Title: PROGNOSTIC VALUE OF RANDOM URINE SODIUM IN PREDICTING OUTCOMES OF PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE

Author: Maria Jhessica Pecson M.D.

ABSTRACT

Background

Heart failure is an urgent public health need being the leading cause of hospitalization and an important cause of morbidity and mortality in the world.[1] The science of prognostication attempts to identify patient's clinical and biological characteristics that are associated with poor outcome.[2] Risk prediction in patients admitted with acute decompensated heart failure remains a challenge hence this study was conducted to determine association between urine Na+ level of patients admitted for acute decompensation of heart failure and outcome.

Method

All patients >19 years old admitted at the Philippine Heart Center for acute decompensation of heart failure with normal creatinine level at admission and with consent to participate were included in the study. Random urine sodium level was determined during first 24 hours of hospitalization. Patients were then followed up and clinical outcomes noted.

Results

Study included 150 patients which were grouped into three groups. First group included 31 patients with low urine Na+ $\leq$30 mmol/L, 48 patients in the second group with normal urine Na+ 31-90 mmol/L and 71 patients in the third group with high urine Na+ >90 mmol/L. Baseline characteristics of the three groups were similar (Table 1). The primary composite outcome of death occurred in 42 patients (28%): 42 patients (58%) in the 1st group, 11 patients (22%) in the 2nd group and 18 patients (25%) in the 3rd group which was statistically significant (p=0.002). Readmission rate did not differ statistically (p=0.889) shown in Table 2.

Conclusion

This study showed that there is an association between random urine sodium level and mortality of patients admitted for acute decompensation of heart failure. Low urine sodium level (uNa+ $\leq$ 30 mmol/L) is associated with poor outcome. Use of urine sodium is attractive because of its low cost and is widely available.

Keywords: random urine sodium, acute decompensated heart failure, cardiovascular event

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from structural and functional impairment of ventricular filling or ejection of blood. [1] It is an urgent public health need with national and global implications. It is one of the most important causes of morbidity and mortality in the world.[1] The prevalence of HF is estimated to be 1–2% in developed countries, increasing with age. HF is the leading cause of hospitalization for patients older than 65 years, raising concerns about the economic burden of this syndrome.[2]

The science of prognostication has been extremely active in HF over the last two decades. In the attempt to stratify patients by risk categories and aiming at applying a staged therapeutic strategy, a number of clinical and biological characteristics, clinical scores as well as a large and ever increasing number of biomarkers have been associated with outcome and a few have been developed as 'predictors' of outcome.[2] Urine sodium measurement estimates tubular reabsortive function. It is affected by dietary sodium, aldosterone secretion, urine volume and drugs. Drugs that can increase urine sodium include diuretics, prostaglandins and certain antibiotics while corticosteroids and NSAIDs can decrease urine sodium level. Urine sodium is decreased when sodium is retained or sodium intake in reduced, which may occur in patients with heart failure and patients receiving diuretic therapy.[2] In a study entitled "Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study", it was found out that sodium intake predicted mortality and risk of coronary heart disease, independent of other cardiovascular risk factors. These results provide the harmful effects of high salt intake in the adult population. [3]

In another study conducted by O'Donnell MJ et al, he found out that there was an association between estimated sodium excretion and CV events was J-shaped. Compared with baseline sodium excretion of 4 to 5.99 g per day, sodium excretion of greater than 7 g per day was associated with an increased risk of all CV events, and a sodium excretion of less than 3 g per day was associated with increased risk of CV mortality and hospitalization for CHF. [4]

In another study by Imamura, T MD et al, he found out that urine osmolality estimated using urine urea nitrogen, sodium and creatinine can effectively predict response to Tolvaptan in decompensated heart failure patients. [5] This was also confirmed by study done by Fadi T Alattar MD et al, where he concluded that a FeNa of greater than 0.4% more than 6 hours after administration of diuretics predicts renal impairment and a complicated hospital course in acute decompensated heart failure patient. [6]

Risk prediction in patients admitted with acute decompensated heart failure (ADHF) remains a challenge. Biomarkers may improve risk prediction, which in turn may help to better inform patients regarding short-term and long-term prognosis, therapy and care. [2] This study aims to determine association of urine sodium with outcomes in patients admitted for acute decompensation of heart failure. [7]

Research Objectives:

This study aimed to correlate random urine sodium level with outcomes in patients admitted for acute decompensated heart failure. The general objective of this study was to determine association between urine sodium with outcomes in patients admitted for acute decompensated heart failure. This study specifically aims to determine random urine sodium level of patients admitted for acute decompensated heart failure, to determine outcomes of patients with acute decompensated heart failure and to determine association between random urine sodium with outcomes in these patients.

METHODOLOGY

Study design

This study is a prospective cohort conducted at Philippine Heart Center last January 2016 to January 2017. Patients age >19 years old who was admitted for acute decompensation of heart failure with normal serum creatinine during admission and with consent to participate in the study were included.

Exclusion criteria

Patients with Syndrome of Inappropriate Antidiuretic Hormone (SIADH), Diabetes insipidus, Post-obstructive diuresis, Adrenal insufficiency, Hyperaldosteronism and Acute tubular necrosis and patients admitted for acute GI losses and patients with Chronic Kidney Disease whether on Hemodialysis or not were excluded in the study.

Sample size calculation

Using Epi Info version 7, the minimum sample size requirement was estimated to be at least 150 based on the following parameters: alpha 0.05, 30-day mortality rate among heart failure patients 11% (*O'Riordan, Michael. Medicare Analysis Shows Hospitals Can Lower Mortality and Readmission Rates. February 13, 2013*) and margin of error = 5%.

Study maneuver

All patients >19 years old admitted for acute decompensation of heart failure with normal creatinine level at admission and consent to participate were included in the study. Random urine sodium was performed during first 24 hours of hospitalization. Patients was followed up and clinical outcomes such as those who had myocardial infarction, fatal arrhythmia, acute kidney injury requiring hemodialysis or not, those who intubated and those who eventually died were determined. For discharged patients, readmission or death within 30 days were noted.

Statistical analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Quantitative variables were summarized and presented as mean and standard deviation while qualitative variables will be tabulated and presented as frequency and percentage. Fisher's Exact/Chi-square test was used to determine the difference of frequency between groups. Predictors of outcome of heart failure patients were determined using logistics regression analysis. Null hypotheses were rejected at 0.05α-level of significance. STATS SE version 13 was used for data analysis.

RESULTS

The study included 150 patients. Patients were grouped into three groups. First group were those with urine Na level below normal (uNa+ ≤30 mmol/L), second group were those with normal level (uNa+ 31-90 mmol/L) and third group were those with above normal level (uNa+ >90 mmol/L).

Table 1. Demographic characteristic of the patients (n=150)

Parameters	**Low Urine Na+ (≤ 30 mmol/L) n=31**	**Normal Urine Na+ (31-90 mmol/L) n=48**	**High Urine Na+ (>90 mmol/L) n=71**	**P value**
	Frequency (%); Mean ± SD			
Age (years)	43.8 ± 15.7 (31)	48.3 ± 14.9 (48)	49.2 ± 15.6 (71)	0.2589
Sex				0.292
Male	28.4 (15)	66.67 (32)	59.15 (42)	
Female	51.6 (16)	33.3 (16)	40.85 (29)	
Smoking history				0.162
Smoker	16.13 (5)	27 (13)	18.7 (28)	
Previous smoker	25.81 (8)	22.9 (11)	32 (48)	
Non smoker	58.1 (18)	50 (24)	45.1 (32)	
Alcohol use				0.240
Non drinker	67.7 (21)	45.8 (22)	49.3 (35)	
Current drinker	32.2 (10)	50 (24)	49.3 (35)	
Previous drinker	0 (0)	4 (2)	1.4 (1)	
History of drug use	0 (0)	14.6 (7)	9.8 (7)	0.71
Medical history				
Hypertension	25.8 (8)	45.8 (22)	42 (63)	0.123
Diabetes Mellitus	6.5 (2)	22.9 (11)	18.6 (13)	0.161
Prior MI	3.2 (1)	16.8 (8)	14.1 (10)	0.180
Prior Stroke/TIA	0 (0)	0 (0)	4.2 (3)	0.307
Medications				
Diuretics	67.7 (21)	68.8 (15)	63.4 (45)	0.855
ACEI	38.7 (12)	29.2 (14)	47.9 (34)	0.127
ARBs	6.5 (2)	4.2 (2)	11.3 (8)	0.390
B-blocker	45.2 (14)	45.8 (22)	39.4 (28)	0.766
Aldosterone antagonist	45.2 (14)	41.7 (20)	31 (22)	0.275
Digoxin	51.6 (16)	50 (24)	50.7 (36)	1.0
Statin	25.8 (8)	27.1 (13)	35.2 (25)	0.529
Antiplatelet	29 (9)	41.7 (20)	45.1 (32)	0.322
Anticoagulant	29 (9)	20.8 (10)	25.4 (18)	0.706

Thirty-one patients were included in the first group, 48 patients in the second group and 71 patients in the third group. Table 1 showed the baseline characteristics of the patients included in the study. All of the variables showed no significant difference among the three groups as shown in Table 1.

The primary composite outcome of death occurred in 42 patients (28%): 19 patients (45%) died during the admission while 23 patients (55%) die within 30 days after discharge. Thirteen patients (58%) died in the 1st group, 11 patients (22%) in the 2nd group and 18 patients (25%) in the 3rd group. The difference is statistically significant (p=0.002) as shown in Table 2. Readmission stay did not differ significantly among the three groups (p = 0.889) as shown in Table 2.

Table 2. Association of Abnormal Urine Na to clinical outcomes of the patients

Parameters	**Low Urine Na+ (≤ 30 mmol/L) n=31**	**Normal Urine Na+ (31-90 mmol/L) n=48**	**High Urine Na+ (>90 mmol/L) n=71**	**P value**
	Frequency (%); Mean ± SD			
Death	58.1 (13)	22.9 (11)	25.4 (18)	**0.002**
Readmission	41.9 (13)	39.5 (19)	64.8 (46)	0.889

DISCUSSSION

Sodium constitutes the primary extracellular solute determining tonicity and thus the major determinant of extracellular fluid volume. In normal humans, the kidney is primarily responsible for maintaining the homeostasis of total body sodium. In normal humans, this exquisite modulation of total body sodium by the kidney involves both acute and chronic mechanisms. Sodium restriction is associated with stimulation of the renin-angiotensin-aldosterone system. Angiotensin II then stimulates the sympathetic nervous system. Both angiotensin and -adrenergic stimulation increases tubular sodium reabsorption very rapidly. [9] Measurement of the urine sodium concentration is vital in determining the integrity of tubular reabsorptive function. [10]

Results of this study showed that random urine sodium level of patients admitted for acute decompensated heart failure may predict outcome. Low urine Na level (uNa+ of < 30 mmol/L) was associated with poor outcome compared with normal & above normal urine Na level. Low urine sodium concentration indicates not only intact reabsorptive function but also the presence of a stimulus to conserve sodium. [10]

Low uNa+ has long been considered as a biomarker of prerenal failure as well as low intravascular volume status and/or low cardiac output. Moreover, low urine Na+ concentration is a biomarker of RAAS activation that may be triggered by various factors. [11]

The study however have several limitations. First, it did not include factors that could affect urine sodium level like diet; dose and duration of prior diuretic therapy; triggering factors that led to acute decompensation. Serum electrolytes and other urine electrolytes and urine osmolality were not obtained. Study also had a relatively small sample size & involved short term follow-up. Finally, etiology of heart failure was not determined & if intervention done to the patient which could affect prognosis of patients.

Nevertheless, the result of this study may help in predicting patients with poor outcome after being admitted for acute decompensated heart failure. It may also guide physicians in managing and caring for their patients. The use of urine sodium level is attractive because of its low cost. Prospective studies with more sample and longer follow-up are encouraged to provide more evidence on the value of urine Na in predicting outcome of patients admitted for acute decompensated heart failure.

CONCLUSION

In this prospective cohort study, it showed that there was an association of random urine sodium of patients admitted for acute decompensation heart failure and outcome. Urine Na+ $\leq$ 30 mmol/L was associated with a higher risk of death and cardiovascular events compared with normal (31-90 mmol/L) and high ($\geq$90 mmol/L) urine sodium level.

ETHICAL CONSIDERATIONS

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to study initiation, there shall be a review and approval of the study protocol and informed consent and subsequent amendments by the Philippine Heart Center Institutional Ethics Review Board (PHC IERB).

Before a subject's participation, a written informed consent was obtained by the investigator after adequate explanation of the aims, methods, anticipated benefits and potential risks of the study. The informed consent was signed and personally dated by the subject and the person who conducted the informed consent discussion. One copy of the informed consent was given to the subject. Since the sample population are vulnerable subjects, informed consent was taken from legally authorized representative.

The investigator preserved the confidentiality of all subjects taking part in the study. The investigator ensured that the subject's anonymity is maintained.

DISCLOSURE OF CONFLICT OF INTEREST: none to disclose

REFERENCES

1. Mann DL, Bonow RO, Zippes DP, Libby P. Braunwald E. Braunwald's Heart Desease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: Elsevier Saunders, 2015.

2. Zannad F, Agrinier N and Alla F. Heart failure burden and therapy. European Society of Cardiology. Europace (2009)11,v1–v9 doi:10.1093/europace/eup304

3. Prof Tuomilehto, Jaakko et. al. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. THE LANCET. 2001 March 17: Volume 357, No 9259, p 484-851.

4. O'Donnell MJ et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA*. 2011 Nov 23;306 (20):2229-38. doi: 10.1001/jama.2011.1729.

5. Imamura, T MD et. al. Urine Osmolality Estimated Using Urine Urea Nitrogen, Sodium and Creatinine Can Effectively Predict Response to Tolvaptan in Decompensated Heart Failure Patients. Circulation Journal Official Journal of the Japanese Circulation Society. *Circulation Journal* 2013; 77: 1208 – 1213

6. Alattar, Fadi T MD et al. Fractional excretion of sodium predicts worsening renal function in acute decompensated heart failure. *Exp Clin Cardiol* 2010;15(3):e65-e69.

7. Bayes-Genis A and Ordonez-Llanos J. Multiple biomarker strategies for risk stratification in heart failure. *Clin Chim Acta*. 2015 Mar 30;443:120-5. doi: 10.1016/j.cca.2014.10.023. Epub 2014 Oct 23.

8. O'Riordan, Michael. *Medicare Analysis Shows Hospitals Can Lower Mortality and Readmission Rates.* February 13, 2013

9. Schrier, Robert. Diagnostic Value of Urinary Sodium, Chloride, Urea,and Flow. *J Am Soc Nephrol* 22: 1610–1613, 2011.

10. Mir, Fazia MD and Eric Staros MD. Urine sodium: Reference range, Interpretation, Collection and Panels. 2013.

11. Legrand, Mattieu et al. Urine sodium concentration to predict fluid responsiveness in oliguric ICU patients: a prospective multicenter observational study. *Critical Care* (2016) 20:165.

12. Brown, Ian et al. Estimating 24-Hour Urinary Sodium Excretion From Casual Urinary Sodium Concentrations inWestern Populations The INTERSALT Study. *American Journal of Epidemiology*. 2013.

13. O'Donnell Martin M.B., Ph.D.et al. Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events. *New England Journal Medicine* 2014.

14. Mann, Samuel MD and Linda M. Gerber, PhD. Estimation of 24-Hour Sodium Excretion from Spot Urine Samples. *The Journal of Clinical Hypertension*. March 2010.