The relationship between fluid intake and hyponatremia detected in the present study was based on the link between fluid intake and the severity of the patients' brain injuries, which was not represented as well by the type of TBI according to the TCDB CT category or the GCS score on arrival.

The same could be said of the relationship between the presence of cranial fractures and hyponatremia. As fluid administration is strictly managed based on factors such as the patients' serum lactate levels and urinary output, we suspect that higher fluid intake reflects the severity of the TBI, rather than that excess fluid intake was associated with hyponatremia. In any case, appropriate fluid management during the first week is important in TBI patients, as this is when hyponatremia frequently occurs. An elevated D-dimer level on admission has been reported to be an independent predictor of patient outcomes [22, 23] and the D-dimer level tended to be higher in the present study's hyponatremic group, but our multivariate analysis revealed no significant difference in this parameter between the hyponatremic and normonatremic groups.

CSWS and SIADH are considered to be the 2 principle causes of hyponatremia in TBI patients, but the mechanisms responsible for hyponatremia and the underlying pathophysiology of the condition are still not fully understood [1]. Assessing whether patients are hypovolemic or euvolemic might be useful only for determining the differences between CSWS and SIADH, which are difficult to distinguish [1, 2, 24]. Other causes of hyponatremia such as hypopituitarism or elevated levels of natriuretic peptides have also been reported [25, 26], which might make obtaining a correct diagnosis more difficult. Thus, the optimal treatment for hyponatremia in TBI patients has not been established, and clinicians should perform thorough work-ups to determine the underlying causes of their patients' conditions and then treat them appropriately.

Potts *et al.* suggested that vasopressin 2 receptor antagonists might be effective against hyponatremia in neurosurgical patients [27]. Further studies about the optimal treatment for hyponatremia in TBI patients, *e.g.*, studies examining the use of active sodium supplementation, mineralocorticoids, and/or vasopressin 2 receptor antagonists, are needed.

This study had several limitations. First, it was a single-center retrospective study involving a small population. Second, no information was obtained about the patients' daily fluid and sodium balance. In addition, the patients' long-term outcomes were not evaluated.

In conclusion, we investigated the prevalence, risk

factors, and short-term outcomes of TBI-associated hyponatremia. Increased fluid intake during the first 3 days after admission and the presence of cranial fractures were suggested to be risk factors for hyponatremia. Hyponatremia tended to result in fewer ventilator-free days, a prolonged time to ICU discharge, and less favorable outcomes, but these tendencies were not significant. Further studies are necessary to identify the optimal management strategy for TBI-associated hyponatremia in the ICU.

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