

Baseline characteristics and the association between hyponatraemia and pulmonary embolism prognosis

Ilhan Korkmaz,¹ Fatma Mutlu Kukul Güven,² Sevki Hakan Eren,³ Inan Beydilli,⁴ Birdal Yildirim,⁵ Can Aktas,⁶ Hakan Alagozlu⁷

Abstract

Objective: To evaluate the effect of hyponatraemia on pulmonary thromboembolism mortality rates.

Methods: The retrospective study was conducted at the Cumhuriyet University Medicine Faculty's Emergency Department, and involved the analysis of records related to all patients who were diagnosed with acute pulmonary thromboembolism between January 2005 and June 2011. Diagnoses were confirmed by pulmonary angiography, multi-slice computed tomography or high-probability ventilation/perfusion scintigraphy. All patients (n=260) were over 16 years of age. SPSS 14 was used for statistical analysis.

Results: Plasma sodium level, platelet count and hospitalisation time were significantly lower among those who died (n=16; 6.29) ($p<0.005$, $p<0.035$, $p<0.035$). Pearson correlation analysis found a negative correlation between plasma sodium level and C-reactive protein, white blood cells and pulmonary artery pressure ($r=-0.238$, $p<0.001$; $r=-0.222$, $p<0.001$; $r=-0.444$, $p<0.018$ respectively). A positive correlation was found between plasma sodium level and hospitalisation time ($r=0.130$; $p<0.039$).

Conclusion: While mortality rates in hyponatraemic pulmonary thromboembolism patients increases, low plasma sodium is an easy parameter that should be kept in mind for the prognosis of pulmonary thromboembolism disease.

Keywords: Hyponatraemia, Pulmonary thromboembolism, Mortality rate, Sodium. (JPMA 63: 331; 2013)

Introduction

Acute pulmonary embolism (PE) is a relatively common cardiovascular emergency. By occluding the pulmonary arterial bed, it may lead to acute life-threatening, but potentially reversible right ventricular failure (RVF). The consequences of acute PE are primarily haemodynamic and become apparent when 30-50% of the pulmonary arterial bed is occluded by thromboemboli. Sudden death may occur, usually in the form of electromechanical dissociation. Alternatively, the patient presents with syncope and/or systemic hypotension, which might progress to shock and death due to acute RVF. Rightward bulging of the interventricular septum may further compromise systemic cardiac output as a result of diastolic left ventricular (LV) dysfunction.

The severity of PE can be classified into three groups: clinical markers (shock, hypotension), markers of RV dysfunction (RV dilatation, hypokinesia or pressure overload on echocardiography, RV dilatation on spiral computed tomography [CT], brain natriuretic peptide

[BNP] or N-terminal pro B-type natriuretic peptide [NT-proBNP] elevation, elevated pressure at right heart catheterisation [RHC]) and markers of myocardial injury (cardiac troponin T or I).¹

Clinical value of hyponatraemia in severely ill patients was first described by Flear and Singh.² They showed that an abrupt fall in sodium concentration was often caused by a widespread increase in membrane permeability. Membrane permeability is increased by many factors: hypoxia, increased catecholamines, viral infection, endotoxins, and malnutrition. As a result of such an increase, some normally non-diffusible solutes 'leak' from cells, taking water with them. The resulting hyponatraemia persists for as long as these solutes remain in the extracellular fluid.²

Over time, hyponatraemia is associated with poor outcomes in patients with severe decompensated heart failure, ST-elevated myocardial infarction (MI), severe multi-organ dysfunction, right heart failure secondary to pulmonary arterial hypertension, pneumonia and in elderly patients.³⁻¹¹

This study set out to examine the association between admission sodium level and PE-related mortality.

Patients and methods

The retrospective study was conducted at Cumhuriyet

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¹⁻³Emergency Service, ⁷Department of Gastroenterology, Cumhuriyet University, Medicine Faculty, Sivas, ⁴Emergency Department, Antalya Education-Research Hospital, ⁵Emergency Department, Mugla State Hospital, ⁶Yeditepe University, Medicine Faculty, Emergency Service, Turkey.

Correspondence: Ilhan Korkmaz. Email: ilhankorkmaz100@hotmail.com

University Medicine Faculty's Emergency Department, in Turkey, and involved patient record of all those diagnosed with acute pulmonary thromboembolism (PE), between January 2005 and June 2011. We included 260 patients with confirmed PE over 16 years of age. Diagnoses were confirmed by pulmonary angiography, multi-slice CT or high-probability ventilation/perfusion scintigraphy. Patients who were accepted and treated as PE, but were not confirmed with pulmonary angiography, multi-slice CT or ventilation/perfusion scintigraphy were excluded. Baseline clinical and laboratory characteristics were recorded from their charts.

The study used the traditional cut-off value for hyponatraemia, which is accepted as 135 mmol/L or lower. Serum sodium level was adjusted in patients with re-distributive hyponatraemia.¹²

Two groups were generated according to their admission sodium level (≤ 135 mmol/L and >135 mmol/L) and in-hospital mortality rates were analysed with chi-square test. Also, we analysed the mean values of laboratory results via Mann-Whitney U test. Pearson correlation analyses for laboratory variables was calculated. SPSS 14 was used, and a p-value below 0.05 was accepted as significant. Ethical approval was taken from the Cumhuriyet University

Medicine Faculty Ethical Board.

Results

Of the 260 patients with confirmed PE, 6 (2.30%) patients were excluded from the study since their admission sodium levels were missing. There were 116 (45.66%) females and 138 (54.33%) males. The ages ranged from 18 to 90 years. Of the total, 86 (33.8%) were found to be hyponatraemic with a mean age of 64.7 ± 15.1 years, while 168 (66.1%) were normonatraemic with a mean age of 60.9 ± 18.1 years (Table-1).

Dyspnoea and chest pain complaints were high in pulmonary embolism in both hyponatraemic and normonatraemic patients (Table-2). Markers showing statistically significant difference at the time of admission of those who suffered from mortality ($n=16$; 6.29%) and those who were discharged alive ($n=238$; 93.70%) included plasma sodium level ($p<0.005$), and hospitalisation time ($p<0.035$) (Table-3).

Pearson correlation analysis found a negative correlation between plasma sodium level and C-reactive protein (CRP), white blood cell, and pulmonary artery pressure ($r=-0.238$, $p<0.001$; $r=-0.222$, $p<0.001$; $r=-0.444$, $p<0.018$ respectively). Also, a positive correlation was found between plasma sodium level and hospitalisation time ($r=0.130$, $p<0.039$).

Table-1: Baseline characteristics between hyponatraemic and normonatraemic patients.

Baseline characteristics	Hyponatraemic patients (n=86) (Mean $\pm$ SD)	Normonatraemic patients (n=168) (Mean $\pm$ SD)	P-value
Age (years)	64.7 $\pm$ 15.1	60.9 $\pm$ 18.1	0.26
Gender (female/male)	39/47	77/91	0.94
Repetition of pulmonary embolism	7/86	11/168	0.54
Malignancy	13/86	15/168	0.13
Deep venous thrombosis	21/86	47/86	0.67
Immobilisation	25/86	71/168	0.04*
Trauma	2/86	9/168	0.26
Pregnancy	5/86	4/168	0.16
Use of contraceptive drugs	0/86	4/86	0.15
C-reactive protein (mg/L)	123.3 $\pm$ 129.2	73.6 $\pm$ 78.6	0.008*
White blood cells (μ L)	13255.5 $\pm$ 6133	10840.5 $\pm$ 4204.9	0.013*
Platelet (μ L)	262465 $\pm$ 97521	291820 $\pm$ 254606	0.83
Plasma sodium (mmol/L)	132.7 $\pm$ 3.2	138.9 $\pm$ 3.7	0.001*
Lactate dehydrogenase (IU/L)	342.8 $\pm$ 289.9	301.9 $\pm$ 229.1	0.62
Conjugated bilirubin (mg/dL)	0.42 $\pm$ 0.33	0.34 $\pm$ 0.25	0.43
Unconjugated bilirubin (mg/dL)	0.69 $\pm$ 0.42	0.70 $\pm$ 0.71	0.56
Aspartate aminotransferase (IU/L)	77.2 $\pm$ 202.7	57.0 $\pm$ 159.0	0.96
D-dimer (ng/ml)	2671.5 $\pm$ 2661.1	2499.9 $\pm$ 2699.9	0.36
Pulmonary artery pressure (mm Hg)	53.9 $\pm$ 24.4	48.4 $\pm$ 12.4	0.57
Troponin (ng/ml)	0.11 $\pm$ 0.21	2.25 $\pm$ 8.74	0.43
Hospitalisation time (days)	10 $\pm$ 5	9.7 $\pm$ 5.1	0.32
Mortality rate	11/86	5/168	0.002*

Table-2: Admission complaints of the patients

Admission complaints	Hyponatraemic patients (n=86)	Normonatraemic patients (n=168)
Dyspnoea	38	68
Chest pain	8	28
Haemoptysis	6	10
Syncope	1	7
Leg swelling and pain	5	6
Dyspnoea and chest pain	26	45
Palpitations	2	4

$\chi^2=4.99$ $p<0.054$.

The effect of hyponatraemia on mortality is explained by several ways in different studies. Hyponatraemia is a well-known marker of neurohormonal activation in patients with LV failure. In low or high cardiac output failure, the arterial circulation fullness is decreased which increases sympathetic discharge, activation of the renin-angiotensin-aldosterone system, and nonosmotic release of vasopressin. Increased sympathetic and angiotensin activity is the cause of increased proximal tubular sodium and water reabsorption. Finally, the nonosmotic stimulation of vasopressin release leads to free water retention and contribute to the development of

Table-3: Demographic and laboratory characteristic according to mortality

Baseline characteristics	Patients who died (n=16) (Mean±SD)	Patients who were discharged alive (n=238) (Mean±SD)	P-value
Age (years)	69.2±15.3	61.7±17.3	0.74
Gender (female/male)	39/47	77/91	0.38
C-reactive protein (mg/L)	121.2 ±78.9	89.4±102.9	0.05*
White blood cells (μL)	12825±5759.1	11586±5020.9	0.46
Platelet (μL)	213446±110827.9	286030±218215	0.035*
Plasma sodium (mmol/L)	133.6±7.2	136.8±4.6	0.005*
Lactate dehydrogenase (IU/L)	539.8±363.4	301.3±236.6	0.003*
Conjugated bilirubin(mg/dL)	0.62±0.5	0.34±0.23	0.19
Unconjugated bilirubin (mg/dL)	0.83±0.6	0.69±0.64	0.31
Aspartate aminotransferase (IU/L)	192.5±330.3	55.1±156.4	0.001*
D-dimer (ng/ml)	4874.8±5450	2388.3±2260.6	0.77
Pulmonary artery pressure (mmHg)	48	50.6±18.2	0.95
Troponin (ng/ml)	0.26±0.41	1.55±7.22	0.62
Hospitalisation time (days)	6.7±6.1	10.0±4.9	0.035*

*P-value<0.05 significant

Discussion

Hyponatraemia is the most common electrolyte abnormality in hospitalised individuals, defined as a relative excess of total body water to sodium and is seen in a variety of medical conditions, including congestive heart failure (CHF), liver disease, inappropriate anti-diuretic hormone syndrome, and as a result of medications.¹³

It is observed that the mortality rates are increased among hyponatraemic patients. A study found that the hyponatraemic patients mortality rates (in-hospital, 1-year, and 5-year follow-up) increased between 9%-33% according to their classification.¹⁴

Association between hyponatraemia and mortality has been found in heart failure, ST segment elevated MI, severe multi-organ dysfunction, right heart failure, increased pulmonary arterial hypertension, hospitalised pneumonia patients and in elderly patients.³⁻¹¹

hyponatraemia.¹⁵ A study found that patients who were hyponatraemic had an increased plasma renin-angiotensin, norepinephrine and epinephrine level compared with the normonatraemics. Also, renal and hepatic blood flows were significantly decreased which showed the severity of the heart failure.¹⁶ Another study evaluated 949 patients with systolic dysfunction, and found admission serum sodium to be an independent predictor of increased number of days hospitalised for cardiovascular causes and increased mortality within 60 days of discharge.¹²

The neurohormonal activation in right heart failure was examined by another study that found plasma norepinephrine, atrial natriuretic peptide and endothelin levels were significantly higher among the isolated right heart failure patients with increased pulmonary artery pressure.¹⁷ It concluded that cardiopulmonary derangements severity is associated with increased

neurohormonal activation, and elevation in endothelin levels is related to pulmonary hypertension. Others evaluated 40 patients with pulmonary hypertension by right heart catheterisation and dichotomised them into hyponatraemic and normonatraemic groups.⁹ Death and hospitalisation rates were significantly higher in the hyponatraemic group. The mean pulmonary artery pressure was also higher among hyponatraemic group which resembled our results.

Evaluating Non-ST elevated MI patients and the association between hyponatraemia and 30-day adverse outcomes, another study found mortality and cardiac failure rates to be significantly higher in hyponatraemics.¹⁸ Likewise, another study found a higher mortality and re-admission rate (due to CHF), in hyponatraemic patients during a 920-day average follow-up period.⁵

Hyponatraemia among patients admitted to Emergency Department (ED) was evaluated by another study and mortality rate was found to be increased with the severity of hyponatraemia.¹⁹

Classifying PE according to severity is important and different criteria have been used in literature. One study evaluated 15531 patients retrospectively and found that the ones who had one of these risk factors; patient over 70 years, cancer, heart failure, chronic lung disease, chronic renal disease, cerebrovascular disease, pulse ≥ 110 beats/min, systolic blood pressure < 100 mm Hg, altered mental status, arterial oxygen saturation $< 90\%$, were at higher risk of short-term mortality and other adverse medical outcomes.²⁰

Others analysed CT pulmonary angiography and found that median obstruction index was significantly higher in patients who were admitted with a systolic blood pressure < 90 mmHg, body temperature ($> 37.5^\circ\text{C}$), and they also observed a correlation between D-dimer, troponin I and median obstruction index.²¹

Another study evaluated patients with newly diagnosed acute PE for accurate risk stratification, prognostication and facilitation of appropriate triage to intensive coronary unit, telemetry unit or outpatient management.²² The study evaluated troponin, electrocardiography (ECG), Echocardiography and chest CT results. Low-limb lead voltage, a pseudoinfarction pattern (Q waves) in leads III and AVF, and ST-segment elevation or depression in leads V4 to V6, elevation of troponin were the ECG findings for poor prognosis. Also, physical examination results like neck vein distension, palpate a prominent pulmonic impulse, and auscultate

tricuspid regurgitant murmur were accepted as bad prognostic factors. RV dysfunction and reconstructed four-chamber CT images in acute PE patients have been validated as an important prognostic tool.

Clinical correlation of hyponatraemia and mortality in PE was evaluated by a study.²³ It analysed 13,728 PE patients charts by use of International Classification of Diseases, 9th Clinical Modification diagnosis of PE or a secondary diagnosis for PE and one of the primary diagnoses that represent complications or treatments of PE. They diverged patients in three groups (< 130 , 130 - 135 , > 135 mmol/L). The hyponatraemia rate was 21.1%, which was lower than our results. Pulmonary severity was quantified with pulmonary emboli severity index and there was a negative correlation between severity index and hyponatraemia degree. Troponin level did not differ among the groups, like our study.

Mean admission serum creatinine and glucose levels were higher in hyponatraemic groups. Our study analysed liver panel, C-Reactive protein and complete blood count (CBC) levels and observed higher mean CRP and white blood cell plasma levels in hyponatraemic patients. Like our results, CRP is associated with RV dysfunction or with complicated clinical outcomes as a predictor of bad prognosis in PE in two studies.^{24,25}

Mortality in these three groups diverged one day after admission, and the difference continued to increase over the 30-day follow-up in one study.²³ The hospitalisation death rate was 6.1% and the adjusted odds ratio for all mortalities was 1.53 in the hyponatraemic groups with 130 - 135 mmol/L, and 3.26 for < 130 mmol/L serum sodium groups. Our mortality rate was 6.2% for all patients and was significantly higher in the hyponatraemic group. The odds ratio for mortality in our hyponatraemic groups was 4.78 (95% CI 1.60-14.24)

Our work has several limitations. It seems that hyponatraemia is the end stage in patients with left or right heart failure due to neurohormonal activation. That is why a prospective study is needed which analyses the renin-angiotensin-aldosterone and vasopressin levels, and echocardiographic management where RV dysfunctions are revealed. Also, the correlation of hyponatraemia and arterial blood gas results can also be useful, and a multivariate analyses according to these parameters can uncover the real effect of hyponatraemia in PE.

Conclusion

Low plasma sodium levels is an easy parameter to work out the prognosis of PE patients with hyponatraemia.

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