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Original Article

A Prospective Comparison Study on the Effectiveness Of 3% Saline and Tolvaptan in Hyponatremia

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ABSTRACT

Hyponatremia is defined as the serum sodium concentration is less than 135 meq [1]. Hyponatremia is the most noticeable electrolyte abnormality in hospitalized patients, which may lead to seizures, prolonged hospitalization and result in an increased rate of mortality. The treatment of hyponatremia is contentious since it was found in the early 1980s that rapid correction of hyponatremia can lead to central pontine myelinolysis and hyponatremia can cause brain damage if not corrected rapidly . Moreover, current studies proved that tolvaptan can improve the treatment outcomes of hyponatremia patient suffering from acute and chronic heart failure, liver disease and end-stage kidney disease This is a prospective observational study was conducted for a period of three months at a tertiary care teaching hospital. Hyponatremia were found in some patients at the time of admission as well as in the hospital stay. Based on volume status of the patient, all the patients are treated with 3% NaCl and Tolvaptan. 100 ml of 3 % saline or 15 mg of Tolvaptan was given for the identified population .In 377 number of patients monitored, 79 patients have found sodium level less than 135 meq/l. . By comparing the efficacy in increasing serum sodium level, NaCl proved to be more effective than tolvaptan, but on concerning safety, the patients' treated with NaCl reported more adverse drug reactions than oral tolvaptan. The major drawback of our study was the limited sample size and not monitoring the serum sodium level at 72hrs and urine osmolality which was shown to have an importance in selecting the choice of treatment to prove the efficacy.The hypertonic saline as well as arginine vasopressin inhibitor Tolvaptan are effective in correcting hyponatremia. They are selected based on the fluid characteristics of the patients. In spite of the infusion site reactions the hyponatremia correction rate was more with 3 % saline compared to Tolvaptan.

INTRODUCTION

Hyponatremia is defined as the serum sodium concentration is less than 135 meq[1]. Hyponatremia is the most noticeable electrolyte abnormality in hospitalized patients, which may lead to seizures, prolonged hospitalization and result in an increased rate of mortality. [2,3].The increased level of antidiuretic hormone (ADH) and non-osmotic stimuli such as volume depletion, pain, stress, administration of hypotonic fluids mayalso be a cause of hyponatremia[4].The hyponatremia can be measured by calculating the serum and urinary sodium concentration and osmolality [5]. Eventually hyponatremia was treated with hypertonic saline [6]. The treatment of hyponatremia is contentious since it was found in the early 1980s that rapid correction of hyponatremia can lead to central pontine myelinolysis and hyponatremia can cause brain damage if not corrected rapidly [7,8]. The cornerstone of hyponatremia treatment is restricted free water intake, Saline infusion [9,10] and tolvaptan. Tolvaptan is the first oral vasopressin (V_2) receptor antagonist approved by FDA, which directly combats elevated ADH level. This medication is commonly used to treat hypervolemic or euvolemic _

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hyponatremia associated with congestive heart failure, hepatic cirrhosis or SIADH [11, 12, and 13]. Moreover, current studies proved that tolvaptan can improve the treatment outcomes of hyponatremia patient suffering from acute and chronic heart failure, liver disease and end-stage kidney disease[12]. The current study evaluate the outcome difference in the hyponatremia treatment with sodium chloride and Tolvaptan. Antidiuretic hormone(ADH) SIADH: Syndrome of Inappropriate Antidiuretic Hormone.

METHODOLOGY

A prospective observational study was conducted for a period of threemonths at a tertiary care teaching hospital. Study has the clearance from institutional ethical committee of Karuna Medical College Vilayodi, Palakkad. All the patients having age more than 30 years regardless of the gender developed or admitted with hyponatremia are included in the study.

A specially designed data collection form was used to collect necessary information's such as demographic details, serum sodium level, treatment provided and associated ADE. All the data are collected by the clinical pharmacist of the hospital.

Serum sodium of the all patients was monitored by reviewing the electronic medical record and patients with Serum sodium level falling below 135 meq were categorized into hyponatremia.

The various management strategies for hyponatremia were analysed by monitoring the medication chart. Types of correction method were recorded and their outcomes measured in the elevation in serum sodium concentration for the first 24 and 48 hour are compared with baseline value.

Adverse drug event associated with the drug used to treat hyponatremia were also monitored to find out the risk with the treatment strategy.

STATISTICAL ANALYSIS

Serum sodium concentration at 24hr and 48 hr after the treatment was determined and compared against the baseline serum sodium concentration.

Statistical analysis was done with IBM SPSS software version 22.20. The collected data was entered in MS Excel 2007 for calculating the percentages. Continuous variables were expressed in Mean ± SD. And the changes in the serum sodium concentration was analysed using students paired t test.

RESULTS

Hyponatremia were found in some patients at the time of admission as well as in the hospital stay. Based on volume status of the patient, all the patients are treated with 3% NaCl and Tolvaptan. 100 ml of 3 % saline or 15 mg of Tolvaptan was given for the identified population.

In 377 number of patients monitored, 79 patients have found sodium level less than 135 meq/l. The identified populations are admitted in various specialities sucah as General medicine, surgery department..Based on the disease severity they are triaged in to ward, high dependency unit and critical care units

From the analysis it is identified that majority (66%, n=52) of the diseased population have more than 70 years old and for only 6.35 % of the study population are fall under 30-50 years category.Based on the volume status or type of hyponatremia the population were categorised into hypervolemia hyponatremia and hypovolemic hyponatremia. Because of the fluid restriction and comorbid condition of the patients the treatment IV saline is given for the hypovolemic hyponatremia and and oral Tolvaptan was administered to hypervolemic hyponatremia patients.

Almost 70 % (n=52) of the affected population are male and 27 numbers are female. When comparing the type of hyponatremia developed in the two gender groups, Hypovolemic hyponatremia are more prevalent in elderly patients (greater than 70years) and hypervolemic hyponatremia in 30 – 50 years.

Table 1: OCCURRENCE OF HYPONATREMIA

Age in groups	Hypovolemic hyponatremia	Hypervolemic hyponatremia
30 – 50 years	2	3
50 – 70 years	13	9
Greater than 70 years	27	25
Mean age ± SD	74.8±15.34	75.95±14.15

For more than 50 % of the population, hypertonic saline was administered were as for 37 patients arginine vasopressin inhibitor Tolvaptan was administered. There is no mean difference in the number of saline treated population and Tolvaptan treated group.

After the administration of corrective measures the rise in sodium level in the first 24 hr and 48 hr are compared from the baseline sodium level of the individual patients. The mean baseline sodium levels of the patients were same in two portion of the population. It is found that in the first 24 hr the effectiveness of saline and Tolvaptan are differing, the mean rises in the saline group are 6.19 meq/ day and 3.9 meq/ day for Tolvaptan group. Similarly after 48 hrs 11.12 meq/day and 8.51 meq /day elevation were observed for saline and Tolvaptan group respectively. When comparing the total rise serum concentration in saline group 55.6 % rise were found in the day 1 but only 45.88 % rise observed with one day therapy with Tolvaptan.

Total rise in serum sodium level (mean 19.63 meq/48hr) were analysed in total population, in which 56.66% of this fall in patients treated with saline treated and only 43.33 % rise in obtained in Tolvaptan treated group. There is a significant difference ($p<0.001$) in the rise in serum level on the day one of therapy as well as in the day two or the therapy.

Table 2: Increase in serum

Serum sodium concentration	3% NaCl	Tolvaptan
Baseline sodium	123.11±2.50	123.51±2.29
After 24hours	129.31±3.1	127.42±1.6
After 48 hour	134.23±2.65	132.02±1.01
Sodium concentration		
After 24hour	6.19 ± 0.6	3.91± 0.69
After 48hour	11.12± 0.15	8.51± 1.28
P value	<0.0001	<0.0001

Adverse drug reactions are developed after the administration of oral Tolvaptanas well as IV 3%NaCl. The identified reactions are thrombophlebitis; swelling, itching and thirst. Thirst is the only ADE observed in the Tolvaptan treated population and it was developed in 11.6% percentage of the treated population. But 3% saline administered population developed ADE in which thrombophlebitis is more prevalent, secondly swelling (21.3%) and itching (12.1%) at the injection site.

DISCUSSION

According to Ewout J. Hoorn et al [14] hyponatremia is a water balance disorder and have difficulty in the diagnosis and treatment. The hypertonic saline and vaptans are the mainstay treatment of choice for the hyponatremia in acute and chronic settings.

Even if there is not clear evidence to the relation between the age and the prevalence of hyponatremia, Robert C. Hawkins et al [15] conducted a study in different population groups and found that the occurrence of hyponatremia is more prevalent in elderly patients > 60 years of age with 18% of the hyponatremia population. Similarly in this current study 18.5 % of the total admitted population had hyponatremia and an increment in the age in 10 years, 65 % of the hyponatremia population have more than

or equal to 70 years of age. This evidence was supported by the study of *Sood et al* [16] found that as goes up the risk of hyponatremia also increases with mean age 62.25 ± 17.7 years but in the current study the mean age was bit higher(74.8±15.34).

The serum level increment achieved after the administration of corrective measures. *Vilapurathu et al* [17] conducted a comparative study on effectiveness Tolvaptan and 3 % saline found that a significant effect is achieved with both populations. With a p value of < 0.001 significant difference improvement with hypertonic saline than the Tolvaptan part of the study. Similarly in the current study similar significance was observed with mean elevation of 11.12 % in the saline population and 8.51 % in the Tolvaptan group. On a daily base evaluation study conducted by Pulak et al [18] in Post-operative hyponatremic population found that after 24 hour correction with hypertonic saline achieved 3.9 meq elevation and after 48 hours 3.1 meq elevation. But in the Tolvaptan group from the baseline after 24 hours 2.5 meq and 3.8 meq elevations achieved after 48 hours. When representing the rise in meq after 24 hrs, 7 meq in 3 % saline groups and 5 meq in Tolvaptan gropup and after 48 hrs 11meq and 8 meq respectively.

By comparing the efficacy in increasing serum sodium level, NaCl proved to be more effective than tolvaptan, but on concerning safety, the patients' treated with NaCl reported more adverse drug reactions than oral tolvaptan. When evaluating the safety profile of the therapy hypertonic saline induced ADR are more against the oral arginine vasopressin antagonist. In 18.1 % of the population developed ADR with Tolvaptan in heart failure patients, a study conducted by the Koichiro Kinugawa et al[6] and the identified reactions are thirst, hypernatremia, renal dysfunction, liver dysfunction. Within first 3 days 6.8% of the population developed thirst. When comparing with the above study the thirst is the only ADE developed with the Tolvaptan population and it is 11.6 %, very less than the compared study. Koichiro found that majority of the ADE developed within days of therapy, but only few ADR's are identified by this study.

Dangerous systemic episodes are not identified in the study but peripheral ADE are more prevalent than the Tolvaptan for hypertonic saline. Phlebitis identified in 50% of the population and others erythema and edema are 25 % in study conducted by Dilon C *et al* [7], similarly in the current study population treated with 3% saline 66.6% population had phlebitis and others reactions in 33.4%.

Thus both the drugs shows a good impact in treatment in hyponatremia, in which 3 % NaCL shows a significant increase in sodium concentration while the patients have more risk to occur adverse drug reactions, while tolvaptan can be used if the patients cannot withstand the adverse drug reactions occur along with it also shows increase in sodium concentration. Studies conducted by Pulak *et al* [18] have also commented on the risk and efficacy of NaCl and Tolvaptan.

The major drawback of our study was the limited sample size and not monitoring the serum sodium level at 72hrs and urine osmolality which was shown to have an importance in selecting the choice of treatment to prove the efficacy.

CONCLUSION

The hypertonic saline as well as arginine vasopressin inhibitor Tolvaptan are effective in correcting hyponatremia. They are selected based on the fluid characteristics of the patients. In spite of the infusion site reactions the hyponatremia correction rate was more with 3 % saline compared to Tolvaptan, but later also showed a progressive improvement in the correction of hyponatremia with minimum adverse effects.

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