Conference Paper

Sodium Imbalance and Mortality Rate in Septic Patients

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Abstract

Sepsis is a life-threatening organ dysfunction caused by an irregular host response to infection. There are cytokines that regulate various inflammatory responses. Dysregulation of cytokines causes endothelial dysfunction, vasodilation and increased capillary permeability, then causes cellular leakage syndrome that interferes with regulation and intravascular hypovolemia, cellular dysfunction, and ultimately tissue death. As the main extracellular cation, sodium (Na) is the most osmotically active solute in the human body. Sodium is usually a parameter that is ignored, but it has a predictive value. This study aimed to evaluate the prognostic value of serum Na in adult patients with a diagnosis of sepsis.A total of 406 patients were diagnosed with sepsis during 2017 at Dr. Moewardi hospital. Data collection was performed in a retrospective cohort during the period of January-December 2017. Data distribution was evaluated by using Kolmogorov-Smirnov test, followed by Kruskal-Wallis analysis for comparison between groups and by using chi-square test. We determined the relative risk (RR) to assess the risk of death. We found that in patients with hypernatremia RR= 7.25 (95% CI 0.91-57.58; p = 0.03), in mild hyponatremia RR= 0.45 (95% CI 0.22 - 0.91; p= 0.02), both were comparable to healthy control. In conclusion, there is no significant difference in the risk of death between patients with hypernatremia group and normonatremia, serum sodium levels are not the main parameters that indicate the risk of death but can be used as a supporting parameter of risk of death in septic patients.

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1. Introduction

Critical diseases such as severe burns, trauma, sepsis, brain damage, and heart failure can cause fluid and electrolyte homeostasis. Acute disorders of sodium concentration in blood, or dysnatremia (hyponatremia and hypernatremia), are usually found in intensive care units (ICU) and have adverse effects on various organ systems especially through changes in plasma osmolality [1]. The prevalence of dysnatremia is around 10-20% of patients with critical illness [2] and the prevalence of hypernatremia around 25 - 45% varies around 25-45% according to the time of onset, threshold for diagnosis, and population [3]. The definition of hyponatraemia and hypernatremia varies in different

studies, but most studies defined hyponatraemia as a serum sodium level of less than 136 mmol/L, while hypernatremia is greater than 145 mmol/L [4].

Sepsis is defined as a life-threatening organ dysfunction caused by an irregular host response to infection. Clinical criteria for sepsis include suspected infection or documented and acute increase of two or more of Sequential Organ Failure Assessment (SOFA) as a reference for organ dysfunction. However, SOFA is a score calculation that has many variables so that it is less applicable for routine use [5].

In sepsis, there are cytokines that regulates various inflammatory responses. Dysregulation of cytokine release causes endothelial dysfunction, vasodilation, and increased capillary permeability which result in cellular leakage syndrome that interferes with fluid regulation and causes intravascular hypovolemia, cellular dysfunction, and finally tissue death. Hemodynamic changes in sepsis are directly related to endothelial disorders, tissue hypoxia, mitochondrial dysfunction, decreased oxygen delivery, and changes in blood flow [6]. Impaired renal function and the effects of fluid loss play important roles in the increase of BUN and creatinine. Moreovers osmotic diuresis due to the high concentration of urea in the blood can cause the kidneys losing free water thus increasing serum sodium levels [4]. Sodium levels are controlled by the mechanism of the arginine, kidney and brain vasopressin system. Abnormalities in serum sodium indicate a disturbance in the body's water balance. Such disorders can cause serious clinical manifestations including seizures, coma and even death [7].

As a major extracellular cation, sodium is the most osmotically active solute in the human body. Under normal conditions, serum sodium is maintained in the physiological range. Even mild hypernatremia or acute changes in serum Na, can trigger rapid changes in serum osmolality with poor results. So that it can give an explanation that sodium as a parameter that is usually ignored can have predictive values [3].

Several previous studies associated sodium levels with sepsis, but still have weaknesses. In their study, Wu et.al. explained the important role of serum Na as a predictor of mortality that can be relied upon patients with enteric fistula who had septic complications; however, the limitation of the study is that it was only conducted for 7 days in certain population groups with male sex dominance [8]. Another study [3] suggested that one third of patients with critical illness experience mild to moderate dysnatremia when entering ICU; the limitation is that the research design did not allow the evaluation of the causes of dysnatremia and factors that influence the therapeutic and fluid balance. This study aimed to determine the relationship of serum sodium levels as a predictor of mortality in patients with sepsis.

2. Methods

2.1. Research design

This study was a retrospective cohort study to determine the relationship of serum sodium levels with the risk of death in septic patients.

2.2. Place and time

The study was conducted in the clinical pathology laboratory of Dr. Moewardi Regional General Hospital from January to December 2017.

2.3. Research population

The target population of this study were all patients diagnosed with sepsis based on International Diagnostic Criteria (ICD) 10 by clinicians at Dr. Moewardi Surakarta between January - December 2017 (total sampling for 1 year).

2.4. Research subjects and methods for taking research subjects

The research subjects were recruited by total sampling within the period of January - December 2017, with the inclusion criteria being the data of patients diagnosed with sepsis by the clinicians based on ICD-X and the subjects were examined for serum sodium levels. We classified the clinical outcome of life and death that matched the subjects of the study based on age parameters. The clinical outcome of the patient is seen when the patient left the hospital; i.e., dead or alive. Exclusion criteria were septic patients who left the hospital forcibly (on their own request).

2.5. Sample size

Data from a total of 406 sepsis patients admitted to DR Moewardi hospital from January to December 2017 were recorded. Analysis was carried out based on the time of examination of serum sodium levels and based on the age of the patient ($\geq$ 18 years). Then, from 338 study subjects, exclusion criteria were re-examined; namely the clinical outcome of patients discharged at their own request or forced return. Based on the inclusion and exclusion criteria, there were 328 subjects included in this study.

2.6. Patient data and laboratory examination

Demographic data were obtained from medical records. The parameters of serum sodium were examined using the AVL electrolite analyzer with the ion-selective electrode (ISE) method, the value ranges from 40-205 mmol/L [9]. Data from the examination of sodium levels were taken when the diagnosis of sepsis was established.

2.7. Identification of research variables

The variables in this study were serum sodium levels that were divided into several groups according to the literature, namely: levels 135 until ≤145 mmol/L are called normonatremia, levels ≤125 mmol/L are called severe hyponatremia, 125 until ≤129 mmol/L are called moderate hyponatremia, levels of 130 until ≤134 mmol/L are called mild hyponatremia, and levels of >145 mmol/L are called hypernatremia [10]. The sepsis type (specific or non-specific) was determined based on examination of blood cultures; a specific sepsis is defined if germs were found and sepsis was not specific if no germs were found or sepsis was considered due to other causes.

2.8. Statistical analysis

Characteristics of research subjects were presented in an observational analytic manner. Test of data distribution was performed using Kolmogorov-Smirnov analysis, test of data distribution shows that the data is not normally distributed so the data is presented as a median, the minimum and maximum value. A comparison of sodium levels among more than two groups of was carried out using the Kruskal-Wallis test. Statistical signification P <0.05. Categorical data uses chi-square and RR (relative risk) assessment using descriptive analysis with SPSS version 16.0

3. Results

A total of 328 patients with a sepsis diagnosis who were treated within 1 year between January 1, 2017 and December 31, 2017 who were examined for serum sodium levels when diagnosed with sepsis were included in the analysis. Approximately 53.3% of the research subjects were male. Median age is 58.14 years (range 21-93). Median length of stay is 9.63 days (range 1 - 69). The mortality rate during the study lasted 76.83%.

The mean value of serum Na 133 mmol / L (range 132.08 - 134.02). Measurement of sodium levels is not normally distributed. Total normonatremia percentage was 22.86%; while in the hypernatremia group it was 9.14%. The highest mortality value was in the hypernatremia group 96.7% and severe hyponatraemia was 88.5%. Sepsis was divided into two specific groups and was not significantly higher in the severe hyponatremia group with non-specific sepsis of 78.8% (p = 0.019) (Table 1). There is a significant difference between survival rate compared to those who died in the sodium group with the value of p <0.001 (Table 2)

Table 1: Basic characteristics of research subjects.

	Normo-natraemic	Severe hyponatraemic	Moderate hyponatraemic	Mild hyponatramic	Hyper-natraemic	*P* value
Count (Total%)	75 (22.86)	52 (15.85)	73 (22.25)	98 (29.87)	30 (9.14)	-
Age						0.219
Median (year)	61	56.5	58	60.5	57	
Range	(26 - 87)	(24 - 88)	(21 - 89)	(24 - 93)	(21 - 93)	
Gender						0.984
Male (%)	41 (54.7)	29 (55.8)	37 (50.7)	52 (53.1)	16 (53.3)	
Female (%)	34 (45.3)	23 (44.2)	36 (49.3)	46 (46.9)	14 (46.7)	
Length of stay						0.686
Median (day)	7	7.5	6	9	8.5	
Range	(1 - 55)	(1 - 48)	(1 - 69)	(1 - 48)	(1 - 55)	
Sepsis						0.019
Specified (%)	26 (34.7)	11 (21.2)	17 (23.3)	37 (37.8)	14 (46.7)	
Unspecified (%)	49 (65.3)	41 (78.8)	56 (76.7)	61 (62.2)	16 (53.3)	
Mortality (%)	60 (80)	46 (88.5)	54 (74)	63 (64.3)	29 (96.7)	0.001
The Kruskall-Wallis test is significant if p <0.05						

The RR value of the hypernatremic group was 7.25 (95% CI 0.91-57.58) (p = 0.03) and in the mild hyponatremia group RR value was 0.45 (95% CI 0.22 - 0.91) (p = 0.02) (Table 3).

4. Discussion

Hai-bin study found that clinical patients with hypernatremia were significantly worse than the non-hypernatremia group [4]. The results of the study by Atalan, that APACHE value (acute physiology and chronic health evaluation) II, SOFA score, low and high pH value, hypernatremia, hyperlactatemia, and low Cl: Na ratio are predictors of increased

Table 2: Comparison of research subjects: survive vs died.

	Survive	Died	P value
Count (%)	76 (23.17)	252 (76.83)	-
Sodium group			< 0.001
Normonatraemi	15 (20)	60 (80)	
Severe hyponatraemic	6 (11.54)	46 (88.46)	
Moderate hiponatraemic	19 (26.03)	54 (73.97)	
Mild hiponatraemic	35 (35.71)	63 (64.29)	
Hypernatraemic	1 (3.33)	29 (96.67)	
Length of stay			0.006
Median (days)	12	7	
Range	119	68	
Age			0.959
Median	60.34	57.19	
Range	(57.1 - 63.6)	(55.4 – 58.9)	
Sepsis			0.19
Specified (%)	29 (27.36)	77 (72.64)	
Unspecified (%)	47 (21.08)	176 (78.92)	
Gender			0.36
Male (%)	43 (24.85)	130 (75.15)	
Female (%)	33 (21.15)	123 (78.85)	
The Chi Square test is significant if p <0.05			

Table 3: The relationship between normonatraemia and disnatremia with the risk of death in septic patients.

		P value
Normonatraemic (Na 135 - 145 mmol/L)		
RR	1	-
95 % CI	-	-
Severe hiponatraemic (Na < 125 mmol/L)		
RR	1.92	0.21
95 % CI	0.69 - 5.32	
Moderate hiponatraemic (Na 125 - 129 mmol/L)		
RR	0.71	0.38
95 % CI	0.33 - 1.54	
Mild hiponatraemic (Na 130 - 134 mmol/L)		
RR	0.45	0.02
95% CI	0.22 - 0.91	
Hipernatraemic (Na > 145 mmol/L)		
RR	7.25	0.03
95% CI	0.91 - 57.58	

mortality in ICU [11]. In this study, the RR value of the hypernatremia group was 7.25 (95% CI 0.91-57.58) (p = 0.03) meaning that there were no significant differences in the risk of death between patients with hypernatremia and normonatremia groups. It can be said that serum sodium level is not the main parameter that indicate the risk of death, but can be used as a risk support parameter for death which refers to the main laboratory criteria and parameter for the diagnosis of sepsis.

In the Whelan study, there was a significant association between hyponatremia and the risk of death in hospital despite adjustment for acute disease scores, age, criteria for sepsis, ICU admission and pre-transfusion requirements, all of which were strong predictors of hospital mortality [7]. Clayton's study in 108 patients with severe hyponatraemia obtained a hospital mortality rate of 20%, compared with normonatremic patients with 7% of mortality over the same period of time. Interestingly, about 2 years later, the mortality rate increased to 45% in the severe hyponatremia group compared to only 22% in normonatremia patients [12]. However, this study found a mild hyponatremia group with RR 0.45 (95% CI 0.22 - 0.91, p = 0.02), meaning that mild hyponatremia was a protective factor against the occurrence of death in septic patients, the risk of death in the hyponatremia group was 2.2 times more low compared to normonatremi group.

5. Study Limitations

The retrospective cohort study design posed a difficult determination when subjects are exposed to the risk factors studied. The diagnosis of sepsis is made by different clinicians so that there was no standardization. Moreover, the proportion of each group is unbalanced. In this study, we did not control other factors that could influence clinical outcomes, such as APACHE II score, SAPS (simplified acute physiology score) score and BMI (body mass index). This study also did not exclude the diagnosis that can affect the levels of the parameters studied (e.g., shock patients, hypoxemia, seizures, chronic kidney disease, dehydration, heavy activities that can affect blood sodium levels).

6. Conclusion

In this study, it can be concluded that there is no significant difference in the risk of death between patients with hypernatremia and those with normonatremia so serum sodium level is not the main parameter that indicates the risk of death but can be used as a supporting parameter of risk of death in septic patients. In mild hyponatraemia, there is a protective factor against the occurrence of death in patients with sepsis, as it was

shown that the risk of death in the mild hyponatremia group is lower than that in the normonatremi group.

Monitoring sodium levels in septic patients can be useful for avoiding dysnatremia caused by excessed fluid therapy or a lack of fluid therapy, and to avoid clinical outcomes in the form of death.Further research can be done by taking more complete additional parameters, scoring data for clinical diagnosis of sepsis and exclusion of diagnosis that can affect the levels of the parameters studied.

References

[1] Lee J W 2010 *Electrolyte Blood Press* **8** 72-8

[2] Lansink-Hartgring A O *et al*. 2016 *Ann Intensive Care* **6** 22

[3] Darmon M *et al*. 2013 *Crit Care* **17** (1) R12

[4] Ni H B. *et al*. 2016 *Am J Med Sci* **351** (6) 601-5

[5] Napolitano L M 2018 *Surg Infect* 19 (2) 117-25

[6] Cunneen J, Cartwright M 2004 *AACN Clin Issues* **15** (1) 18-44

[7] Whelan B *et al* 2008 *Q J Med* **102** 175-182

[8] Wu Y *et al* 2015 *J Invest Surg* **28** 131-9

[9] AVL Scientific Corporation 1996 *9180 Electrolyte analyzer operator manual* (USA: AVL Scientific Corporation) p.14

[10] Asadollahi K, Beeching N, Gill G 2006 *Q J Med* **99** 877-80

[11] Atalan H K, Gucyetmez B 2017 *Turk J Med Sci* **47** 435-42

[12] Clayton J A, Le Jeune I R, Hall I P 2006 *QJM* **99** 505-11