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Frequency and Comparison of Hyponatremia in Patients Taking ACE Inhibitors and ARB in a Tertiary Level Hospital

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Abstract **Original Research Article**

Background: Major electrolyte imbalance during various organ dysfunction is a condition that can be overcome. Unfortunately, some antihypertensive, such as ACE inhibitors and ARBs, can produce silent hyponatremia, which is exceedingly harmful to the human body. ***Aim of the study:*** The purpose of this study was to determine the frequency of hyponatremia in patients taking ACE inhibitor and ARB. ***Methods:*** From May 2019 to October 2019, this cross sectional observational study was conducted at Department of Medicine, Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh. Purposive sampling was used to choose a sample of patients attending the Medicine department who were on ACE inhibitors and ARB medicines. Following that, they were evaluated using eligibility criteria, and 100 patients were chosen. All of the patients had been diagnosed with hypertension. Data on clinical biochemistry and surgical profile were collected. Data were analyzed using SPSS (version 23). ***Results:*** Among 50 patients in each group, the highest 19(38%) and 21(42%) belonged to ARB group and ACEi group respectively from age group (61-70 +). The male to female ratio in ARB and ACEi groups were 2.57:1 and 1.77:1 respectively. Among 50 patients in each group 4(8%) and 11(22%) patients in ARB and ACEI group respectively developed hyponatremia. The mean of total 15 hyponatremia patients was 128.73±2.17 mmol/L. Besides ARB group and ACEi group hyponatremia patients had mean serum sodium value like 130.31±1.79 mmol/L and 127.79±2.73 mmol/L respectively which shows statistically significant difference (P=<0.001). ***Conclusion:*** Hyponatremia was discovered in 31% of AECI and ARB patients. Though the amount is not excessive, it is disturbing. The incidence of hyponatremia among patients on these two medications varied statistically.

Keywords: Hyponatremia, electrolyte, ACE, ARB.

INTRODUCTION

Hyponatremia is defined as serum sodium ion concentrations less than 135 mmol/L [1]. Hyponatremia is classified as "mild" when the serum sodium concentration is between 130 and 134 mmol/L, "moderate" when the concentration is between 125 and 129 mmol/L, and "profound" when the concentration is less than 125 mmol/L [1]. Serum sodium concentrations and osmolality are precisely controlled by homeostatic mechanisms such as thirst stimulation, vasopressin secretion, and renal sodium processing [2]. Tonicity refers to the osmolality contribution of solutes that do not freely traverse cell membranes, such as sodium and glucose. Changes in serum osmolality cause the signs and symptoms of hyponatremia, as well as complications during therapy in the presence of high risk factors [3]. Hyponatremia is the most prevalent electrolyte anomaly seen in clinical practice, both in hospitals and in the outpatient sector [4]. Hyponatremia affects around 1.72% of the general population [5]. In acute hospital settings, its prevalence ranges from 4% to 45% [6]. Hyponatremia causes a wide range of clinical symptoms, from minor to severe, and has the potential for considerable mortality, morbidity, and extended length of hospital stay in patients with a variety of illnesses [7]. The most serious complication is the onset of cerebral

oedema, which causes headaches, nausea, vomiting, seizures, and coma [8]. The mortality rate linked with hyponatremia ranges between 5 and 50%, depending on the severity and acuity of onset [9]. Hyponatremia is thus both common and significant. Hyponatremia can be caused by diseases or as a side effect of some medications. According to reports, medicines account for 30% of hyponatraemia instances [10]. Hyponatremia can occur during treatment with medications commonly used in clinical practice. ACEI and ARB, also known as AT1 receptor antagonists or Sartans, are medications that affect the Renin Angiotensin Aldosterone system. They are generally used to treat hypertension, diabetic nephropathy, and congestive heart failure. In this subcontinent, ACE inhibitors are prescribed at a rate of approximately 13.5%, whereas AT1 receptor antagonists are prescribed at a rate of 24% [11]. Enalapril, Captopril, Ramipril, and Lisinopril (ACEI) are routinely recommended medicines, as are losartan, olmesartan, telmisartan, candesartan, and irbesartan (ARB). Drug side effects noted include hypotension, cough, hyperkalemia, headache, dizziness, nausea, and renal impairment. Importantly, euvolemic hyponatremia is more prevalent in the elderly. It is usually caused by an increase in free water along with little change in body sodium. This syndrome is most usually linked to non-osmotic vasopressin secretion. Euvolemic hyponatremia can be caused by some medicines (for example, hydrochlorothiazide), glucocorticoid deficit, hypothyroidism, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [12]. Izzedine H *et al.*,'s case report on blood sodium level monitoring before and after medication indicated severe hyponatremia caused by enalapril, which was attributed to ACEl-induced Syndrome of Inappropriate Antidiuretic Hormone (SIADH) [13]. Reports suggest the impact of ACEI and ARB on sodium channels: ACEl therapy affects the subcellular distribution of sodium transporters, blunting sodium re-absorption along the nephron [14]. ACEI and ARBs have also been shown to down regulate sodium channel and renin expression in renal tubules. These effects would act to suppress sodium re-absorption via sodium channel and neutralises the mechanism that would elevate blood pressure in response to increased salt intake [15]. ARB has been shown to inhibit angiotensin II's vasoconstricting mechanism and aldosterone secreting actions, resulting in reduced salt re-absorption and potassium secretion in the renal tubules [16]. The main aim of this study is to determine the frequency of hyponatremia in patients taking ACEI/ARB and comparison between them.

METHODOLOGY

From May 2019 to October 2019, this cross sectional observational study was conducted at Department of Medicine, Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh. Purposive sampling was used to choose a sample of patients attending the Medicine department who were on ACE inhibitors and ARB medicines. Following that, they were evaluated using eligibility criteria, and 100 patients were chosen. All of the patients had been diagnosed with hypertension. They were briefly informed about the study and gave their signed consent. Before beginning the study, a pre-tested, observation-based, peer-reviewed data collection sheet was constructed. Data on clinical biochemistry and surgical profile were collected. Data were analyzed using SPSS (version 23).

Inclusion Criteria:

- Patients having ACE inhibitors or ARB drugs minimum for one month.

Exclusion Criteria:

- Patients with known case of renal failure.
- Patient with known case of liver disease, heart failure or hypothyroidism.
- Patient having no history of obstructive lung disease, CNS infection, Stroke.
- Patients having history of diarrohea during last one week.
- Intake of additional drugs that is known to cause hyponatremia like thiazide ARB combination.

RESULT

Table-1 displays the distribution of patients according to age and sex. Among 50 patients in each group, the highest 19(38%) and 21 (42%) belonged to ARB group and ACEi group respectively at the age of (61-70yrs). The mean age of the respondents of ARB group was 59.73 plus/minus 8.61 (age range: 41-85) years and ACEI group is 61.75 plus/minus 9.13 (age range: 40-86) years. Out of 50 patients in ARB group there 36(72%) were male whereas 32(64%) were male in same number of patients in ACEi group. Regarding female sex it was revealed that, out of 50 patients in each group, 14(28%) and 18(36%) were female in ARB and ACEi group respectively. The male to female ratio in ARB and ACEi groups were 2.57:1 and 1.77:1 respectively. Table-2 demonstrates that out of 50 patients in ARB group 32(64%), 15(30%) and 3(6%) were prescribed Olmesartan, Losartan and Telmisartan respectively. On the contrary, in ACEi group, among 50 patients, 42(84%), 7(14%) and 1(2%) patients were prescribed Ramipril, Captopril and Metosartan respectively. Table-3 displays that among 50 patients in each group 4(8%) and 11(22%) patients in ARB and ACEi group respectively developed hyponatremia. Table-4 reveals that among 3 patients getting Telmisartan in ARB group and 1 patients getting Enalapril in ACEi group, no single patient developed hyponatremia. Besides 3 (9.3%) patients out of 32 Olmesartan users developed hyponatremia in ARB group. On the contrary, 10 (23.8%) patients out of 42 Ramipril users and 1 (14%) out of 07 Captopril users in ACEi group developed hyponatremia. None of the statistics showed statistically significant differences (P=>0.05). Table-5 reveals that out of 4 hyponatremia

patients in ARB group 3(75%) had mild hyponatremia and 1(25%) had moderate hyponatremia. On the contrary, out of 11 diagnosed hyponatremia in ACEi group 07 (63.6%) had mild hyponatremia 03(27.27%) had moderate hyponatremia and 01 (9.09%) had severe hypontremia. None of the statistics showed statistically significant difference (P=>0.05). Table-6 shows that out of 31 hyponatremia cases, 19(61.29%), 11(35.48%) and 1(3.22%) developed mild, moderate and severe hyponatremia respectively. Majority hyponatremia (75%) in ARB group showed non-neurological symptoms as well as majority cases (74.07%) cases of ACEi hyponatenia patients (P=>0.05). Table-7 shows that the mean of total 31 hyponatremia patients was 128.73±2.17 mmol/L. Besides ARB group and ACEi group hyponatremia patients had mean serum sodium value like 130.31±1.79 mmol/L and 127.79±2.73 mmol/L respectively which shows statistically significant difference (P <= 0.001).

Table-1: Distribution of patients according to age and sex (N=100)

Age distribution (in years)	ARB group (n=50) No. (%)	ACEi group (n=50) No. (%)	Total (N=100) No. (%)
≤50	9 (18)	3 (6)	12 (12)
51-60	11 (22)	14 (28)	25 (25)
61-70	19 (38)	21 (42)	40 (40)
71-80	8 (16)	7 (14)	15 (15)
.>80	3 (6)	5 (10)	8 (8)
Mean±SD (in years)	59.73±8.61	61.75±9.13	
Age range (in years)	41-85	40-86	
Sex			
Male	36 (72)	32 (64)	68 (68)
Female	14 (28)	18 (36)	32 (32)

Table-2: Distribution of patients according to types of prescribed drugs in both groups (N=100)

Prescribed drugs	Frequency No. (%)
ARB (n=50)	
Losartan	15 (30)
Olmesartan	32 (64)
Telmisartan	3 (6)
ACEi (n=50)	
Captopril	7 (14)
Enalapril	1 (2)
Ramipril	42 (84)

Table-3: Distribution of development of hyponatremia in ARB and ACEi groups (N=100)

Hyponatremia	ARB group (n=50) No. (%)	ACEi group (n=50) No. (%)	P-value
Hyponatremia developed	4 (8)	11 (22)	
Hyponatremia not described	46 (92)	39 (88)	$<0.00002^{S}$

Table-4: Distribution of patients according to individual drug induced hyponatremia (N=100)

Groups	Drugs	Total use	Hyponatremia developed No. (%)	P-value
ARB (n=50)	Telmisartan	3	0 (0)	0.50^{NS}
	Olmesartan	32	3 (9.3)	
	Losartan	15	1 (6.66)	
ACEi (n=50)	Captopril	7	1 (14)	0.84^{NS}
.	Ramipril	42	10 (23.8)	
	Enalapril	1	0 (0)	

Table-5: Distribution of patients according to severity of hyponatremia (N=31)

Severity of hyponatremia	ARB group hyponatremia (n=4) No. (%)	ACEi group hyponatremia (n=15) No. (%)	P-value
Mild	3 (75)	7 (63.6)	0.95^{NS}
Moderate	1 (25)	3 (27.27)	
Severe	0 (0)	1 (9.09)	

Table-6: Distribution of hyponatremia patients according to severity and its correlation with types of features (N=31)

Severity of hyponatremia	ARB group hyponatremia (n=4)		ACEi group hyponatremia (n=27)		P-value
	Neurological No. (%)	Non-neurological No. (%)	Neurological No. (%)	Non-neurological No. (%)	
Mild	1 (25)	2 (50)	4 (14.81)	12 (44.44)	0.81^{NS}
Moderate	0 (0)	1 (25)	3 (11.11)	7 (25.92)	
Severe	0 (0)	0 (0)	0 (0)	1 (3.70)	

Table-7: Mean serum sodium values of different hyponatremia groups (N=31)

	Total (n=31)	ARB group hyponatremia (n=4)	ACEi group hyponatremia (n=27)	P-value
Serum sodium values (mean±SD) (mmol/L)	128.73±2.17	130.31±1.79	127.79±2.73	<0.0001^{S}

DISCUSSION

Hyponatremia can arise when there is an overabundance of fluid compared to the typical level of sodium.or owing to a lack of both salt and bodily fluid. In this study, the mean age of the 50 respondents in the ARB group was 59.73± 8.61 (age range: 41-85) years, whereas the ACEi group was 61.75± 9.13 (age range: 40-86) years. These findings were comparable to those of other prior research [17]. A prior investigation on solely losartan found that females were more susceptible to hyponatremia than males [18]. However, the current study's findings reveal that males are more susceptible than females; the male to female ratio was 4.16.1 (25:6). The current study found that 15% of patients using ACEI and ARB experienced hyponatremia. Of these 15% patients, 4% were from the ARB group and 11% from the ACEI group. These findings are consistent with the higher incidence of hyponatremia reported in case reports of ACEI-induced hyponatremia [19]. In our study, the majority of the patients exhibited mild hyponatremia (10.66%) out of 15 cases, followed by moderate (4.66%) and severe (6.66%) hyponatremia, and similar results were observed in other studies such as MY Rao *et al.*, [20]. In the current investigation, neurological symptoms such as disorientation, delirium, abnormal behavior and speech, and seizures were reported among the patients, which is nearly identical to the study conducted by MY Rao *et al.*, [20]. Studies have demonstrated that both aging and male gender protect against hyponatremia-induced seizures, however the reasons are unknown [21]. The majority of patients in our study had numerous co-morbidities, with hypertension and diabetes being the most common. Glucose is an osmotically active chemical. Hyperglycemia can cause a decrease in serum sodium levels by transferring water from intracellular to extracellular compartments. Serum sodium levels decrease by 1.6 to 2.4 mmol/L for every 100 mg/dL increase in serum glucose levels [22]. Enalapril, ramipril, captopril, telmisartan, metosartan, and losartan are among the medications recommended to the patients in this study. Only one patient was prescribed metosartan, and he had hyponatremia. None of the three captopril-treated patients in the trial had hyponatremia; however, previous case reports on enalapril, lisinopril, captopril, ramipril, and losartan documented hyponatremia [23]. Because 15% of the research group suffered hyponatremia, the findings of this study emphasize the importance of monitoring serum sodium levels in patients using ACEI and ARBs. The mechanism of ACE inhibitor and ARB-induced hyponatremia has not been determined. A syndrome of improper antidiuretic hormone production linked with ACE inhibitor and ARB medication that causes symptomatic hyponatremia could be regarded an uncommon but plausible cause [24]. With ACEI medication, more circulating Angiotensin I enters the brain and is converted to Angiotensin II, which may promote thirst and antidiuretic hormone production from the hypothalamus, finally leading to hyponatremia [25]. According to reports, Aldosterone-induced renal tubular sodium reabsorption and potassium secretion are

blocked, potentially leading to a decrease in serum sodium levels [26].

Limitation of the study:

This is a cross-sectional study. This study was a single-center study with a small sample size and a short duration of follow-up, so these findings may not reflect the actual scenario.

CONCLUSION & RECOMMENDATION

Hyponatremia is a common electrolyte disorder. It can be accurately identified using a history of concomitant disease and drugs, as well as a measurement of extracellular volume during a physical examination. If hyponatraemia is not thoroughly investigated, the management plan implemented may be unsuitable and ineffective. Hyponatremia was discovered to be related with 15% of individuals receiving AECI and ARB.ACEI and ARB account for 11% and 4%, respectively. Even while the amount is not excessive, it is nonetheless disturbing. The incidence of hyponatremia among individuals taking these two medications varied statistically. However, metosartan is a somewhat worrisome medicine in this aspect. The current study underscores the importance of monitoring serum sodium levels in patients on ACEIs and ARBs to avoid unexpected adverse events.

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