Efficacy and Safety of Oral Tolvaptan Therapy in Hospitalized Cirrhotic Patients with Hyponatremia

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Abstract

Background: Tolvaptan is an orally administered, nonpeptide, selective arginine vasopressin V(2) receptor antagonist that increases free water clearance, thereby correcting and increasing the low serum sodium levels in patients of cirrhosis, where hyponatremai is am major encountered problem.

Aims: Evaluate the efficacy and tolerabilty of tolvaptan in cirrhotics with symptomatic hyponatremia that resist correction with fluid restriction. Intellectual improvement assessed using Short Portable Mental Status Questionnaire (SPMSQ) pre and post therapy(on conclusion). Adverse drug reactions monitored to assess safety.

Methdology: Study design: Prospective, pre and post drug efficacy and safety evaluating study with permission from ethical committe. Study Population: one hundred cirrhotic patients, irrespective of etiology, with hyponatremia, who fulfill the inclusion criteria. Protocol: All enrolled patients, treated with oral Tolvaptan at doses of 15 mg once daily in addition to the concurrent treatment regimen. Tolvaptan therapy was concluded as soon as the patient reached the normal sodium levels, which were monitored daily.

Results: Our study population had a majority of Hepatitis C patients (49%). Mean sodium levels at baseline were 125.79 + 3.49 which had a significant (130.25+3.28), and highly significant (133+ 3.19) change post 48 and 72 hours. In clinical parameters, urine output was altered significantly (pre drug mean 1530.76+619.02 to post drug mean of 1783+563.01. Body weight and Abdominal girth changes were not significant.

Introduction

Hyponatremia has been shown to be an independent predictor of mortality.[1] Even mild asymptomatic hyponatremia has been shown to be associated with attention impairment, falls, fractures and osteoporosis in elderly patients.[2,3] It is further classified as:

a. Hypervolemic Hyponatremia: It is due to excessive retention of water and sodium, usually as a result of congestive heart failure or cirrhosis and Nephrotic syndrome.

b. Hypovolemic Hyponatremia: It is caused by excessive loss of water and electrolytes from the gastrointestinal tract or kidneys, usually as a result of severe diarrhea or abuse of diuretic drugs.

c. Euvolemic Hyponatremia. Euvolemic hyponatremia is caused by a primary defect in urinary dilution Example syndrome of inappropriate antidiuretic hormone secretion (SIADH) and can be caused by several different abnormalities in osmoregulation.[4]

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The symptoms are primarily neurological and relate to the rapidity of fall of serum sodium.

Usually from no symptoms at mild hyponatraemia to seizures, coma, permanent brain Hyponatraemia in clinical practice damage, respiratory arrest, brain-stem herniation and death may occur if severe low levels of sodium occurs.[5] The options for treatment of euvolemic hyponatremia and hypervolemic hyponatremia are fluid restriction, 3% saline administration and use of loop diuretics.[6] The major problems encountered in this conventional therapy are:

- Water restriction is slow to work and difficult to sustain due to inherent increased thirst sensation in these patients resulting in poor compliance.
- Saline administration can also be problematic in patients with hypervolemic hyponatremia as it can further cause volume expansion.[7]

One major class of upcoming drugs approved for hyponatremia are the VAPTANS.[8] Vaptans are vasopressin receptor antagonists, they acts by increasing electrolyte free-water excretion and thereby increasing serum sodium concentration and can be a better treatment option citing two reasons:[9]

- Greater ease in terms of titrating the correction rate of hyponatremia with vaptan than with hypertonic saline.
- No risk of pulmonary edema in response to vaptan as opposed to hypertonic saline

Considering the scarcity of data from Indian context, the present study was envisaged to assess efficacy and safety of tolvaptan in cirrhotic patients.

Material and Methods

Study Population: The study population included a total of 100 clinically and radiologically confirmed cirrhotic patients with hyponatremia, irrespective of etiology, who fulfilled the inclusion criteria and gave a written consent to participate in the study. Cases were enrolled from the Department of Medicine, G.G.S. Medical College & Hospital, Faridkot. ***Sample size:*** Using a two sided paired t test, achieving at least 80% power and a significance level of 0.05, the sample sizes calculated (Mean=1 meq/l, SD=1 meq/l) t73 patients. (Mean=1 meq/l, SD=3 meq/l). Recruitments of 100 patients were planned keeping in view the drop outs. The ***Inclusion criteria*** were as follows: (a) Age more than 18 years; (b) Hospitalised patients with clinically and radiologically confirmed cirrhosis; (c) Serum sodium level less than 135mmol/L; The ***Exclusion criteria*** included those with (a) Hypovolemic hyponatremia (b) Anuria (c) Patients who are unable to respond appropriately to thirst (d) Serum creatinine more than 3.5 mg/dl (e)Pregnant females (f) Concurrent drug therapy of CYP3A4 inhibitors like (ketoconazole, itraconazole, ritonavir, clarithromycin (g) Any co-morbid cognitive disorder (like Alzhiemer's) (h) Those not responding post 7 days of therapy (i) Hepatic encephalopathy.

After ethics committee approval (*vide letter no BFUHS/2015/156*), all enrolled patients, according to our study protocol, were treated with oral Tolvaptan at doses of 15 mg once daily in addition to the concurrent treatment regimen. As per the study protocol Tolvaptan administration was restricted to 7 days. Tolvaptan therapy was concluded as soon as the patient reached the normal sodium levels, which were monitored daily. Those with unaltered levels were labelled as non responders to 15 mg Tolvaptan and were excluded from the study. Comparison of clinical and investigational parameters (reduction of ascites, body weight, abdominal circumference) between day of enrolment (i.e before the therapy) and at conclusion of therapy were done. All patients underwent the following investigation performed after hospital admission.

- Complete hemogram, blood sugar, liver function test, Renal function test, PTI, INR, Total Serum Proteins, Serum Albumin.
- Serum electrolytes (daily until 7th day or discharge).
- Ultrasound, Chest X-ray and electrocardiogram.

Efficacy assessment

Primary Outcome Measure: The proportion of subjects with normal serum sodium level (135-145 mmol/l) evaluates the efficacy of tolvaptan in cirrhotic patients with hyponatremia

Secondary Outcome Measures

- o Change in sodium level from baseline and other electrolytes.
- o Change in body weight.
- o Reduction in Ascites (measuring urine volume over 24 hrs, abdominal circumference and edema).
- o Intellectual improvement.

Intellectual improvement was assessed using Short Portable Mental Status (SPMSQ) pre and post therapy(on conclusion).[10] This Questionnaire consists of ten questions which are to be answered without any memory aid. Total numbers of errors based upon the answers to the 10 questions were compared and analysed accordingly.

Addressing safety:

- By monitoring the adverse drug reactions after inclusion of the tolvaptan in treatment schedule.
- Renal function monitoring.

Statistical Analysis

Paired t test, pre and post drug therapy, was applied with presentation of data in appropriate mean and Standard deviations wherever required.

Results

Out of 100 patients recruited, 5 were labelled as non-responders, amid the unaltered levels of electrolytes (specifically sodium) to 15 mg of Tolvaptan. Excluding the non responder group from the results, 95 patients showing a positive response post 15 mg of therapy constituted our study group of responders. 3 other patients were excluded because of progressive hepatic encephalopathy in the disease course. So a total of 92 patients were included. The baseline demographic and clinical profile of patients is shown in Table 1.

Based on sodium level the patients were categorised in three groups A, B, C and D as shown in Table 2. Maximum number of patients presented with sodium levels between 125 and 130 (i.e Group B 44.5%), followed by sodium levels of 120-124.meq/L (i.e Group C) as evident.

The results of comparison of clinical and investigational parameters before and after the drug administration drug are tabulated in Table 3. A significant increase in serum sodium concentration post 24 and 48 hours and highly

Table 1: Demographic profile

Baseline characteristic		Value	
Total number of patients		92	
Age (year)		56.25± 9.45 (Mean±SD)	
Sex	Male	67	72%
	Female	25	27%
Education	Educated	36	40%
	Uneducated	56	60%
Occupation	Farmer	48	52%
	Self employed	21	23%
	House wife	23	25%
History of previous blood transfusion	Present	57	61%
	Absent	35	41%
Marital status	Married	90	98%
	Unmarried	2	2%
Cirrhosis etiology	Alcohol	49	53%
	HCV	45	49%
	HBV	22	24
Co-morbidity	Diabetes	08	8.7%
	Wilsons disease	01	1%
	Oesophageal varices	22	24%
Body weight (kg)		65.21 ± 12.62 (Mean ± SD)	

Table 2: Baseline sodium levels of the patients

Serum Sodium (meq/L)	Total no. of patients (n=92)	Percentage (%)
Group A (>131)	17	18.5%
Group B (125-130)	41	44.5%
Group C (120-124)	29	31.5%
Group D (<120)	05	5.5%

significant after 72 hours seen. Other electrolytes like potassium, chloride did not show any significant change. Liver injury biomarkers (trans-aminases) which were closely monitored during the therapy, the change reported was non- significant. Dry mouth and increased thirst were seen in 44% of patients, no other major side effect was noted. Apart from the five non responders (where sodium levels were unaltered) out of 92 patients, Tolvaptan therapy 15mg was continued to a maximum of seven days in 9%, six days in 8%, five days in 31%, four days in 49%, and 3 days in 4% of the patients. In clinical parameters, apart from urine output which significantly increased from its pre drug value i.e (1530.76 ±619.02 to1783±563.01), no significant reduction was seen in abdominal girth which was increased due to ascites or body weight pre and post therapy.

SPMSQ Score

Intellectual improvement using Short Portable Mental Status Questionnaire (SPMSQ) pre and post therapy (on conclusion) was done and a significant change in group C which included patients with sodium levels in range of 120-24. In group D, lesser number of patients, yielded a non significant result as shown in Table 4.

Table 3: Clinical and Investigational parameters before and after the drug

Variable	Pre drug value Mean± (SD)	Post drug value Mean± (SD)	p value
Sodium baseline (meq/L)	125.79 ±3.49	-	-
Post 24 hours	125.79 ± 3.49	127.28±3.23	0.0290*
Post 48 hours	125.79 ±3.49	130.25±3.28	0.001*
Post 72 hours	125.79 ±3.49	133±3.19 (sample size decreased)	0.001*
>72 hrs	125.79 ±3.49	134.17±3.17	0.001*
Potassium (meq/L)	4.05±0.611	4.03±0.57	0.81
Chloride (meq/L)	91.9±4.25	92.11±4.54	0.74
Blood urea (mg/dl)	44.16±3.96	45.53±4.22	0.068
Serum Creatinine (meq/L)	1.26±0.49	1.35±0.48	0.29
Clinical parameters			
Abdominal girth	59.83±16.26	58.91±16.144	0.7
Body weight	65.21±12.62	64.846±12.786	0.84
Urine output	1530.76±619.02	1783±563.01	0.043*

The p values with *marks are significant.

Table 4: Comparison of SPMSQ score

SPMSQ Score	No. of patients(n)	Pre drug score (Mean +SD)	Post drug score (Mean +SD)	p value
Group A	17	9.85+0.36	9.93+0.27	0.16 (NS)
Group B	41	9.53+1.45	9.62+1.57	NS
Group C	29	9.2+0.68	9.7+0.57	<0.5(S)
Group D	05	8.60+0.55	9.40+0.55	0.09(NS)

Discussion

Male predominance was clearly seen with Male to female ratio being 2.6:1. Alcoholism predominantly in males can be attributed as one of the major contributors of CLD and hence this ratio. Earlier reports too cite alcohol as a major contributor of cirrhosis.[11] Decrease in initiating age to consume alcohol in on rise in India.[12] Looking at etiology, despite alcohol, HCV seropositivity was found 49% of our study group patients. This is at variance with early reports from other regions in India where hepatitis B (rather than hepatitis C) Followed by cryptogenic chronic liver disease alcohol which were reported as a major contributors to portal hypertension and cirrhosis.[13] However one recent study in from our institution which was conducted to highlight the importance of screening for hepatitis B and C in farmers in which 1219 farmers were screened and prevalence of anti HCV sero-positivity was found to be 5%, and that of Hepatitis B was 0.32%. Our study too reflected a HCV seropositivity of 49 % of patients with a blood transfusion history in 61 % patients thereby stressing the need for safer blood supply, safe injection practices especially in Malwa region of Punjab.[14]

In cirrhosis, treating hyponatremia is a prudent step because it helps reduce the frequency and severity of complications such as encephalopathy. The initial research started with Studies of Ascending Levels of Tolvaptan (SALT1 and SALT2) Trials which first assessed the use of tolvaptan for hyponatremia were designed to focus specifically on changes in serum sodium in patients with hyponatremia from multiple disorders including cirrhosis, SIADH, heart failure.[15] The superiority was apparent in all end points like change from baseline, time to serum sodium normalisation, percentage with serum normalisation, in cirrhotic subgroup as compared to placebo. These results first established that improvements in serum sodium concentration were well maintained over longer periods with an acceptable adverse event profile. Other Studies with shortterm administration of tolvaptan (up to 1–2 weeks) and have shown a significant improvement with p value <0.003.[16,17]

As per our knowledge, none of the studies in Indian cirrhotic population has been reported so far, except from south Indian centre by Patra et al[18] which established the efficacy in acute decompensated heart patients. In our study too, significant changes in serum sodium status of the patients were

observed. We further compared the values post 24, 48 and 72 hours with the baseline as the results were evident in many patients post 24 hours itself.

Ascites reduction by tolvaptan therapy reported in previous studies is reported in patients of ascites in hepatic oedema[16] as well as in refractory ascites[19] However in our study, though urine output was increased significantly but the change in ascites measured by abdominal girth was not very appreciating. As per our study protocol we terminated the therapy as soon as sodium levels were normal, this could explain the non significant change in ascites and the body weight. However, further studies with longer duration of therapy and with dose escalation are warranted in this regards.

The improvement of hyponatremia and its co-relation with reduced occurrence of hepatic encephalopathy[20,21] and improved quality of life[22] is well documented. In our study too, the patients of group C with sodium levels of <124 were gaffe prone reflected with a mean score of 9.2+0.6 which however significantly improved at conclusion of therapy. Group A and B patients did show a pre drug value of 10 itself unlike most of patients in group C (with mean values as shown in Table 3) supporting the fact that progressive decreasing sodium affect the mental status.

Limitation of the study

Controlled studies during longer periods of time are needed to evaluate the safety, efficacy, and applicability of these agents in patients with cirrhosis with hyponatremia.

Conclusion

Hyponatremia has long been associated with worsened clinical outcomes in patients with cirrhosis and can be an important survival predictor. Our study concludes 15 mg of Tolvaptan therapy is safe and effective in reversing hyponatremia in cirrhotic patients patients and can help preventing the neurological complications occurring due to hyponatremia.

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