

Hyponatremia and SIADH Frequency in Clinically Euvolemic Patients Receiving Chemotherapy: Prospective Study in Unselected Patients' Cohort

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Abstract

Purpose: Biochemical hyponatremia is a common electrolyte abnormality in patients with cancer. In this prospective single center trial we aim to study the frequency of hyponatremia in patients receiving chemotherapy with special emphasis on syndrome of inappropriate secretion of anti-diuretic hormone (SIADH).

Patients and Methods: This is a prospective study of consecutive patients receiving different types of outpatient chemotherapy between January 2013 and June 2014. Serum Sodium was measured as part of routine assessment for all patients receiving chemotherapy. Euvolemic patients with hyponatremia (Na <135 mmol/L) were also tested for Serum and urine osmolality and urinary Na excretion. Criteria of SIADH are: serum Osmolality <275 mOsmol/kg, urine Osmolality >100 mOsmol/kg and urinary Sodium >30 mmol/L.

Results: 1254 patients received different chemotherapy regimens were screened and 1150 fulfilled the inclusion criteria. Median age was 55 year (19-75). Biochemical hyponatremia developed in 105 (9.1%) of all patients and in 42/298 (14%), 25/357 (7%) and 38/495 (7.7%) of patients who received cisplatin, carboplatin/oxaliplatin and non-platinum chemotherapy regimens respectively. 68/105 (65%) fulfilled biochemical criteria of SIADH of which 26/42 (62%), 13/25 (52%) and 29/38 (76%) of hyponatremic patients received cisplatin, carboplatin/oxaliplatin and non-platinum regimens respectively. Cisplatin based regimens were significantly associated with SIADH compared to non-cisplatin regimens (OR: 1.521, 95% CI: 1.105-2.093; p=0.022).

Conclusion: 9.1% of euvolemic patients receiving out-patient chemotherapy manifest a degree of biochemical hyponatremia with highest risk associated with cisplatin based regimens. Hyponatremia can be attributed to SIADH in two thirds of cases.

Keywords: Hyponatremia; SIADH; Renal salt-wasting syndrome; Chemotherapy

Introduction

Hyponatremia (defined as a serum sodium concentration <135 mmol/L) is the most frequently encountered electrolyte disturbance in clinical practice [1]. It can present with nausea, vomiting and generalized weakness. Severe hyponatremia (sodium <125 mmol/L), particularly if develops rapidly (within 48 hours) may lead to confusion, hallucinations, seizures, coma, and respiratory arrest [2]. Severe hyponatremia is reported to be associated with significant morbidity and increased mortality (up to 60 folds) compared with normo-natremic controls [3-6].

There are three main pathophysiological forms of hyponatremia [7]. (a) Hypovolemic hyponatremia caused by intravascular volume depletion and is treated by volume replacement. (b) Hypervolemic hyponatremia caused by dilutional effect of fluid overload which is treated by diuresis. (c) Euvolemic hyponatremia caused by excessive sodium excretion. SIADH is an example of the latter. Recently, a new class of drugs, vasopressin V2-receptor antagonists (vaptans), showed promising efficacy in SIADH patients [8,9].

Hyponatremia is a common electrolyte abnormality in patients with cancer. Causes of hyponatremia in this specific population include chemotherapy, decreased fluid intake, diuretics, intravascular volume changes, renal salt-wasting syndrome and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The most

frequently reported chemotherapeutic drugs causing hyponatremia are cisplatin, vincristine, vinblastine, and cyclophosphamide [10]. The pathophysiology of hyponatremia induced by these drugs is only partly known. Renal salt wasting is described with cisplatin and carboplatin [11]. The syndrome of inappropriate antidiuretic hormone secretion was reported secondary to vinca alkaloids and cisplatin and other agents [11].

Early recognition of hyponatremia enables prompt intervention leading to less complications, shorter hospitalization time and improvement of outcome. We studied the frequency of hyponatremia in patients receiving systemic chemotherapy at our hospital with special emphasis on SIADH.

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Patients and Methods

This is a prospective study of all patients attending for administration of different types of out-patient chemotherapy between January 2013 and June 2014. All patients ≥ 18 year and receiving chemotherapy in metastatic or curative setting for malignant disease were screened. Measurement of serum electrolytes (including sodium) was part of routine assessment prior to administration of each chemotherapy cycle. Only those patients who developed hyponatremia after chemotherapy were further investigated by measuring urine sodium (mmol/l), serum osmolality (mOsmol/kg) and urine osmolality (mOsmol/kg). Patients with hyponatremia and clinical signs of dehydration (history of poor fluid intake, recent diarrhea and vomiting) prior to start of chemotherapy were excluded. Patients on diuretics or psychotropic drugs and those with abnormal cortisol, TSH and fT4 levels were also excluded. Hyponatremia was classified as mild, moderate and severe according to the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), represented by European Renal Best Practice (ERBP) [12] (Table 1). SIADH was diagnosed according to criteria for diagnosis of SIADH developed by Thompson, et al. [6] (Table 2). The study was designed to evaluate the rate of hyponatremia and SIADH among unselected patients receiving different chemotherapy regimens with palliative or curative intent in daily practice.

The intention of this study is to represent the heterogeneity of tumor types treated by various chemotherapy regimens in routine daily practice. Due to diversity of administered chemotherapy protocols, they were identified into 3 broad categories (a) cisplatin, (b) carboplatin or oxaliplatin and (c) non-platinum based regimens. The association between SIADH and relevant factors was tested. These factors include gender, age, chemotherapy regimen (cisplatin and others), cycles of chemotherapy, hemoglobin, creatinine, uric acid and urea. Two sided Chi-square test was applied for univariate analysis and binary logistic regression test has been used for multivariate analysis using SPSS version 20. The study was approved by the ethical committee.

Results

104/1254 (8.3%) patients receiving narcotics or diuretics were excluded. Patients' characteristics are listed in Table 3. The median age of our patient population was 55 years. Gastrointestinal tract primary 34/105 (32%) was the commonest diagnosis followed by breast cancer (21%) and 74/105 (70.5%) of patients were receiving chemotherapy in the first line setting. 1150 patients fulfilled the inclusion criteria.

| | |
|-----------------------|--|
| Mild hyponatremia | Biochemical finding of a serum sodium concentration between 130 and 135 mmol/l |
| Moderate hyponatremia | Biochemical finding of a serum sodium concentration between 125 and 129 mmol/l |
| Severe hyponatremia | Biochemical finding of a serum sodium concentration <125 mmol/l |

Table 1: Definition of hyponatremia based on biochemical severity [12].

| |
|--|
| Plasma sodium <135 mmol/l |
| Urine osmolality >100 mOsm/kg |
| Urine sodium >30 mmol/l |
| Patient clinically euvolemic |
| Exclusion of glucocorticoid deficiency |
| Hyponatraemia |
| Normal salt intake |

Table 2: Essential criteria for the diagnosis of SIADH [6].

298 (26%), 357 (31%) and 495 (43%) patients received cisplatin, carboplatin/oxaliplatin and non-platinum based chemotherapy regimens respectively. 105/1150 (9.1%) patients had hyponatremia and are the subject of subsequent analysis. (Table 3)

Hyponatremia was mild, moderate and severe in 3.4%, 5.7% and 0.09% respectively. Table 4 illustrates the frequency and degree of hyponatremia among patients receiving different chemotherapy regimens. Overall 68/105 (65%) fulfilled biochemical criteria of SIADH. 26/42 (62%), 13/25 (52%) and 29/38 (76%) of patients receiving cisplatin, other platinum and non-platinum based regimens respectively fulfilled biochemical criteria of SIADH. In univariate analysis cisplatin based regimens were significantly associated with SIADH compared to non-cisplatin regimens (OR: 1.521, 95% CI: 1.105-2.093; $p=0.022$) and other platinum regimens (OR: 1.51, 95% CI: 1.189-1.917; $p=0.008$). However, the statistical significance was lost on multivariate analysis. Additionally, there was no association between SIADH and gender (male vs. female; $p=0.22$), age (<60 vs ≥ 60 years; $p=0.836$), number of chemotherapy cycles (1-2 vs >2 cycles; $p=1.0$), hemoglobin, creatinine, uric acid and urea.

Discussion

The frequency of hyponatremia in cancer patients receiving chemotherapy is not well documented in the literature. To study chemotherapy associated hyponatremia, we screened a large unselected cohort ($n=1254$) of patients with cancer receiving different chemotherapy regimens. Subsequently, we excluded those with clinical hypovolemia and those receiving non-chemotherapy drugs that may cause hyponatremia [13-15]. We found that 9.1% of these patients manifest hyponatremia which was mostly of mild to moderate severity. 26% (298/1150) of screened patients received cisplatin based regimens. Platinum compounds, in particular cisplatin are recognized to induce sodium loss through renal tubular toxicity [11]. Grade 3/4 hyponatremia was reported in 15% and 30.7% of 79 patients receiving brand and generic cisplatin respectively [16]. In our larger cisplatin treated cohort ($n=298$), all degree hyponatremia and moderate to severe hyponatremia was observed in 14.1% and 10% of patients respectively. In line with previous reports, hyponatremia was also associated with other platinum (7%) and non-platinum (7.7%) agents albeit less frequently than with cisplatin [11].

Several case reports about salt wasting and SIADH in patients receiving chemotherapy were published [17-19]. Examples for drugs that were reported to cause SIADH include platinum, vincristine

| Patient Demographics | n=105 |
|-----------------------------|------------------|
| Gender | |
| Female | 59 (56%) |
| Male | 46 (44%) |
| Median age | 55 (19-75) years |
| Primary tumor | |
| Gastrointestinal | 34 (32%) |
| Breast | 22 (21%) |
| Gynecological | 13 (12%) |
| Lymphomas | 11 (10.5%) |
| Lung | 10 (9.5%) |
| Urological | 9 (8.5%) |
| Others | 6 (5.5%) |
| Line of chemotherapy | |
| First line | 74 (70.5%) |
| Subsequent | 31 (29.5%) |

Table 3: Patients' characteristics.

| | Cisplatin based chemotherapy (n=298) | Carboplatin or oxaliplatin based chemotherapy (n=357) | Non-platinum based chemotherapy (n=495) | Total (n=1150) |
|-------------------------------|--------------------------------------|---|---|----------------|
| Hyponatremia | 42 (14.1%) | 25 (7%) | 38 (7.7%) | 105 (9.1%) |
| SIADH | 26 (8.7%) | 13 (3.6%) | 29 (5.9%) | 68 (5.9%) |
| Mean serum Na (mmol/L) | 128.9 | 129.1 | 129.5 | 129.2 |
| Range | (123-133) | (126-133) | (127-133) | (123-133) |
| Grade of hyponatremia | | | | |
| Mild (130-135) | 12 (4%) | 8 (2.2%) | 19 (3.8%) | 39 (3.4%) |
| Moderate (125-130) | 29 (9.7%) | 17 (4.8%) | 19 (3.8%) | 65 (5.7%) |
| Severe (<125) | 1 (0.3%) | None | None | 1 (0.09%) |
| Hyponatremia fulfilling SIADH | 26/42 (62%) | 13/25 (52%) | 29/38 (76%) | 68/105 (65%) |

Table 4: Details of hyponatremia among patients receiving different chemotherapy regimens.

| Factor | Odds ratio- 95% CI | P-value |
|---|--------------------|---------|
| Gender | 1.55 (0.64-3.71) | 0.32 |
| Age (median: 55 years) | 1.02 (0.98-1.05) | 0.22 |
| Chemotherapy Regimen (Cisplatin vs. others) | 0.87 (0.36- 2.06) | 0.75 |
| Chemotherapy cycles (1-2 vs. >2 cycles) | 0.84 (0.34- 2.05) | 0.70 |
| Hemoglobin | 1 (0.98- 1.03) | 0.62 |
| Serum Creatinine | 0.98 (0.95- 1.01) | 0.29 |
| Uric Acid | 1 (0.99- 1) | 0.16 |
| Urea | 0.97 (0.84- 1.11) | 0.67 |

Table 5: Multivariate Analysis.

[20,21], cyclophosphamide [17], vinorelbine [22-25], docetaxel [26]. In the majority of those cases platinum was the main reason for hyponatremia [16,18,19,27-30]. New targeted therapies like imatinib [31], alemtuzumab [32] have been reported to cause SIADH also.

Our study is the first in the literature investigating the frequency of SIADH in unselected patients' cohort regardless of the type of antineoplastic agents or the cancer type. We rigorously attempted to exclude patients with other causes of hyponatremia as those with dehydration and those receiving diuretics and/or psychotropic drugs which are known to cause disturbance of the sodium balance [13-15,33].

In our results and considering all patients, SIADH was more frequent with cisplatin 26/298 (8.7%) than other platinum regimens 13/357 (3.6%). Around two thirds 68/105 (65%) of patients with hyponatremia fulfilled the criteria of SIADH. Hyponatremia and SIADH were more frequently associated with cisplatin than other platinum regimens (Table 4). These findings were supported by the results of univariate analysis which showed cisplatin based regimens were statistically significantly associated with SIADH compared to non-cisplatin and other platinum regimens. However, this statistical significance was lost in multivariate analysis which included other potential factors that could influence SIADH (Table 5). This could be explained by the extensively heterogeneous tumor sites and chemotherapy protocols also. Feature studies should focus on groups of patients with particular tumor sites and receiving specific chemotherapy regimen. Literature on carboplatin and oxaliplatin associated hyponatremia and SIADH are scarce and are limited to case reports and very small patients' series [34,35]. Grade III hyponatremia was observed in phase II study of oxaliplatin in patients with unresectable, metastatic or recurrent hepatocellular cancer (n=15) [36]. Our findings indicate that carboplatin and oxaliplatin associated hyponatremia and SIADH are commoner than expected.

The broad heterogeneity of tumor sites and chemotherapy regimens (24 regimes) used in our patients cohort practically preclude analysis of each individual tumor site and chemotherapy regimen.

Hyponatremia is associated with poor prognosis and has a negative

impact on quality of life [37-40]. Our relatively large study sheds light on the scale and magnitude of frequency of hyponatremia in patients receiving systemic chemotherapy. However, the heterogeneity of patients, broad cancer sites, chemotherapy regimens (24 regimens), stages of disease and lines of treatment practically precludes any meaningful survival analysis or analysis of each individual tumor site and chemotherapy regimen separately. Relevant blood and urine tests were carried out on the date of each chemotherapy cycle. We did not routinely perform tests between cycles, which may limit our end results and can underestimate the real frequency of hyponatremia in our patients.

Conclusion

To our knowledge this is the first published prospective study analyzing frequency and grade of hyponatremia and SIADH in unselected euvolemic patients' population receiving chemotherapy. About 9% of these patients manifest a degree of hyponatremia which fulfills the biochemical criteria of SIADH in 65% of these patients. Cisplatin poses higher risk of hyponatremia and SIADH than other platinum and non-platinum regimens. Chemotherapy induced hyponatremia is frequently observed and is commonly attributed to SIADH. Treating oncologists should be aware of this complication particularly in patient undergoing cisplatin based therapy.

Author contributions

Dada, Zekri, Farag and Bayoumy contributed on the design, patients' selection, data collection and processing and manuscript writing.

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