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The relationship between cerebral salt wasting syndrome and clinical outcome in severe and moderate traumatic brain injury patient at Sanglah Hospital, Bali, Indonesia

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ABSTRACT

Introduction: Intracranial and extracranial factors causing secondary Traumatic Brain Injury (TBI) are the primary targets for medical intervention and preventing brain damage. One of the extracranial factors that worsen the prognosis of TBI is Cerebral Salt Wasting (CSW) syndrome. There are only a few articles that report CSW in TBI patients, and no studies are describing the relationship between CSW and clinical outcome of head injury. This study aimed to determine the relationship between CSW and clinical outcome of TBI patients.

Methods: This was a prospective cohort study conducted from October 2018 to May 2019. Data collection was carried out in a surgical emergency and inpatient ward at Sanglah Hospital. The outcome was assessed using the Glasgow Outcome Scale (GOS) 3 months after head injury. The relationship between variables was analyzed and using Chi-square analysis. Data were analyzed using SPSS version 23 for Windows.

Results: Most of respondents are male (83.3%), severe head injury (73.3%), mild hyponatremia (90.0%), and negative fluid balance (100.0%) in CSW (+) group (Table 1). However, in CSW (-) group, most of respondents are male (70.0%), moderate head injury (85.0%), normal serum natrium (80.0%), and positive fluid balance (60.0%). CSW increased the risk of unfavorable outcomes, 5.7 times in moderate and severe head injuries (95% CI=1.8 – 18.4; p=< 0.001).

Conclusion: CSW syndrome increased the risk of unfavorable outcomes in moderate and severe traumatic brain injury patients.

Keywords: cerebral salt wasting, hyponatremia, outcome, traumatic brain injury.

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INTRODUCTION

One of the extracranial factors that worsen the prognosis of traumatic brain injury (TBI) patients is hyponatremia. Hyponatremia frequently happened in TBI patients because the central nervous system plays an important role in water and natrium homeostasis.[1] Sherlock et al.[2] reported that hyponatremia was experienced by 46.8% of TBI patients, 50.7% of subdural hematoma, 25% of epidural hematoma, 47.9% of cerebral contusion, and 50% of diffuse axonal injury patients. Albanese et al.[3] also reported that hyponatremia in TBI patients increases mortality by up to 14.3%.

A traumatic brain injury could cause disturbance of natrium regulation by the kidney. Natriuresis further caused hypovolemic status and developed to Cerebral Salt Wasting (CSW) syndrome.[4] CSW syndrome is a collection of symptoms as consequences of natrium and water regulation failure because of brain disorder with normal kidney function.[5] This syndrome characterized by hyponatremia associated with hypovolemia because of natriuresis. As hyponatremia occurs, it will cause astrocyte apoptosis because of cell swelling due to low osmolality. The death astrocytes will cause disturbance of the blood-brain barrier and cause brain edema and high intracranial pressure in the end.[6] This study's objective was to determine the relationship between cerebral salt wasting syndrome and clinical outcome of moderate and severe traumatic brain injury patients.

METHODS

This study was an observational analytic study using a prospective cohort design. This research begins by identifying subjects with risk factors and subjects without risk factors, followed up to the time specified to assess outcomes. Data retrieval was carried out in a surgical emergency installation and inpatient ward at Sanglah Hospital. Examination of serum sodium levels was carried out at the Clinical Pathology Laboratory of Sanglah Hospital Denpasar. Whereas outcomes according to the Glasgow outcome scale were assessed three months after head injury when the patient was still being treated or polyclinic control. The time of the study was carried out in the period of October

2018 - May 2019 or until the number of samples was fulfilled.

The target population in this study were < 13 GCS head injury sufferers with age > 18 years. This study's affordable population was patients who suffered head injuries with GCS < 13 who were diagnosed and hospitalized in the Sanglah Hospital Denpasar ward for the period October 2018 to May 2019.

The research sample is part of an affordable population that meets the inclusion and exclusion criteria. The determination of samples is done by consecutive sampling, which is sampling sequentially during the period of the study until the required number of samples is fulfilled. The inclusion criteria for this study were adult patients > 18 years old with GCS head injury < 13, agrees to participate in this study, followed by the signing of an agreement after explanation.

Patients with a history of brain tumors, cerebrovascular accident (hemorrhagic or non-hemorrhagic stroke), history of previous episodes of seizures or epilepsy, diabetes insipidus, thyroid disorders, and kidney disorders were excluded from this study. Patients with a history of using diuretics, who have performed trepanation surgery, and bilateral negative pupillary reflexes were also excluded from the study.

The cerebral salt wasting syndrome was defined as a collection of symptoms characterized by hyponatremia findings and decreased extracellular volume. Hyponatremia was defined as blood sodium levels through an examination of serum electrolytes at first arrival (24 hours) less than 136 meq/L before receiving fluid therapy. A decrease in extracellular volume measured by a negative fluid balance for 24 hours (with maintenance crystalloid fluid therapy 16 drops per minute). The outcome was assessed with GOS-E. The unfavorable outcome was defined as GOS-E value shows a scale of 1 – 2 and the outcome severe disability if the GOS-E value shows a scale of 3 – 4. Favorable outcome was defined as score 5 – 8 in GOS-E value. The relationship between variables was analyzed and presented using Chi-square to test the significance of the comparative hypothesis of two categorical samples with the significance limits used were $p < 0.05$ and 95% confidence intervals. Data analysis was carried out using SPSS for Windows version 23.0.

Table 1 Baseline characteristics of the sample

Variable	CSW (+) n = 30	CSW (-) n = 40
Gender, n (%)		
Male	25 (83.3)	28 (70.0)
Female	5 (16.7)	12 (30.0)
Age	39.47±19.36	38.88±20.08
Severity of injury, n (%)		
Moderate head injury	8 (26.7)	34 (85.0)
Severe head injury	22 (73.3)	6 (15.0)
Serum natrium, n (%)		
Normal	0 (0.0)	32 (80.0)
Mild hyponatremia	27 (90.0)	8 (20.0)
Severe hyponatremia	3 (10.0)	0 (0.0)
Fluid balance, n (%)		
Positive	0 (0.0)	24 (60.0)
Negative	30 (100.0)	16 (40.0)

RESULTS

The characteristic of the sample can be seen in Table 1. In this study, there were 70 patients with moderate and severe TBI patients over 18 years old. Forty-two (60%) patients were classified as moderate TBI while the other 28 (40%) patients were classified as severe TBI. There were 30 moderate and severe TBI patients (42.8%) who experienced CSW and 40 patients (57.2%) who did not experience CSW (Table 1). Most of respondents are male (83.3%), severe head injury (73.3%), mild hyponatremia (90.0%), and negative fluid balance (100.0%) in CSW (+) group (Table 1). However, in CSW (-) group, most of respondents are male (70.0%), moderate head injury (85.0%), normal serum natrium (80.0%), and positive fluid balance (60.0%) (Table 1).

As we can see in Table 2, there is relationship between the severity of the head injury and the presence of CSW syndrome. CSW syndrome tends to present in more severe TBI patients (RR=4.12; 95%CI=2.14-7.92; p<0.001).

In Table 3, we can see that there is a significant relationship between the severity of hyponatremia and the clinical outcome of TBI patients (p=0.003). Most of patients with severe hyponatremia condition was in the unfavorable outcome (66.67%) and normal serum natrium levels was predominant in the favorable clinical outcome (96.9%) (Table 3).

Based on Table 4, it can be seen that the presence of CSW increased the risk of unfavorable outcomes 5.7 times in moderate and severe TBI patients significantly (95% CI=1.8 – 18.4; p<0.001).

DISCUSSION

Although the incidence of CSW in head injuries is unknown, the relationship between the two is described by several case reports and case series. A study by Steelman et al.[7] reported 5% to 10% of TBI patients had natriuresis. Donati et al.[8] mentioned

Table 2 The relationship between the severity of the head injury and the presence of the cerebral salt wasting syndrome

Severity of injury	Cerebral Salt Wasting (N=70)		RR	CI 95%	P-value
	Present (N=30)	Absent (N=40)			
Severe TBI, n (%)	22 (73.3)	6 (15.0)	4.12	2.14 – 7.92	< 0.001
Moderate TBI, n (%)	8 (26.7)	34 (85.0)			

Table 3 The relationship between clinical outcome and serum natrium

Serum natrium	Clinical outcome		P-value
	Unfavorable	Favorable	
Severe hyponatremia (< 125), n (%)	2 (66.67)	1 (33.3)	0.003
Mild hyponatremia (125 – 134), n (%)	13 (37.1)	22 (62.9)	
Normal (135 – 145), n (%)	1 (3.1)	31 (96.9)	

Table 4 The relationship between clinical outcome and the presence of the cerebral salt wasting syndrome

Cerebral salt wasting syndrome	Clinical outcome		RR	CI 95%	P-value
	Unfavorable	Favorable			
Present	13 (43.3%)	17 (56.7%)	5.7	1.8 – 18.4	< 0.001
Absent	3 (7.5%)	37 (92.5%)			

the incidence of CSW after TBI ranges from 0.8% to 34.6%, and they found the highest prevalence in patients with GCS < 9.

In this study, we found eight patients with mild hyponatremia without CSW. The cause of hyponatremia in these samples is Syndrome of Inappropriate Anti Diuretic Hormone (SIADH). SIADH and CSW both have low sodium levels; however, the volume status of the patient can differentiate between CSW and SIADH. SIADH is a euvolemic hyponatremia syndrome characterized by euvolemic or positive fluid balance, hyponatremia (100 mOsm / kg H^2O serum sodium in adults), and an increase in urinary sodium concentration (> 40 mmol / L) in individuals with normal salt and water intake. They are the result of excessive secretion of the antidiuretic hormone, which causes reabsorption in the distal nephron, resulting in concentrated urine despite serum hyposmolality.[1]

We found that severe TBI increased the risk of CSW 4.12 times higher than in moderate TBI patients. This ultimately relates to the outcome of head injury patients. In a study conducted by Navdeep et al.[9] with 110 samples found that GCS scores at hospital admission have proven to be reliable predictors for assessing outcomes in patients with TBI. In addition, older age, hypoxia, midline shift from abnormal CT scan and reflex pupil findings were significant predictors of unfavorable outcomes in patients with head injuries.[9]

We found a significant relationship between sodium level and clinical outcome of patients with moderate and severe TBI. This is in line with the research of Verbalis *et al.*,[10] which states that hyponatremia significantly results in high morbidity and mortality rates of 38% in hospitalized patients. Hannon *et al.*[11] stated 25% mortality of patients with sodium levels < 125 mmol / l and 48% were occurred after being evaluated on three months post-trauma. Moro *et al.*[12] reported that 18% of TBI patients with hyponatremia had a poor outcome compared to normo-natremia patients that only 5% had a poor outcome.

TBI causes a stress response and activation of the hypothalamic-pituitary-adrenal-axis. This causes an increase in the atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which increases arginine vasopressin resulting in hyponatremia.[13] Furthermore, hyponatremia that occurs also disrupts the kidney's mechanism in regulating fluid body volume. As a result of the released natriuretic peptide, resistance occurs in the renin-angiotensin-aldosterone cascade, so that sodium reabsorption in the proximal tubule of the kidney decreases. This lost sodium also attracts water according to the osmotic pressure gradient balance. This then causes a hypovolemic condition, which then develops into Cerebral Salt Wasting (CSW) syndrome.[4]

This condition is more common in patients with moderate and severe TBI patients (GCS < 13),

indicating the severity of brain damage also increases the risk of CSW incidence. When hyponatremia occurs, plasma osmolality decreased, which causes the movement of water to the brain tissue according to the osmosis gradient, causing cerebral edema. The cells most commonly affected are astrocytes, one type of glial cell that forms the blood-brain barrier and has an important role in maintaining fluid and electrolyte concentrations of the extracellular space in the brain. CSW will further cause swelling of this cell and induce apoptosis of astrocytes. The blood-brain barrier is disturbed, and intracranial pressure increases causing brain herniation and mortality of patients.[6]

Currently, research examining the relationship between TBI and incidence of CSW syndrome is limited in several case reports. In a prospective cohort study that we conducted, we reported a relative risk value of 5.7, which means that CSW syndrome increased the risk of unfavorable outcomes by 5.7 times in moderate and severe TBI patients. The unfavorable outcomes were assessed with the Glasgow Outcome Scale Extended (GOSE), which are death, persistent vegetative state, lower severe disability, and upper severe disability.[14]

The outcome of severe TBI patients was worse than moderate TBI patients. The role of severe TBI on outcomes is undoubted. However, in this study, the role of CSW could not be doubted either because in moderate TBI patients with CSW syndrome also had unfavorable outcomes. Indeed, in severe TBI patients, the role of CSW on outcomes appears biased but statistical tests showed the role of CSW in outcomes was not dependent on GCS score.

CONCLUSION

The presence of cerebral salt wasting syndrome increased the risk of unfavorable outcomes by 5.7 times. Monitoring of sodium levels and fluid balance in TBI patients with GCS score < 13 is suggested to prevent poor outcomes that can be avoided with appropriate early management.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this study.

AUTHOR'S CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Nyoman Golden, Jeffrey Ariesta Putra, Wayan Niryana, and Putu Eka Mardhika. The first draft of the manuscript was written by Nyoman Golden and Jeffrey Ariesta. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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