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SHORT COMMUNICATION

Diuretic Induced Hyponatremia in Hypertensive Patients

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ABSTRACT

Diuretics are the recommended antihypertensive by several international guidelines. This study was designed to determine the association of hyponatremia in hypertensive patients on diuretic therapy. This was a case control study conducted at the Aga Khan University Hospital, Karachi in adult inpatients (> 18 years) who were known hypertensive. Cases were defined as hypertensives with hyponatremia and controls were defined as hypertensives without hyponatremia. Outcome was hyponatremia. Exposed were those using diuretics. Out of 1800 hypertensive patients sampled by the ICD-9-Coding; 1191 (66%) fulfilled the inclusion criteria. Cases n (%) were 553 (46.4) and controls were 638 (53.5). Among 553 cases (%) 180 (32.5) were exposed (on diuretics) and in controls 189 (29.6) were exposed (on diuretics) p=0.15. The association of hyponatremia with diuretic use was not significant with OR=1.11 (95% CI=0.86 - 1.45, p=0.40), after adjusting for chronic kidney disease, ischemic heart disease and chronic liver disease, in the final model. Diuretics were not associated with hyponatremia in hypertensive adult patients in this study.

Key Words: *Hyponatremia. Hypertension. Diuretics.*

Hypertension is an increasingly important medical and public health issue.[1] In developing countries like Pakistan, India, and China, where hypertension has reached epidemic proportions affecting more than 20% of the adult population, the control rates are less than 6%.[2] In trials comparing diuretics with other classes of antihypertensive agents, diuretics have been virtually unsurpassed in preventing the cardiovascular complications of hypertension.[3]

Many physicians tend not to prescribe thiazide diuretics as first line antihypertensive agents recommended by most international guidelines.[4] Low prescribing rate of thiazides has been attributed to concerns about electrolyte disturbance. Diuretics tend to be under used in management of hypertension due to concern of electrolyte imbalance. Hence, this study was conducted to determine association of hyponatremia in hypertensive patients using diuretic as an antihypertensive therapy.

This was a case control study conducted at the Aga Khan University Hospital, Karachi, Pakistan. Ethical approval from the ethics review committee of the Aga Khan University Hospital (ERC/AKU;16-08-2009) was taken for conduct of the study.

All adult inpatients (> 18 years), over a 1.5 years period (2008 - 2009), who were known hypertensive (diagnosed on having an average blood pressure of ≥ 140/90 mmHg on atleast 2 clinic visit) and were on antihypertensive therapy for atleast 6 weeks were included.[5] Cases were defined as hypertensive with hyponatremia (sodium < 135 mmol/l) on admission.[6] Controls were defined as hypertensive without hyponatremia (sodium > 135 mmol/l) on admission. Cases and controls were not matched for any characteristics. Exposure was defined as the use of diuretics at 6 weeks prior to recruitment. This was assessed by recording data on antihypertensive therapy.

This sample was drawn using computerized medical record system International Classification of Diseases - 9-coordination and maintenance (ICD-9-CM) at health information management system in the hospital. Patients admitted either with primary or secondary diagnosis of hypertension was used for selection through the ICD-9-CM. Cases were selected if in addition these patient had associated diagnosis of hyponatremia and controls were selected if the associated diagnosis was not hyponatremia. Those patients who did not have a documented record of the antihypertensive therapy or who had recent history of fluid loss (for example diarrhea) were excluded from the study.

Primary outcome variable was hyponatremia in hypertensives. Data on demographics, co-morbid conditions, type and number of antihypertensive agents and mean duration of antihypertensive therapy was recorded by trained data collectors, from the medical record of the patient. A history of physician-diagnosed diabetes, stroke, ischemic heart disease (IHD), chronic kidney disease (CKD) as documented in the medical records was noted.

Statistical Package for Social Sciences (SPSS) version 17.1 was used for the analysis. Mean and standard deviation was used for quantitative variables and

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frequency and percentage for qualitative variables. Distribution of variables was compared between cases and controls; comparison of qualitative variables was done by chi-square test and of quantitative variables by independent sample t-test and analysis of variance value of < 0.05 was taken as significant. Subgroup analysis was done to see association of exposure (use of diuretics) and with hyponatremia, stratified for age, gender, IHD, CKD and CLD to check for confounding. Crude odds ratio and its 95% confidence interval (95% CI) were computed through logistic regression for each independent variable. Multiple logistic regression models were built to determine the association of exposure (use of diuretics) with hyponatremia.

A sample of 1800 participants was drawn during the study period. Out of these, 1191 (66) fulfilled the inclusion criteria. Cases n (%) (hypertensives with hyponatremia) on admission were 552 (46.3) and controls (hypertensives without hyponatremia) were 639 (53.7). All participants were followed back in time for exposure of being on diuretics versus not on diuretics.

Mean age was 62.5 ± 12.4 years; 65.8 ± 11.1 years in cases and 59.6 ± 11.1 years in controls. Males were 540 (45.3%); 197 (35.6%) in cases and 343 (53.8%) in controls. Mean systolic blood pressure was 136.2 ± 25 mmHg; 137.0 ± 26 mmHg in cases and 135.5 ± 24.3 mmHg in controls. Mean sodium was 133.1 ± 9.4 meq/L; 126 ± 9.9 meq/L in cases and 139 ± 2.5 meq/L in controls. Overall prevalence of hypertensives on diuretics was 369 (30.9%). Out of them, 126 (34.1%) were on loop diuretics, 73 (19.7%) were on loop + potassium sparing diuretics, 47 (12.7%) were on thiazide diuretic, 15 (4%) were on potassium sparing diuretic. Among cases (n=552), 300 (54.3%) had mild hyponatremia, 162 (22.3%) had moderate hyponatremia and 90 (7.5%) had severe hyponatremia.

Among cases, 180 (32.5%) were exposed (on diuretics) and in controls, 189 (29.6%) were exposed (on diuretics, p-value 0.15). Mean sodium level in exposed group was125.4 ± 9.1 meq/L in cases and 139.3 ± 2.22 meq/L in exposed group in controls. OR of having hyponatremia and being exposed was 1.14 (95% CI; 0.89 - 1.46, p=0.27). On further stratification of the exposed group (on diuretics); there was no statistically significant difference with age > 63 years (58.3 years vs. 39.7 years; p < 0.19) and female gender (65% vs. 46.6%, p=0.35, Table I). On subgroup analysis of the exposed group into those who were on thiazide diuretics versus those on other diuretic the association was not significant with hyponatremia. (17% vs. 19.4% {OR 1.16 (0.61 - 2.18) p=0.63}.

On logistic regression analysis taking outcome hyponatremia; OR (95% LCI, UCI) for association of having hyponatremia with exposure was 1.13 (0.87, 1.46, p=0.33) after adjusting for age and gender in model 1. Further adjustment for CKD, IHD and CLD is shown in model 2, 3 and 4 respectively (Table II). No significant association is shown of having hyponatremia with exposure in the final model; OR (95% CI) 1.11 (0.86 - 1.45; p=0.40).

Diuretics make up one of the most common causes of hyponatremia, with an estimated incidence of 11% in 1 series of 114 geriatric patients.[7] It was found in this study that the association of hyponatremia with diuretic use in hypertensive is not significant in adults. However, there was significant hyponatrermia in elderly and female patients. In the Systolic Hypertension in the Elderly Program (SHEP), which focused on older patients, hyponatremia was observed in 4.1% of patients treated with chlorthalidone versus 1.3% in the control group.[8] In this study, this proportion of patients showed no significant association with hyponatremia The reason for this could also be that primarily 3 main factors;

Table I: Association of hyponatremia with diuretic use in hypertensive patients^.

Variables	Cases on diuretics (exposed) n=180 % (n)	Controls on diuretics (exposed) n=189 % (n)	OR(95%CI)	p-value
Age: > 63 years	58.3 (105)	39.7 (75)	1.34 (0.85,2.11)	0.19
Gender: female	65 (117)	46.6 (88)	0.80 (0.51,1.27)	0.35
CKD	13.9 (25)	11.1 (21)	1.19 (0.59,2.4)	0.61
IHD	38.3 (69)	45 (85)	1.00 (0.63,1.5)	0.98
CLD*	10 (18)	5.8 (11)	-	-

^ *Continuous variables are reported as mean ± standard deviation, and categorical variables are reported as %(n) CKD : Chronic kidney disease, IHD : Ischemic heart disease, CLD : Chronic liver disease.*OR was in exponential value.*

Table II: Regression models for factors associated with hyponatremia in hypertensives.

Candidate variables	Model 1*		Model 2**		Model 3***		Model 4****	
	OR(95%CI)	p-value	OR(95%CI)	p-value	OR(95%CI)	p-value	OR(95%CI)	p-value
Diuretic use	1.13(0.87,1.46)	0.33	1.12 (0.87,1.45)	0.36	1.15 (0.88,1.48)	0.29	1.11 (0.86,1.45)	0.40
Age: > 63 years	2.41(1.90,3.05)	< 0.001	2.40 (1.89,3.05)	< 0.001	2.46 (1.93,3.13)	< 0.001	2.49 (1.96,3.17)	< 0.001
Male: gender	0.47(0.37,0.60)	< 0.001	0.47 (0.37,0.60)	< 0.001	0.48 (0.38,0.61)	< 0.001	0.49 (0.38,0.62)	< 0.001
CKD	-	-	1.14 (0.75,1.73)	0.53	1.13 (0.74,1.71)	0.56	1.11 (0.73,1.69)	0.61
IHD	-	-	-	-	0.81 (0.63,1.05)	0.11	0.83 (0.64,1.07)	0.15
CLD	-	-	-	-	-	-	1.78 (1.0,3.16)	0.04

Outcome; cases (hypertensives with electrolyte imbalance) / controls (hypertensives without electrolyte imbalance).
Model I adjusted for age > 63 years and gender.*
*Model 2** adjusted for age > 63 years, gender and Chronic kidney disease (CKD).*
*Model 3*** adjusted for age > 63 years, gender, CKD and ischemic heart disease (IHD).*
*Model 4**** adjusted for age > 63 years, gender, CKD : Chronic kidney disease, IHD : Ischemic heart disease, CLD : Chronic liver disease.*
Hosmer lameshow test:0.12.

stimulation of vasopressin secretion, reduced free-water clearance, and increased water intake all contribute in development of thiazide induced hyponatremia.[9] Any change in these factors can hence confound the effect of thiazide induced hyponatremia. The risk of thiazide induced hyponatremia is 3-fold higher in patients older than 70 years and is higher among women, possibly because of smaller body size or lower sodium intake.[10] In a study of Chinese population, in 2759 Chinese population thiazides were associated with low prevalence of hyponatremia and hence it was recommended that physicians should not deter from prescribing thiazide diuretics as first-line antihypertensive agents as recommended by most international guidelines.[4]

The strength of the study is the large sample size and a case control design. It is the first to report the association of diuretics with hyponatremia in a multivariable model. However, there are several limitations in this study. Firstly, the group on thiazide diuretic is very small, hence the entire results cannot be related largely to them. Secondly, information regarding the different dosages of diuretics has not been recorded which may be a confounder. Thirdly, contribution of other agents causing hyponatremia like antidepressants causing hyponatremia has not been recorded.

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

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