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Research Article

COMPARATIVE STUDY ON RAMIPRIL AND TELMISARTAN-ASSOCIATED HYPONATREMIA

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ABSTRACT

Objectives: This study was planned to study the association of ramipril and telmisartan with hyponatremia and to compare the hyponatremia effect of ramipril and telmisartan.

Methods: The study was conducted in a tertiary care hospital. Serum sodium levels were assayed in patients taking ramipril and telmisartan. Fifty-one patients were recruited. The patient's age, gender, drug dosage, and frequency of drug administration were collected using a pro forma. Statistical analysis of data was performed using SPSS version 23.0.

Results: About 35.3% (28 out of 51) of the study population administered with ramipril and telmisartan developed hyponatremia. Predisposition to develop hyponatremia was high in males compared to females. Incidence of hyponatremia was 43.8% (7 out of 16) in the age group of 50–60 years. Although, incidence of hyponatremia was 56.5% (13 out of 23) in ramipril group compared to 17.9% (5 out of 28) in telmisartan group, it was not statistically significant.

Conclusion: The current study laid emphasis on the requisite for monitoring of serum sodium level in patients on ramipril and telmisartan administration to avoid morbidity and mortality due to unexpected adverse reactions.

Keywords: Ramipril, Telmisartan, Hyponatremia, Serum sodium level.

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INTRODUCTION

Hyponatremia, serum sodium concentration <135 mmol/L is a very common electrolyte disorder, is associated with increased morbidity, length of hospital stay and hospital resource use, as well as significant mortality and disability. Serum sodium levels can be lowered either due to disease conditions or as a side effect on the administration of certain drugs. Studies indicate that 30% of hyponatremia cases are drug-induced [1]. Angiotensin-converting enzyme inhibitor (ACEI) is a drug primarily for the treatment of hypertension and congestive heart failure. Common drug reactions are hypotension, cough, hyperkalemia, headache, dizziness, nausea, and renal impairment [2]. In a study done by Izzedine *et al*. [3], severe hyponatremia have been reported to have been caused by ACE therapy which was found by monitoring the sodium levels done before and after the start of the therapy. This is due to ACEI-induced SIADH which led to the hyponatremia. The majorly prescribed drugs include enalapril, ramipril, and lisinopril. Angiotensin II receptor antagonists (ARBs), also known as AT1 receptor – antagonists/sartans, have been used for the treatment of hypertension, diabetic nephropathy, and congestive heart failure. The known side effects include dizziness, headache, and hyperkalemia. Infrequent side effects include orthostatic hypotension, rash, diarrhea, dyspepsia, abnormal liver function, muscle cramp, myalgia, nasal congestion, and back pain. The drugs prescribed often include telmisartan, losartan, candesartan, and irbesartan [4]. Studies also indicate effects of ACEI and ARB on sodium channels. ACEI-treatment alters Na transporter subcellular distribution in a method that would blunt sodium reabsorption along the nephron [5]. ACEI and ARB's have been stated to down-regulate the sodium channel and renin expression in renal tubules. These properties would act to decrease sodium reabsorption through sodium channel and neutralizes the mechanism that would increase blood pressure in response to increased salt intake [6]. ARB prevents the vasoconstricting mechanism and aldosterone releasing effects of angiotensin II which leads to reduced renal tubular sodium reabsorption and potassium secretion [7]. Telmisartan and ramipril are a safe and effective alternative for the management of hypertension [8]. A pilot study report has indicated that usage of ACEI (enalapril and ramipril) and ARB's (telmisartan and losartan) leads to clinically significant fall in serum sodium levels in th majority of the patients (50%) [9]. Hence, this study was planned to study the association of ramipril and telmisartan with hyponatremia and to compare the hyponatremia effect of ramipril and telmisartan.

METHODS

A cross-sectional study was conducted on the patients who visited the tertiary care hospital at Tamil Nadu, India, from August 2017 to July 2018 after approval from the Institutional Human Ethics Committee. Patient's above 18 years, both genders, having ramipril and telmisartan for more than 10 days were included in the study. Patients with known renal failure, history of diarrhea during the past 1 week, and intake of additional drugs that have been known to cause hyponatremia were excluded from the study. Written informed consent was obtained from eligible patients based on inclusion and exclusion criteria. A 3 mL of venous blood was collected in sterile conditions for assay of serum sodium level. The patient's age, gender, drug dosage, and frequency of the drug administration were collected using pro forma and serum sodium levels were assayed by direct ISE method.

Statistical analysis

Statistical analysis of data was performed using SPSS version 23.0. Chi-square test was used to compare occurrence of hyponatremia among patients taking ramipril and telmisartan. Mean sodium levels of ramipril and telmisartan were done using unpaired student t-test. Comparison of mean using unpaired student t-test was performed to compare ramipril and telmisartan induced hyponatremia. $p<0.5$ was considered as statistically significant.

Table1: Gender and age distribution of participants with hyponatremia

Participant distribution	Total number of participants		Participants with hyponatremia	
	n (%)	Mean sodium level (mEq/L)	n (%)	Mean sodium level (mEq/L)
Total	51 (100)	135.7	18 (35.3)	130.9
Male	39 (76.5)	135.7	15 (38.5)	130.6
Female	12 (23.5)	135.7	3 (33.3)	132.3
40–50 years	7 (13.7)	138.3	1 (14.3)	132
51–60 years	16(31.4)	135.3	7 (43.8)	131
61–70 years	18 (35.3)	136.2	6 (33.3)	131.7
>70 years	10 (19.6)	133.7	4 (40)	129.3

Table 2: Occurrence of hyponatremia with ramipril and telmisartan

Drug	Total participants n (%)	Participants with with hyponatremia n (%)	p value
Ramipril	23 (45.1)	13 (56.5)	0.004*
Telmisartan	28 (54.9)	5 (17.9)	

*p<0.05 is statistically significant

Table 3: Mean sodium level with ramipril and telmisartan

Drug	Mean Sodiumlevel of total total participants (mEq/L)	p value	Mean sodium level of participants with hyponatremia (mEq/L)	p value
Ramipril	133.8	0.001*	130.5	0.07
Telmisartan	137.3		132	

*p<0.05 is statistically significant

RESULTS

A total of 51 participants recruited for the study, 23 on ramipril and 28 on telmisartan. Approximately 35.3% (18 out of 51) of patients administered with ramipril and telmisartan developed hyponatremia. Predisposition to develop hyponatremia was found to be more in males compared to females, 38.5% of males developed hyponatremia compared to 33.3% of females. Mean sodium levels were equal in both males and females. However, the magnitude of lowering of sodium level was higher in males (Table 1). Incidence of hyponatremia was more (43.8%) in the 50–60 years age group compared to the other age groups. However, the magnitude of lowering of sodium level was higher in patients above 70 years indicating a higher drop in serum sodium level as age advances (Table 1). There was a significant occurrence of hyponatremia with ramipril and telmisartan (Table 2). There was a significant difference in the mean sodium level with ramipril and telmisartan (Table 3). Ramipril had a higher rate of inducing hyponatremia compared to telmisartan (Fig. 1 and Table 3).

DISCUSSION

The present study revealed the occurrence of hyponatremia in 35.3% of the participants on ramipril and telmisrtan (Table 1). This finding coincides with more incidence of hyponatremia with ACEI-induced hyponatremia [9].

A previous study on losartan had reported higher susceptibility of females to hyponatremia compared to men [9]. However, the present study results indicate a higher susceptibility of males compared to females (Table 1). This may also be due to the fact that cardiovascular diseases are more predominant in males than in females, and thus, the proportion of male population receiving the drugs is more in number.

Incidence of hyponatremia was high in the age group 50–60 years compared to the other age groups. However, the magnitude of serum sodium lowering was found to be higher in patients above 70 years of age (Table 1). A study on patients receiving losartan had also reported the incidence of hyponatremia at a mean age of 76.4 years [10]. Differences in the kinetics and dynamics of drugs in elderly patients could be the basis for this finding.

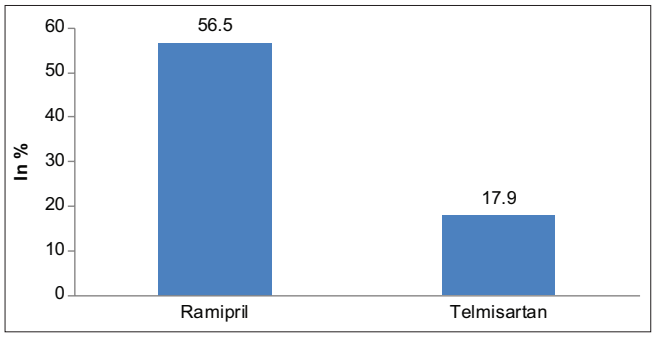

Fig. 1: Hyponatremia with ramipril and telmisartan

The mean sodium levels were lower (133.8 mEq/L) in ramipril group than in telmisartan group (137.3 mEq/L). Moreover, the incidence of patients who developed hyponatremia was higher in ramipril group than telmisartan group, it was statistically significant (p>0.05) (Table 3). However, the magnitude of hyponatremia with these two drugs was not statistically significant. Furthermore, literature search on earlier case reports revealed that ramipril-induced hyponatremia had been reported more [11].

CONCLUSION

Hyponatremia was found to be associated in nearly 35.3% of patients taking ramipril and telmisartan. The incidence of hyponatremia among patients on these two drugs showed statistical variation. However, the magnitude of hyponatremia with these two drugs was not statistically significant. The current study laid emphasis on the requisite for monitoring of serum sodium level in patients on ramipril and telmisartan administration to avoid morbidity and mortality due to unexpected adverse reactions.

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AUTHORS CONTRIBUTIONS

Both the authors contributed to the concept, design, screening of patients, selection and recruitment of patients, Informed consent, Laboratory investigations, Laboratory report interpretation, data collection and monitoring of data, interpretation of data, statistical analysis and interpretation, maintaining master file of project, drafting final report, submission of final report to the funding agency and IHEC, and publication.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest regarding the research, authorship, and publication of this article.

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