Efficacy of conivaptan and hypertonic (3%) saline in treating hyponatremia due to syndrome of inappropriate antidiuretic hormone in a tertiary Intensive Care Unit

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Abstract

Background: Hyponatremia is one of the most common electrolyte abnormalities encountered in clinical practice and has a significant impact on morbidity and mortality in hospitalized patients. The optimal management of hyponatremia is still evolving. Over the last decade, vaptans have been increasingly used in clinical practice with promising results.

Materials and Methods: The study included eighty patients with symptomatic hyponatremia due to syndrome of inappropriate antidiuretic hormone (SIADH) admitted and treated in Intensive Care Unit (ICU) with either conivaptan or hypertonic (3%) saline. They were compared for time taken to achieve normal serum sodium, length of ICU and hospital stay, and adverse effects.

Results: The demographic data and serum sodium levels at admission were comparable between the two groups. After initiating correction, sodium levels at 6, 12, and 24 h were similar between the two groups. However, at 48 h, patients in the conivaptan group (Group C) had higher sodium levels (133.0 ± 3.8 mEq/L) as compared to hypertonic saline group (Group HS) (128.9 ± 2.6 mEq/L), which was statistically significant (P < 0.001). The length of ICU stay was less in the Group C (3.35 ± 0.89 days) when compared with the Group HS (4.61 ± 0.91 days) (P < 0.001). There was no significant difference in mortality between the two groups. Conclusion: In patients with symptomatic hyponatremia due to SIADH, conivaptan with its “aquaretics” property can achieve a significantly better sodium correction, resulting in reduced ICU and hospital stay with no significant adverse effects.

Keywords: Conivaptan, hypertonic saline, hyponatremia, syndrome of inappropriate antidiuretic hormone

Introduction

Hyponatremia is defined as a serum sodium concentration below 135 mEq/L (mmol/L) and is the most frequently encountered electrolyte abnormality in hospitalized patients. Although it is a common electrolyte disorder, it remains incompletely understood in many basic areas because of its association with a plethora of underlying disease states, its causation by multiple etiologies with differing pathophysiological mechanisms, and marked differences in symptomatology and clinical outcomes, based on acuteness or chronicity of hyponatremia. Hyponatremia can be associated

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with low, normal, or high tonicity. The most common classification of hyponatremia refers to volume state, that is, hypovolemic, hypervolemic, and euvoletic hyponatremia. Euvolemic hyponatremia due to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) accounts for 15%-45% of cases. Although most cases are mild and relatively asymptomatic, severe hyponatremia can manifest as cerebral edema leading to coma, irreversible neurological damage, and even death.

The traditional treatment approach of SIADH involves restriction of free water intake, use of loop diuretics, oral salt tablets, demeclocycline, urea, and intravenous administration of normal or hypertonic saline. Although hypertonic saline is still accepted as the treatment of choice in symptomatic hyponatremia, its use demands careful monitoring to avoid osmotic demyelination syndrome (ODS), a feared neurologic disorder that manifests as progressive and sometimes permanent neurologic deficits.

Vaptans are the new group of drugs which directly block the action of vasopressin on its receptors, thus promoting renal free water excretion while sparing electrolytes. Conivaptan, a nonselective V1A/V2 vasopressin receptor antagonist, is the only intravenous vaptan approved for clinical use in the treatment of hyponatremia due to SIADH. Although rapid correction of sodium with the use of conivaptan has been documented, it is still thought to be an effective method of correcting hyponatremia due to its availability as an intravenous formulation.

The aim of our study is to compare the efficacy of conivaptan with that of hypertonic saline in improving serum sodium levels and its impact on the length of Intensive Care Unit (ICU) and hospital stay.

Materials and Methods

This is a single center study and included eighty patients admitted to the ICU with symptomatic hyponatremia due to SIADH, from January 2012 to December 2013. Of the eighty patients, forty were treated with hypertonic saline and the rest with conivaptan. The inclusion criteria were patients above 18 years of age, admitted to ICU for symptomatic hyponatremia, with clinical and laboratory evidence of SIADH, defined as euvoletic hypoosmolar hyponatremia (serum sodium <130 mEq/L and serum osmolality <280 mOsm/kg) with inappropriate urinary concentration (urine osmolality >100 mOsm/kg and urine sodium >20 mmol/L). Patients with head injury, women with a positive pregnancy test, those on diuretics, antidepressants, on thyroid or steroid supplements, and neurosurgical patients were excluded from the study.

In the conivaptan group (Group C) (n = 40), patients received a bolus dose of 20 mg conivaptan over 30 min followed by an infusion of 40 mg over 24 h for the next 72 h or until serum sodium level is above 130 mEq/L. We selected a 40 mg infusion over 24 h based on the study by Zeltser et al. In hypertonic (3%) saline group (Group HS) (n = 40), patients received 3% saline according to Adrogue–Madias formula, whereby a bolus dose was given followed by an infusion until 72 h or until serum sodium is above 130 mEq/L whichever is earlier. In Group HS, data were retrieved from medical records. We recorded patients’ demographic data, clinical presentation, comorbidities, and regular medications. We also collected the admission serum sodium levels, serum osmolality, urine sodium, urine osmolality, serum thyroid-stimulating hormone, and cortisol in addition to other tests as deemed appropriate at the time of admission. Serum sodium levels at 6, 12, 24, 48, and 72 h were collected. Our primary end point was the rate of correction of serum sodium levels. The secondary end points were length of ICU stay, length of hospital stay, potential complications, and mortality. Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated in all patients to compare the severity of presentation among the two groups. Overcorrection is defined, according to hyponatremia treatment guidelines, as a change in serum sodium of 6 mEq/L at 12 h, 12 mEq/L at 24 h, or 18 mEq/L at 48 h, after initiation of therapy. In case of overcorrection, the study drug was stopped, and patients were given a 5% dextrose infusion if serum sodium levels remained persistently high.

Data analysis was performed using Chi-square test for categorical data, summarized as percentages and paired Student’s t-test for quantitative data. Results were presented as a mean ± standard deviation. Statistical significance was defined as P < 0.05 and highly significant when P < 0.001.

Results

A total of eighty patients were enrolled in this study, out of which forty patients received conivaptan and the rest 3% saline. About 65% of patients in Group C and 50% of patients in Group HS were in the age group of 76–80 years, implying that our study included predominantly geriatric population. The etiology for SIADH in both the groups was comparable and included pulmonary, neuro-infections, but in majority of the
cases, it was idiopathic, as most of our study population was elderly. Among comorbidities, most of our patients had diabetes, hypertension, and ischemic heart disease. The patient demographics are summarized in Table 1. The admission serum sodium and sodium levels at 6, 12, 24, 48, and 72 h are presented in Table 2. There was no significant difference in baseline sodium levels among the two study groups and that patients in both the groups had severe hyponatremia. There was no statistically significant difference in serum sodium levels at 6, 12, and 24 h, but after 48 h, the difference did become statistically significant, with patients in Group C having a faster correction in sodium levels compared to Group HS. In 70% of patients in Group C, conivaptan infusion was stopped at 48 h as serum sodium levels were above 130 mEq/L, but we continued to monitor sodium levels among these patients to watch the trends and also to look for the need to treat for overcorrection. At 72 h, although most patients in Group HS had sodium levels above 130 mEq/L, the average sodium levels in Group C still remained higher compared to Group HS and were statistically significant. The average time to achieve sodium levels of above 130 mEq/L was significantly lower in Group C (54.60 ± 13.30 h) compared to Group HS (66.15 ± 13.29 h) (P < 0.001). Other variables such as serum osmolality, urine sodium, and urine osmolality were consistent with a diagnosis of SIADH and comparable among both the groups. The length of ICU stay and hospital stay is significantly decreased in Group C compared to Group HS as shown in Table 3. Among the adverse effects, thrombophlebitis was far more common in Group HS with 75% of its patients affected as compared to just 10% in Group C. Three patients died in each group, all of them presented to ICU intubated, ventilated, and on inotropes, indicating severe illness at the time of admission. The mean APACHE II score was 17.05 in Group HS and 17.1 in Group C, with a predicted mortality rate of 26% in both groups.

**Discussion**

Hyponatremia is a serious but often overlooked electrolyte imbalance that has been independently associated with a wide range of deleterious changes involving many different body systems. The diverse etiologies and comorbidities associated with hyponatremia pose substantial challenges in managing this disorder. Untreated acute hyponatremia can cause substantial morbidity and mortality as a result of osmotically induced cerebral edema whereas excessively rapid correction of chronic hyponatremia can cause severe neurological impairment and death as a result of osmotic demyelination.

In SIADH, hyponatremia results from ADH-induced retention of ingested or infused water. Although water excretion is impaired, sodium handling remains intact as there is no abnormality in volume regulating mechanisms such as the renin-angiotensin-aldosterone system or atrial natriuretic peptide thus resulting in euvoletic hypoosmolar hyponatremia.

Although administration of hypertonic saline is effective in correcting hyponatremia in SIADH, it entails a salt load that may be undesirable in some scenarios. Intake of salt does not address the causative factor in SIADH, which is free water excess. Intravenous conivaptan is an attractive option to treat SIADH, particularly in cases when the underlying cause of SIADH is time limited or could be eradicated with appropriate treatment such as postoperative states, pulmonary consolidation, or other conditions where the stimulus for inappropriate release of vasopressin is expected to be transient.
In this study, we found that correction of sodium levels in hyponatremia due to SIADH is much faster with conivaptan as compared to 3% saline. There were no similar studies in literature to compare our results. A retrospective study by Dominguez et al.\(^\text{[19]}\) compared the efficacy of 3% saline versus conivaptan in achieving hyponatremia treatment goals and found no significant difference between them and also noted the rate of correction was slow in both the groups, but the study population was small and included a complex mix of neurosurgical, neurological, and surgical patients, where the cause of hyponatremia was not well defined.

A few other studies\(^{[7,14]}\) which compared conivaptan with a placebo in euvoletic and hypervolemic patients found that conivaptan increased serum sodium promptly and safely. The median baseline sodium levels in our study were much lower as compared to these studies, indicating that patients in our study had more severe hyponatremia.

Since conivaptan is a relatively new drug, there are no clear guidelines regarding the exact dosage and duration of therapy. We used conivaptan 20 mg bolus over 30 min followed by 40 mg infusion over 24 h for next 72 h, based on a few reported studies\(^{[7,20]}\) who showed that conivaptan significantly increased serum sodium and was well tolerated at these doses.

The magnitude of increase in serum sodium levels is a bit higher in our study compared to previous studies\(^{[7,21,22]}\) though the rate of correction is still within the recommended treatment guidelines for hyponatremia.\(^{[2]}\) The faster correction of sodium in our study could be possibly due to the presence of a more elderly population and low baseline serum sodium levels. A study by Velez et al.\(^{[13]}\) showed that baseline serum sodium levels significantly correlated with the subsequent rise in serum sodium resulting from treatment. Metzger et al.\(^{[21]}\) observed that responders had lower mean serum sodium compared to nonresponders.

In terms of safety, though rapid correction was noticed in few patients, there was no incidence of ODS\(^{[23]}\) or severe neurological damage. Our findings resembled those of other studies,\(^{[13,14,21,22]}\) where there were no reports of neurological damage despite rapid correction.

The interesting finding in this study is that the duration of ICU stay and hospital stay was significantly less in Group C as compared to the Group HS [Figure 1]. This reduces overall health care costs for patients and would alleviate concerns about conivaptan being costlier than 3% saline.

There was no significant difference in mortality among the two study groups. The only significant adverse event noticed in both the groups was thrombophlebitis, which is consistent with previous studies.\(^{[13,14]}\)

Our study included a specific cohort of patients with symptomatic and severe hyponatremia due to SIADH, where conivaptan therapy was more appropriate. We made an attempt to look into the length of ICU and hospital stay, which are relevant to health-care costs and policymaking although our study is underpowered to determine such an effect.

The main limitation of our study is the small sample size and is thus underpowered. Other limitations are a lack of follow-up beyond the hospital stay.

Since SIADH and hyponatremia are common entities and conivaptan is a relatively new drug, there is a need for more research in this field to work out the appropriate dosage and duration of therapy and to study potential complications by long-term follow-up. With many newer vaptans in the pipeline, well-designed, large, prospective studies comparing vaptans with other established modalities of therapies for hyponatremia would help in incorporating this group of drugs into routine clinical practice.

**Conclusions**

In summary, conivaptan shows promising results in achieving hyponatremia treatment goals, particularly in SIADH. It increases serum sodium levels rapidly without any adverse consequences and thus has a positive impact on the duration of ICU and hospital stay.

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Conflicts of interest
There are no conflicts of interest.

References