



TOLVAPTAN IN HYPONATREMIA- AN OBSERVATIONAL STUDY

General Medicine

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ABSTRACT

Introduction- Hyponatremia is a common disorder of water and sodium occurring in patients in wards and intensive care units of hospitals. Various modalities of treatment are tried to overcome this disorder including free water restriction, use of salt capsules and extra salt in diet, etc. **Objectives-** To study the efficacy of tolvaptan in correction of hyponatremia; the use of tolvaptan in patients with hyponatremia- euvolemic / hypervolemic / hypovolemic type; the adverse effects of the drug – as witnessed by the patients receiving the drug; the frequency and duration for which the drug is prescribed on a day-to-day basis for hyponatremia, in a clinical setting by different medical practitioners, the correlation between other laboratory parameters like cbc, creatinine, electrolytes, liver enzymes (sgot, sgpt, bilirubin) and - sodium correction by the drug. **Methodology:** A prospective observational study was conducted among 50 patients admitted to a tertiary care centre with hyponatremia during the period of study from January 2022 to January 2023. Type of hyponatremia was documented along with serial serum sodium measurements after treatment with tolvaptan were noted, among side effects and other laboratory parameters. **Results:** The data suggests that Tolvaptan is efficacious drug in the treatment of hyponatremia specially when it is not corrected with standard treatment. The mean sodium levels prior to starting the drug and after the drug were compared by t test and results were $p < 0.001$ thus found to be statistically significant indicating that Tolvaptan was efficacious in improving sodium levels in these patients. It was further observed that Tolvaptan was prescribed most in patients who had SIADH or Euvolemic hyponatremia. **Conclusion:** The drug Tolvaptan was found to be efficacious with statistically significant results in treating hyponatremia in Euvolemic/SIADH (Syndrome of inappropriate anti diuretic hormone secretion) and Hypervolemic states like in heart or liver diseases.

KEYWORDS

Hyponatremia, Tolvaptan, SIADH

INTRODUCTION-

Hyponatremia (typically defined as serum sodium level < 135 meq/L) is a common electrolyte abnormality observed amongst hospitalized patients. (1) The normal serum sodium concentration is between 135-145 meq/L. Hyponatremia is classified according to volume status, as follows- Hypovolemic hyponatremia: decrease in total body water with greater decrease in total body sodium. Euvolemic hyponatremia: normal body sodium with increase in total body water. Hypervolemic hyponatremia: increase in total body sodium with greater increase in total body water. The presence and severity of clinical symptoms largely depends on the rate and extent of the decline in serum sodium; rapid or large declines may lead to serious neurological complications. The approach to treatment depends on the presence and severity of neurological complications, the underlying aetiology, and the patient's volume status. Patients with euvolemic or hypervolemic hyponatremia usually have inappropriately elevated levels of arginine vasopressin, which stimulates water reabsorption even in the presence of low serum osmolality. Tolvaptan is an orally active, selective V2-receptor antagonist that blocks the effects of arginine vasopressin in the renal collecting duct thus causing an increase in the urinary water excretion, resulting in an increase in the free water clearance, promotes aquaresis, a decrease in urine osmolality and it increases serum sodium in a controlled manner (2). Tolvaptan offers a mechanism-based treatment option for patients with hyponatremia who have serum sodium levels < 125 meq/L or persistent symptoms resistant to fluid restriction in cases of euvolemic hyponatremia e.g. in Syndrome of inappropriate anti diuretic hormone secretion and hypervolemic hyponatremia e.g., in congestive cardiac failure (3) or liver cirrhosis (4) The above background will help us in the study of Vasopressin antagonist Tolvaptan (5) in the treatment of hyponatremia in a group of hospitalised patients in a Tertiary care centre.

MATERIALS AND METHODS

A prospective observational study was conducted among 50 patients admitted to a tertiary care centre with hyponatremia during the period of study from January 2022 to January 2023. Adults aged > 18 years, who were hospitalized with Hyponatremia (with serum sodium less than 130 meq/L) categorised into Euvolemic Hyponatremia, Euvolemic is defined as absence of clinical and historical evidence of extracellular fluid volume depletion or sequestration and absence of

oedema or ascites; Hypervolemic hyponatremia Hypervolemia is defined as an excess extracellular fluid volume in dependent oedema or ascites; Hypovolemic hyponatremia Patients on diuretic therapy as Thiazides, or history of diarrhoea or vomiting or any volume depleted state.

OBSERVATIONS AND RESULTS

The study participants had a mean age of 62.9 ± 13.5 years. 70% were males and 30% were females. 36% of patients who had hyponatremia and received Tolvaptan were admitted with complaint of drowsiness. It was the most common chief complaint observed in the study. Other complaints included cough (14%), weakness (12%), breathlessness (10%), dyspnea on exertion (10%), headache (8%), irrelevant talk (4%), admitted for surgery (4%) and loss of appetite (2%). It was observed that 50% patients had hypertension followed by diabetes mellitus in 38%. Other co-morbidities are as depicted in the graph below-

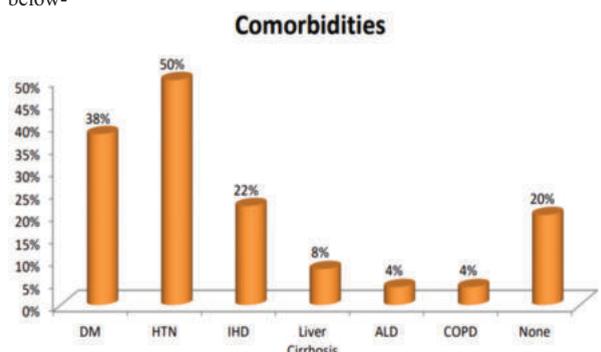


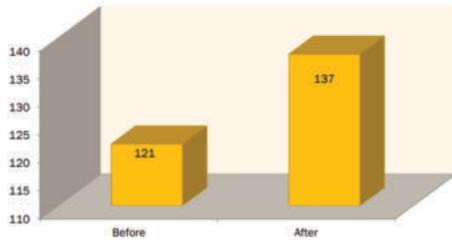
Fig.1 Comorbidities of patients included in the study

It was observed that 48% of patients had medication history mainly chlorthalidone or frusemide. 52% were not on any medication.

Table 1 & Fig.2- Mean sodium levels before and after starting Tolvaptan

	Before	After	significance
Mean Na Levels	121 ± 3.75	137 ± 5.62	P<0.0001 *
			significant

*ttest was used to compare the mean sodium levels.
Mean Na Levels



The above graph depicts the efficacy of tolvaptan in treating hyponatremia. It is observed that the mean sodium levels before and after starting tolvaptan were 121 and 137 respectively. The p value < 0.0001 shows that the results are statistically significant and Tolvaptan is efficacious in correcting low sodium levels.

Table 2- Side effects seen in patients on Tolvaptan

	No. of patients	No. of days drug given (mean)
Cerebral myelinolysis	1	6
Dry mouth	7	4.43
Nausea	7	4.71
Polyurea	6	3.57
None	29	5.82
Total	50	

The above table depicts the side effects of the drug TOLVAPTAN showing that majority of patients in the study, receiving tolvaptan, did not have any adverse effects upon consuming the drug. However, Nausea, Polyurea and Thirst were most commonly reported when the drug was taken for an average duration of 2-5 days. Cerebral Pontine Myelinolysis is a rare condition, observed in one patient, that occurs due to rapid correction of sodium in cases with moderate to severe hyponatremia.

Table 3- Laboratory parameters before and after in patients on Tolvaptan

	Before	After	significance
S. Creatinine	1.37 ±0.56	1.35 ±0.55	P>0.05 NS *
SGOT	63.38 ±64.69	60.2 ±51.65	P>0.05 NS **
SGPT	69.94±71.75	63.08±54.64	P>0.05 NS **
K	3.83±0.55	3.9±0.38	P>0.05 NS *

*ttest was used to compare mean Creatinine levels, K levels.

**Mann-Whitney test was used to compare mean SGOT and SGPT values.

In these group of patients, to assess the effects of TOLVAPTAN on the laboratory parameters, they were measured before the start of the drug and after the drug was stopped and a comparison is made between the two. The above table indicates that in a group of 50 patients who received TOLVAPTAN, there was NO significant effect on the Serum creatinine, serum potassium levels or liver enzymes observed.

It is shown that Tolvaptan was given in majority of patients with EUVOLEMIC HYPONATREMIA OR SIADH (52%) followed by Hypervolemic hyponatremia (35%). Tolvaptan most commonly advised by physicians (44%) followed by cardiologists (16%) followed by gastroenterologists (12%), neurologist (10%) and neurosurgeons (10%).

DISCUSSION

All cases of hyponatremia who have been advised tolvaptan in addition to the standard treatment for hyponatremia e.g., fluid restriction and diuretics in cases of hypervolemia or fluid restriction and high salt diet in cases of euvolemia other conditions etc. but have not adequately responded to the treatment have been included in this study. Out of 50 cases selected, 70% of the patients were Males and 30% were Females. Hyponatremia was found to be more common in age groups 50-70 years (56%). Least incidence (6%) of hyponatremia was seen in 30-40 years of age. It was observed that majority of patients who developed hyponatremia had chief complaints of drowsiness (36%), followed by cough (14%), weakness (12%) and breathlessness (10%). About (8%) of them had headache and altered sensorium, and (4%) had complaints of irrelevant talks. About (4%) of the patients were admitted for surgery and developed hyponatremia post operatively. Thus indicating that hyponatremia is more common in patients with altered hemodynamic status and morbid conditions. Various co morbid conditions were observed in relation to low sodium levels, e.g., Hypertension was seen in about (50%) of these patients followed by Diabetes Mellitus accounting to (38%). About (22%) of the patients had a history of ischemic heart disease. (8%) of patients were a known case of Liver Cirrhosis and (4%) had Alcoholic Liver Disease. (4%) of patients also had a history of Chronic Obstructive Pulmonary Disease. Rest 22% had nil co morbidities. Thus, depicting that Hyponatremia is more prone in patients HTN, DM along with patients with Cardiac and Liver diseases. There are about 4% patients included in the study who had a history of recurrent hyponatremia and were on tolvaptan for a period of 2-3 months intermittently and their sodium levels were regularly monitored with baseline sodium levels between 129-132. In these patients the sodium levels would fall once tolvaptan was stopped and hence had to be restarted and continued for a long period of time. 48% patients with hyponatremia had a history of medications/drugs for coexisting illness. Most encountered drugs were Thiazides like Chlorthalidone given mainly for Hypertension or Frusemide in patients with Heart failure with reduced ejection fraction (6)(7). Other medication involved oral hypoglycemic agents for diabetes mellitus, ACE/ARBs for blood pressure. Patients with chronic liver disease were on Aldactone. All the above drugs mentioned did not necessarily lead to low sodium levels except Chlorthalidone which is the thiazide (8) diuretic which was found to be more commonly associated with hyponatremia.

The data obtained suggest that Tolvaptan is a highly efficacious drug in the treatment of hyponatremia specially when it is not corrected on standard treatment for the same. The mean sodium levels prior to starting the drug and after the drug were compared by t test and results were p <0.001 thus found to be statistically significant indicating that Tolvaptan was efficacious in improving sodium levels in these patients. It was further observed that Tolvaptan was prescribed most in patients who had SIADH (9) or Euvolemic hyponatremia. These patients were initially treated with Fluid restriction and high salt diet. Due to lack of response to the above, Tolvaptan was added. About 52% of such patients constituted this group and were either diagnosed with Subdural hematoma, sub arachnoid hemorrhage/Intra cerebral hemorrhage, demyelinating neuropathy or post operatively (cancer surgeries). The next most common group of patients who were given Tolvaptan were those who developed hyponatremia due to Hypervolemic status. About 34% of these patients were in Fluid overload/ Edematous status. 22% of them had a history of ischemic heart disease with reduced systolic function (EF20-25%). About 4 % of the patients had a history of Liver cirrhosis with Portal hypertension and ascites. They were initially treated with Fluid restriction and diuretics but did not respond to the standard treatment. Tolvaptan was found to significantly improve sodium levels in these patients and also caused significant weight reduction by increased urine formation. (Diuresis) About 10% of the patients observed in this study were admitted with gastroenteritis or dehydration and were prescribed tolvaptan. They were in hypovolemic states. These patients developed increased thirst and polyurea (discussed below) and thus the drug had to be discontinued after approximately 1-2 days as it caused minor worsening of the clinical status. Thus, inferred that Tolvaptan should

not be used in this subset of patients with low volume status (hypovolemic hyponatremia). Standard Fluid therapy was sufficient in these subsets of patients. Drug induced hyponatremia comprised 4% of these patients and the most common drug associated with this was Thiazide diuretic namely Chlorothalidone at a dose of 12.5 mg taken for Hypertension. This group of patients also comprised the hypovolemic group. Adverse effects noted in these patients were mainly Dry mouth and Polyuria with Nausea. About 28% of the patients did not complaint of any side effects on receiving tolvaptan. Nausea and dry mouth were observed in 7% of these patients and 6 % patients had polyuria. 1 patient developed Cerebral Pontine Myelinolysis (as per MRI report) (10)who had received tolvaptan for hyponatremia (SIADH). The duration of tolvaptan given in this patient was for 6 days. The patient died due to multiple co-morbid conditions and septic shock. The side effects of this drug were co-related with the duration of the drug given. It was found that Dry mouth and thirst were seen when the drug was given for an average of 4-5 days. Polyuria was observed within the duration of 3-4 days. The effect of Tolvaptan on various Laboratory and Hemodynamic parameters was also noted. Laboratory parameters mainly Complete blood count, Serum creatinine, Liver enzymes, Bilirubin and Serum electrolytes were noted at the start of the study and these parameters mainly Creatinine, SGOT/SGPT and Potassium were noted after completing the course of Tolvaptan. It was observed that Tolvaptan had NO significant effect on Creatinine, Liver enzymes or potassium levels. Thus, concluding that Tolvaptan has no adverse effects on kidney and liver or electrolytes, when given for a short duration. Although Tolvaptan is known to cause liver dysfunction as a potential side effect, the results from this study showed $p > 0.05$ which is insignificant. Urine spot sodium was measured in all the patients was measured in all the patients who had hyponatremia and mean value was 51. Most cases were euvoletic with urinary spot sodium more than 20.

Hemodynamic parameters were observed in these patients. Vitals like blood pressure, heart rate, saturation varied in these patients depending on the clinical diagnosis and was dependent on the treatment of the underlying condition. Although, Body weight was one parameter that was affected on giving tolvaptan. Patients receiving tolvaptan showed statistically significant reduction in weight. It was observed that prior to starting tolvaptan, the average weight was 70.16 ± 9.37 and afterwards was 68.35 ± 8.91 . It showed statistically significant ($p < 0.001$) reduction in weight after receiving tolvaptan, attributed to increased urine formation. (Diuresis) The duration of tolvaptan was given for 3 days in majority of patients with an average of 4-5 days. It is observed that tolvaptan is given most commonly for 4-5 days till the mean sodium levels are achieved. As this is a study on hospitalized patients, Tolvaptan was given for a shorter duration till the sodium levels normalized. Tolvaptan was used by doctors of all specialties to treat hyponatremia. In the study, the majority of doctors as per their specialty, prescribing tolvaptan to patients in hyponatremia were General Physicians (Most common) comprising (44%), followed by Cardiologists (16%) and Gastroenterologists (12%). Neurologist and neurosurgeons constituted (10%) and General surgeons and oncosurgeons comprised and respectively. Thus Tolvaptan is increasingly used by 6%) 2% medical practitioners in a cli based on their nical care setting for the treatment of judgement and clinical decision making.

CONCLUSION

Tolvaptan was found to be highly efficacious with statistically significant results in treating hyponatremia in Euvoletic/SIADH (Syndrome of inappropriate anti diuretic hormone secretion) or Hypervolemic states like in heart or liver diseases. In hypervolemic patients, like in cardiac failure or liver cirrhosis, resistant to standard treatment like fluid restriction or diuretics, or in non-compliant patients for correction of hyponatremia. It was not only efficacious in correcting sodium levels but it was also helpful in the improvement of overall clinical status of the patient by causing diuresis and reducing length of hospital stay.

Same applies to hyponatremia associated with SIADH, where low sodium levels when did not respond to fluid restriction and high salt diet, Tolvaptan produced improvement in sodium levels in 3-5 days. It was found to be less efficacious when used in hypovolemic states as it caused increased fluid loss and dehydration, causing mild worsening of clinical condition. The mean duration of giving Tolvaptan as per the study ranged between 3-5 days. Common Side effects observed in these subsets of patients were Dry mouth, polyuria and nausea when

given for a short duration of time, but were not severe enough for the patients to stop therapy. The side effects were reversed when the drug was stopped. Cerebral pontine myelinolysis is a rare side effect and was observed in one patient who was advised tolvaptan. Tolvaptan caused significant reduction in weight attributed to fluid loss (Diuresis) but other hemodynamic parameters like Blood pressure, Heart rate, oxygen saturation were not affected. Laboratory parameters like renal parameters (creatinine), liver enzymes (SGOT, SGPT, Bilirubin) or serum electrolytes (Potassium/ chloride) were not affected when given for a short duration.

To conclude, Tolvaptan shows promising results in the treatment of hyponatremia.

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