



**TO STUDY THE SAFETY AND EFFICACY OF TOLVAPTAN IN HYPONATREMIC
PATIENTS**

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Received 20th Jan. 2025; Revised 19th March 2025; Accepted 5th May 2025; Available online 1st April 2026

<https://doi.org/10.31032/IJBPAS/2026/15.4.10022>

ABSTRACT

Background: Hyponatremia, a electrolyte imbalance as serum sodium concentration of less than 135mEq/L. Hyponatremia is most common electrolyte disorder, with prevalence of 20% to 35% among the hospitalized patients. This is more common in the elderly patients due to the multiple comorbidities, multiple medications and lack of access to food. Tolvaptan is a selective, nonpeptide antagonist that blocks the arginine vasopressin from binding to V2 receptors of distal nephron, induces the excretion of electrolyte-free water without changing the total level of electrolyte excretion.

Objective: To study the safety and efficacy of tolvaptan in hyponatraemic patients.

Methodology: An ambidirectional cohort study design was conducted at Mallige Hospital, located in the heart of Bengaluru, the capital of Karnataka state of India. This study recorded 300 patients according to inclusion and exclusion criteria from ICU, Male ward and female ward and medical record department.

Result: This study shows that sodium level of patients before administration of tolvaptan is 121 mEq/L in 21 patients (14.1%), 125 mEq/L in 19 patients (12.9) and 131 mEq/L in 1 patient (0.7%). The sodium level after the administration of tolvaptan is 138 mEq/L in 42 patients (28.4%), 136 mEq/L in 26 patients (17.6%) and 135 mEq/L in 1 patient (0.7%).

Conclusion: The study revealed that the hyponatraemic patients who is treated with tolvaptan having higher efficacy than the patients who is treated with the IVF NS as a standard treatment.

Keywords: Hyponatremia, chronic kidney disease, SIADH, Tolvaptan, ADPKD

INTRODUCTION

Hyponatremia is an electrolyte imbalance as a serum sodium concentration of less than 135 mEq/L but can vary to some extent depending upon the set values of varied laboratories. Hyponatremia is a common electrolyte abnormality caused by excess of total body water in comparison to that of total body sodium content. Hyponatremia represents an imbalance in the ratio where total body water is more than total body solutes. Total body water has two main compartments, extracellular fluid and intracellular fluid, accounting for the remaining two-thirds. Sodium is the major solute of the extracellular fluid, and potassium for the intracellular fluid.

Hyponatremia is the most common electrolyte disorder, with a prevalence of 20% to 35% among hospitalized patients. The incidence of hyponatremia is high among critical patients in the intensive care unit and also in the postoperative patients. This is more common in the elderly patients due to the multiple comorbidities, multiple medications and lack of access to food [1]. It is usually classified as the hypovolemic, euvolemic and hypervolemic. The secretion of arginine vasopressin appears to be of central importance in the decline of serum sodium concentrations in all of these conditions. Hyponatremia is reported to be associated with increased morbidity and mortality among patients with heart, liver and neurologic

disease. Even mild chronic hyponatremia has been associated with subtle neurologic defects, manifested as impairments in balance and attention that can increase the incidence of falls. These deficits may be reversed with the correction of hyponatremia [2].

Tolvaptan is a selective, nonpeptide antagonist that blocks the arginine vasopressin from binding to V2 receptors of the distal nephron, inducing the excretion of electrolyte-free water without changing the total level of electrolyte excretion. Patients with heart failure, tolvaptan appears to decrease body weight and edema, increase serum sodium concentrations without adversely affecting serum electrolyte levels, vital signs and renal function [3].

The primary aim of the study was to evaluate the safety and efficacy of tolvaptan in a hyponatremic patient and other secondary objectives include its dosage regimen, effectiveness and adverse effect of tolvaptan in a hyponatremic patient.

MATERIALS AND METHODS

This was an ambidirectional cohort observational study. Patients above 18 years of age of both genders with existing or newly diagnosed hyponatremia prescribed with Tolvaptan and IV-fluids were selected and the purpose of the study was fully explained to the participants and they were asked to sign the informed consent form.

All assessments were performed at baseline and any adverse events occurring during the study were recorded throughout the study. The ethical approval for the study was granted by the Mallige Hospital. After the approval from IEC, voluntary written informed consent was obtained from the subjects and their legal representative before the start of the enrollment. The study was followed and conducted based on Ethics Committee notifications as per the GCP guidelines issued by the Central Drugs Standard Control Organization (CDSCO) and ethical guidelines for biomedical research on human subjects issued by the Indian Council of Medical Research (ICMR).

For this study data of patient was collected using the data collection form if the patient gives the data voluntarily after signing the consent form or from medical record department after their approval. After collecting the data, effectiveness and safety of tolvaptan in patients with pre-existing/current hyponatremia was analyzed from their medication chart.

In this study 300 patients who fulfilled the inclusion criteria were included and whereas the pregnant women were excluded. The eligible participants underwent detailed assessment of their medication chart for their age, gender, type of renal impairment, class of antibiotics, dosage regimen, drug-drug interactions (DDI) and Adverse drug effects

(ADR).

Any ADRs reported by patients or attenders were noted using Naranjo scale at clinical visits. The DDIs were assessed using the online database such as Micromedex and Medscape. If any ADR or DDI occurred, then it was reported and recorded.

STUDY SETTING AND POPULATION

The study was conducted at Mallige Hospital, Crescent Road, Bangalore, Karnataka, India. A total of 300 subjects were enrolled in the study (166 males & 134 females). In-patients attending nephrology department, general medicine and cases from medical record department were included.

DATA ANALYSIS

Data was analysed using MS-Excel and SPSS. The results were obtained in the form of graphs and tables.

RESULTS

Out of 300 cases of hyponatremia, 166 patients (56%) were males and 134 patients (43%) were females. Most number of patients were seen within the age group of 51-60(24.8%) and weight category of 61-70 kg (132 patients). Hypertension was the major risk factor and was observed in 178 patients (71.2%) followed by diabetes mellitus (66.4%). In the present study, majority of patients having sodium level between 130-132mEq/L for 109 patients (36.6%) and least observed sodium value between 110-115mEq/L for 41 patients

(1.3%).

1. SODIUM LEVEL BEFORE ADMINISTRATION OF IV-FLUIDS

It shows that most of the patient before administration of IV-Fluids having sodium level of 133mEq/L for 29 patients (18.8%),

132mEq/L for 27 patients (17.5%), 134mEq/L for 17 patients (11%), 131mEq/L for 14 patients (9.5%), followed by 114,116,135,136 mEq/l for 1 patient (0.6%).

SODIUM LEVEL (mEq/L)	NO OF PATIENTS	PERCENTAGE (%)
133	29	18.8
132	27	17.5
134	17	11
131	14	9.5

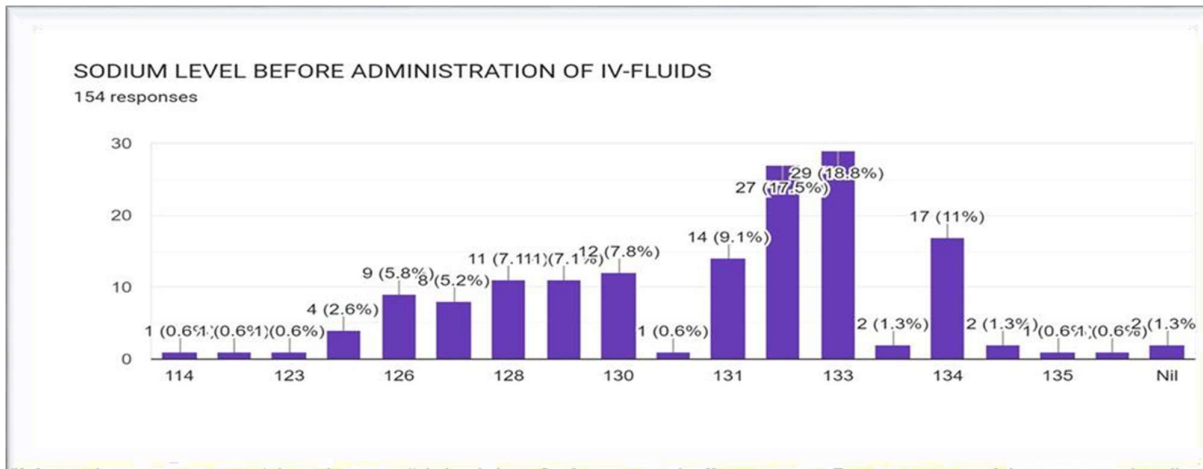


Figure 1: Sodium level before administration of IV-Fluids

2. SODIUM LEVEL AFTER ADMINISTRATION OF IV-FLUIDS

Sodium level after administration of IV fluids in 153 patients are depicted in graph as follows; It shows that most of the patient

having sodium level 138mEq/L for 26 patients (17%) followed by 139mEq/L for 16 patients (10.5%) and least observed sodium level is 135,145 mEq/L for 1 patient (0.7%).

SODIUM LEVEL (mEq/L)	NO OF PATIENTS	PERCENTAGE (%)
135	1	0.7
136	27	2
137	35	0.7
138	26	17
139	16	10.5
140	13	8.5
141	18	5.2
142	10	6.5
143	7	4.6
144	3	2
145	1	0.7

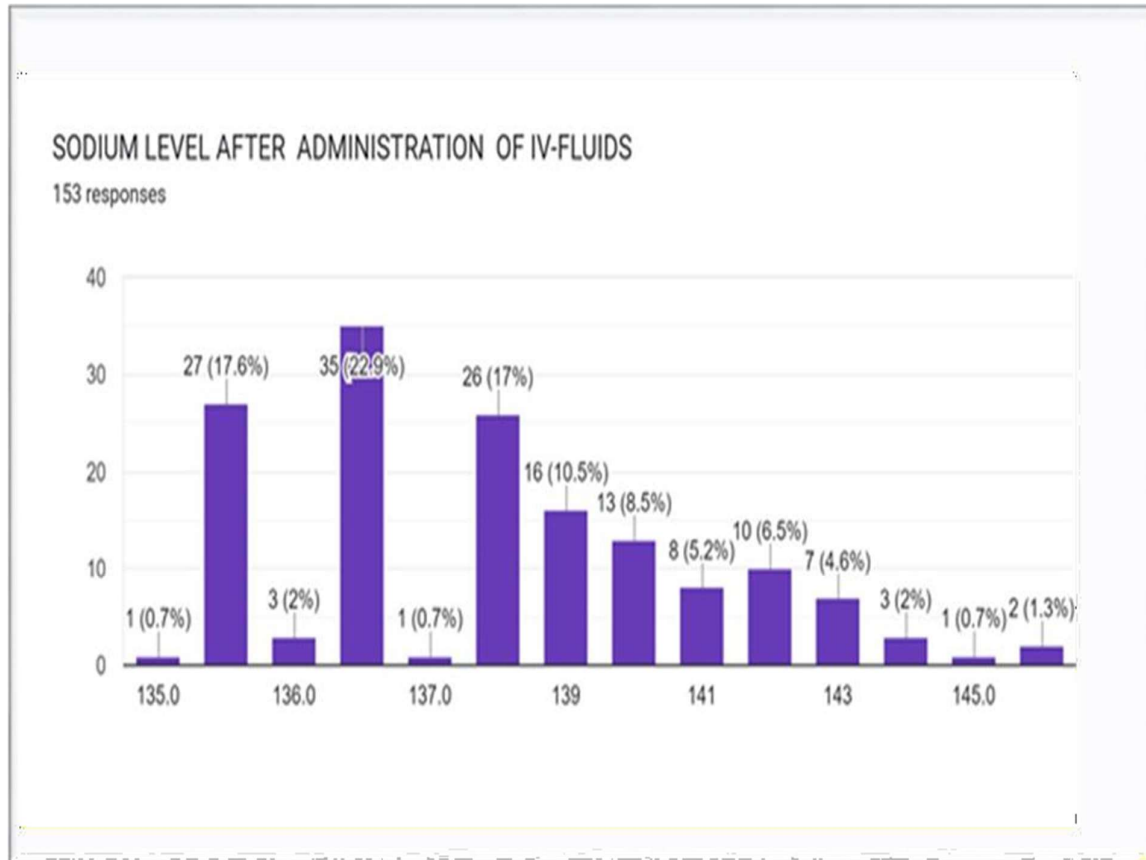


Figure 2: Sodium level after administration of IV-Fluids

3. SODIUM LEVEL BEFORE ADMINISTRATION OF TOLVAPTAN

Sodium level before administration of tolvaptan in 149 patients are depicted in graph as follows; It shows that most of the

patient having sodium level 121mEq/L for 21 patients (14.1%) followed by 124, 125mEq/L for 19 patients (12.9) and least observed sodium level is 111,131mEq/L for 1 patient (0.7%).

SODIUM LEVEL (mEq/L)	NO OF PATIENTS	PERCENTAGE (%)
111	2	1.3
112	1	0.7
114	5	3.4
116	7	4.7
117	2	1.3
118	3	3.2
119	1	0.7
120	7	4.7
121	21	14.1
122	13	8.7
123	16	10.7

SODIUM LEVEL BEFORE ADMINISTRATION OF TOLVAPTAN

149 responses

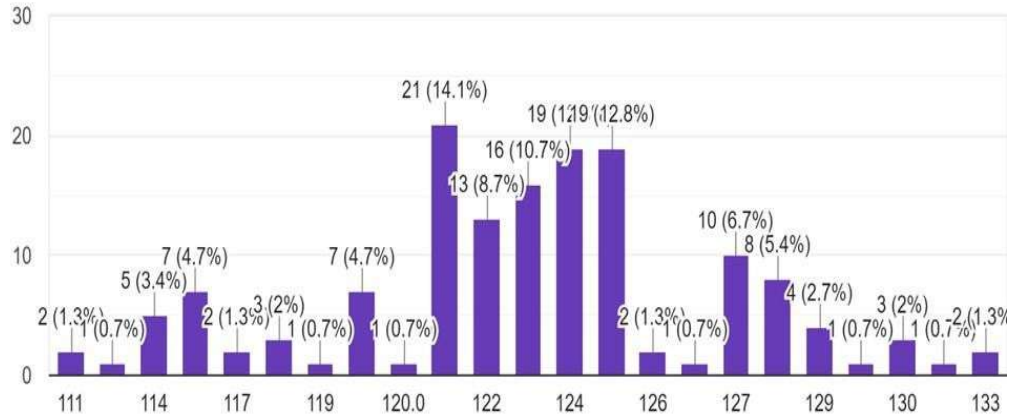


Figure 3: Sodium level before administration of Tolvaptan

4. SODIUM LEVEL AFTER ADMINISTRATION OF TOLVAPTAN

Sodium level after administration of tolvaptan in 148 patients are depicted in graph as follows; It shows that the most of

the patient having sodium level 138mEq/l for 42 patients (28.4%) followed by 136mEq/l for 26 patients (17.6%) and least observed sodium level is 130,135mEq/L for 1 patient (0.7%).

SODIUM LEVEL (mEq/L)	NO OF PATIENTS	PERCENTAGE (%)
130	1	0.7
133	2	1.4
135	1	0.7
136	26	17.6
137	37	25
138	42	28.4
139	12	8.1
140	2	1.4
141	2	1.4
142	5	3.4
143	5	3.4

SODIUM LEVEL AFTER ADMINISTRATION OF TOLVAPTAN
148 responses

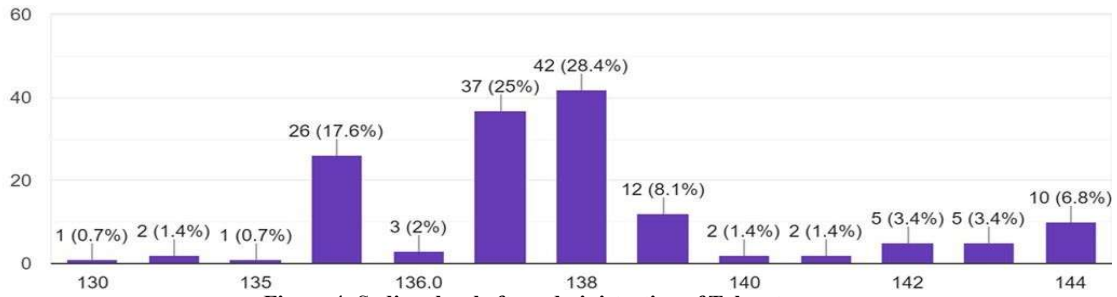


Figure 4: Sodium level after administration of Tolvaptan

5. ADVERSE DRUG REACTION

Among the 189 patients following graph show the adverse drug reaction occurred. The most occurred adverse drug reaction

was thirst, which was seen in 63 patients (33.3%) followed by nausea in 53 patients (28%) and the least observed adverse drug reaction is pollakiuria in 1 patient (0.5%).

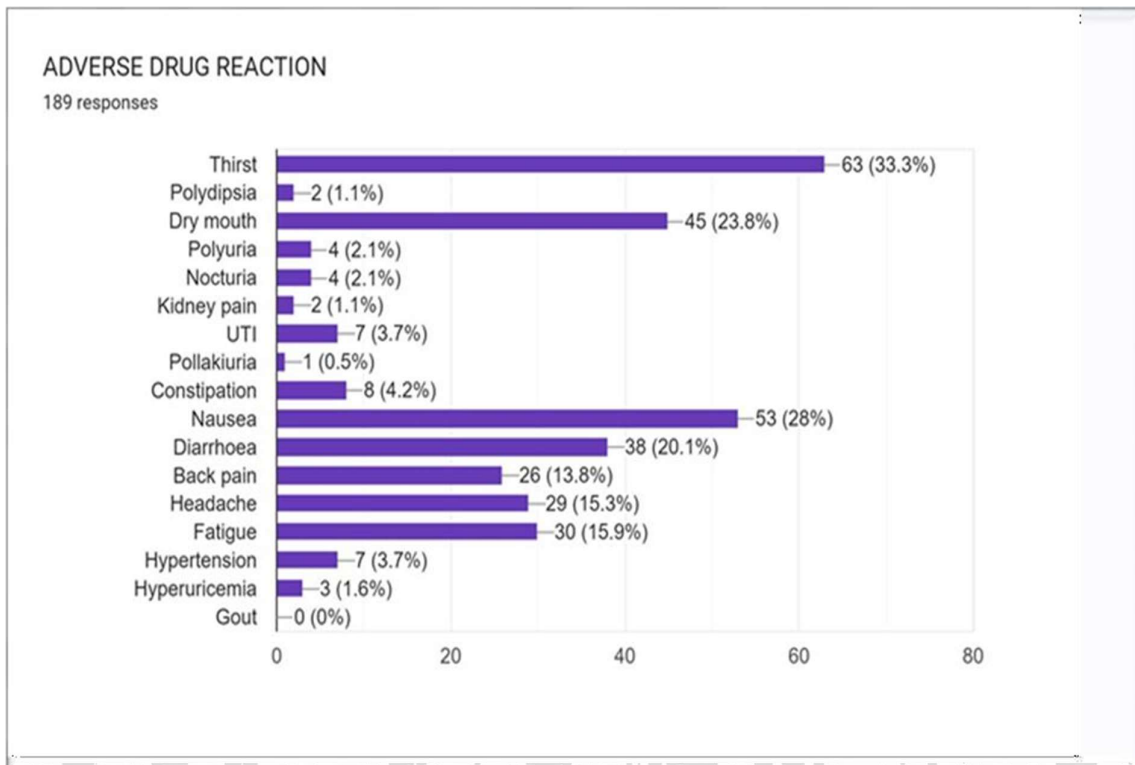


Figure 5: Adverse Drug Reaction of patients

6. DRUG INTERACTIONS

The study showed that the drug interaction between tolvaptan and diclofenac was the most reported. One (19 cases) followed by

tolvaptan and spironolactone (14 cases) and the least observed drug interaction was tolvaptan with itraconazole and ritonavir (1 case).

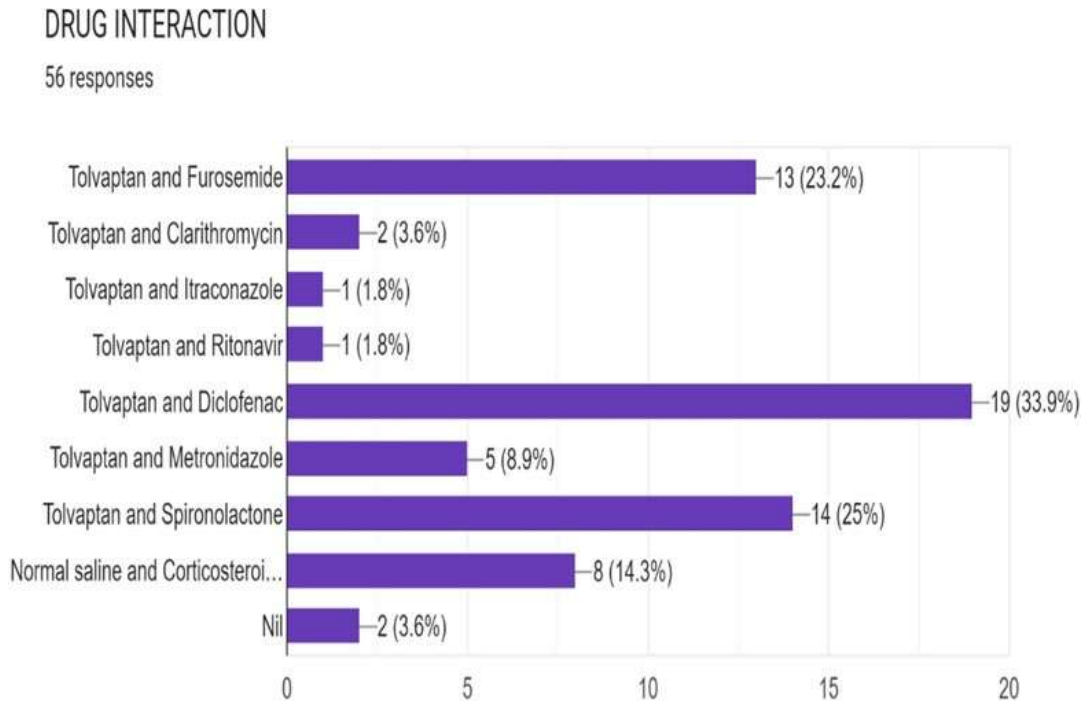


Figure 6: Drug interactions

DISCUSSION

Hyponatremia is a condition characterized by an abnormally low level of sodium in the blood. Sodium is an essential electrolyte that helps regulate water balance in and around cells, and it is crucial for Proper nerve and muscle function. The causes of hyponatremia are typically classified by a person's body Fluid status into low volume, normal volume, or high volume.

Low volume hyponatremia can occur from Diarrhoea, vomiting, diuretics, and sweating hyponatremia can occur from heart

failure, liver failure, and kidney failure the prevalence of hy The incidence of the hyponatremia is high among critical patients in the intensive care unit and also in the Postoperative. This is more common in the elderly patients due to the multiple comorbidities, Multiple medications and lack of access to food. Very often hyponatremia patients are treated with tolvaptan and normal saline.

Tolvaptan is a selective, nonpeptide antagonist that blocks the arginine vasopressin from binding to V2 Receptors of

distal nephron, induces the excretion of electrolyte-free water without changing the total level of electrolyte excretion. Just like tolvaptan, another treatment option for hyponatremia is administration of intravenous normal saline. For severe hyponatremia, a doctor may administer 100 mL boluses of 3% hypertonic saline every 10 minutes, up to three times. This can raise sodium levels by 4–6 mEq /L per day. Hypertonic saline can be administered through a peripheral IV, but central venous access is preferred. This study was done to evaluate the safety and efficacy of tolvaptan in hyponatremia patients at a tertiary care hospital.

This study recorded 300 patients according to inclusion and exclusion criteria from ICU, Male ward and female ward and medical record department. Out of 300 patients in the study 56.1% was male and 43.9% was female. Hence majority of patients with hyponatremia was male. Many possible conditions and lifestyle factors and certain medications can cause hyponatremia in male.

This study was conducted between Age group of 0-100 and it was found that the majority of the patients were in the age group 51-60 around 74 patients (24.8%) and the second major age group was 61-70 around 67 patients (22.5%) were affected by the condition. It occurs because in this age group patient are more likely to take medicines or

medical problems that cause this condition.

This study revealed that majority of patients was suffering from hyponatremia are from the weight category of 61-70 kg (132 patients) followed by 51-60 kg (74 patients). The major risk factors that was observed in the patients who were taken under the studies are hypertension- 178 patients (71.21%), second major risk factor was Diabetes mellitus- 166 (66.4%). Other risk factors such as Thyroid illness, Cardio vascular accident, Ischaemic heart disease, COPD, Asthma, Bronchitis are significantly involved. Hypertension patients are more likely to take some certain medications like thiazide, which leads to this condition. Ponatremia is 20% to 35% among the hospitalized patients.

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The major biochemical marker used in the study was sodium levels. The majority of patients 36.6% were having sodium value in between 130-135 mEq/L. Second significant around 83 patients (27.9%) were having sodium level 120-130 mEq/L. Among 300 patients, in 148 patients Tolvaptan was used, mostly they were having sodium level below 125 mEq/L.

Most of the patients around 21 (14.1%) got administered with sodium level 121 mEq/L. And second major number of patients are 19 (12.8%) got administered with sodium level 124 mEq/L. On administering tolvaptan 15mg, there was significant rise in sodium level in the 149 patients. Around 42 (28.4%) patients the sodium levels raised to 138 mEq/L and in 37 (25%) patients raised to 137 mEq/L.

In this study 154 patients were administered 30ml IV Fluid for the same condition. And the sodium level in these patients were between 125-135 mEq/L. Majorly 29 patients (18.8%) were having sodium level

133 mEq/L and around 27 patients (17.5%) were having sodium level 131 mEq/L. On administration of IV Fluids the sodium level raised majorly till 137 mEq/L in 35 patients (22.9%). In this study among 300 patients, 151 patients (51.40%) were treated with Tab Hyponat (Tolvaptan) 15mg orally and 142 patients (48.30%) were treated IV NS 0.9% in 100ml. Tolvaptan is preferred more in patients with hyponatremia because it shown more prominent and prompt action in patients below 125 mEq/L sodium level.

This study has shown that around 63 (33.3%) patients had an adverse drug reaction of Thurst followed by 53 (28%) patients were suffering from Nausea. Other significant adverse drug reaction was Dry mouth (45%), Diarrhoea (38%), Fatigue (30%), Headache (29%), Back pain (26%) This study shows that the drug interaction between tolvaptan and diclofenac was more frequent (19 patients), because both the drug increases serum potassium and the second major drug interaction was found in between Tolvaptan and Spironolactone (14 patients) because of the same reason.

CONCLUSION:

Hyponatremia is a electrolyte imbalance as a serum sodium concentration less than 135 meq/l The incidence of hyponatremia is high among critical patients in the ICU and also in post operative patients. This is more common in elderly patients due to the multiple comorbidities and multiple

medications and lack of access to food. The present study demonstrate the safety and efficacy of tolvaptan in hyponatremic patients. The study was conducted on 300 individuals from a tertiary care hospital. The findings indicate that elderly patients having higher prevalence of renal Impairment.

The study discovered that majority of Patients were affected by CKD, DM, HTN The diagnosis was made based on the observation of sodium level. The study revealed that the hyponatremia patients who is treated with tolvaptan having higher efficacy than the patients who treated with the IVF NS as a standard treatment.

Acknowledgement

For the successful completion of this project, we required a lot of guidance, supervision and support from many people and we are extremely happy and feel privileged to get such support. We take this opportunity to express our gratitude to all of them.

We would like to express our heartfelt gratitude to respected Dr. Shailesh Yadav, ASOCIATE PROFESSOR & HOD, Department of Pharmacy Practice, Mallige College of Pharmacy, for his valuable guidance, inspiration, unflinching encouragement, and moral support throughout this project work. We thank our guide Dr. Shailesh Yadav, Associate Professor & HOD, Department of Pharmacy Practice, Mallige College of Pharmacy for

his immense support and guidance in technical matters of this study, which made us complete the project.

We take our deep sense of gratitude and reverence to Dr. S.V RAJENDRA, Principal of Mallige College of Pharmacy, for providing us the requisite opportunities and facilities during PharmD academic program.

We are thankful and fortunate enough to get constant encouragement, support and guidance from all the teaching staffs of Mallige College of Pharmacy, which helped a lot in successful completion of this project work. We do love to express our sincere thanks to our juniors and non-teaching staffs for supporting us throughout our work in their own way.

Our heartfelt gratitude is extended to all our dear classmates for their encouragement.

We are greatly indebted to our beloved parents for their countless prayers, love, faith, encouragement and support throughout this wonderful journey. We also express our sincere gratitude to the Renal Dialysis Unit, In-patient Department, Medical Records Department, Supporting Doctors, Nurses, Pharmacists and Medical Laboratory Department who supported us their own way for the successful completion of this study.

Thank you one & all.

Source of Funding: No source of funding was provided.

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Table Analyzed	Col. One-way ANOVA				
Data sets analyzed	A-D				
ANOVA summary					
F	830.6				
P value	<0.0001				
P value summary	****				
Significant diff. among means (P < 0.05)?	Yes				
R squared	0.8070				
Brown-Forsythe test					
F (DFn, DFd)	13.79 (3, 596)				
P value	<0.0001				
P value summary	****				
Are SDs significantly different (P < 0.05)?	Yes				
Bartlett's test					
Bartlett's statistic (corrected)	70.43				
P value	<0.0001				
P value summary	****				
Are SDs significantly different (P < 0.05)?	Yes				
ANOVA table					
	SS	DF	MS	F (DFn, DFd)	P value
Treatment (between columns)	24171	3	8057	F (3, 596) = 830.6	P<0.0001
Residual (within columns)	5781	596	9.700		
Total	29952	599			