Factors predicting postoperative hyponatremia and efficacy of hyponatremia management strategies after more than 1000 pituitary operations

Clinical article

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Object. Syndrome of inappropriate antidiuretic hormone secretion–induced hyponatremia is a common morbidity after pituitary surgery that can be profoundly symptomatic and cause costly readmissions. The authors calculated the frequency of postoperative hyponatremia after 1045 consecutive operations and determined the efficacy of interventions correcting hyponatremia.

Methods. The authors performed a retrospective review of 1045 consecutive pituitary surgeries in the first 946 patients treated since forming a dedicated pituitary center 5 years ago. Patients underwent preoperative and daily inpatient sodium checks, with outpatient checks as needed.

Results. Thirty-two patients presented with hyponatremia; 41% of these patients were symptomatic. Postoperative hyponatremia occurred after 165 operations (16%) a mean of 4 days after surgery (range 0–28 days); 19% of operations leading to postoperative hyponatremia were associated with postoperative symptoms (38% involved dizziness and 29% involved nausea/vomiting) and 15% involved readmission for a mean of 5 days (range 1–20 days). In a multivariate analysis including lesion size, age, sex, number of prior pituitary surgeries, surgical approach, pathology, lesion location, and preoperative hypopituitarism, only preoperative hypopituitarism predicted postoperative hyponatremia (p = 0.006). Of patients with preoperative hyponatremia, 59% underwent medical correction preoperatively and 56% had persistent postoperative hyponatremia. The mean correction rates were 0.4 mEq/L/hr (no treatment; n = 112), 0.5 mEq/L/hr (free water restriction; n = 14), 0.7 mEq/L/hr (salt tablets; n = 22), 0.3 mEq/L/hr (3% saline; n = 20), 0.7 mEq/L/hr (intravenous vasopressin receptor antagonist Vaprisol; n = 22), and 1.2 mEq/L/hr (oral vasopressin receptor antagonist tolvaptan; n = 9) (p = 0.002, ANOVA). While some patients received more than 1 treatment, correction rates were only recorded when a treatment was given alone.

Conclusions. After 1045 pituitary operations, postoperative hyponatremia was associated exclusively with preoperative hypopituitarism and was most efficiently managed with oral tolvaptan, with several interventions insignificantly different from no treatment. Promptly identifying hyponatremia in high-risk patients and management with agents like tolvaptan can improve safety and decrease readmission. For readmitted patients with severely symptomatic hyponatremia, the intravenous vasopressin receptor antagonist Vaprisol is another treatment option.

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Key Words • hyponatremia • pituitary surgery • postoperative • transsphenoidal • tolvaptan

Abbreviations used in this paper: ADH = antidiuretic hormone; SIADH = syndrome of inappropriate ADH secretion.
Postoperative hyponatremia after pituitary surgery

Preoperative pituitary function or whether a patient had undergone prior pituitary surgeries. Studies to date have also not reported the efficacy of commonly used interventions, with treatments such as 3% saline and salt tablets continuing to be used despite little evidence for their efficacy. To fully calculate the frequency of postoperative hyponatremia and the efficacy of various interventions in correcting hyponatremia in a comprehensive series of pituitary patients representative of the wide spectrum seen in practice, we retrospectively analyzed postoperative hyponatremia after 1045 consecutive operations done in the past 5 years since the establishment of our dedicated pituitary center of excellence.

Methods

Case Collection

This study was approved by our institutional Committee on Human Research. We retrospectively reviewed 1045 consecutive pituitary surgeries in the first 946 patients treated in the 5 years since the establishment of the California Center for Pituitary Disorders, a dedicated multidisciplinary center of pituitary expertise. Per institutional protocol, patients underwent preoperative and daily sodium checks while hospitalized after surgery, which for the patients in this series lasted for a mean period of 3 days (median 2 days), with outpatient checks performed in patients with mild hyponatremia or high urine output at the time of discharge or in patients who contacted the center reporting symptoms that could be consistent with SIADH or diabetes insipidus. Hyponatremic patients admitted to the hospital for corrective measures underwent sodium checks every 6 hours as inpatients until symptoms of hyponatremia resolved or near normalization of serum sodium occurred (133 mEq/L or higher), while hyponatremic outpatients, who were asymptomatic, underwent twice weekly sodium checks until near normalization of serum sodium. Parameters recorded for each case included lesion size, age, sex, number of prior pituitary surgeries, surgical approach (endoscopic endonasal, microscopic endonasal, or craniotomy), lesion type (endocrine-inactive adenoma, endocrine-active adenoma, Rathke cleft cyst, apoplexy, craniopharyngioma, or other), lesion location (sellar, suprasellar, or sellar with suprasellar extension), and the presence of preoperative hypopituitarism. Preoperative hypopituitarism was defined by low levels of an anterior pituitary lobe laboratory value on the blood work checked closest to the time of surgery or preoperative diabetes insipidus and was noted in 210 patients. Because our center does not routinely correct preoperative hormone deficits until after surgery, only 8% (n = 16) of patients were started on hormone replacement for all hormone deficits noted on their last set of preoperative pituitary laboratory values.

Postoperative Variables Recorded

Postoperative hyponatremia was defined as a serum sodium below normal (< 135 mEq/L) occurring within 30 days of surgery. The efficacies of treatment measures were documented by recording the rate of correction in cases in which the treatment was used as the sole treatment for hyponatremia. This rate of correction was calculated by taking the units that the sodium increased during correction and dividing it by the number of hours that the correction was implemented, which in the case of medications such as tolvaptan and Vaprisol included the half-life of the medication added on to the time of the last dose.

Statistical Analysis

Binary logistic regression was used to determine the correlation between these parameters and postoperative hyponatremia, defined as serum sodium levels lower than 135 mEq/L. Analysis of variance was used for parametric comparisons of more than 2 variables when the dependent variable was continuous while a chi-square test was used to compare more than 2 proportions. Parametric comparison between 2 variables was performed using the Student t-test. The Fisher exact test was used to compare 2 proportions. The p values are 2-tailed and p < 0.05 was considered statistically significant.

Results

Patient Preoperative Characteristics

The mean age of patients before the 1045 operations was 46 years (range 4–93 years). There were 576 female patients (55%). The mean lesion size was 2.0 cm (range 3 mm to 6.7 cm).

Preoperative Hyponatremia

Thirty-two patients (3%) presented with preoperative hyponatremia, 41% of whom were symptomatic. A multivariate analysis including patient age, patient sex, lesion size, lesion location (sellar, suprasellar, or sellar with suprasellar extension), preoperative hypopituitarism, operation number, and pathology revealed none of these 7 variables to be predictive of preoperative hyponatremia (Table 1). Of 32 patients with preoperative hyponatremia, only one had preoperative diabetes insipidus managed with desmopressin prior to surgery, while another had nephrogenic diabetes insipidus due to the use of lithium. Nineteen (59%) of 32 patients with preoperative hyponatremia underwent medical correction preoperatively and 18 (56%) had postoperative hyponatremia.

Postoperative Hyponatremia

Pathologies included 340 endocrine-active adenomas, 381 endocrine-inactive adenomas, 124 Rathke cleft cysts, 50 craniopharyngiomas, and 150 miscellaneous pathologies. Postoperative hyponatremia occurred after 165 of the 1013 operations performed in patients without preoperative hyponatremia (16%) a mean of 4 days after surgery (range 0–28 days), with the largest peak of incidence occurring on postoperative Day 2, followed by a smaller delayed peak on postoperative Day 7 (Fig. 1).

Thirty-one of the 165 operations leading to postoperative hyponatremia (19%) were associated with postoperative symptoms attributable to hyponatremia a mean of 6
days after surgery (range 1–29 days; Fig. 1B). Twenty-four of the 165 operations leading to postoperative hyponatremia (15%) involved readmission due to hyponatremia for a mean of 5 days (range 1–20 days). Of the 31 cases of symptomatic postoperative hyponatremia, 38% involved dizziness and 29% involved nausea or vomiting. The risk of permanent diabetes insipidus was comparable in patients with or without postoperative hyponatremia (1.6% vs 0.9%; p = 0.2).

### Risk Factors for Postoperative Hyponatremia

In a multivariate analysis including patient age, patient sex, lesion size, lesion location (sellar, sellar with suprasellar extension, or suprasellar), preoperative hypopituitarism, operation number, surgical approach, and pathological diagnosis, only preoperative hypopituitarism predicted postoperative hyponatremia (p = 0.006) (Table 2). Patients with preoperative hypopituitarism had a 32% (67 of 210) rate of postoperative hyponatremia compared with a 24% (115 of 470) rate of postoperative hyponatremia in those without preoperative hypopituitarism (p < 0.05) (Fig. 2). We then looked at rates of postoperative hyponatremia in patients with or without deficiencies in each of the 5 individual endocrine axes (gonadal, thyroid, adrenal, growth hormone, and prolactin). Of the 5 possi-

### TABLE 1: Results of multivariate analysis of variables predicting the presence of preoperative hyponatremia*

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>1.1 per decade</td>
<td>0.1</td>
</tr>
<tr>
<td>male sex</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>lesion size (mean diameter)</td>
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</tr>
<tr>
<td>suprasellar extension</td>
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</tr>
<tr>
<td>preop hypopituitarism</td>
<td>4.2</td>
<td>0.4</td>
</tr>
<tr>
<td>op no.</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>pathological diagnosis</td>
<td>1.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* HR = hazard ratio.
ble anterior pituitary hormone deficiencies, 3 elevated the risk of postoperative hyponatremia (Fig. 2). First, patients with preoperative central hypothyroidism had a 51% (42 of 83) rate of postoperative hyponatremia compared with 10% (33 of 322) in those without preoperative central hypothyroidism (p < 0.001) (Fig. 2). Second, patients with preoperative central hypogonadism had a 37% (29 of 79) rate of postoperative hyponatremia compared with 17% (34 of 200) in those without central hypogonadism (p < 0.001) (Fig. 2). Third, patients with preoperative central hypoadrenalism had a 38% (21 of 55) rate of postoperative hyponatremia compared with 10% (15 of 150) in those without central hypoadrenalism (p < 0.001) (Fig. 2).

**Correction of Hyponatremia**

The mean correction rates in mEq/L/hour were 0.4 (no treatment, n = 112), 0.5 (free water restriction, n = 24), 0.7 (salt tablets, n = 14), 0.3 (3% saline, n = 20), 0.7 (intravenous vasopressin receptor antagonist Vaprisol, n = 22), and 1.2 (oral vasopressin receptor antagonist tolvaptan, n = 9) (p = 0.002 ANOVA; p < 0.05 for paired comparisons of tolvaptan or Vaprisol vs no treatment; p > 0.05 for free water restriction, salt tablets, or 3% saline vs no treatment) (Fig. 3). While some patients received more than 1 treatment, correction rates were only recorded when a treatment was given alone. The mean time to sodium normalization in all hyponatremic patients was 23 hours (range 3 hours to 27 days). Hyponatremia in 1 patient receiving Vaprisol was overcorrected, with a resulting sodium of 150 mEq/L.

**Discussion**

After 1045 pituitary operations, postoperative hyponatremia was associated exclusively with preoperative hypopituitarism and was most efficiently managed with the vasopressin receptor antagonists Vaprisol and tolvaptan, with other interventions not significantly different from no intervention. Preoperative hypopituitarism appears to be a marker for lesions whose removal will require the surgeon to dissect close to the posterior lobe of the gland or pituitary stalk, potential risks factors for postoperative SIADH. As such, patients with preoperative hypopituitarism may warrant closer follow-up for postoperative hyponatremia than patients with normal preoperative pituitary function.

Our finding that postoperative hyponatremia occurred after 16% of pituitary surgeries is consistent with other recent series, which have reported 18%–23% incidences of postoperative hyponatremia. An earlier study from our institution reported a 2% incidence of postoperative hyponatremia in surgeries done between 1971 and 1993; the vast majority of those cases were symptomatic. The more frequent identification of asymptomatic hyponatremia without change in incidence of symptomatic hyponatremia between that study and the current study likely results from the implementation of standardized postoperative sodium checks since the completion of that study, identifying more asymptomatic cases of hyponatremia.

The timing of postoperative hyponatremia in our study was comparable to that in other studies, which have reported both an early incidence peak occurring around postoperative Day 2 as well as a slightly more delayed peak typically occurring between postoperative Days 7 and 9. While the fact that all patients underwent sodium checks in the hospital after surgery meant that the first peak captured a number of asymptomatic patients, the delayed peak only captured symptomatic patients since

**TABLE 2: Results of multivariate analysis of variables predicting the occurrence of postoperative hyponatremia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>age (per decade)</td>
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<tr>
<td>male sex</td>
<td>1.0</td>
<td>0.9</td>
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<td>suprasellar</td>
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</tr>
<tr>
<td>op no.</td>
<td>1.9</td>
<td>0.4</td>
</tr>
<tr>
<td>surgical approach</td>
<td>2.9</td>
<td>0.1</td>
</tr>
<tr>
<td>pathological diagnosis</td>
<td>1.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

![Fig. 2.](image_url) The frequency of postoperative hyponatremia in patients with various preoperative anterior pituitary deficits. Patients with any anterior pituitary deficit (p < 0.05) or deficits in the gonadal (follicle-stimulating hormone, luteinizing hormone, estrogen, progesterone, or testosterone), thyroid (thyroid-stimulating hormone, T3, or T4), or adrenal (adrenocorticotropic hormone or cortisol) axes had an increased risk of postoperative hyponatremia compared with those without. GH = growth hormone.
asymptomatic patients did not undergo outpatient serum sodium checks; limiting the analysis to patients with symptomatic hyponatremia also revealed a large early peak and a smaller delayed peak (Fig. 1B). The delayed peak has been described in other studies as the predominant time for postoperative hyponatremia, unlike in our study where it was smaller than the postoperative Day 2 peak. The delayed peak has been reported to occur in patients who do not excrete an administered water load and suppress plasma arginine vasopressin normally. In that same study, patients with postoperative hyponatremia occurring around Day 7 were more natriuretic; had lowered dietary sodium intake; and had similar fluid intake, cortisol, and atrial natriuretic peptide as normonatremic patients. The delayed peak in postoperative hyponatremia occurring between postoperative Days 7 and 9 could represent the antidiuretic interphase seen in a triphasic progression of diabetes insipidus. Despite this possibility that postoperative hyponatremia occurring between postoperative Days 7 and 9 could be the second phase of a 3-phase process ultimately leading to postoperative diabetes insipidus, we found the rate of postoperative diabetes insipidus to be comparable in patients with postoperative hyponatremia to those without.

In terms of risk factors for postoperative hyponatremia, our findings differ from other series that analyzed smaller series of patients than ours and suggested that factors such as age older than 60 years and lesion size contribute to postoperative hyponatremia after pituitary surgery. Our multivariate analysis of more than 1000 operations revealed neither age nor lesion size to be risk factors. A study that identified lesion size as a risk factor for postoperative hyponatremia could reflect the fact that larger lesions require manipulation of the pituitary stalk for resection. However, the fact that neither lesion size nor stratification of lesions as sellar, suprasellar extension, or purely suprasellar proved predictive of postoperative hyponatremia in our large series argues against this hypothesis. Another hypothesized risk factor would be pathology, with lesions such as craniopharyngiomas that typically occur closer to the pituitary stalk theoretically increasing the risk for postoperative hyponatremia. However, our analysis failed to identify pathology as a risk factor for postoperative hyponatremia. The one factor we found to increase the risk of postoperative hyponatremia was preoperative hypopituitarism. Given that lesion size, suprasellar location, and pathology failed to predict postoperative hyponatremia, the correlation between preoperative hypopituitarism and postoperative hyponatremia is unlikely to reflect lesion anatomy, but it is possible that preoperative hypopituitarism could increase the risk of postoperative hyponatremia after pituitary surgery through exacerbation of the underlying mechanisms through which hyponatremia is often a transient self-correcting phenomenon, but when medical intervention is indicated, measures designed to replete sodium or deplete water are no more effective than no intervention and are far less effective in terms of the rate of correction than medicines directly targeting the downstream effects of the inappropriate ADH secretion. These findings support SIADH rather than cerebral salt wasting as the etiology of most cases of postoperative hyponatremia after pituitary surgery.

Vasopressin receptor antagonists such as tolvaptan or Vaprisol are a relatively new therapeutic class of agents for the management of hyponatremia. Nephrologists have long believed that vasopressin receptor antagonists may be particularly effective at treating SIADH due to CNS disorders, trauma, or neurosurgery since they are the most physiological approach to the treatment of this common electrolyte disturbance. While vasopressin receptor antagonists are costly, with tolvaptan costing $250 per day, recent analysis of the Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT-1 and SALT-2) trial showed that the reduction in admission rates and durations associated with tolvaptan led to cost reductions of nearly $700 per case in the US. Despite the ability of tolvaptan to offset some of its cost by correcting hyponatremia more rapidly than other measures, mild to moderate hyponatremia that is minimally symptomatic should still be managed with measures that are less costly and less aggressive, such as fluid restriction, with tolvaptan reserved for cases that are more severe in terms of the magnitude of hyponatremia or symptoms.

There are a number of limitations of our study that...
must be acknowledged. The percentage of patients with hyponatremia after discharge that we report is not the true prevalence since not every patient was tested on each of the 29 postoperative days for which we reported the percentage of patients with hyponatremia (Fig. 1C). While a previous publication reported the incidence of postoperative hyponatremia using a standardized prospective protocol in which 247 patients were screened for serum sodium on postoperative Day 7,19 screening a sample size as large as ours for 29 consecutive postoperative days would be cost prohibitive. Thus, our early peak of hyponatremia shown in Fig. 1A likely captured a number of asymptomatic cases simply because all patients underwent daily sodium checks while recovering from surgery. The fact that limits cases because all patients underwent daily sodium in Fig. 1A likely captured a number of asymptomatic cases may be more readily detected while a patient is in the hospital recovering from surgery than when he or she is at home and might not report symptoms to care providers. Furthermore, our findings of different rates of correction between different corrective measures could reflect the fact that, while our frequency of sodium checks did not vary depending on which corrective measure was being used, the frequency of sodium checks did vary between inpatients and outpatients and some corrective measures (3% saline and Vaprisol) could only be given to inpatients.

Conclusions

Despite these limitations, the information we report on the 2 peaks of overall and symptomatic postoperative hyponatremia and modern strategies for correcting this phenomenon provides valuable insight for neurosurgeons managing patients after transsphenoidal surgery. Our findings suggest that prompt identification of hyponatremia in high-risk patients and management of significant symptomatic cases with the oral vasopressin receptor antagonist tolvaptan can improve patient safety and decrease the rates and duration of readmission to the hospital after otherwise successful elective pituitary surgery. For readmitted patients with severely symptomatic hyponatremia, the intravenous vasopressin receptor antagonist Vaprisol is another treatment option.

Disclosure

Arman Jahangiri is a Howard Hughes Medical Institute Research Fellow. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Aghi. Acquisition of data: Aghi, Jahangiri, Wagner, Tran, Miller, Tom. Analysis and interpretation of data: Aghi, Jahangiri, Wagner, Tran, Miller, Tom. Drafting the article: Aghi. Critically revising the article: all authors. Reviewed submitted manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Aghi. Statistical analysis: Aghi. Study supervision: Aghi.

References


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