Original Research Article

Hyponatremia and Infection-related hospitalisation in ESRD patients undergoing maintenance hemodialysis: An observational study

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Abstract

Background: Hyponatremia is one of the common dyselectrolytemia encountered in ESRD patients. Existing evidence suggests that hyponatremia contributes to the impairment of host immunity by interfering with the function of helper T-cells. This results in higher rate of infections among the patients undergoing maintenance hemodialysis.**Objectives**: To study the levels of serum sodium in ESRD patients undergoing maintenance hemodialysis and to establish the association between the severity of hyponatremia and infection-related hospitalisation in these patients.**Methods**: Study was conducted on 60 patients with ESRD undergoing maintenance hemodialysis thrice a week. Serum sodium was measured on admission and patients were categorized based on the severity of hyponatremia which was statisticallycorrelated with infection-related hospitalisation.**Results**: Among the 60 patients studied, 87% were hospitalised with infections, among whom 50% had moderate and 50% had severe hyponatremia. The mean total leucocyte count was 16010±1295 cells/cubic mm, mean ESR was 80±12 mm/hour and mean CRP was 8.7±0.8 mg/L in the severe hyponatremia group which was higher than moderate and mild hyponatremia groups (p-value=0.0001, r-value: -0.746, -0.716 and -0.704 respectively). **Conclusion:** There was a significant negative correlation between serum sodium and infection risk in admitted patients as assessed by the total leucocyte count, ESR and CRP values. Serum sodium can be an independent marker for risk assessment and prediction of mortality in ESRD patients undergoing hemodialysis.

Keywords: Hyponatremia, ESRD, Hemodialysis, Infection-related hospitalisation.

Introduction

Hyponatremia is defined as a plasma Na+ concentration <135 mEq/L, occurs in up to 22% of hospitalized patients.[1]Prevalence estimates in End Stage Renal Disease (ESRD) vary depending on the underlying study population characteristics and dialysis modality. Epidemiologic data suggest that approximately 6-29%of hemodialysis (HD) patients have serum sodium levels <135mEq/L, which is substantially higher than that of the general population.[2-7] Hyponatremia in ESRD is based on accompanying changes in extracellular volume (ECV) status.

I. An increase in ECV suggests that a gain in electrolyte-free wateris the basis for the sodium derangement, and may be aconsequence of high free water intake, and potentially excess sodium intake relative to the capacity forexcretion although not to the same degree as free water.

II. No change in ECV status suggests a gain of osmotically active solutes restricted to the extracellularfluid compartment (e.g., glucose, paraproteins).Alternatively, loss of intracellular solutes (e.g., potassium, inorganic phosphate) due to protein-energy malnutrition leads to a compensatory shift of sodiumfrom the extracellular to intracellular fluid compartments. In the presence of vasopressin and non-functioning kidneys, electrolyte-free water accumulates in extracellular fluid compartment, leading to hyponatremia.[8]Helper T lymphocytes are crucial in the antimicrobial defense. They activate and modulate immune responses by producing cytokines. Type 17 helper T (Th17) lymphocytes produce the prototype cytokine interleukin-17 (IL-17), as well as interleukin-21 and interleukin-22, cytokines that are pivotal in the defense against bacteria and fungi. [9,10] Sodium binding activates Th17 cells and directly induces the Serine /threonine-protein kinase SGK1, which stabilizes the messenger RNA (mRNA) of the interleukin-23R and reinforces the Th17 phenotype. It also activates p38 mitogen-activated protein kinase and nuclear factor of activated T cells 5 (NFAT5) transcription factor, which induce expression of SGK1. By means of the enhanced production of cytokines suchas interleukin-17A and interleukin-17F, granulocyte-macrophage colony stimulating factor (GM-CSF), and tumor necrosis factor (TNF), the stimulated Th17 cells modulate the host defense.[11]The impaired function of Th17 cells and breakdown of microbial barrier function due to cellular edema or mucosal membranes in hyponatremia increases the susceptibility to infections in an already compromised renal function state. [12] Infections related to vascular access are the most common source of bacteremias in hemodialysis patients. Non-access related infections among dialysis patients include infections of the upper and lower respiratory tract, gastrointestinal infections, including hepatitis and Clostridium difficile colitis, genitourinary tract infections, cellulitis and osteomyelitis, infections due to antibiotic-resistant organisms, and tuberculosis.It is well known thatinfection can result in hyponatremia through various mechanisms including hypovolemia, hyperglycemia, renal failure, heart failure, or syndrome of inappropriate ADH secretion (SIADH). But our objective is to assess whether the existence of hyponatremia and its severity predicts infection.

Methodology

A cross-sectional observational study was conducted on 60 patients with ESRD undergoing maintenance hemodialysis thrice a week. Relevant data was collected after taking informedconsent from all the participants. Patients included were older than 18 years diagnosed to

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have ESRD of varied etiology undergoing maintainence HD thrice weekly in our dialysis unit. Patients who are taking ADH antagonist drugs like Tolvaptan and those with underlying decompensated cirrhosis were excluded from the study. All the patients had hyponatremia (serum Na+: <135 mEq/L) on admission. They were categorized based on the severity of hyponatremia as: Mild (130-135 mEq/L), Moderate (125-129 mEq/L) and Severe (<125 mEq/L). Complete hemogram, ESR, CRP, RFT, LFT, Serum electrolyte panel and urine microscopy were done for all patients. Chest X-ray, Ultrasound abdomen, Blood, sputum and urine culture with sensitivity were done wherever required. Infection-related hospitalisation (IRH) was defined whenprimary diagnosis on admission was an infectious disease as suggested by clinical examination and investigations. IRHs were divided into four broad categories: Respiratory infections, Genitourinary infections, Others (skin/soft tissue infections and joint/bone infections) and Septicemia (catheter related bloodstream infection).

Statistical analysis: The study data has been coded and entered in Microsoft Excel for windows 10 and analysed using the statistical software SPSS version 23. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. p-value <0.05 is taken as significant. Chi-square test has been used to find the significance of study parameters on categorical scale between two or more groups. Pearson correlation co-efficient has been used to establish correlation between the variables. Unpaired t test, ANOVA and Post hoc ANOVA are used wherever found appropriate.Linear regression analysis has been performed to find out the prediction.Classification of Correlation Co-efficient (r): 0.1-0.3 = Small correlation, 0.3-0.5 = Moderate correlation, 0.5-0.7= Large correlation, 0.7-0.9=Very large correlation, 0.9-1.0=Nearly perfect correlation and 1=Perfect correlation. Significant figures: p-value ≤ 0.01=Strongly significant, 0.01-0.05=Moderately significant and 0.05-0.10=Suggestive significance.

Results

Among the 60 study participants, 60% (n=36) were males and 40% (n=24) were females. 45% (n=27) of the study population were smokers and 35% (n=21) were alcoholics, 70% (n=42) had diabetes and all 100% (n=60) had hypertension. Out of 60, 18% (n=11) had mild, 38% (n=23) had moderate and 44% (n=26) had severe hyponatremia.Among the study participants, 87% (n=52) were hospitalised with IRH, out of whom, 33% (n=20) had respiratory infections, 27% (n=16) had genitourinary infections, 12% (n=7) had other infections and 15% (n=9) had septicemia. Among the patients hospitalised with respiratory infections (n=20), 55% (n=11) had moderate and 45% (n=9) had severe hyponatremia. Among those with genitourinary infections (n=16), 25% (n=4) had mild, 31% (n=5) had moderate and 44% (n=7) had severe hyponatremia (p-value=0.672). Among the patients hospitalised with other infections (n=7), 43% (n=3) had moderate and 57% (n=4) had severe hyponatremia (p-value=0.213).Among the patients with septicemia (n=9), 33% (n=3) had moderate and 67% (n=6) had severe hyponatremia. There was a significant correlation of severe hyponatremia with respiratory infection group (p-value=0.004) and suggestive correlation with septicemia group (p-value=0.090). The mean total leucocyte count was 16010±1295 cells/cubic mm in severe, 14186±1554 cells/cubic mm in moderate and 10255±2758 cells/cubic mm in mild hyponatremia groups. There was a significant negative correlation between serum sodium levels and total leucocyte count (p-value=0.0001,r-value: -0.746). The mean ESR was 80±12 mm/hour in severe, 66±15 mm/hour in moderate and 41±15 mm/hour in mild hyponatremia groups. There was a significant negative correlation between serum sodium levels and ESR (p-value=0.0001, r-value: -0.716). The mean CRP was 8.7±0.8 mg/L in severe, 7.7±1.1 mg/L in moderate and 5.3±1.7 mg/L in mild hyponatremia groups. There was a significant negative correlation between serum sodium and CRP (p-value=0.0001, r-value: -0.704).

Table 1: Relation between hyponatremia and IRH

Hyponatremia	Respiratory infection (n)		Total	p-value
	NO	YES		
Severe	17	9	26	0.004
Moderate	12	11	23	
Mild	11	0	11	
Total	40	20	60	
	Genitourinary infection (n)			
	NO	YES		
Severe	19	7	26	0.672
Moderate	18	5	23	
Mild	7	4	11	
Total	44	16	60	
	Other infections (n)			
	NO	YES		
Severe	22	4	26	0.213
Moderate	20	3	23	
Mild	11	0	11	
Total	53	7	60	
	Septicemia (n)			
	NO	YES		
Severe	20	6	26	0.090
Moderate	20	3	23	
Mild	11	0	11	
Total	51	9	60	

Table 2: Relation between serum sodium and Total leucocyte count, ESR and CRP

	Hyponatremia	Number (n)	Mean	Std. Deviation	p-value(ANOVA)
WBC COUNT (cells /cu mm)	Severe	26	16010.385	1295.1092	0.0001
	Moderate	23	14186.087	1554.4357	
	Mild	11	10254.545	3069.6070	
	Total	60	14255.833	2748.1287	
ESR (mm/hour)	Severe	26	80.538	12.3101	0.0001
	Moderate	23	66.609	15.2933	
	Mild	11	41.182	15.2828	
	Total	60	67.983	19.8780	
CRP (mg/L)	Severe	26	8.727	.8623	0.0001
	Moderate	23	7.700	1.0715	
	Mild	11	5.318	1.7360	
	Total	60	7.708	1.6662	

Discussion

We studied a total of 60 patients diagnosed as ESRD of varied etiology undergoing maintenance HD in our dialysis unit. They were categorised into 3 groups: Mild, Moderate and Severe hyponatremia based on their serum sodium levels. 87% of the study population had IRH. Among them, 50% had moderate and 50% had severe hyponatremia. The patients in the severe hyponatremia group had higher total leucocyte count, higher ESR and higher CRP values compared to moderate and mild hyponatremia groups. Our study showed a significant negative correlation between serum sodium and IRH as assessed by leucocyte count, ESR and CRP.Mandai S et al [12] studied 332 patients undergoing maintenance HD whose mean serum Na+ was 138.9 mEq/L (1st tertile:<138, 2nd tertile:138–140,3rd tertile:>140).The hazard ratio(HR) for IRH was higher for the 1st and 2nd tertiles than the 3rd tertile (unadjusted HR=3.20, p=0.002; adjusted HR=2.36, p=0.027 and unadjusted HR=2.07, p=0.058;adjusted HR=2.11, p=0.054 respectively). In a continuous model, higher serum Na+ wasassociated with lower risk of IRH (p=0.040), and lower all-cause mortality(p=0.049). The study confirmed the established relationship between lower serum Na^+ and higher mortality, even after adjustments for various covariates. Waikar et al[7] showed a continuous relationship betweenlower serum Na^+ and higher mortality in the HD population without residual renal function, indicating that thisrelationship is independent of ADH secretion related tounderlying disease. Each 4mEq/L increment in baseline pre-dialysis serum sodium concentration was associated with a hazard ratio for all-cause mortality of 0.84. Hoorn et al [13] showed that hyponatremia has been associated with mortality in long-term hemodialysis patients without residual function in whom the underlying disease cannot be responsible for hyponatremia.The HEMO study group [14]undertook a randomized clinical trial in 1846 patients undergoing thrice-weekly dialysis. They concluded that the relationship between lower serum Na^+ and higher mortality was significant in analyses of cardiovascular and non-cardiovascular mortality.Hyponatremia has a significant contribution to the increased risk of IRH among maintenance HD patients. Lower serum Na+ results in mucosal edema associated with extracellular hypotonicity and water transfer into the intracellular space. This decreases the mucosal microbial barrier function in the respiratory, genito-urinary tract, skin and soft tissue given that infections of these organs were more frequent in the present study. The decreased function of Th17 cells plays a pivotal role. Th17 cells and IL-17 play an important role inhost immunity, with the capacity of protection against extracellular pathogens and fungi, whereas they are also important drivers of autoimmune disease. Kleinewietfeld M et al [15]showed that elevated sodium chloride concentration generates Th17 cells which display a highly pathogenic and stable phenotype characterized by the upregulation of the pro-inflammatory cytokines GM-CSF, TNF-α and IL-2in a mouse model. Likewise, decreased sodium chloride concentration or hyponatremia can reduceit through inhibition of Th17 cells.However, this was an observational single centre study. The limited outcome may not be sufficient to generalise for a larger population. Further studies are required to associate serum sodium and the functioning of Th17cells to clarify the relation between hyponatremia and host immunity.

Conclusion

Hyponatremia is an independent predictor of higher risk forinfection-related hospitalization in maintenance HD patients. It is possible that hyponatremia is not only a marker of severe underlying disease that results in poor outcome, but is also a direct contributor to mortality in addition to various disease co-morbidities.

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