Journal of Research in Pharmacy Practice

Brief Communication

A prospective study to compare the clinical efficacy of Tolvaptan with 3% hypertonic saline solution in hospitalized patients having hyponatremia

Jobin Kunjumon Vilapurathu[1], S. Rajarajan[2]

[1]Department of Pharmacy Practice, The Erode College of Pharmacy and Research, Veppampalayam, Erode, India

[2]Department of Medicine and Cardiology, N. S. Memorial Institute of Medical Sciences, Palathara, Kollam, India

ABSTRACT

Objective: Hyponatremia is one of the most common electrolyte abnormalities in hospitalized patients. The treatment of hyponatremia is controversial as rapid correction of serum sodium can give rise to neurologic disorder and at the same time if not corrected timely, it can lead to brain damage. The aim of this study was to compare the efficacy of Tolvaptan with 3% hypertonic saline solution for the management of hyponatremia in hospitalized patients.

Methods: In this prospective observational study, data of 60 hospitalized patients having hyponatremia from February 2013 to July 2013 were collected and analyzed. Patients either received oral Tolvaptan or intravenous infusion of 3% hypertonic saline solution. The serum sodium concentration before administration of treatment and 24 h and 48 h after the administration of the drugs were recorded and analyzed. Data were analyzed using GraphPad Software, by Student's paired *t*-test and one-way analysis of Variance (ANOVA).

Findings: Tolvaptan and 3% hypertonic saline solution had significant effects in raising serum sodium level in hyponatremic patients at both 24 h and 48 h ($P < 0.0001$). This increase was about 8.030 ± 0.6507 mEq/L and 12.33 ± 0.6489 mEq/L for 3% hypertonic saline and about 5.111 ± 0.6616 mEq/L and 10.11 ± 0.6230 mEq/L for Tolvaptan, after 24 h and 48 h, respectively.

Conclusion: Both drugs had significant effects in raising serum sodium level in hyponatremic patients; however administration of 3% hypertonic saline solution had a slightly superior efficacy in raising the serum sodium concentration at both 24 h and 48 h periods in Hyponatremic patients compared with oral Tolvaptan.

Keywords: Arginine vasopressin receptor antagonists; hypertonic saline solution; hyponatremia; Tolvaptan

Received: October 2013
Accepted: November 2013

Corresponding author:
Mr. Jobin Kunjumon Vilapurathu,
E-mail: jobinkunjumon@yahoo.com

INTRODUCTION

Hyponatremia is an electrolyte disturbance in which the serum sodium concentration is lower than normal.[1] It is one of the most common electrolyte abnormalities in hospitalized patients and may lead to complications such as prolonged hospitalization, seizures and increased mortality.[2,3] The first step in the treatment of hyponatremia is to determine the underlying cause by proper clinical assessment and also to establish the severity of hyponatremia by measuring serum and urinary sodium concentrations and osmolality.[4] The treatment should be based on the severity of hyponatremia as the magnitude and rate of increase in serum sodium is critical. Under-correction of chronic hyponatremia may prolong the length of hospitalization and may fail to prevent life-threatening manifestations while sudden over-correction of sodium concentration may lead to osmotic myelinolysis.[5]

Access this article online

Website: www.jrpp.net

DOI: 10.4103/2279-042X.132710

The treatment of hyponatremia was controversial since it was found in the early 1980's that the rapid correction of hyponatremia can lead to central pontine myelinolysis and it was also reported that severe hyponatremia itself can lead to brain damage if not corrected rapidly.[6,7] The correction of serum sodium levels has a history even long before the measurements of serum sodium became available to clinicians. Clinicians understood that severe water intoxication can lead to cerebral edema and death can be prevented through reducing brain swelling by administration of hypertonic saline solution.[8] Today, the treatment of hyponatremia has progressed a lot with a greater understanding of the human body and by developing accurate methods for the measurements of electrolyte levels. The mainstays of hyponatremia treatment were restricted free water intake and saline infusion.[9,10] These conventional approaches are effective, but the results are often unpredictable. The new studies have demonstrated the effectiveness of Vaptans (non-peptide arginine vasopressin receptor antagonists) in the treatment of hyponatremia.[11,12] Tolvaptan, the first orally acting vasopressin receptor antagonists induce aquaresis[13] (formation of solute free urine) resulting in correction of osmolality and serum sodium concentration without the activation of the renin-angiotensin-aldosterone system or changes in blood pressure or renal function.[14,15] Furthermore current studies have proved that Tolvaptan can improve the treatment outcomes of hyponatremic patients suffering from acute and chronic heart failure, liver disease and end stage kidney disease.[16]

METHODS

The study was conducted in accordance with the ethical principles originated from the Declaration of Helsinki and also with the permission of Institutional ethics committee (The Erode College of Pharmacy Ethics Committee on Research on Human Subjects located at Erode, Tamil Nadu, India). Around 60 hospitalized patients having either euvolemic or hypervolemic hyponatremia and were not previously treated with Tolvaptan were randomly selected for the study during the period of February 2013-July 2013. The patients were randomized using 2:1 method and were either receiving oral Tolvaptan 15-30 mg once daily depending upon the severity of hyponatremia or intravenous infusion of 3% hypertonic saline solution based on their body weight and baseline serum sodium concentration in order to correct the plasma sodium deficiency. The parameters for inclusion of subjects into the study were hyponatremic hospitalized patients aged 25-70 years who were either being treated with oral Tolvaptan or 3% hypertonic saline solution. Although the exclusion parameter were patients with hypovolemic hyponatremia, patients who were not willing to stay in hospital, patients treated with either of the study drugs 6 months prior to the onset of study, patients with severe renal impairment and patients who were hypersensitive to Tolvaptan or similar class of drugs. The electrolyte levels of the patients were closely monitored in order to determine if there are any fluctuations. The initial serum sodium concentration before the administration of the study drugs were compared with the values obtained 24 h and 48 h after the administration of either oral Tolvaptan or 3% hypertonic saline solution. The primary end point of the study was to determine the acute effect of Tolvaptan and 3% hypertonic saline solution on serum sodium concentration. Serum Sodium concentration at 24 h and 48 h after the administration of the study drug was determined and compared against the baseline serum sodium concentration. Data were analyzed using GraphPad Prism (Inc. 7825 Fay Avenue, Suite 230 La Jolla, CA 92037 USA), Version 6.0. The results were presented using absolute percentages. Analysis was performed using Student's paired *t*-test One-way analysis of variance.

RESULTS

Out of the 60 enrolled patients, Tolvaptan 15-30 mg was administered to 37 patients depending upon the severity of hyponatremia. Serum sodium concentration was significantly increased at 24 h while the effect persisted at 48 h in this group of patients. Similarly, serum sodium concentration was found to be increased significantly at both 24 h and 48 h when compared with the baseline values in 23 patients who received 3% hypertonic saline solution [Table 1].

On evaluation of the efficacy of both oral Tolvaptan and 3% hypertonic saline solution on hyponatremic hospitalized patients, it was concluded that both drugs had significant effects on serum sodium concentration. Statistical analysis proved that 3% saline solution had a greater efficacy in increasing the serum sodium concentration than Tolvaptan on the study population [$P < 0.001$; Table 1] at both 24 h and 48 h analysis

DISCUSSION

SALT Investigators studied the clinical efficacy of Tolvaptan in patients with hyponatremia due to multiple disorders including syndrome of inappropriate antidiuretic hormone secretions,[17] chronic heart failure or cirrhosis.[18] Studies of ascending levels of Tolvaptan (SALT-1 and SALT-2) enrolled 205 and 243 patients, respectively. The patients were given

Table 1: The effect of oral Tolvaptan and 3% hypertonic saline solution on serum sodium concentration in hyponatremic patients

Serum Sodium Concentration	Tolvaptan	3% hypertonic saline solution
Serum [Na^+] concentration, mEq/L		
Baseline	123.3±0.5239	121.8±0.4639
After 24 h	128.4±0.4040	129.8±0.4562
After 48 h	133.4±0.3372	134.1±0.4537
Increase in serum [Na^+] concentration from baseline		
After 24 h	5.111±0.6616	10.11±0.6230
After 48 h	8.030±0.6507	12.33±0.6489
P value	<0.0001	<0.0001

Data presented as Mean ± standard deviation

daily oral doses of placebo or Tolvaptan 15 mg with titration to 30 and 60 mg, 4 times a day, with a 7 days follow-up visit after the end of the study. Primary end points were changes in sodium from baseline to day 4 and day 30 of treatment. SALT-1 patients who received Tolvaptan had a daily area under the curve change in serum sodium by day 4 of 3.62 ± 2.68 mEq/L when compared with 0.25 ± 2.08 mEq/L in the placebo group ($P < 0.0001$). At day 30, this averaged 1.66 ± 3.59 mEq/L for placebo and 6.22 ± 4.10 mEq/L for Tolvaptan ($P < 0.0001$). SALT-2 showed the similar results; so in both studies, serum sodium improved in Tolvaptan treated patients. Tolvaptan was fond to be superior to placebo in raising and maintaining serum sodium concentration; also, Tolvaptan treated patients required less fluid restrictions

Hyponatremia is one of the most common electrolyte disturbances occurring in hospitalized patients and may result in many serious discomforts and adverse events including prolongation of hospitalization and even death. The treatment options of hyponatremia changed dramatically after the understanding of the molecular level of the condition which led to the discovery of a new class of drugs, arginine vasopressin-2 (AVP) receptor antagonists. Tolvaptan, the first orally acting AVP receptor antagonist is now used widely for the correction of hyponatremia and associated conditions.

REFERENCES

1. Joy MS, Hladik GA. Disorders of sodium water calcium and phosphorous homeostasis. In: Dipiro JT, Talbert RL, Yees CG, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach. McGraw Hill, Medical Publishing Division. 2005. p. 937-67.
2. Zenenberg RD, Carluccio AL, Merlin MA. Hyponatremia: Evaluation and management. Hosp Pract (1995) 2010;38:89-96.
3. Hyponatremia: The Merck Manuals: The Merck Manual for Healthcare Professionals. Available from: http://www.merckmanals.com/proessional/print/sec/12/ch156/ch156d.html. [Last accessed on 2013 Aug 04].
4. Craig S, Schraga ED. Hyponatremia in emergency medicine. Medscape. Retrieved from: http://www.emedicine.medscape.com/article/767624-overview. [Last accessed on 2013 Jul 10].
5. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. Semin Nephrol 2009;29:282-99.
6. Norenberg MD, Leslie KO, Robertson AS. Association between rise in serum sodium and central pontine myelinolysis. Ann Neurol 1982;11:128-35.
7. Kleinschmidt-DeMasters BK, Norenberg MD. Rapid correction of hyponatremia causes demyelination: Relation to central pontine myelinolysis. Science 1981;211:1068-70.
8. Helwig FC, Schutz CB, Kuhn HP. Water intoxication. Moribund patient cured by administration of hypertonic salt solution. J Am Med Assoc 1938;110:644-5.
9. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: Expert panel recommendations. Am J Med 2007;120:S1-21.
10. Hyponatremia, Clinical Key; Elsevier. Retrieved from http://www.clinicalkey.com/topics/nephrology/hyponatremia.html#sectionTreatmentManagement. [Last accessed on 2013 Jul 10].
11. Thompson C, Hoorn EJ. Hyponatraemia: An overview of frequency, clinical presentation and complications. Best Pract Res Clin Endocrinol Metab 2012;26 Suppl 1:S1-6.
12. Fenske W, Maier SK, Blechschmidt A, Allolio B, Störk S. Utility and limitations of the traditional diagnostic approach to hyponatremia: A diagnostic study. Am J Med 2010;123:652-7.
13. Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, *et al*. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol 2010;21:705-12.
14. Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders. New York: McGraw-Hill; 2001. p. 583-8.
15. Wells BG, Dipiro JT, Schwinghammer TL, Dipiro CV. Electrolyte homeostasis. Pharmacotherapy Handbook. The McGraw-Hill Companies, Inc; 2009. p. 881-96.
16. Reilly T, Chavez B. Tolvaptan (Samsca) for hyponatremia: Is it a worth salt? Pharm Ther 2009;34:543-7.
17. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, *et al*. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-112.
18. Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS, *et al*. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur J Endocrinol 2011;164:725-32.

How to cite this article: Vilapurathu JK, Rajarajan S. A prospective study to compare the clinical efficacy of Tolvaptan with 3% hypertonic saline solution in hospitalized patients having hyponatremia. J Res Pharm Pract 2014;3:34-6.

Source of Support: Nil, **Conflict of Interest:** None declared.