Clinical Investigation

Effectiveness of single dose conivaptan for correction of hyponatraemia in post-operative patients following major head and neck surgeries

Address for correspondence:
Dr. Sunil Rajan, Department of Anaesthesiology, Amrita Institute of Medical Sciences, Kochi, Kerala, India.
E-mail: sunilrajan@aims.amrita.edu

Sunil Rajan, Soumya Srikumar, Jerry Paul, Lakshmi Kumar
Department of Anaesthesiology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/0019-5049.160943
Quick response code

ABSTRACT

Background and Aims: Conivaptan, a vasopressin receptor antagonist, is commonly used for the treatment of euvolaemic, hypervolaemic hyponatraemia. Usually, an intravenous (IV) bolus followed by infusion is administered for many days. We decided to assess the effectiveness of single dose conivaptan for correction of hyponatraemia in post-operative patients. **Methods:** This was a prospective, randomised trial conducted in 40 symptomatic post-operative Intensive Care Unit (ICU) patients with a serum sodium level of ≤130 mEq/L. Group A patients received IV conivaptan 20 mg over 30 min, whereas in group B infusion of 3% hypertonic saline was started as an infusion at the rate of 20–30 ml/h. Serum sodium levels were measured at 12, 24, 48 and 72 h and the daily fluid balance was measured for 3 days. The Chi-square test, Wilcoxon signed rank test and Mann–Whitney tests were used as applicable. **Results:** The serum sodium levels before initiating treatment were comparable between groups. However, subsequent sodium levels at 12, 24 and 48 h showed significantly high values in group A. Though at 72 h the mean sodium value was high in group A, it was not statistically significant. Group A showed a significantly high fluid loss on day 1, 2 and 3. The mean volume of hypertonic saline required in group B showed a steady decline from day 1 to 3 and only 13 patients required hypertonic saline on the 3rd day. **Conclusion:** Single dose conivaptan is effective in increasing serum sodium levels in post-operative ICU patients up to 72 h associated with a significant negative fluid balance.

Key words: Conivaptan, hypertonic saline, hyponatraemia, intensive care unit patients, post-operative

INTRODUCTION

Hyponatraemia is the most commonly encountered electrolyte abnormality in hospitalised patients particularly in the intensive care unit (ICU).[1,2] In a post-surgical ICU, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a frequent cause for hyponatraemia. Vaptans, a new group of vasopressin receptor antagonists, are increasingly being used for the treatment of euvolaemic, hypervolaemic forms of hyponatraemia. Conivaptan is now gradually becoming the most popular drug among the vaptans for correction of this condition in the ICU. This is administered as an initial intravenous (IV) bolus followed by an infusion, which may be continued for days. In this study, we aimed to assess the effectiveness of a single dose IV conivaptan for correction of hyponatraemia in post-operative ICU patients.

METHODS

This was a prospective, randomised trial conducted in 40 patients from April 2013 to December 2014. Based on the key article,[3] and due to the availability of limited number of cases satisfying the inclusion criteria, the study was restricted to 40 patients, with 20 in each group (A and B). Patients were recruited after obtaining consent and approval from Hospital Ethical Committee. Post-operative ICU patients who had undergone major head and neck surgeries for malignancies with a serum

How to cite this article: Rajan S, Srikumar S, Paul J, Kumar L. Effectiveness of single dose conivaptan for correction of hyponatraemia in post-operative patients following major head and neck surgeries. Indian J Anaesth 2015;59:416-20.

sodium level of ≤130 mEq/L and were symptomatic (headache, nausea, vomiting, lethargy, confusion, disorientation) were included in the study. Patients with hypovolaemia, hepatic cirrhosis, congestive cardiac failure and anuria were excluded.

Patients were randomly allocated to one of the two groups (A and B) using computer generated sequence of random numbers. Pre-operative nutritional status and hydration of the patients in both groups were assessed with body mass index (BMI), haemoglobin, serum albumin and sodium levels, pre-operative heart rate (HR) and mean arterial pressures. Perioperative normovolaemia was assessed by comparing pre-operative and post-operative urea levels in addition to intraoperative urine output per hour. The 24 h fluid balance of the patients 2 days and 1-day prior to commencement of study was also documented.

When symptomatic, for correction of hyponatraemia, Group A patients received IV conivaptan 20 mg over 30 min, whereas in group B infusion of 3% hypertonic saline was started as an infusion at the rate of 20–30 ml/h, the exact dose being calculated using the formula,

$$\text{Changes in Na} = \frac{\left(\text{infusate Na} + \text{infusate } K\right) - \text{serum Na}}{\text{total body water} + 1}$$

The rate of correction in serum sodium was aimed to be 6–8 mEq/L in 24 h, 12–14 mEq/L in 48 h and 14–16 mEq/L in 72 h. No diuretics were concurrently administered and there was no fluid restriction. HR, blood pressure (BP) and urine output were checked hourly. Hypotension was defined as a reduction of >30% of systolic BP from baseline value. Serum sodium was checked at beginning of treatment, 12, 24, 48 and 72 h after initiation of treatment. The daily fluid balance was recorded at 24, 48 and 72 h following initiation of treatment. Development of thrombophlebitis was also noted.

The statistical software IBM SPSS version 20.0 was used for data analysis. For comparing American Society of Anesthesiolgists (ASA) physical status, gender and thrombophlebitis, Chi-square test was used. Mann–Whitney test was used to compare the pre-operative nutritional status and hydration, post-operative serum sodium values, fluid balance and volume of hypertonic saline used at different time periods. Wilcoxon signed rank test was used to analyse changes in the blood urea levels. Significance was assumed for $P < 0.05$.

RESULTS

Mean age, weight, BMI, distributions of sex and ASA physical status among patients in group A and B were comparable [Tables 1 and 2]. Pre-operative haemoglobin, serum albumin, sodium, HR and mean arterial pressures of both groups were also comparable [Table 2]. Comparison of pre-operative and post-operative urea levels, intraoperative urine output as well as the post-operative daily fluid balance 2 days and 1-day prior to commencement of study didn't show any significant difference between the groups [$P < 0.05$, Table 3].

The serum sodium level before initiating treatment for hyponatraemia was also comparable between the groups. However, the subsequent sodium level measured at 12, 24 and 48 h showed significantly high values in group A ($P < 0.05$). At 72 h the mean sodium value was high in group A but the difference was not statistically significant [$P = 0.159$, Table 4 and Figure 1].

Group A showed a significantly high fluid loss (negative fluid balance) on day 1, 2 and 3 following initiation of treatment as compared to group B. In addition, it was also observed that on day 3, the fluid balance in group B had become positive [Table 4]. The mean volume of hypertonic saline used in group B showed a steady decline from

Table 1: Comparison of demographics and ASA physical status

Parameters	Mean±SD		*P*
	Group A	Group B	
Age	66.5±5.1	65.5±8.0	0.827
Weight	67.0±9.2	63.9±11.2	0.591
	Patient *n* (%)		
Female	9 (45.0)	10 (50.0)	0.752
Male	11 (55.0)	10 (50.0)	
ASA I	12 (60.0)	13 (65.0)	0.744
ASA II	8 (40.0)	7 (35.0)	

SD – Standard deviation; ASA – American Society of Anaesthesiologists physical status

Table 2: Comparison of pre-operative nutritional status and hydration

Variables	Mean±SD		*P*
	Group A	Group B	
BMI (kg/m^2)	25.85±4.54	25.40±6.28	0.978
Haemoglobin (g/dL)	12.07±0.95	12.28±1.10	0.597
Albumin (mg/dL)	3.51±0.45	3.69±0.63	0.308
Blood urea (mg/dL)	28.33±7.05	27.09±6.35	0.636
Serum sodium (meq/L)	137.56±4.29	135.86±4.09	0.155
Pre-operative HR (bpm)	76.00±8.16	74.15±7.55	0.464
Pre-operative MAP (bpm)	104.55±4.76	104.75±3.67	0.957

HR – Heart rate; MAP – Mean arterial blood pressure; SD – Standard deviation; BMI – Body mass index

day 1 to 3 [430 ± 92.3–211.5 ± 65 ml, Figure 2] and only 13 patients required hypertonic saline on the third day. This could probably explain the reason for a positive fluid balance observed in group B on the third day.

Though less number of patients in group A developed thrombophlebitis compared to group B (10 vs. 50%), the difference was not statistically significant ($P = 0.014$).

Table 3: Comparison of perioperative fluid volume status

Groups	Mean±SD		*P*
	Pre-operative urea mg/dl	Post-operative day 1 urea mg/dl	
Group A	28.33±7.05	29.23±5.81	0.542
Group B	27.09±6.35	27.95±5.35	0.130
Parameters	**Group A**	**Group B**	
Intraoperative urine output in mL/kg/h	3.08±0.74	2.89±0.40	0.449
Post-operative fluid balance 2 days before study (mL)	845.00±192.29	971.50±200.40	0.058
Post-operative fluid balance 1-day before study (mL)	864.00±189.22	966.50±199.14	0.131

SD – Standard deviation

Table 4: Comparison of serum sodium levels and daily fluid balance during study

Variables	Time	Mean±SD		*P*
		Group A	Group B	
Serum sodium levels in meq/L	At beginning of study	125.5±2.4	123.9±2.9	0.098
	12 h	129.4±2.8	127.7±1.1	0.006
	24 h	131.5±2.1	127.3±2.8	<0.001
	48 h	130.5±2.6	126.5±1.9	<0.001
	72 h	129.4±2.5	127.5±3.8	0.159
Daily fluid balance in mL	Day 1	−1094.3±286.7	−425.0±165.0	<0.001
	Day 2	−579.0±375.8	−260.5±282.5	0.005
	Day 3	−370.0±219.9	263.5±546.0	<0.001

SD – Standard deviation

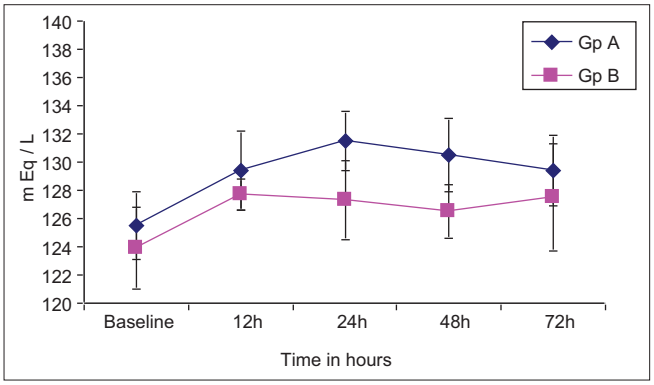

Figure 1: Changes in sodium levels

DISCUSSION

Dysregulation of arginine vasopressin (AVP) frequently occurs in hospitalised patients resulting in hyponatraemia and is associated with increased morbidity and mortality. Non-osmotic secretion of AVP is the main pathophysiology in patients with euvolaemic, hypervolaemic hyponatraemia.[5]

Hyponatraemia is defined as a serum sodium concentration <135 mmol/L. Acute onset hyponatraemia (duration of <48 h) requires prompt correction, whereas chronic hyponatraemia should be corrected cautiously as there is a higher risk of development of central pontine myelinolysis following rapid correction.[6] Although earlier recommendations supported a correction of <10–12 mmol/L of sodium during the first 24 h of treatment and a target <18mmol at the end of 48 hrs,[7] the occurrence of osmotic demyelination[8] even at these values has led to caution in the rates of correction. Currently the target rise in sodium is set at 6–8 mEq/L in 24 h, 12–14 mEq/L in 48 h and 14–16 mEq/L in 72 h[9] to ensure a safety in neurological events. However, in symptomatic patients regardless of chronicity, a rapid rise of 4–6 mEq/L is adequate.[9]

Conivaptan is a non-selective vasopressin receptor antagonist available in an IV form and is approved by the Food and Drug Administration to treat euvolaemic, hypervolaemic hyponatraemia.[3] It acts by inhibiting ADH, also known as AVP. It competitively and reversibly binds to selected AVP receptors and inhibits actions of ADH. Though conivaptan has high affinity for both V1A (vascular) and V2 (renal) receptors, affinity for V2 is tenfold higher and the aquaretic effect is pre-dominantly V2-associated.[3,10] The term aquaretics denotes drugs that can induce electrolyte-free water excretion. V1 receptor antagonism in vascular

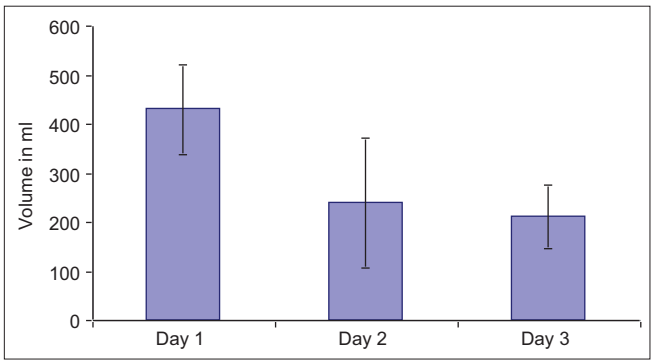

Figure 2: Hypertonic saline requirement in group B

smooth muscle cells results in vasodilatation whereas antagonism of V2 receptors present in the renal collecting duct results in aquaresis.[4]

Side effects of conivaptan include minimal to clinically significant fall in BP, postural hypotension[11,12] and hypokalaemia. Though in most patients rate of increase in sodium level is moderate, there are reports of rapid correction as fast as 14 mEq/L within 4 h when conivaptan 40–80 mg/day was used.[12] Even though no serious neurological sequelae had been reported because of rapid correction, possible development of osmotic demyelination syndrome should be kept in mind. The most common adverse events reported during studies were dry mouth and thirst.[13]

Other possible side effects include rebound hyponatraemia and renal damage due to significant hypovolaemia leading to hypotension and acute tubular necrosis. Increased frequency of adverse cardiac events, atrial dysrhythmias and sepsis in the presence of congestive cardiac failure have been reported.[10] However, V2 receptor antagonists (V2RA) are now indicated selectively for the treatment of hyponatraemia caused by congestive cardiac failure.[14] Tolvaptan or other V2RA may be of benefit in selected patients with severe congestive symptoms.[15] Oral tolvaptan is being evaluated for the management of hyponatraemia in heart failure.[4] Recent research indicates that conivaptan and tolvaptan are safe and not associated with increased morbidity such as renal failure and arrhythmias.[16]

Conivaptan is usually started at a dose of 20 mg IV over 30 min, followed by an infusion of up to 20 mg over the next 24 h, given to a maximum of 4 days, closely monitoring serum sodium levels, BP and volume status. The maximum daily dose is 40 mg.[17] Though conivaptan treatment is costlier, it involves a significantly lower volume of medication[13] and possibly reduces ICU stay.

Data from the study by Galton *et al*. suggest that in non-hyponatraemic patients with severe traumatic brain injury, the use of single dose conivaptan is safe and may reduce intracranial pressure.[18] A single bolus dose of 20 or 40 mg was found to be effective for the correction of acute hyponatraemia in neurologically injured patients and the effect of intermittent bolus dosing lasts up to 72 h.[19] Similar results were obtained in our study also though the study population was different.

While giving an IV infusion, to avoid the risk of an accidental administration of a bolus dose, it is always preferable to administer the drug using an infusion pump. However, this adds to the cost of treatment. The advantages of using single dose conivaptan are that only a lesser amount of the drug is required, which will reduce the cost of treatment by avoidance of an infusion, which requires careful monitoring or an infusion pump for safe administration.

The superiority of 3% hypertonic saline in raising the serum sodium concentration in hyponatraemia patients is well proven.[20] It is less expensive but carries a risk of volume overload in oliguric or anuric patients. A drawback of hypertonic saline is that it has to be given as an infusion and the duration of drug administration may extend over many hours.

In the present study, the pre-operative nutritional and hydration status of patients in both the groups were comparable and well within normal limits [Table 2]. Perioperative normovolaemia was ensured as reflected by adequate urine output and comparable pre-operative and post-operative blood urea levels [Table 3]. The positive daily fluid balance observed 2 days prior to patients becoming symptomatic indicated the gradual onset of development of hyponatraemia [Table 3].

The main limitations of our study were a low sample size and the fact that urine osmolarity was not analysed. We did not statistically analyse the haemodynamic parameters during the period of the study, but there were no alterations in HR or BP during the 72 h study period. None of the patients developed hypokalaemia during our study, but another limitation was that this was again not statistically analysed.

Based on the results of our study we suggest that a single dose of conivaptan can be considered for the initial correction of hyponatraemia, with serial serum sodium level monitoring, rather than prescribing a bolus dose followed by an infusion. The drug can be considered for an infusion if the correction is not satisfactory.

CONCLUSION

A single dose of conivaptan was found to be effective in increasing the serum sodium levels up to 72 h, with a significantly negative fluid balance, in post-operative ICU patients following major head and neck surgeries.

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