DISORDERS OF SODIUM BALANCE AFTER TRAUMATIC BRAIN INJURY IN ADULT PATIENTS: A PROSPECTIVE STUDY IN A SINGLE CENTRE

BY

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DR TAN ZI HAN

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LIST OF ABBREVIATIONS

1.	DI	DIABETES INSIPIDUS
2.	SIADH	SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE
3.	CSW	CEREBRAL SALT WASTING SYNDROME
4.	TBI	TRAUMATIC BRAIN INJURY
5.	SHI	SEVERE HEAD INJURY
6.	MHI	MODERATE HEAD INJURY
7.	RTA	ROAD TRAFFIC ACCIDENT
8.	WDT	WATER DEPRIVATION TEST
9.	NA	SODIUM
10.	OSMO	OSMOLALITY
11.	SE	SERUM
12.	UR	URINE
13.	HSAJB	HOSPITAL SULTANAH AMINAH JOHOR BAHRU
14.	GCS	GLASGOW COMA SCALE
15.	I/O	INPUT/OUTPUT
16.	DDAVP	DESMOPRESSIN
17.	CT	COMPUTED TOMOGRAPHY
18.	ADH	ANTI-DIURETIC HORMONE

ABSTRAK

Latar Belakang dan Objektif

Kecederaan otak trauma adalah punca utama kematian dan kecacatan pada masa dewasa muda sebagai masalah kesihatan awam utama. Endokrinopati selepas trauma telah dilaporkan sebagai salah satu komplikasi TBI yang menyebabkan defisit fizikal dan mental yang serius. Walaupun banyak kajian yang menumpukan pada kekurangan pituitari anterior, fungsi pituitari posterior pada mangsa yang selamat dari TBI kekal disiasat dengan baik. Oleh itu, matlamat kajian ini adalah untuk menilai masalah natrium dalam fasa awal dan kronik TBI dan protokol yang dicadangkan untuk pengenalan awal dan rawatan segera masalah natrium.

Kaedah

Ini adalah kajian kohort membujur pusat tunggal. Jumlah 270 pesakit yang berumur di antara 18 hingga 65 tahun dengan GCS 3-13 yang memenuhi kriteria telah dimasukkan ke Jabatan Neurosurgeri, HSAJB dari 1 Januari 2018 hingga 31 Disember 2018. Pesakit akan diuruskan berdasarkan protokol yang dicadangkan. Data demografi: umur pesakit, jantina, mekanisme kecederaan, jenis kecederaan kepala dan jenis campur tangan akan dinilai. Serum dan urine Osmolality akan diperolehi jika pesakit mengalami hypernatremia dengan poliuria (serum Na> 145). Jika pesakit mengalami hyponatremia (serum Na <130), osmolality serum dan urine, urine Na, serum kortisol dan ujian fungsi tiroid akan diperolehi. Semua pesakit yang mengalami awal DI dan yang mengalami gejala DI semasa susulan klinik, akan tertakluk untuk ujian kekurangan air pada 6 bulan selepas TBI

Keputusan

36 pesakit (13.3%) mengalami DI dalam fasa awal TBI dengan usia 31.4 (± 12.6) tahun dengan 35 pesakit yang mengalami kecederaan otak yang teruk. GCS median adalah 6. Purata permulaan DI dalam fasa akut TBI ialah 2.0 hari (± 1.0), julat natrium serum semasa permulaan DI adalah 149-162 mmol / l dengan natrium 153.5 mmol / l (± 3.3). Untuk hari normalisasi tahap natrium, min ialah 4.5 hari (± 1.7). Dari regresi logistik berganda (Jadual 6), kecederaan pada asal tengkorak ($p < 0.001$), edema serebrum ($p = 0.040$) dan skor GCS ($p = 0.009$) adalah signifikan. Ini menunjukkan bahawa asas fraktur tengkorak, edema serebrum dan skor GCS adalah faktor yang dikaitkan ke arah DI tanpa mengira kewujudan polytrauma dan SAH di tangki basal. 2 pesakit mempunyai WDT yang tidak normal pada 6 bulan selepas TBI. Kadar kematian bagi DI akut ialah 13%

24 pesakit (8.9%) membangunkan SIADH dalam fasa akut TBI dengan semua pesakit yang mengalami kecederaan kepala yang teruk dengan kecekapan adrenal dan tiroid yang diketepikan. Median GCS ialah 6. Kegagalan awal natrium abnormal adalah 7.7 hari (± 3.4), pelbagai natrium serum semasa permulaan SIADH adalah 114-128 mmol / l dengan natrium min 125.3 mmol / l (± 2.9). Hanya satu faktor yang berkaitan dengan SIADH yang merupakan edema serebrum ($p = 0.018$) apabila diselaraskan ATAU bagi kedua-dua faktor yang menggunakan ujian regresi logistik multivarian (Jadual 8). Semua SIADH diselesaikan terlebih dahulu dan tidak ada kes baru yang didiagnosis SIADH. CSW dilihat dalam 3 pesakit dengan natrium serum 120 atau kurang dengan natriuresis.

Kesimpulan

Hasil kajian menunjukkan kekerapan gangguan natrium dalam fasa awal dan kronik TBI dan dapat menentukan faktor-faktor penting yang berkaitan dengan DI dan SIADH pada fasa awal TBI. Oleh itu, pengiktirafan awal dan rawatan segera dengan protokol rawatan

yang betul adalah sangat penting untuk mengurangkan morbiditi dan mortaliti ketidakseimbangan natrium. WDT adalah ujian yang paling baik untuk membezakan DI tengkorak dari nefrogenik dan pengenalan tengkuk parsial atau teruk dalam fasa kronik TBI.

Kata kunci

Kecederaan otak trauma; diabetes insipidus; SIADH; sindrom pembuangan garam serebrum; ujian kekurangan air

ABSTRACT

Background and Objective

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults remain a major public health concern (1–3). Post-traumatic endocrinopathy has been reported as one of the complications TBI which causes serious physical and mental deficit (4–6). While many studies focus on anterior pituitary insufficiency, the function of posterior pituitary in survivors of TBI remains poorly investigated. Hence, the aim of this study is to evaluate the sodium abnormality in patients in the acute and chronic phase of TBI and a proposed protocol that was developed for the early identification of sodium abnormality for prompt treatment.

Methods

This was a single centre longitudinal cohort study. A total of 270 patients aged between 18 to 65-year-old with Glasgow Coma Scale (GCS) 3-13 who fulfilled the inclusion criteria admitted to the Department of Neurosurgery, Hospital Sultanah Aminah (HSAJB) from 1st January 2018 to 31st December 2018 were included. Patients were managed based on the proposed protocol. Demographic data: age of patients, gender, mechanism of injury, types of head injury and types of intervention were evaluated. Serum and urine Osmolality were obtained if the patients developed hypernatremia with polyuria (serum Na >145). If the patients developed hyponatremia (serum Na < 130), serum and urine osmolality, urine Na, serum cortisol and thyroid function test was obtained. All the patients who were diagnosed with acute diabetes insipidus (DI) and who developed symptoms of DI during clinic follow-up, were subjected for water deprivation test at 6 months post TBI

Results

In all 36 patients (13.3%) developed DI in the acute phase of TBI, with a mean age 31.4 (± 12.6) year old with 35 patients suffering severe head injury. The median GCS was 6. The mean onset of DI in the acute phase of TBI was 2.0 days (±1.0), the range of serum sodium during onset of DI was 149-162 mmol/l with mean sodium 153.5 mmol/l (±3.3). For the day of normalization of sodium level, the mean was 4.5 days (±1.7). From the multiple logistic regression (Table 6), base of skull fracture ($p<0.001$), cerebral oedema ($p=0.040$) and GCS score ($p=0.009$) were significant. This indicated that the base of skull fracture, cerebral oedema and GCS score are associated factor towards DI regardless of the existence of polytrauma and SAH at basal cistern. Two patients had abnormal WDT at 6 months post TBI. The overall mortality rate for acute DI is 13%

A total of 24 patients (8.9%) developed Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) in the acute phase of TBI with all patients suffering severe head injury with adrenal and thyroid sufficiency being ruled out. The median GCS was 6. The mean onset of sodium abnormality was 7.7 days (±3.4), the range of serum sodium during onset of SIADH was 114-128 mmol/l with mean sodium 125.3 mmol/l (±2.9). Only one factor associated with SIADH, which is cerebral oedema ($p=0.018$) when adjusted OR for both factors using multivariate logistic regression test (table 8). All SIADH resolved prior discharge and there was no new case of SIADH being diagnosed. Cerebral salt wasting (CSW) syndrome was seen in 3 patients with serum sodium 120 or less with natriuresis.

Conclusion

Study results showed significant frequency of sodium disorder in acute and chronic phase of TBI and it was possible to determine the significant factors that were associated with DI and SIADH at the acute phase of TBI. Hence, early recognition and prompt

treatment with proper treatment protocol is extremely important in order to reduce the morbidity and mortality of sodium imbalance. Water deprivation test (WDT) is a gold standard for differentiation of cranial DI from nephrogenic and identification of partial or severe cranial in chronic phase of TBI.

Keywords

Traumatic brain injury; diabetes insipidus; SIADH; cerebral salt wasting syndrome; water deprivation test

1. INTRODUCTION & LITERATURE REVIEW

Traumatic brain injury (TBI) is an insult to the brain from an external force causing temporary or permanent neurological dysfunction, that neither due to degenerative nor congenital conditions (6,7). It is the leading cause of death and disability in young adults with resultant consequences that range from physical disabilities to long term cognitive, behavioural, psychological and social defect (7,8). TBI is also often referred as the "silent epidemic" and it remains as a major public health concern, and it is a major cause of mortality and morbidity in developed and developing countries (1–3). It was estimated that approximately 69 million people suffer from TBI each year with the greatest proportion from Southeast Asia and Africa (both 56%) and lowest proportion from North America (25%) (1). In the developed world, North America and Europe the estimated incidence is 1,299/100,000 and 1,012/100,000 per year, respectively (1,9). People who suffered from TBI are those aged between 15-30 years old, children less than 5 year old and those more than 75 year old (5). Males are twice as likely to experience TBI compared to females (5). The major causes of TBI cases are due to road traffic accidents (RTA) (50%) followed by falls (30%) and violence-related injuries (20%) (5). Head injury was the fifth (7.86%) commonest cause of hospitalization in Malaysian public hospitals in 2014 with RTA being the commonest cause of injury-related hospitalization (10). In the Global Status Report on Road Safety 2013 of the World Health Organization (WHO), the road traffic fatality rate in Malaysia was higher than the global rate (25 versus 18 per 100,000 population)(10). The number of admissions of into the department of Neurosurgery, Hospital Sultanah Aminah (HSAJB) was about 998 cases and 982 cases each in 2016 and 2017. Out of the 998 cases of head injury cases, severe head injury comprised 335 cases and moderate head injury comprised of 102 cases. For 2017, there were 324 cases with severe head injury and 98 cases with moderate head injury (11,12).

Survivors of TBI sustained multiple complications such as impaired movement, cognitive deficit, seizure or hydrocephalus (4). Post-traumatic endocrinopathy (PTE) has been reported as one of the complications as TBI causes serious physical and mental deficit (4–6). PTE was first reported in 1918 and was originally thought to be a rare complication (13). However, since then many studies reported a wide range of incidence rates from 2% to 90%(4,14–18). The pituitary gland is located within the bony sella turcica which is lined superiorly by the diaphragmatic sellae. About 70-90% of the blood supply to the anterior lobe of the pituitary is derived from the superior hypophyseal artery which is a branch of the ophthalmic portion of internal carotid artery (ICA) and this artery forms the hypophyseal portal circulation that carries hypothalamic neuropeptides from hypothalamus to adenohypophysis. However, the blood supply to the small part of adenohypophysis and entire neurohypophysis are derived from inferior hypophyseal artery which is the branch of meningohypophyseal trunk of the cavernous portion of ICA.

There are a few proposed mechanisms of injury that ultimately lead to pituitary insufficiency. These include compression of the long hypophyseal vessels, pituitary gland or hypothalamus by oedema, haemorrhage, skull fracture, raised intracranial pressure or any cause of hypoxic insult(13,19). The mechanisms above cause anterior pituitary infarction which lead to anterior pituitary insufficiency. The inferior hypophyseal blood vessels are not transacted with stalk ruptured hence the posterior pituitary infarction is not common. However, injury to the paraventricular and supraoptic nuclei of hypothalamus, pituitary stalk or the axon terminals of the posterior pituitary can result in denervation which ultimate lead to diabetes insipidus (DI) (5,17,19). Inflammatory oedema around the hypothalamus or the posterior pituitary may also result in DI, which recovers once the oedema is resolved(5,17,19).

While many studies have evaluated the anterior pituitary insufficiency in survivors of TBI, the posterior pituitary function remains poorly investigated. Posterior pituitary comprises of Anti-diuretic hormone (ADH) and oxytocin. Serum ADH is measured biochemically via serum and urine osmolarity or serum ADH itself. However, oxytocin is not related to traumatic brain injury and the testing of oxytocin is usually complicated as it is not confined to only one. ADH is produced by the supraoptic nuclei in hypothalamus which then migrates along the axons to the posterior pituitary gland where it is stored as granules and secreted in the circulation when stimulated. It is regulated by plasma osmolality(20). ADH acts on the vasopressin receptors (three subtypes of vasopressin receptors V1a, V1b and V2) and it stimulates the V2 receptor to promote the expression of specific water channel proteins (aquaporins) on the luminal surface of the collecting duct(20). Serum ADH dysregulation will lead to either hypernatremia or hyponatremia which is also known as disorder of sodium balance.

Disorder of sodium balance, in particular DI and SIADH are the commonest medical complications in the acute phase of head injury. DI is a well-recognized complication of TBI. Acute DI is usually due to indirect mechanism which is small vessel damage or inflammatory oedema during acute traumatic brain injury. However, patients with partial DI can be easily missed due to lack of severe symptoms and their clinical course of DI which is often complicated with significant neurological and cognitive disabilities. In the acute phase, the percentage of patients developing cranial DI again varies markedly between studies, ranging from 2.6% to 51%(20,21). This wide range of prevalence might be due to differences in the diagnostic criteria used, characteristic of study population and time of evaluation(20). In two series of cases by Agha et al., 21.6%-26% of the patient developed post-traumatic DI in acute setting which is a relatively high prevalence. Of those, 7 persistent DI after confirmation with water deprivation test(14,15). Amaretti et

al who re-examined 100 patients with TBI at 3 months, 6-9 months, 12 months and 17 months, found that only 4% had DI at 3 months and 1.4% – 8% at 6 months and beyond(22). Hadjizacharia et al., reported that 15.4% of the TBI cases were diagnosed with post-traumatic DI, mostly in the first few days after the injury (mean 1.2 days)(23). Furthermore, in a series of cases by Benvenga et al., 20% of the post traumatic brain injury hypopituitary patients also developed transient DI(24). Boughey et al. found a prevalence of 2.9% but in their series of cases only severe cases were included(25). In the prospective study of severe traumatic brain injury patients, 28% developed acute DI(26). Most cases of acute post-traumatic DI were transient in nature (usually 3 to 5 days) and permanent DI were considered as rare occurrence. In the study of Agha et al, the onset of DI was on day 1 to 3 in 11 patients, day 5 on 1 patient and day 11 in one patient(14,15). Hadjizacharia et al reported that the mean of onset of DI was 1.7 days(23). Retrospective case note analysis in the same patient cohort revealed that 22% that have acute DI was closely related to severity of head injury, base of skull fracture and cerebral oedema. Agha et al concluded that acute DI was associated with lower GCS scores and cerebral oedema but not related to age, gender, BMI, operative mass evacuation, diffuse injury or basal skull fractures(14,15). Diagnostic criteria for DI are plasma sodium >145 mmol/l, in the presence of polyuria more than 3 litre/24 hour or more than 3cc/kg/hour for 3 consecutive hours, dilute urine (urine osmolality <300 mOsm/kg) and serum Osmolality > 300 mOsm/kg(14,15,20,27).

Water Deprivation test (WDT) is a common, dynamic and semiquantitative test done in Endocrinology units for the assessment the ability of the kidney to concentrate urine when fluids are withheld. This test also used as an investigation of suspected cranial or nephrogenic diabetes insipidus and primary polydipsia(29). WDT is rarely done in post-traumatic DI since most cases are transient and chronic DI is rare. Hence, the purpose of

WDT in this study is to identify incidence of chronic or partial DI in patients who has been diagnosed with DI in the acute phase(30,31). The measurement of urinary osmolality at the end of WDT and post desmopressin (DDVAP) administration is usually referred to as “indirect testing” because ADH secretion is indirectly assessed through changes in urinary osmolalities(30). The patient is maintained on a complete fluid restriction regimen until urinary osmolality reaches a plateau, as indicated by an hourly increase of less than 30 mOsmol/kg for at least three successive hours. After measuring the serum osmolality, 2 mg of DDAVP is then administered subcutaneously. Urinary osmolality is measured again 60 minutes later. The last urinary osmolality value obtained before the DDAVP injection and the highest value obtained after the injection are compared. In patients with severe neurogenic DI, urinary osmolality after dehydration is usually low (<300 mOsmol/kg) and increases more than 50% after DDAVP administration. In patients with severe nephrogenic DI, the urinary osmolality after dehydration is also low (<300 mOsmol/kg) but does not increase after the administration of DDAVP. In patients with partial cranial DI, urinary osmolality increases to variable degrees (10 to 50%) after administration of DDAVP(30,31). In patients with primary polydipsia, maximum urinary osmolality will be obtained after dehydration (>295 mOsmol/kg) and does not increase after administration of DDAVP (<10%)(30,31).

The common causes of hyponatremia in TBI are inadequate salt intake, hypopituitarism, SIADH and CSW(32). Differentiation between SIADH and CSW is made based on the hydration status of TBI patients. About 15% of patients recovering from head injury develop hyponatremia in the acute phase of head injury(33). In 80% of these cases, hyponatremia is due to SIADH(28). Although ACTH deficiency occur in approximately 15% of head injury cases in acute recovery phase, hyponatremia rarely due to glucocorticoid insufficiency. SIADH has been reported with a prevalence of 2.3% to

36% in patients with TBI(16,34–37). In a retrospective study conducted by Rajagopal R et al, findings showed that the prevalence of 13% of patients with hyponatremia are with natriuresis(32). A prospective study by Aghe et al showed that 12.7% of their patients with TBI developed SIADH with a median plasma sodium of 128mmol/liter (range between 118-131)(15). The onset of SIADH is usually between day 3 to day 8(about 92%) and only 8% of patients developed SIADH on day 18(14,15). After treatment for SIADH has commenced, median time for sodium normalization (more than 130 mmol/l) is about 7 days (range from 2 to 26 days)(14). Prospective data on cohort study of 50 patients with TBI showed that 14% had acute hyponatremia but none had hyponatremia at 6 or 12 months after head injury(15). Chronic hyponatremia is rare and is usually associated with usage of drugs such as carbamazepine(28). It was reported that SIADH was closely related to low GCS and cerebral oedema. However, from Agha et al, multiple logistic regression analysis was failed to prove the association between SIADH with other variables such as age, BMI, gender, GCS, diffuse brain injury, the presence of cerebral oedema or operative mass evacuation(14,15). The diagnostic criteria for SIADH are serum sodium < 130mmol/L, decreased effective serum osmolality (<275 mOsm/kg of water) with simultaneous urine Osmolality > 100 mOsm/kg water, urine Na more than 40 mEq/l with normal dietary intake, clinically euvolemia, cardiac, hepatic, renal, thyroid or adrenal failure had been ruled out, normal thyroid and adrenal function and no recent diuretic use(14,15,27).

CSW is characterized by renal loss of sodium due to intracranial pathology, resulting in hypovolemia and hyponatremia(38–40). Until now, the mechanism leading to CSW remained poorly understood and there is no single aetiology proven to be the only cause of CSW(39). The hypothesis is that development of CSW as a result of increased levels of natriuretic peptides and changes in sympathetic nervous system, the renin-angiotensin-

aldosterone system and adrenomodulin(39). CSW has rarely been studied in patients with TBI. Most of the literature reviews on TBI are based on case reports, reviews and cohort studies that focus on the incidence, aetiology and biochemical changes(39). The incidence of CSW post TBI ranged from 0.8 to 34.6%(39,41). Study by Agha et al showed that CSW only had incidence about 1% with the onset of CSW was 8 days post TBI(14,15). There is much variation in the duration of time from injury to the development of CSW. Moro et al reported that most patients with TBI developed hyponatremia within 3 days of injury(33) whereas Lohani et al reported that CSW developed in the late first week and early in the second week(13). However, none of these cohort studies stated the timing of surgery performed in relationship to the development of CSW and timing of injury to the onset of CSW(39). In the case report of Lu DC et at, it was reported that one patient developed CSW 1-week post injury whereas the occurrence in another patient was not specified(42). CSW may be over diagnosed unless certain measurements are taken into account to exclude a number of circumstances which are not commonly seen in neurosurgical units. There are still lack of well-defined diagnostic criteria for CSW. Leonard et al(39) recommended that number of criteria should be fulfilled before a diagnosis of CSW is made: The presence of brain pathology, new onset of hyponatremia(validated by at least one simultaneously low serum osmolality), hypovolaemia based on clinical assessment of intravascular volume, urinary salt loss. Despite criterias being given, there is no definite cut-off value for each criterion. Hence, diagnostic criteria for CSW has been established for this prospective study: presence of new brain pathology, serum sodium <125mmol/L with low serum osmolality <275 mOsm/kg of water, urine Na more than 40 mEq/l despite excessive intake, clinically hypovolaemia (tachycardia >100 and CVP less than 6 cm H20), normal thyroid and adrenal function and no recent use of diuretic medications

2. STUDY PROTOCOL

This was the single centre prospective longitudinal cohort study where moderate and severe head injury patients graded according to GCS who were admitted to the Hospital Sultanah Aminah, Johor Bahru from 1st of January 2018 to 31st of December 2018. The aim of this study was to evaluate the incidence of sodium imbalance of TBI patients in the acute and chronic phases. The inclusion criteria for patients in this study were those aged between 18 to 65 years, GCS 3-13 regardless of CT brain findings, polytrauma, were at least 6 months post TBI and having motor score of 6 for WDT. The exclusion criteria were namely: pregnant women; patients with established chronic kidney disease; those with raised creatinine levels of more than 120; patients on lithium or other medications which is known to cause renal insensitivity; patients with uncontrolled diabetes with blood glucose levels more than 10 mmol/l; hypokalaemia or hypercalcemia; patients with GCS 3/15 and fixed and dilated pupils; and finally patients with established heart diseases regardless types.

A treatment protocol was developed in managing patients who sustained TBI and subsequently encountered of sodium abnormality (Figure 1,2 and 3) according to the diagnostic criteria. Protocol for WDT also developed based on various references.

Approval was obtained from the Medical Research & Ethics Committee of the Ministry of Health Malaysia and registered in the national register for clinical trials registration ID: NMRR-17-3310-38100.

Sample Size

Universal sampling was used in this study. All the adult patients who were aged from 18 to 65-year-old with GCS 3-13 who were admitted to the neurosurgical

department, Hospital Sultanah Aminah from 1st of January 2018 to 31st December 2018 was included in the study based on the inclusion and exclusion criteria.

Declaration of Interest Conflict

There was no conflict of interest in this study. The standard operating procedure of management of severe and moderate head injury was incorporated into this study protocol. Only one procedure, the Water Deprivation Test (WDT) was not routine. However, WDT is a standard and dynamic test to differentiate the neurogenic DI from nephrogenic DI and those patients suspected of chronic and subtle DI. The only risk of water deprivation test is dehydration. However, the following measures were taken (as stated above) to ensure the safety of the patient:

a) WDT will NOT be carried out if serum osmolality >300 mOsm/kg (patients admitted one day earlier and serum and urine Osmolality will be taken);
b) Lost more than 5% of body weight;
c) If serum Osmolality more than 300 mOsm/kg during testing; and
d) PR more than 100 or BP less than 90/60

Hence with strict monitoring via clinical parameters and also biochemically, the risk of study to the patients was minimal. This study provided direct benefit to the participants as the early phases of diagnosis, prompt treatment, proper follow-up and detection of potential chronicity of the disease.

This study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki (2013) and the Malaysian Good Clinical Practice Guideline (2016). Approval was obtained prior to the initiation of this study. As this was a prospective study, therefore the consent of patients and their relatives were obtained. Names of patients was kept in a password-protected database and linked only via a study identification number during this research. The patient identification numbers rather than

patient identifiers was used on data sheets. All data was entered into a computer that was password protected. On the completion of this study, the data in the computer will be copied to a USB drive and other softcopies will be erased while the hardcopy data will be kept and locked in the office cabinet located in the Department of Neurosurgery, Hospital Sultanah Aminah for 3 years, after which time, the data will be removed permanently.

TITLE PAGE

DISORDERS OF SODIUM BALANCE AFTER TRAUMATIC BRAIN INJURY IN ADULT PATIENTS: A PROSPECTIVE STUDY IN A SINGLE CENTRE

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3.2 Abstract

Background and Objective

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults remains a major public health concern in the developed and developing countries(1–3). Post-traumatic endocrinopathy which still remains poorly investigated and has been reported as one of the complications TBI which results in serious physical and mental deficit(4–6). This study is to evaluate the sodium abnormality in the acute and chronic phase of TBI in adult patients and a protocol is proposed for the early identification and prompt treatment and management of sodium abnormality.

Methods

This was the single centre longitudinal cohort study. A total 270 patients aged between 18 to 65-year-old admitted to Department of Neurosurgery, Hospital Sultanah Aminah Johor Bahru (HSAJB) from 1st January 2018 to 31st December 2018. with Glasgow Coma Index (3-13) who fulfilled the inclusion criteria were included in the study. Demographic data were obtained: age of patients, gender, mechanism of injury, types of head injury and types of intervention to be evaluated. Serum and urine Osmolality were obtained if patients developed hypernatremia with polyuria (serum Na >145). If the patients developed hyponatremia (serum Na < 130), serum and urine osmolality, urine Na, serum cortisol and thyroid function test were done. All the patients who were diagnosed acute diabetes insipidus (DI) and who later developed symptoms of DI during clinic follow-up, were subjected to water deprivation test at 6 months post TBI

Results

In all 36 patients (13.3%) developed DI in the acute phase of TBI with mean age of 31.4(± 12.6) year old and 35 patients suffered severe head injury. The median GCS was 6. The mean onset of DI in the acute phase of TBI was 2.0 days (±1.0), the range of serum sodium during onset of DI was 149-162 mmol/l with mean sodium 153.5 mmol/l (±3.3). The mean of the day of normalization of sodium level, was 4.5 days (±1.7). From the multiple logistic regression (Table 6), the base of skull fracture was ($p<0.001$), cerebral oedema ($p=0.040$) and GCS score of ($p=0.009$) were significant. This indicates that base of skull fracture, cerebral oedema and GCS scores are associated factors towards DI regardless the existence of polytrauma and SAH at basal cistern. Two patients had abnormal WDT at 6 months post TBI. The mortality rate for acute DI is 13%

A total of 24 patients (8.9%) developed Syndrome of Inappropriate Anti-diuretic hormone (SIADH) in the acute phase of TBI with all patients suffering severe head injury with adrenal and thyroid sufficiency being ruled out. The median GCS was 6. The mean onset of sodium abnormality was 7.7 days (±3.4), the range of serum sodium during onset of SIADH was 114-128 mmol/l with mean sodium 125.3 mmol/l (±2.9). Only one factor was associated with SIADH which is cerebral oedema ($p=0.018$) when adjusted OR for both factors using multivariate logistic regression test (table 8). All SIADH resolved prior discharge of patients and there was no new case of SIADH diagnosed. Ceberal Salt wasting syndrome (CSW) was seen in 3 patients with serum sodium 120 or less with natriuresis.

Conclusion

This study showed that significant frequency of sodium disorders occur in acute and chronic phase of TBI and we were able to determine the significant factors that are associated with DI and SIADH during the acute phase of TBI.

Keywords

Traumatic brain injury; diabetes insipidus; SIADH; cerebral salt wasting syndrome; water deprivation test

3.3 Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults with the injuries ranging from physical disabilities to long term cognitive, behavioural, psychological and social defects(7,8) and is one of the major cause of mortality and morbidity in the developed and developing countries(1–3). Head injury was the fifth (7.86%) commonest cause of hospitalization in Malaysian public hospitals in 2014 with road traffic accident (RTA) being the commonest cause of injury-related hospitalization(10).

Post-traumatic endocrinopathy has been reported as one of the complications TBI which cause serious physical and mental deficit(4–6). While many studies have evaluated the anterior pituitary insufficiency, posterior pituitary function in survivors of TBI remained poorly investigated. Disorders of sodium balance, DI and SIADH are well recognised in the acute phase of head injury. While most of the sodium disorders appeared to be transient, chronic DI and SIADH are rare.

Hence, the purpose of this study was to evaluate the incidence of sodium disorders in adult patients in the acute and chronic phase of TBI and the association risk factors. This study is also aimed to develop a treatment protocol for such disorders.

Water Deprivation test (WDT) is a common, dynamic and semiquantitative test done in Endocrinology unit for the assessment of the ability of kidneys to concentrate urine when fluids are withheld. It is rarely done in post-traumatic DI because in most cases they are transient and chronic DI is rare. Hence, the purpose of WDT done in this study is to

identify incidence of chronic or partial DI in adult patients who has been diagnosed DI in acute phase(30,31).

3.4 Methodology

3.4.1 Research design

This was the single centre prospective longitudinal cohort study where patients with moderate and severe head injury based on GCS admitted to the Department of Neurosurgery, Hospital Sultanah Aminah (HSAJB), Johor Bahru who fulfilled the inclusion criteria. The aim of this study was to evaluate the incidence of disorders of sodium balance in adult patients who sustained severe head injury and moderate head injury. In addition to that, this study aimed to develop a treatment protocol for sodium disorders in the Neurosurgical department, Hospital Sultanah Aminah.

Approval for this study was obtained from the Medical Research & Ethics Committee of the Ministry of Health Malaysia and registered in the national register for clinical trials registration ID: NMRR-17-3310-38100.

3.4.2 Research location and duration

Patients who fulfilled the inclusion criteria among those admitted to Department of Neurosurgery HSAJB for the treatment of severe head injury and moderate head injury during the period of 1st of January 2018 to 31st of December 2018. HSAJB was the first trauma centre to be established in Malaysia and is tertiary referral centre for the southern region of peninsular Malaysia, consisting of a multidisciplinary team in providing trauma services, including TBI. The Department of Neurosurgery, HSAJB is the only neurosurgical centre on southern region with 2 operative theatres, 10-beds NeuroHDU and 2 neurosurgery wards with 30 beds. Apart from that, this centre is led by consultant

neurosurgeons who able to facilitate the treatment of TBI and provide guidance in terms of surgical skills and academic expertise to all the residents in his region.

3.4.3 Study population and sample size

Universal sampling was used in this study. All the adult patients after RTA admitted to the neurosurgical department, were included based on the inclusion and exclusion criteria. The inclusion criteria for patients were those aged between 18 to 65 years, GCS 3-13 regardless CT brain findings, polytrauma, who were at least 6 months post TBI and motor score of 6 for WDT. The exclusion criteria were: pregnant woman, patients with established chronic kidney diseases, patients with raised creatinine of more than 120, patients who are on lithium or other medications which are known to cause renal insensitivity, patients with uncontrolled diabetes with blood glucose level of more than 10 mmol/l, hypokalaemia or hypercalcemia, patient with GCS 3/15 and fixed and had dilated pupils and patients with established heart diseases regardless the types.

3.4.4 Method of research

Details of all patient who were admitted were entered into data collection form (Appendix 1). Proposed treatment protocols were then developed for patients with normal sodium (Figure 1), hypernatremia, (Figure 2) and hyponatremia (Figure 3). Apart from that the diagnostic criteria of DI, SIADH and CSW(9,14,15,20,27,39) was discussed with the endocrinologist and chemical pathologist. This information is summarized in Table 1. Result of serum and urine osmolalities (osmo) were endorsed by the chemical pathologist prior to being released.

Once patients are admitted to the Neurosurgical HDU/ward, daily I/O chart and plasma sodium was obtained for the duration of their hospital stay. If sodium and urine

output of the patients were normal, patients were discharged and followed-up at neurosurgical clinic on the 1st, 3rd and 6th month post-trauma. During the follow-up clinic, patients were evaluated for symptoms of hypernatremia or hyponatremia by assigned medical personnel. Serum Na was obtained if patients had symptoms of hypernatremia or hyponatremia. If there was evidence of hypernatremia (Na more than 145) or hyponatremia (Na less than 130), their serum and urine osmo was taken for confirmatory diagnosis of DI, SIADH or CSW. Once the diagnosis was confirmed, patients were referred to the endocrinologist and managed accordingly. If there was evidence of DI during follow-ups, patients were then subjected for WDT at post-trauma 6 months.

For patients with hypernatremia (Na > 145) with concurrent polyuria (more than 3cc/kg/hour for 3 consecutive hours) diuretic such as mannitol was given in order to determine if osmotic diuretic was present. Once mannitol was given, serum Na was repeated after 48 hours. If serum Na persisted to be more than 145 (after 48 hours of last dose of mannitol), serum osmolality and urine osmolality were taken. If diagnostic criteria were not fulfilled, other causes of hypernatremia were looked for and serum Na was repeated at post trauma day 7 to day 21 based on the clinical symptoms of the patients. If DI was confirmed based as on the criteria on Table 1, the patient was referred to the endocrinologist and treatment commenced based on the severity of hypernatremia and urine output. If the was Na less than 155, fluid replacement was started based on the clinical parameters (pulse rate, urine output and CVP monitoring). Fluid replacement usually resolved DI if Na is less than 155. If the sodium level was more than 155, sodium correction was started by using D5 or water followed by stat dose of s/c desmopressin while monitoring of the clinical parameters and CVP status. Once the condition is resolved, the patient was then followed-up in the Neurosurgical clinic on 1st, 3rd and 6th

months post trauma. During each of the follow-up, patients were monitored for symptoms of DI and serum sodium was obtained. If serum Na was found to be abnormal, patients were admitted to ward for further evaluation of serum and urine osmolality. Patients who developed DI in acute phase, were subjected to water deprivation test on 6th month post-traumatic brain injury.

If patients developed hyponatremia (Na < 130), Determination whether osmotic diuretic such as mannitol was given. If mannitol was given, serum Na was repeated after 48 hours. This is because mannitol infusion can cause hyponatremia and elevated serum Osmo whereas hypertonic saline can cause hypernatremia and elevated serum Osmo(43–45). If serum Na still persistently less than 130 (after 48 hours of last dose of mannitol), serum osmolality and urine osmolality were checked for further evaluation. If diagnostic criteria were not fulfilled, other causes of hypernatremia were sorted out and serum Na was repeated at post trauma day 7 to day 21 based on the clinical symptoms of the patients. SIADH or CSW will be diagnosed based on criteria listed on Table 1. Once diagnosis was confirmed, the patient was referred to the endocrinologist and treatment commenced. For patients with SIADH, fluid restriction was commenced but sodium replacement was only carried out based on the severity of the sodium levels. For CSW, fluid resuscitation was started and sodium replacement carried out based on the severity of the sodium levels. Once the hyponatremia resolved (Na > 130), serum osmolality and urine osmolality were repeated 24 hours after the treatment being stopped. Once SIADH resolved, patient was followed-up in the neurosurgical clinic on the 1st, 3rd and 6th month. During each follow-up, patients were monitored for symptoms of hyponatremia and serum sodium was obtained. If Serum Na was found to be abnormal, patients were admitted to the ward for further evaluation.

WDT was performed in all patient who developed DI in the acute phase of TBI. This procedure was modified based on the Malaysian's Endocrine protocol, Hospital Putrajaya, Department of clinical biochemistry, North Bristol NHS and Department of Biochemistry, Sandwell and West Birmingham NHS Trust(46–48). Not all trauma patients underwent water WDT. Patient will be tested at 6 months post traumatic brain injury if they: developed DI in acute phase, developed polydipsia and polyuria with suspicious of cranial DI during follow-up in neurosurgical clinic based on figure 1 and 2, and motor score at least 6 with ability to obey simple commands. Testing was done in Neurosurgical ward, HSAJB which monitored by the primary investigators and the endocrinologist. The aim of this test was to determine whether the patient has developed neurogenic DI in chronic phrase of traumatic brain injury and also determine the severity whether it was partial or severe based changes in urine osmolality.

For procedure of WDT, patient was admitted a day earlier. The patient was advised to avoid nicotine and caffeine for 48 hours before this procedure. At 10.00 pm, the patient was weighed and the plasma and urine sample were collected for osmolality. The procedure was only conducted if the serum osmolality was less than 295 mOsm/kg. If the serum Osmolality was more than 300 mOsm/kg and urine osmolality less than 300 mOsm/kg, DI was confirmed and no further testing was needed. Fluid was allowed until 7 am on the day of procedure. Procedure began at 8.00am and ended at 4pm. At 8.00am, the weight of patient was documented again. Serum Na, serum and urine osmolality was measured every 2 hours (0800, 1000, 1200, 1400 and 1600) Apart from that, hourly urine output and patient's weight were documented. Patient's vital signs (blood pressure and pulse rate) were closely monitored. S/C desmopressin 2mcg if: urine osmolality was stable (a change of less than 30mOsmol/kg for 3 successive sample), urine osmolality still less than 750 mOsm/kg at 4pm, patient lost more than 3% of body weight. One hour

after s/c desmopressin. Serum Osmo and urine Osmo were taken and for subsequent interpretation. All the information was documented in WDT form (Appendix 2). Interpretation of water deprivation test is summarized in table 2(30,31). This procedure was terminated if the patient: lost more than 5% of their body weight, serum osmolality > 300 mOsm/kg, if blood pressure was less than 90/60 and PR >100. The contra-indication for water WDT was hypernatremia, evidence of dehydration, confirm diabetes insipidus and exclusion criteria of this study.

3.4.5 Statistical analysis

The data obtained was analysed using SPSS version 20. The descriptive statistic was used which categorical variables analysed by frequency and percentage while numerical variables was analysed by central tendency either mean, median, standard deviation and inter-quatile range. This analysis was presented in graph and table. The statistical analysis used in this study were chi square and logistic regression. They were used to test the association between two independent sample. In order to test the association between more than two independent sample and to identify the significant factors that associated with sodium imbalance, the binary logistic regression was used.

3.5 Results

3.5.1 Demographic and Clinical Characteristic

A total of 307 patients aged between 18 to 65-year-old with GCS 3-13 were admitted to the Department of Neurosurgery, HSAJB and of these 270 patients were enrolled into this study and 37 patients were excluded (Figure 4). Reason for exclusions (Table 3) were for the following reasons: pupils fixed and dilated (19 cases), uncontrolled DM (5 cases), CKD (6 cases), pregnancy (2 cases), long term medications used (2 cases) and established

heart diseases regardless types (3 cases). Clinical characteristic of patients being included (n=270) is summarized in Table 4. Of the 270 patients, 242 (89.6%) were males and 28 (10.4%) were females with a mean age of 32.75 ± 14.23. The male: female ratio was 8.6. There were 231 (85.6%) patients who sustained SHI (GCS 3-8) and 39 (14.4%), who sustained MHI (GCS 9-13). A total of 129 (47.8%) patients sustained polytrauma with TBI and 141(52.2%) patients only had isolated TBI. The mechanism of TBI showed that RTA in 241 (90.2%) patients, alleged fall in 18 patients (6.4%), assault in 3 patients (0.8%) and others in 8 patients (2.6%). Out of 270 patients, 50 (18.5%) patients were given treatment conservatively. The remaining 220 patients underwent surgical intervention with 104 (38.5%) decompressive craniectomy, 30 (11.1%) craniotomy and 86 (31.9%) ICP-guided management (Figure 5). 63 patients developed sodium abnormality during the acute phase of TBI: 36 (13.3%) patients with DI, 24 (8.9%) patients with SIADH and 3 (1.1%) patients with CSW.

3.5.2 Diabetes Insipidus

In all 36 patients (13.3%) developed DI in the acute phase of TBI and the mean age was 31.4(± 12.6) years old. Of 36 patients, 35 patients suffered severe head injury where the other one patient sustained moderate head injury. The median GCS of the patients was 6. The mean onset of DI in the acute phase of TBI was 2.0 days (±1.0) with 13 patients on day 1, 18 patients on day 2, 2 patients on day 3, 2 patients on day 4 and 1 patient on day 5. The range of serum sodium during onset of DI was 149-162 mmol/l with mean sodium 153.5 mmol/l (±3.3). For the day of normalization of sodium level, the mean was 4.5 days (±1.7). Table 5 indicates the clinical characteristic of DI. Based on univariate analysis (Table 5), acute DI was significantly associated with base of skull fracture ($p < 0.001$), cerebral oedema ($p < 0.001$), SAH at basal cistern ($p = 0.006$) and lower GCS

score (p <0.001). This study attempted to investigate to what extent base of skull fracture, cerebral oedema, SAH at basal cistern, polytrauma and GCS score were associated with DI. From the multiple logistic regression (Table 6), base of skull fracture (p<0.001), cerebral oedema (p=0.040) and GCS score (p=0.009) are significant. This indicates that base of skull fracture, cerebral oedema and GCS score were factors associated towards DI regardless the existence of polytrauma and SAH at basal cistern. The model fits with p-value of Homer and Lemeshow = 0.936 and R2 = 0.291. The AOR for base of skull fracture is 7.248 with 95 % CI (2.833, 18.543). Hence, patients with a base of skull fracture was 7.248 were more likely to experience DI compared than those patients who did not have base of skull fracture. Fracture of the base of skull has more impact towards DI compared with cerebral oedema and GCS score. Five (13%) patients who developed DI died in the acute phase of TBI within 3 days onset of the DI.

As for the treatment protocol stated in the methodology, all patients with DI were followed-up in the Neurosurgery clinic at 1st, 3rd and 6th months post TBI. During follow-ups, clinical symptoms and serum sodium were monitored. Out of the 36 patients, 5 patients were died during the acute phase TBI during the hospital stay, 2 patients defaulted follow-up after 2nd visit. A total of 29 patients who had DI in the acute phase of TBI were successfully followed-up till 6 months post TBI. Five patients were not proceeded for WDT due to refusal from family members. In all 24 patients underwent WDT and 22 patient had normal results in the WDT, 1 patient with partial cranial DI (changes in urine Osmo 10%-50% post DDAVP) and 1 patient with cranial DI (changes in urine Osmo >50% post DDAVP)(30,31). For the one patient who was diagnosed with partial DI, he sustained DI at the acute phase of TBI but was subsequently discharged with full GCS without any oral desmopressin. Rapid feeling of thirst, polydipsia and polyuria (about 2 litre/24 hour) were the main symptoms but serum sodium showed no abnormality. For

the patients with cranial DI, he was discharged with GCS with motor score of M5 which subsequently improved to M6 at 3rd month post-trauma. Upon discharge the patient was prescribed oral desmopressin by the endocrinology team. His serum sodium level was 150 at 1st month, 147 at 3rd month and 146 at 6th month. Oral desmopressin was withheld 24 hours prior to the WDT. No new DI was observed from the Non-DI group during follow-up. Median GOS at 6 months post TBI was 4 for patient who developed acute DI.

3.5.3 SIADH and CSW

Table 7 shows the clinical characteristic of SIADH**.** In all 24 patients (8.9%) developed SIADH in the acute phase of TBI with all patients suffering from severe head injury and mean age of 33.4 (± 12.6) year old. Their median GCS was 6. Thyroid and adrenal insufficiency were ruled out in these 24 patients. The mean onset of sodium abnormality in the acute phase of TBI was 7.7 days (±3.4) with 2 patients on day 4, 6 patients on day 5, 4 patients on day 6, 2 patients each on day 7, day 8, day 9 and day 10 and one patient each on day 11, day 12, day 15 and day 17. The range of serum sodium during onset of SIADH was 114-128 mmol/l with mean sodium 125.3 mmol/l (±2.9). For the day of normalization of sodium level, the mean was 3.9 days (±0.7). Based on univariate logistic regression test (table 7), only two factors were significantly associated with SIADH which are cerebral oedema ($p=0.002$) and GCS score ($p<0.05$). The OR of cerebral oedema and GCS score are 4.473 with 95 % CI (1.618, 12.360) and 0.762 with 95 % CI (0.612, 0.949) respectively. However, only one factors was associated with SIADH which was cerebral oedema ($p=0.018$) when adjusted OR for both factors using multivariate logistic regression test (Table 8). The OR for cerebral oedema was 3.511 with 95 % CI (1.238, 9.959). Hence, a patient with a cerebral oedema was 3.511 more

likely to experience SIADH compared than those patients who did not have cerebral oedema.

All patients with SIADH were followed-up in clinic at 1st, 3rd and 6th months post TBI. During follow-up, their clinical symptoms and serum sodium were monitored. Out of the 24 patients, 5 patients were transferred to other centres for further treatment and follow-up, 1 patient defaulted follow-up after 2nd visit and 1 patient during the first admission. In all 17 patients who sustained SIADH in the acute phase of TBI were successfully followed-up till 6 months post TBI. All the 17 patients with acute phase of SIADH had normal serum sodium and absence of clinical symptoms during follow-up. No new SIADH was detected during follow-up. Median GOS at 6 months post TBI was 3 for patient who developed SIADH in acute phase of SIADH

Three patients with severe head injury developed CSW at the acute phase of TBI. For the first patient who was 50-year-old gentleman, diagnosed at day 5 post TBI with serum sodium 120 mmol/l, serum osmo of 268 mOsmo/kg, urine sodium 143 mmol/l and hypovolaemia as evidence of polyuria more than 3 litre/24-day, PR range between 90-110 beats/minute and CVP 4-6 cm H20. The normalization of sodium for this first patient was 5 days after the onset. The second patient aged 43 years, developed CSW at 4 days after TBI with serum sodium 120, serum osmo of 264 mOsmo/kg, urine sodium 159 mmol/l and hypovolaemia as evidence of polyuria more than 3litre/day, PR range between 110-130 beats/minute, and CVP 3-5 cm H20. The normalization of sodium for the second patient was 4 days. The third patient with the age of 28-year-old, was diagnosed CSW at day 6 post TBI with serum sodium 118, serum osmo 261 mOsmo/kg, urine sodium of 201 mmol/l, polyuria more than 3l/day, PR range between 120-130, CVP 1-3 cm H20. The normalization of sodium for the third patient was 6 days. The second patient died at the acute phase of TBI and we managed to follow-up only 2 patients till 6