Original Article

Prevalence and incidence of hyponatremia and their association with diuretic therapy: Results from North India

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Abstract

Introduction: Hyponatremia is associated with substantial morbidity and mortality. Correct estimation of their prevalence, incidence and risk factors, especially the diuretics in Indian patients is important in determining preventive strategies. **Methods:** This multistage mixed methods-based study was conducted in a high-volume cardiac care center to ensure the correct estimation. Patients receiving oral diuretics on an outpatient basis and those admitted to hospital for hyponatremia were enrolled. **Results:** The prevalence of hyponatremia was 27% while the incidence rate was 18% and 29% after 3- and 6-month of the diuretic therapy. The highest rates of hyponatremia were observed in warm season (45%, 111 in 247 patients). Multivariate logistic regression analysis revealed that low solute and nutritious intake and edematous state were negatively correlated with serum sodium levels. Neither diarrhea/vomiting nor diuretic use were found to be associated with hyponatremia. **Conclusions:** Diuretics use was not associated with hyponatremia in adults in this population cohort. However, elderly people on diuretics are comparatively more likely to have hyponatremia. However, a randomized parallel arm trial comparing diuretics with other antihypertensives be done to establish whether diuretics are associated with hyponatremia in this patient population.

Keywords: Loop diuretics, seasonal variation, serum sodium

Introduction

Hyponatremia is the most common electrolyte disorder ranging from 5.2 to 28.8% in hospitalized patients, with an average of about 25.98% for elderly patients experiencing this disorder.[1-3]

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Hyponatremia is not a disease but rather a pathologic alteration in water homeostasis.[4] Causes of hyponatremia include certain drugs (such as hydrochlorothiazide), gastrointestinal loss, corticosteroid withdrawal, hypothyroidism, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[4]

In most cases, patients with hyponatremia are asymptomatic, but sometimes it may present with neurologic and gastrointestinal symptoms if serum sodium concentration drops below 120 mEq per liter.[5,6] Although the past several years have seen major progress in the field of hyponatremia, it remains unclear which factors mainly contribute to hyponatremia. Several studies have

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reported severe hyponatremia after the use of thiazide-type diuretic for hypertension.[7-9] However, most of these studies were performed in a non-controlled fashion or conducted in selected subpopulations.[7,9] Since diuretics are still recommended as first line treatment for hypertension, it is important to identify the risk factors associated with the development of hyponatremia.

Primary care physicians (PCPs) play an extremely important role as they are often the initial point of contact for patients in obtaining the treatment for common electrolyte disorder including hyponatremia. So, knowledge regarding the risk factors for hyponatremia and their treatment is very important as advice from PCPs has been shown to influence behaviors.[10]

The aim of this research was to undertake the most detailed study to date on the etiology of hyponatremia in general Indian population and report its prevalence, incidence, and correlation with risk factors, specially the diuretic. This study used multistage mixed methods to estimate (prevalence, incidence) and test in a case control study the correlation between various risk factors and the hyponatremia.

Methods

This multistage mixed methods study was carried out in Gandhi Memorial (GM) and Associated Hospitals, King George's Medical University (KGMU), Lucknow from over a period of one year. Informed consent was obtained from all participants. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the GM and Associated Hospitals, KGMU, Lucknow, in accordance with its guidelines for the protection of human subjects.

In the first stage, the study assessed the prevalence of hyponatremia through cross-sectional survey of anationally representative sample (Prevalence survey). In the second stage, the incidence of hyponatremia was recorded in patients started on diuretics for edematous disorders (Incidence study). In the third stage, a case control study was conducted to assess the independent association between various risk factors and the incidence of hyponatremia (Case-control study).

Study population

Prevalence survey (Stage 1)

Those >18 years of age, treated with diuretics for ≥6 months and attending the Medicine OPD/consultant's office of G.M. and Associated Hospitals were included in the survey.

Incidence study (Stage 2)

This prospective study was conducted in the patients attending the Medicine OPD/consultant's office of G.M. and Associated Hospitals and those discharged from G.M. and Associated Hospitals.

Case-control study (Stage 3)

Patients aged ≥18 years with moderate-to-severe hyponatremia (<135 mEq/L) admitted to the medical ward were included in the study. The exclusion criteria comprised of cases with hyperglycemia, hyperlipidemia, and paraproteinemia. Age and sex matched patients with normal serum sodium levels hospitalized in medical ward during same period for any illness and consenting to participate constituted the controls for case control study.

Data collection

This study used a case report form (CRF) that included four major sections. The first section included demographics and the status of the patient at the time of inclusion (outpatient). In the second section of the CRF, several questions regarding diagnosis, degree of physical activity, and number of visits to medical OPD were included. The third section of the CRF included several questions about the pharmacotherapy. In the fourth and last section of the CRF, the results of the following tests (at baseline, 3-months and 6-months): serum sodium, serum potassium were requested.

Prevalence survey (Stage 1)

Age, gender, physical activity and diuretic therapy were determined from CRF questionnaires. Primary outcome variable was hyponatremia in those receiving diuretics >6 months. We attempted to identify patients with several co-morbidities using a combination of laboratory results, and responses to disease specific questions. Specifically, we identified participants who were using diuretics for various conditions including hypertension, diabetes, congestive heart failure, coronary artery disease, hypersensitivity pneumonitis, chronic lung disease, chronic renal failure, and chronic obstructive pulmonary disease etc., Participants with hypernatremia, defined as sodium above the reference ranges, were excluded.

Incidence study (Stage 2)

Those >18 years of age started newly on diuretics and will continue for at least 6 months for edematous disorders were included in the study. Participants with hypernatremia were excluded. Primary outcome variable was development of hyponatremia in these patients. Data on demographics, co-morbid conditions, type and number of diuretic agents and impact of seasonal variation was recorded by trained data collectors on CRF. A history of physician-diagnosed hypertension, diabetes, congestive heart failure, coronary artery disease, hypersensitivity pneumonitis, chronic lung disease, chronic renal failure, and chronic obstructive pulmonary disease was noted.

Case-control study (Stage 3)

All adult inpatients (>18 years) with mild, moderate or severe hyponatremia (serum sodium ≤135 mEq/L) were eligible for inclusion in the study. Controls were defined as those received hospital treatment for any other illness and not for hyponatremia (serum sodium >135 mEq/L). Cases and controls were comparable in terms of sex and age group, and who gave written consent. Patients who refused participation in the study or had cognitive impairment, were excluded from the study. Each patient data was considered only once. The frequency of

laboratory tests or the treatments of hyponatremia were not affected by the study.

Statistical analysis

Statistical analyses were performed using STATA 9.2. Categorical variables were presented as numbers and percentages, while continuous variables as mean ± SD. Student's *t*-test was used for assessing change from baseline in continuous variables and Chi square test compared categorical variables. We performed univariate logistic regression analysis to determine the association between clinical variables and hyponatremia following diuretic therapy. We also performed univariate and multivariate logistic regression analyses in case control study to determine the association between clinical variables and hyponatremia. *P* value less than 0.05 was considered to be statistically significant.

Results

Prevalence survey (Stage 1)

The population (n = 109) had a mean age of 48.6 years and was largely male (64.2%). 29% of patients were sedentary while 71% were physical active. Most patients (50/109 [45.9%]) were receiving thiazide diuretics followed by loop diuretics in 39 patients (35.8%). Twenty patients were taking two diuretic agents concomitantly, the most frequent combination being loop diuretics and potassium sparing diuretics (n = 16). The major indication for diuretics was hypertension alone (20.2%), followed by hypertension and diabetes mellitus (12.8%), hypertension and coronary artery disease (11.0%), congestive heart failure (CHF; 9.2%), chronic liver diseases (CLD; 7.3%), and others (39.5%), respectively. Hyponatremia was present in 29 (27%) patients. Of these, 13 patients had mild hyponatremia and 16 had moderate hyponatremia [Figure 1]. No one had severe hyponatremia. In addition, hypokalemia was present in 8 (7%) patients. Univariate logistic regression analysis demonstrate an increase in the prevalence of hyponatremia with age ($P = 0.0023$) and during heat periods ($P = 0.012$).

Incidence study (Stage 2)

A total of 87 patients were included. The mean age at presentation was 50 ± 10 years and 63% were men. Of the 87 patients, 44 (51%) had documented peripheral edema. 38% patients were sedentary while 62% were physical active. 36% (n = 31) patients were prescribed with loop diuretics followed by 34% (n = 30) receiving thiazides, and 14% (n = 12) receiving potassium sparing diuretics. Twelve patients (14%) used a combination of loop diuretics and potassium sparing diuretics. In addition, one patient used a combination of thiazide and potassium sparing diuretics and other one used combination of thiazide and loop diuretics. Diuretics were prescribed mainly for hypertension (51%) in patients with non-edematous disorders while CHF was the most common (30%) reason for their use in patients with edematous disorders. A significant decrease was found in mean serum sodium levels after 3-and 6-months of diuretic therapy (138.5 ± 2.5 mEq/L vs. 136.7 ± 3.4 mEq/L and 135.5 ± 4.5 mEq/L; $P < 0.0001$). Total 16 (18%) and 25 (29%) patients experienced hyponatremia after 3- and 6-month of the therapy. Also, 3% and 10% experienced hypokalemia, respectively. Univariate logistic regression analysis demonstrated an increase in the incidence of hyponatremia with edematous disorders ($P = 0.0390$). Neither age ($P = 0.134$) nor physical activity ($P = 0.459$) was associated with hyponatremia.

Case-control Study (Stage 3)

A total of 247 cases and 247 controls were matched using a 1:1 ratio for gender (38% female, 62% male). Most of the patients were aged between 35 and 65 years. The mean age was 50.3 ± 15.5 years for cases and 48.6 ± 12 years for control [Table 1].

Out of 247 hyponatremic patients, 106 patients (43%) had a serum sodium of 130-134 mEq/L while 125 (51%) had 120-129 mEq/L. Severe hyponatremia (serum sodium < 120 mEq/L) was detected in 16 patients (6%). Hypokalemia (<3.5 mEq/L) was seen in 27% (95% CI; 22-34) cases. Patients with hyponatremia were older and more likely to have edematous states, more severe symptoms of diarrhea/vomiting and frequent use of diuretics.

Hyponatremia and seasonal variation

The prevalence of patients with profound hyponatremia (<135 mmol/l) in each month is shown in Figure 2. The incidence was 24.3% between January and March, 44.9% between April and June, 8.5% between July and September and 22.3% between

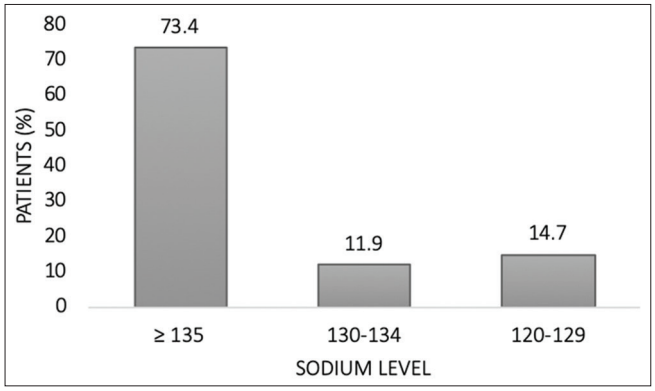

Figure 1: Distribution of serum sodium in the study population

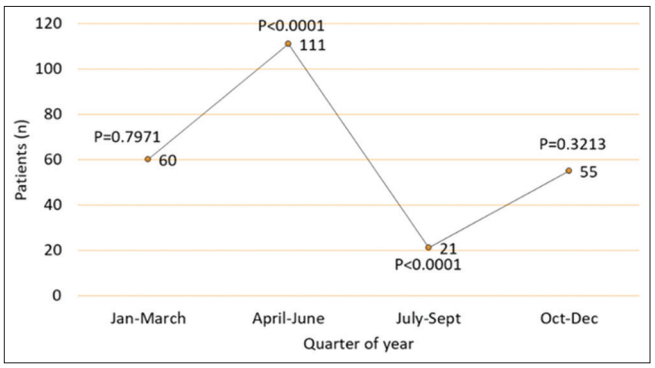

Figure 2: Seasonal variation and prevalence of hyponatremia

October and December. Statistically significant difference was observed in incidence rate of hyponatremia between second quarter (Apr-June months) and third quarter (Jul-Sep months) of the year ($P < 0.0001$). Thus, the prevalence of hyponatremia in the warm season of April to June (44.9%, 111 in 247 patients) was significantly ($P < 0.0001$) higher than that in the rainfall season (9%, 21 in 247 patients) and the cold season of October to March (46.6%, 115 in 247 patients).

Risk factors for developing hyponatremia

Univariate and multivariate logistic regression analyses were performed to evaluate the determinants of hyponatremia. Table 2 lists the results of both logistic regression analyses. In univariate analysis, diuretics use, presence of diarrhea/vomiting, poor solute and nutrients intake, and edematous states were significantly associated with hyponatremia [Table 1]. Patients on diuretics increased their risk by 160%. Conditions like diarrhea/vomiting increased risk by 250%, edematous states by 620%, and poor solute and nutrients intake by 200%. However, in the multivariate analysis, only poor solute and nutrients intake (2.2; $P = 0.010$) and edematous states (6.40; $P = 0.001$) were independently associated with the development of hyponatremia (acute hospital population). Neither diarrhea/vomiting ($P = 0.287$) nor diuretics use ($P = 0.664$) was associated with hyponatremia [Table 2].

Discussion

The multistage study method is the most general framework among advanced designs. We report, for the first time in India, the prevalence, incidence and correlation of various risk factors with hyponatremia in a multistage design and establish that diuretics are not associated with hyponatremia in adult patients, after controlling the confounding factors. The study estimated prevalence and incidence of hyponatremia in separate samples of general Indian population receiving regular diuretics for at least 6 months in ambulatory settings. Univariate analysis of stage 3 case control study demonstrates an increase in the prevalence of hyponatremia with diuretic use, diarrhea/vomiting, low solute and nutritious intake, and edematous states. However, multivariate analysis determined that only subjects with low solute and nutrients intake and edematous states were significantly more likely to have hyponatremia. Neither diarrhea/vomiting nor diuretic use were found to be associated with hyponatremia.

Table 1: Demographic details in the case control study

	Cases (*n*=247)	Control (*n*=247)
Age (mean±SD)	50.3±15.5	48.6±12
Male [*n* (%)]	153 (62)	153 (62)
Female [*n* (%)]	94 (38)	94 (38)
Physical activity		
Sedentary [*n* (%)]	60 (24)	63 (26)
Moderate [*n* (%)]	187 (76)	184 (74)

Table 2: Predictors of developing hyponatremia by logistic regression analysis

Risk factors	Odds ratio	95% CI	*p*
Univariate logistic regression analysis			
Diuretic use (yes vs. no)	1.6	1.1-2.4	<0.0001
Diarrhea/vomiting (yes vs. no)	2.5	1.2-5.0	0.0063
Poor solute and nutrients intake (yes vs. no)	2.0	1.1-3.8	0.0236
Edematous states (yes vs. no)	6.2	3.4-11.7	<0.0001
Multiple logistic regression analysis			
Diarrhea/vomiting	1.5	0.7-2.9	0.287
Poor solute and nutrients intake	2.2	1.2-4.0	0.010
Edematous states	6.40	3.4-12.2	0.001
Diuretics use	0.90	0.6-1.43	0.664

The prevalence rate of hyponatremia in our study was 27%, which is consistent with the previous findings that have estimated the prevalence of hyponatremia to 5.2%-28.8% of Indian patients admitted to hospitals.[1-3] According to a study from the Netherlands in 2013, the prevalence of hyponatremia was 7.7%, a marked less prevalence rate from the 27% reported in our study.[11] The larger prevalence obtained in Indian studies may be attributed to inadequate nutrition and low solute intake as well as tropical weather conditions. In 2002, Chakrapani *et al.* from India reported the important role of humidity and temperature in the manifestation of hyponatremia.[12] During the study period of two years, they found an increased incidence of hyponatremia in the peak southwest monsoon season.[12] In contrast, our study reported higher incidence of hyponatremia during the warm season of April to June (45%, 111 in 247 patients) than in the rainfall season (9%, 21 in 247 patients). Studies from Switzerland and Japan have also reported a higher risk of hyponatremia during the hot weather.[13,14] So we could validate the prevalence and incidence in separate groups of population through multistage design.

Previous studies have shown higher risk of hyponatremia in patients using certain drugs (e.g. diuretics, antidepressants, antiepileptics, tramadol, and codeine) and those with compromised age-related physiology and multiple comorbidities.[15,16] In 2018, a study by Imai *et al.* reported significantly higher prevalence of hyponatremia in the elderly group than in the adult group (17.0% vs. 5.7%, $P < 0.001$).[17] However, several studies suggest that age alone does not appear to be an independent risk factor for hyponatremia after controlling all other confounding variables.[18,19] A study by Al Mawed *et al.* has shown significantly higher hyponatremia-associated mortality in younger versus older patients.[20] In order to identify more reliable and validated risk factors for hyponatremia, both univariate and multivariate logistic regression analyses were performed in our matched case–control study (stage 3). Univariate analysis found hyponatremia to be elevated in subjects with edematous states, diarrhea/vomiting, low solute and nutrients intake, and those using diuretics.

The cause of hyponatremia may be renal (nephritis, diuretics, mineralocorticoid deficiency) and/or extrarenal (vomiting, diarrhea, burns).[21] Hyponatremia due to water excess is attributable to heart failure, nephrotic syndrome, cirrhosis and

others (infusion 5% glucose solutions and drugs that stimulate antidiuretic hormone (ADH) secretion).[21] In our study, subjects with edematous states were significantly more likely to have hyponatremia compared to those without edematous states meaning that edematous states had lower levels of serum sodium.

Hyponatremia due to poor solute and nutrients intake is described only in individual case reports.[22] In 1972, Gwinup *et al.* found that administration of more than 5 liters of beer daily for seven days results in hyponatremia, weight gain, strongly positive fluid balance and inappropriate urinary concentration.[23] Both American (2013) and European (2014) clinical practice guidelines considered urine osmolality of <100 mOsm/kg in hyponatremia and low dietary solute intake as a major cause of this condition.[24,25]

Thiazide type diuretics are associated with an increased risk of hyponatremia.[26] In 2006, a study that prospectively looked at patients hospitalized with severe hyponatremia; a greater proportion of patients were on loop diuretics than thiazides.[27] In consistent with these previous studies, diuretics use ($P = 0.664$) was also found not to be associated with hyponatremia in multivariate analysis of our study; though several study considered thiazide type diuretics as a major cause of hyponatremia.

Multivariate logistic regression analysis of our case-control study also suggested that if all other confounding factors are controlled, then only edematous disorders states, and poor salt and nutrients intake seem to be independent risk factors for development of hyponatremia. This is also in agreement with the results of previous studies showing that patients with diuretic hyponatremia frequently have other conditions like hot weather contributing to the hyponatremia.[14,28,29] Thus, it is fair to conclude that diuretics may be associated with hyponatremia but do not directly cause it.

The strength of the study is the multistage mixed methods design, and separate population evaluation leading to large sample size. To the best of our knowledge, this is the first Indian study to systematically evaluate and quantify various risk factors for hyponatremia in patients taking diuretic therapy. The study differs from already published case reports detailing limited number of severe hyponatremic cases. Also, this study describes the risk factors with certainty in both ambulatory and hospital settings; though this is a fundamental difficulty in the geriatric population. However, the study has several methodological limitations. Firstly, information regarding the different dosages of diuretics has not been recorded which may be a confounder. Secondly, contribution of other agents causing hyponatremia like other medications causing hyponatremia has not been recorded.

Conclusion

It is concluded that diuretics are not associated with hyponatremia in adult patients in this cohort of patients. However, elderly population on diuretics is more likely to have hyponatremia compared to the adult population. The authors recommend that a randomized parallel arm trial comparing diuretics with other antihypertensives be done to establish whether diuretics are associated with hyponatremia in this patient population.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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