



Profound Hyponatremia: Prevalence, Underlying Disorders and Outcome in Tertiary Care Hospital

Parminder Singh¹, Amarinder Singh^{1*}, Jasneet Chawla¹, Amitoj Singh¹,
Satinder Kaur² and Manikant Singla¹

¹Department of Endocrinology, Dayanand Medical College and Hospital Ludhiana, Punjab, India.

²Department of Biochemistry, Dayanand Medical College and Hospital Ludhiana, Punjab, India.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Profound hyponatremia (<125 mmol/l) is a serious electrolyte disturbance often encountered in tertiary care setting and is associated with increased morbidity and mortality. Does hyponatremia per se or the underlying disorder contribute to increased mortality remains a controversial point. Clinical records of profound hyponatremia patients were explored with the aim of finding its cause and contribution of hyponatremia in final outcome.

Materials and Methods: All the inpatients with serum sodium \leq 125 mmol/L were identified from laboratory data over a period of four months in a tertiary care hospital. Outpatients and cardiac patients were not included in the study. They were classified into three groups according to serum sodium levels in mmol/l (group I: 121-125, group II: 116-120, group III: \leq 115). Clinical data was obtained from medical record office. Clinical diagnosis, extent of hyponatremia correction and mortality rates were studied.

Observations: One thousand and fifty patients were identified as having profound hyponatremia (sodium \leq 125 mmol/l). Prevalence of profound hyponatremia was recorded as 6.35%. Majority of profound hyponatremic patients (70.54%) had sodium levels in range of 121-125 mmol/l. Very

*Corresponding author: E-mail: sandhu_amarindersingh@yahoo.co.in;

profound hyponatremia (≤ 115 mmol/l) was noted in 17.6% patients. Mortality rate was significantly higher than the general mortality rate of hospital during that period (8.83% vs 4.6%, $p < 0.001$). Mortality in group III was highest (12%) followed by patients in group-I (8.42%). Most common cause of hyponatremia was chronic liver disease (20.9%), followed by infectious disease (17.04%), chronic and acute renal disease (15.4%). Diabetes mellitus along with its complications and endocrinological cause were present in 12.1% patients. Other causes include malignancy (11%), neurological (7.04%), pulmonary and trauma (6.4% and 5.17% respectively). Some miscellaneous causes like burns, psychological, skin disease were also noted.

It was observed that patients died mainly because of underlying disease as in majority of subjects (75.72%) hyponatremia was corrected either fully or partially ($\text{Na} \geq 130$ mmol/l and $\text{Na} \geq 125$ respectively) before demise.

Conclusion: High prevalence of hyponatremia was recorded in inpatients making it a common electrolyte disturbance. Underlying disease and severity of hyponatremia have a bearing on final outcome of patients.

Keywords: Hyponatremia; incidence; mortality; sodium levels.

1. INTRODUCTION

Hyponatremia defined as serum sodium concentration < 135 mmol/l is the most prevalent electrolyte abnormality encountered in 30% of hospitalized patients and can lead to wide spectrum of clinical symptoms ranging from subtle to severe and even life threatening [1,2]. Hyponatremia can result from a varied spectrum of conditions and can occur by different pathophysiological mechanisms. It can be classified as mild, moderate and profound depending upon the serum sodium level; mild denoting serum sodium level of 130 to 135 mmol/l, moderate 125-129 mmol/l and profound hyponatremia as serum sodium level of < 125 mmol/l [3]. The defined threshold of profound hyponatremia published in scientific literatures have values varying from 110-125 mmol/l [4,5]. Several studies report that when serum sodium concentration drop below 125 mmol/l, symptoms become more common [6,7]. There are other ways to classify hyponatremia like depending upon duration and speed of development as acute or chronic [8] depending on serum osmolality and volume status as hypovolemic, euvolemic and hypervolemia; based on symptoms moderately severe and severe. From clinical point of view hyponatremia is classified as non-hypotonic hyponatremia and hypotonic hyponatremia. Non-hypotonic hyponatremia can be isotonic or hypertonic resulting from the presence of additional osmoles. Hypotonic hyponatremia is further subdivided into three categories depending upon adequacy of extracellular water; decreased extracellular water resulting from renal, non-renal and third space losses; normal extracellular fluid volume resulting from syndrome of inappropriate ant diuresis, secondary adrenal insufficiency, hypothyroidism

and increased extracellular water from kidney disease, heart failure, liver failure, nephrotic syndrome.

Hyponatremia is basically a disorder of water balance, with relative excess of water compared to total sodium content. It results from disturbed activity of water balancing hormone, vasopressin. Vasopressin secretion is regulated by various mechanisms. Osmoreceptors located in hypothalamus, and peripherally stretch receptors present in left atrium, carotid sinus, aortic arch are the main effector sensors for the release of vasopressin from posterior pituitary gland. Unregulated release of vasopressin (without osmo or baro signals) under pathological circumstances can also occur eutopically or ectopically.

Hyponatremia affects body by extracellular hypo-osmolarity, causing free water to shift from vascular space to intracellular space. Therefore clinical manifestations of hyponatremia are related primarily to cerebral edema. Adaptatory mechanisms of brain can take care of this edema if hyponatremia occurs slowly. This adaptation process takes 24-48 hours hence the reason for using 48 hours threshold to distinguish between acute (< 48 hours) and chronic (> 48 hours) hyponatremia. Unfortunately the distinction between acute and chronic hyponatremia becomes unclear in clinical practice, especially in emergency ward. Unless there is clinical or amnesic evidence to suggest acute hyponatremia, it is considered to be chronic in nature. Even patients with chronic hyponatremia with no apparent symptoms can have subtle clinical abnormalities when analyzed in detail like gait disturbance, concentration, cognitive deficits, repeated falls and fractures [9]. Hyponatremia is

associated with increased hospitalization and risk of death [10,11]. Whether these are casual association or merely symptoms of underlying medical conditions such as heart or liver failure remains unclear.

Correct diagnosis of etiology causing hyponatremia and its treatment can definitely alter the prognosis when it is recognized timely. Proper correction of serum sodium level is necessary in patients of severe acute hyponatremia to avert brainstem herniation and death. On the other hand slow correction is the key for chronic hyponatremia. Present study is undertaken to study prevalence, underlying disorder causing hyponatremia, clinical outcome and whether severe hyponatremia was corrected prior to demise so as to know the contribution of hyponatremia.

2. MATERIALS AND METHODS

In this observational study conducted at Dayanand Medical College and Hospital, Ludhiana in North Indian state of Punjab, after ethical clearance from institution, data for all patients admitted in Hospital was screened for hyponatremia ($\text{Na} \leq 125$ mmol/l) from biochemistry laboratory. Ion Specific Electrode analyzed electrolytes on auto analyzer Cobas 6000 (Roche Diagnostics). Outpatients and cardiac patients data were not included in the study. Profound hyponatremia patients were identified and divided arbitrarily into three groups according to $[\text{Na}^+]$ levels in mmol/l (group I: 121-125, group II: 116-120 and group III: ≤ 115 , corrected for pseudo-hyponatremia). Their clinical data was obtained from medical record office. Main parameters studied were clinical diagnosis [International Classification of Disease (ICD)-10], mortality, and correction of hyponatremia in each group. Serum sodium

levels and status of correction of sodium on the day of demise was recorded. Sodium levels > 130 mmol/l was taken as corrected and ≥ 125 -129 mmol/l as partially corrected. The data collected were statistically analyzed. Mean and standard deviation were computed. t-test was used to compare the difference between means and Chi square test was used to evaluate differences in mortality rate. A p value < 0.05 was considered as significant.

3. RESULTS

Twelve thousand four hundred and seventy five patients admitted over period of four months were studied. One thousand and fifty patients were identified as having profound hyponatremia ($\text{Na} \leq 125$ mmol/l) from laboratory data at the time of admission. After excluding subjects with insufficient data for analysis, 792 patients were analyzed for clinical diagnosis and outcome from medical record office data. Prevalence of hyponatremia (sodium ≤ 125 mmol/l) was recorded as 6.35%. Table 1 shows distribution of patients according to sodium levels. Majority of patients (70.54%) had sodium levels in range of 121-125 mmol/l.

Mortality rate during this period in all the hospitalized patients was 4.6% as compared to 8.83% in profound hyponatremic patients ($p < 0.001$). Mortality in group III was highest (12%) followed by patients in group I (8.42%) Table 1. Status of hyponatremia on day of demise is shown in Table 2. About 48% patients had hyponatremia corrected (> 130 mmol/l) and another 28.57% got it partially corrected (125 – 130 mmol/l) at time of demise. Only 22.85% patients died with uncorrected hyponatremia. On the other hand all the patients discharged had sodium > 130 mmol/l.

Table 1. Incidence and mortality in hyponatremia patients, n=792

Groups	[na+] Levels mol/l	No of patients	% of total	Mortality N=70	% Age
I	121-125	570	70.54	49	8.59
II	116-120	122	11.86	9	7.3
III	< 115	100	7.6	12	12

Table 2. Status of hyponatremia in mortality patients before demise, n=70

[Na+] status	Group III n=12	Group II n=9	Group I n=49	Total n=70
Corrected ≥ 130 mmol/l	4 33%	3 33%	27 55%	34 48.6%
Partially corrected ≥ 121 -130 mmol/l	5 41%	2 22%	13 26.5%	20 28.57%
Uncorrected/ No significant change	3 25%	4 44%	9 18.4%	16 22.85%

Table 3. Clinical profile of hyponatremia patients n=792

	Clinical diagnosis	Group I	Group II	Group III	Total	%
Git	Chronic liver disease	115	34	17	166	20.9
	Pancreatitis	9	2	1		
Infectious disease		102	16	13	135	17.04
Nephrology	Arf	20	2	4	122	15.4
	Crf	29	8	5		
	Miscellaneous	39	6	9		
Endocrinology	Dm and it's complications	57	17	8	96	12.12
	Hypopituitarism	8	2	4		
Oncology	Heamatology	16	4	6	87	11.23
	Tumor	29	10	9		
	Miscellaneous	5	1	1		
	Nhl	4	1	1		
Neurology	Cns(cva)	7	2	2	56	7.07
	Cns infection	9	2	4		
	Miscellaneous	24	5	1		
	Cancer neuro	1	-	-		
Pulmonary medicine	Pulmonary infection	24	1	6	51	6.43
	Copd/asthma	12	5	3		
Trauma	Trauma cns	9	-	9	41	5.17
	Spinal cord	1	1	-		
	Miscellaneous	18	2	1		
Miscellaneous	Dengue	1	-	-	1	3.2
	Rheumatology	2	1	1	4	
	Skin	4	1	-	5	
	Burns	3	1	-	4	
	Surgery	9	1	-	10	
	Psychiatry	1	-	-	1	

4. DISCUSSION

Hyponatremia is the frequent electrolyte abnormality encountered in hospitalized patients. Hyponatremia is generally a consequence of systemic diseases and it adds to morbidity and mortality of subjects. These conditions are diverse in etiology and may alter the dynamics in their unique ways. By elucidating various causes one can plan the treatment strategies [12]. So the present work was carried out to identify various clinical conditions associated with hyponatremia. Data of cardiology patients was not included in this study as these patients need separate study, analysis and discussion.

Various authors have reported different prevalence rates with wide variations of 2.5 to 30%. This variation in prevalence has been because of number of factors like definition, level and severity of hyponatremia, method of testing, health care setting, total patient number and population. We studied profound hyponatremia (<125 mmol/l), as symptoms and effects of

hyponatremia are pronounced below these levels [13,14].

As the symptoms of hyponatremia are nonspecific and causes can be multifactorial, so manifestation of the underlying disease takes the precedence. In our study, in association with hyponatremia most common disease happens to be chronic liver disease (CLD) (20.09%). Advanced liver disease generally is associated with impairment in renal capacity to eliminate solute free water causing hypo-osmolality. Systemic vasodilatation in arteriovenous shunting of blood may reduce effective arterial blood flow. This lead to neurohumoral activation and water retention due to baroreceptor mediated vasopressin release. In addition use of mineralocorticoid antagonist spironolactone alone or in combination with loop diuretic reduces sodium retention in liver failure thereby contributing to hyponatremia [15]. CLD is very common in this part of country due to extensive burden of hepatitis C and alcoholism. A good number of our inpatients had CLD and probably

due to this reason it was most common cause of hyponatremia in our study. Chronic and acute renal disease was noted in 15.7% patients. When glomerular filtration rate falls or if there is tubular injury in kidney disease, renal ability to excrete water declines resulting in hyponatremia, if patient do not adhere to fluid restriction. Infectious diseases which include gastroenteritis, malaria, dengue, enteric, lower UTI all cause hyponatremia by diverse mechanisms [16]. In other studies GI losses remains the major cause of hyponatremia followed by use of medication (diuretics) and kidney disease [17,18]. Diabetes mellitus and other endocrinological causes, like hypopituitarism secondary adrenal insufficiency were noted in 12.1% patients.

In our study 11% patients had various types of malignancies. Hyponatremia in the cancer patient is usually as a result of SIADH. SIADH may be driven by ectopic production of arginine vasopressin (AVP) by tumors or by effects of anticancer and palliative medications on AVP production or its action. Diarrhea and vomiting caused by cancer therapy may also cause hypovolemic hyponatremia [19].

In pulmonary diseases patients (6.4% in our study) SIADH is the most probable cause, mechanism of which is poorly understood. CNS disease/ infections were noted in 7.3% patients and probably hyponatremia results from neurohormonal response [20].

In our study significantly higher mortality rate was noted in hyponatremia patients, as reported by other workers also [21]. But mortality rates were significantly higher in the severest grade of hyponatremia (<115). Out of 792 subjects with profound hyponatremia 70 patients expired. When analysis of serum sodium was done it was noted that hyponatremia was corrected either partially (125-130 mmol/l) in 28.57% or completely (>130 mmol/l) in 46.8% patients who expired. Only 22.8% patients had uncorrected hyponatremia at the time of demise. This finding reflects that severity of the underlying disease has a significant bearing on the mortality in association with hyponatremia. In line with this finding another study has also concluded that underlying disease process rather than the severity of hyponatremia explains the mortality rate [22].

5. CONCLUSIONS

Timely diagnosis of hyponatremia and evaluating its possible cause is very important as outcome

of these patients is governed by etiology as well as by Sodium [Na⁺] levels.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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