Original Article

Management of Hyponatremia

# Prevalence, Etiology and Management of Hyponatremia in Hospitalized Patients

**Shafiq Cheema[1], Sidra Cheema[2] and Aqsa Rahman[2]**


## ABSTRACT

**Objective:** The objective was to alleviate cerebral edema, not to correct sodium. So give to only severely symptomatic patients.

**Study Design:** Cross-sectional study

**Place and Duration of Study:** This study was conducted at the National Hospital and Medical Center, Lahore, Pakistan over 90 days period from October 1, 2016 till December 31, 2016.

**Materials and Methods:** Total of 108 (4.2%) patients out of 2560 patients had hyponatremia defined as serum sodium level of less than 135 mmol/L. There were 60 (55.5%) male patients and 48 (44.4%) female patients, Average age was 56 years.

**Results:** Severe hyponatremia (defined as Na+ < 120 mmol/L) was detected in 24 patients (22.2%). The largest group of hyponatraemic patients were euvolemic [48 (44.4%)], followed by hypervolemic [32 (29.6%)] and hypovolemia [28 (25.9%)].Out of total 108, thirty (27.7%) patients fulfilled the criteria for syndrome of inappropriate anti diuretic hormone (SIADH). During the hospital stay, 4/108 (3.7 %) hyponatraemic patients died. None of the deaths were secondary to hyponatremia. Tolvaptan (a V2RA) was not given to any patient and only 4/108 (3.7%) received 3% saline. At discharge, 84/108 (77.7%) had serum sodium more than 135 mmol/L.

**Conclusion:** Hyponatremia is common in hospitalized patients of Pakistan. Euvolemic hyponatremia was the most common type, a significant number of which was secondary to SIADH. Management of hyponatremia is challenging but we were able to manage hyponatremia in most of our patients despite non-availably of 3% saline or V2 receptor antagonists.


**Key Words:** Euvolemic, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion.

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## INTRODUCTION

Hyponatremia is very common in hospitalized patients worldwide. The prevalence varies in different studies and range from 5-30 %[1-3].The etiology also varies in different clinical settings and patient population. Euvolemic hyponatremia and syndrome of inappropriate antidiurtic hormone (SIADH) being the most common cause in hospitalized patients in most studies[1-2]. Management of hyponatremia has always challenged clinicians and nephrologists. Newer agents are changing the way we manage hyponatremia. Lack of V2 receptor antagonists and scarcity of hypertonic saline is making the management even more difficult in hospitalized patients in Pakistan. No data is available on prevalence, etiology and management related to hyponatremia in hospitalized patients in Pakistan.

[1.] Department of Nephrology, Allama Iqbal Medical College, Lahore.

[2.] Department of Pathology, CMH Lahore Medical College, Lahore.

Correspondence: Dr. Shafiq Cheema, Associate Professor & Head of Nephrology, Allama Iqbal Medical College, Lahore.
Contact No: 0311-2381111
Email: shafiqcheema@yahoo.com

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We did this cross sectional study to determine the prevalence, etiological factors and management of hyponatremia in a private hospital of Lahore, Pakistan. We also reviewed the literature to discuss available options for the management of different types and degrees of hyponatremia in hospitalized setting.

## MATERIALS AND METHODS

All patients hospitalized at National Hospital and Medical Center, Lahore, Pakistan over 90 days period (October 1, 2016 till December 31, 2016) with serum sodium (Na+) level of less than 135 mmol/L (Normal 135-145 mmol/L) were included in this study. Patients who have had prior history of chronic hyponatremia or hyponatremia during previous hospitalization were also included.The first admission serum electrolyte report was used as inclusion criteria. Patients who developed hyponatremia during hospitalization were also included. All patients with pseudo hyponatremia (secondary to Hyperlipidemia & hyperproteinemia) or hyponatremia secondary to mannitol or hyperglycemia were excluded thus including true hyponatraemic patients only. Standard diagnostic criteria were used to diagnose different etiologies of hyponatremia. Patients' volume status was assessed clinically as hypervolemic, euvolemic & hypovolemic.

Patients suspected of having pseudohyponatremia were excluded from study group. Only patients with 'true' hyponatremia were included. Following labatory tests were obtained in all of the patients with hyponatremia. Serum electrolytes, complete blood count, renal function tests including blood urea nitrogen, serum creatinine, thyroid function tests, serum cortisole, serum uric acid, serum osmolality, random urine sodium, random urine osmolality, urine complete and chest x-rays. Ultrasound KUB, 2D Echocardiogram and serum BNP were done in selected cases as indicated. Normal serum sodium range in our hospital lab (Chughtai's Lab) is 135–145 meq/l, serum osmolality is 275–293 mosm/kg of water, and urine osmolality is 500–850 mosm/kg water. Hyponatremia is defined as Na+ < 135 meq/l and severe hyponatremia defined as serum Na+ < 120 meq/l. Endocrinology, cardiology and nephrology consultations were requested as needed.

SIADH is diagnosis of exclusion and was defined by the classic Bartter-Schwartz criteria, which can be summarized as follows:

- Hyponatremia with corresponding hypo-osmolality
- Continued renal excretion of sodium
- Urine less than maximally dilute
- Absence of clinical evidence of volume depletion
- Absence of other causes of hyponatremia
- Correction of hyponatremia by fluid restriction

Patients were managed based on standard guidelines. If patient had hyponatremia of unknown duration or for more than 48 hours than that was considered chronic hyponatremia. For chronic hyponatremia sodium was not increased more than 10-12 meq in first 24 hours to avoid central pontine myelinolysis. Acute hyponatremia was defined as low serum sodium level developed within last 48 hours. Hypertonic saline, demeclocycline and tolvaptan were not available. Hyponatremia was managed by treating underlying cause, water restriction, oral salt tablets, normal saline with or without sodium bicarbonate and furosemide in various combinations. Hypertonic saline was given to only four patients who had very severe symptomatic hyponatremia, three with serum sodium of 105,109,110 mmol/L and fourth with sodium of less than 100 mmol/L. It was not easy to arrange hypertonic saline and in most cases family made this arrangements.

# RESULTS

Total of 2560 patients were hospitalized during this 90 day time period and 108/2560 (4.2%) had hyponatremia with serum sodium of less than 135 mmol/L. Twenty two (20.3%) patients out of 108 had serum sodium less than 120. There were 60 (55.5%) males, 48 (44.4%) females. Mean age was 56 years. In most patients with mild hyponatremia stopping the causative drug or treating the underlying cause along with water restriction corrected sodium. In patients with hypovolemia hyponatremia correcting the fluid deficit with normal saline helped correct serum sodium.

Following were the causes of hyponatremia:

**Table No.1: Etiology of Hyponatremia. CLD = chronic liver disease, CHF = congestive heart failure.**

| | | |
|---|---|---|
| Total with hyponatremia | 108 | (100%) |
| Euvolemia | 46 | |
| SIADH | 30 | (27.7%) |
| Hypothyroidism | 2 | (1.85%) |
| Adrenal insufficiency | 2 | (1.85%) |
| Drugs | 10 | (9.25%) |
| Primary polydipsia | 2 | (1.85%) |
| Hypervolemia | 34 | |
| CHF | 12 | (11.11%) |
| CLD | 18 | (16.6%) |
| Nephrotic syndrome | 2 | (1.85%) |
| ESKD on dialysis | 2 | (1.85%) |
| Hypovolemia | 28 | (25.9%) |

Two patients each with hypothyroidism and adrenal insufficiency received thyroxin and steroids to correct sodium. A patient with primary polydipisa was counseled to restrict fluid and it corrected her sodium in hospital. But she was hospitalized again after 2 weeks with hyponatremia secondary to poor compliance with fluids and she was referred to pyschiatry. Hypontremia secondary to idiopathic SIADH, chronic liver disease (CLD), congestive heart failure (CHF) were most difficult to manage. Serum sodium stayed around 128-136 in most of these patients despite the use of furosemide. Four patients with very severe hyponatremia (serum sodium less than 100, 105, 109, 110 mmol/L) needed almost a liter of 3% saline to correct sodium initially and this helped to bring sodium to safe range of above 115-120 mmol/L. Many patients also responded to normal saline with sodium bicarbonate to create relatively hypertonic IV fluid (tonicity 1.5-2.5%).This bicarbonate solution was especially used in patients who had some degree of metabolic acidosis. Depending on the degree of serum bicarbonate, sodium and need to correct sodium, this fluid was prepared based on the recommendations of nephrologist. One patient had low sodium of unclear etiology but responded to holding pregabalin. Pregabalin was restarted by her physician and she came back in OPD with low sodium of 121 which responded again to just stopping pregabalin.

None of the patients developed any complications as a result of hyponatremia or treatments of hyponatremia. Most of these patients were managed in general ward except few with acute and severe hyponatremia who were managed in ICU. Almost 50% of patients lost for follow up but most of others had their serum sodium well in range except few with CLD, advanced CHF and idiopathic SIADH.

# DISCUSSION

The prevalence of hyponatremia in our cohort of patients was 4.2%. Epidemiological studies have shown prevelance between 5-30% in various clinical settings depending on different etiological risk factors[1-3]. The prevalence of hyponatremia in our study is somewhat lower than values mostly reported in western literature. Our slightly low prevalence could have been secondary to the fact we included all patients including obstetrics & gynecology, surgical, medical and short stay hospitalization. Many of these patients were otherwise healthy and had been hospitalized for short stay for elective surgery or delivery of newborn or for procedures like angiogram to rule out acute coronary syndrome etc. Recently, Sandar Win, Komal Patel, Maria V DeVita et al. reported a prevalence of 4.7% in their hospitalized patients. Our data showing prevalence of 4.2 % corresponds to the prevalence reported by them.

In terms of etiology of hyponatremia, we found, like others, SIADH as being the most common cause of hyponatremia in hospitalized patients[1-2]. CLD was also very common cause of hyponatremia .This was probably secondary to the fact that hepatitis B & C and hence cirrhosis and CLD are prevalent in south East Asia and Pakistan. In terms of etiological factors our study findings are consistent with other studies[4].

Management of hyponatremia remains challenging and needs vast knowledge, multidisciplinary approach, non-pharmolgical, pharmacological measures and availability of hypertonic saline, vasopressin receptor antagonist etc. Hyponatremia among hospitalized patients has been associated with increased morbidity and mortality, but whether the mortality is associated with hyponatremia itself or the underlying illness remains unclear[5-8]. Evaluation of the patients' volume status is important in assessing the type of hyponatremia, which will guide the type of management required. If the patient has serious symptoms of hyponatremia (e.g., seizures), then more rapid correction through the use of hypertonic saline may be necessary to prevent cerebral edema and complications[8]. Since hypertonic saline is not freely available and tolvaptan is not available at all, treatment of patients with severe hyponatremia could be difficult and challenging. We were able to manage all patients except few who required 3% saline. Based on our experience and after review of literature following could be the possible recommendations in our set up.

Treat underlying Cause: stop diuretics like hydrochlorothiazide, selective serotonin uptake inhibitors and other possible drugs. Treating underlying correctable cause of hyponatremia.

Water restriction: will work in all cases and should be the first recommendation irrespective of etiology. It will work wonders in patients with primary polydipsia. How much water should be restricted can be estimated based upon patients sodium level, urine osmolality and current water intake. Fluid restriction is usually 1 to 1.5 L per day.

Salt Intake: can be increased to raise serum sodium. Salt restriction should be removed and salt can be liberalized in diet. Salt can be given in the form of salt (NACL) tablets or capsules. Each capsule or tablet usually has around 500 mg of NACl. Blood pressure and volume status should be monitored closely. Oral rehydrating solutions should be avoided given higher content of potassium unless potassium is low also.

Normal saline: The most common treatment option proposed for patients with hypovolemic hyponatremia is replacement of both salt and water through the intravenous infusion of sodium chloride solutions (6-8). Normal or hypotonic fluids should be avoided unless there is clear evidence of hypovolemia and dehydration. It can also make hypervolemic hyponatremia worse. In cases of SIADH the utilization of normal saline depends on urine osmolality which is usually fixed. If urine osmolality is less than 308 mmol/L, it might help to correct hyponatremia. If urine osmolality is more than 308 (usually more than 450 mOsm/kg H2O in SIADH), hypotonic or normal saline will make hyponatremia worse since urine osmolality is fixed and free water will be retained after urine is excreted at higher osmolaity. Addition of sodium bicarbonate can help increase the tonicity of solution and it will help correct hyponatremia. Furosemide can also help normal saline improve hyponatremia quicker by dumping more free water in urine since furosemide impairs renal tubular responsiveness to ADH.

Demeclocycline: it has been recommended in case of SIADH but not very useful secondary to side effects and poor efficacy. The effect of demeclocycline was non-significant in all analyses[10] and its role is declining with the invent of newer V2 receptor antagonists like tolvaptans.Moreover it is not available in Pakistan.

Hypertonic saline: very useful when acute symptomatic and severe hyponatremia must be corrected promptly. Some center like SIUT, Shifa and shoukat khanum prepare their own 3% saline but it is not commonly available in pharmacies. In terms of replacement, desired sodium deficit can be calculated using the following formula.

Na+ (mEq given as 3%) = (Na+ desired) – (Na+ measured) X estimated TBW

This gives the amount of sodium in mEq to be given as 3% saline over time t

There are 513 mEq of sodium in one liter of 3% saline. To determine the volume of hypertonic saline to be given over time t, divide the number of mEq of sodium to be given by 513 mEq/L

Then give this volume over time t. Addition of lasix can increase the efficacy of 3% saline.

The patient who had serum sodium of 105 and marked neurological symptoms of altered mental status, we decided hypertonic saline (3% saline, OSM =1026) should be given initially in view of the marked hyponatremia and neurologic symptoms. This is how we calculated the desired sodium rise of 15 mmol/L over first 30 hours.

Na+ deficit = 0.6 × 70 × (120-105), = 630 meq =1200mL of 3% saline

At 40 ml/h over 30 h to raise the plasma Na+ concentration by 0.5 meq/L/h.

Usually 50-100 ml/hr for 4-6 hours will increase sodium by 6-8 meq/L which is usually enough to reduce symptoms acutely

V2 Receptor Antagonist: Oral Tolvaptan is easily available in USA and has been recommended and approved to manage hyponatremia secondary to idiopathic SIADH, CHF and CLD. Tolvaptan is the only V2R antagonist available in Canada and is a selective oral antagonist of the V2 receptor, causing a dose-dependent increase of dilute urine (13-16).A four-year open-label extension study of the SALT trials, known as SALTWATER, found that the increases in serum sodium levels were maintained over longer periods of time.[12-15]

Unfortunately tolvaptan is not available in Pakistan. But if and when available the dose must be started at 15 mg daily and incrementally increased to maximum dose of 60 mg daily as needed. During tolvaptan use, water or fluids are not restricted to avoid rapid correction of sodium. It causes aquaresis or free water loss by inhibiting ADH receptor. It is indicated and FDA approved for hyponatremia due to SIADH, cirrhosis or CLD and CHF when aquaresis rather diuresis is needed because of hyponatremia. By causing free water loss and retaining sodium, it corrects sodium and treat fluid overload especially in CHF & CLD.

# CONCLUSION

Hyponatremia is common in hospitalized patients of Pakistan. Euvolemic hyponatremia was the most common type, a significant number of which was secondary to SIADH. Management of hyponatremia is challenging but we were able to manage hyponatremia in most of our patients despite non-availably of 3% saline or V2 receptor antagonists.

**Author's Contribution:**

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|---|---|
| Concept & Design of Study: | Shafiq Cheema |
| Drafting: | Sidra Cheema |
| Data Analysis: | Aqsa Rahman |
| Revisiting Critically: | Sidra Cheema, Shafiq Cheema |
| Final Approval of version: | Shafiq Cheema |

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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