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Prediction of post-operative delayed hyponatremia after endoscopic transsphenoidal surgery

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ABSTRACT

Objectives: Delayed symptomatic hyponatremia is a known phenomenon occurring ≥ 3 days after transsphenoidal surgery. This is a significant cause of post-operative emergency room visits and re-admissions. We describe and characterize post-operative hyponatremia in patients undergoing endoscopic transsphenoidal surgery, identify predictive factors, and create a clinical tool for predicting high risk patients.

Patients & methods: We retrospectively reviewed a series of over 300 consecutive patients undergoing endoscopic transsphenoidal surgery and identified patients with delayed hyponatremia as well as patient, tumor, and surgical characteristics. In addition, we recorded inpatient post-operative sodium and specific gravity values as well as treatment upond discharge. Univariate and multivariate analyses were carried out to identify predictors of delayed hyponatremia and stratify patients into risk groups.

Results: We found that 15% of patients developed delayed hyponatremia and that this occurred most commonly on post-operative day 7. This accounted for more than half of re-admissions after this type of surgery. Female patients and patients needing fluid restriction or fludrocortisone upon discharge were more likely to develop delayed hyponatremia. Patients with post-operative diabetes insipidus were less likely to develop delayed hyponatremia. Using ROC analysis we developed a score which reliably could stratify patients at risk for delayed hyponatremia.

Conclusions: We confirm the risk of delayed hyponatremia after transphenoidal surgery and identify factors that are revealed before discharge to identify patients at higher risk of delayed hyponatremia. These data may help identify patients who require treatment upon discharge and short interval follow up to avoid significant costs of re-admission.

1. Introduction

Microscopic and endoscopic transsphenoidal surgery is a common approach for sellar and suprasellar lesions. A well-described issue in these patients is delayed symptomatic hyponatremia (DSH). This is defined as hyponatremia that occurs ≥ 3 days after transsphenoidal surgery with symptoms including headache, nausea, vomiting, altered mental status, seizures, and even death [3,17].

The pathophysiology of DSH is unknown. One proposed mechanism is delayed release of antidiuretic hormone from the traumatized normal posterior pituitary gland after transsphenoidal surgery. Indeed, three studies have identified elevated plasma arginine vasopressin in patients with post-operative hyponatremia, suggesting inappropriate secretion of vasopressin [11,13,14]. Another possible mechanism is cerebral salt wasting syndrome or salt wasting secondary to perturbed ACTH secretion [1,11].

There have been several studies investigating DSH [2,3,5–8,10,13,14,16–19]. In these studies, the overall reported incidence of DSH ranged between 4–23%. Previously reported rates in both series with endoscopic and microscopic transsphenoidal surgery have had similar results [3]. The lowest sodium levels reported to occur on post-operative day 7 [3,5,6] with the range of symptomatic hyponatremia occurring between post-operative day 4 and 7. [4] In regards to risk factors for DSH, the data are unclear. Five studies identified advanced age as a risk factor for DSH [6,6,7,8,16,18], two studies associated female gender as a risk factor [13,19], two studies associated Cushing disease as a risk factor [6,13], and one study associated elevated thyroid stimulating hormone level with DSH [16]. Other studies

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did not find a significant association between these potential risk factors and the development of DSH. Most of these studies did not publish data describing the patient's post-operative course before discharge.

In this study, we retrospectively review a series of over 300 consecutive transsphenoidal procedures for sellar pathology to confirm previously described characteristics regarding DSH and identify risk factors for DSH that can be identified before discharge. We present the first study to evaluate immediate post-operative (day 1–2) inpatient laboratory values and need for treatment upon discharge. We develop the first model using inpatient data to predict patients who will be at risk for DSH as targets for closer outpatient follow up in hopes to decrease emergency room visits and re-admissions in this cohort of patients.

2. Patients & methods

Institutional review board approval was obtained for this study and informed consent was obtained in all cases. We retrospectively reviewed all patients with endoscopic transnasal transsphenoidal surgery for sellar pathology at our institution between 2013 and 2016. All surgeries were performed by senior authors. Pre-operative and intra-operative data were gathered. Post-operative inpatient sodium levels, specific gravities, and medications were reviewed as well as sodium levels after discharge. Emergency room visits and readmissions were recorded as well as laboratory analysis upon arrival.

2.1. Post-operative sodium management

Pre-operative sodium levels, presence of pre-operative diabetes insipidus (DI) were recorded. Following endoscopic transnasal transsphenoidal surgery, patients are typically admitted to a floor level bed. All patients have serum sodium levels checked every 6 h. A foley catheter is placed intraoperatively and urine output is recorded every hour. A specific gravity is checked for elevated urine output, which is defined as 400 cc of urine over one hour for two consecutive hours. The number of times a specific gravity was ordered as well as the value was recorded. Patients with hyponatremia are treated with a combination of salt Table 1 gram three times a day for 7 days), free water / fluid restriction (total free water restriction and < 1 L fluid over 24 h), and/or fludrocortisone ($0.1-0.2$ gram twice a day). We identified patients with delayed symptomatic hyponatremia as previously described in the literature: patients with hyponatremia $\geq$ 3 days after surgery with symptoms including significant headache, nausea/vomiting, or altered mental status.

Table 1
Pre-operative, intra-operative, and post-operative statistics of a series of 367 consecutive patients with transsphenoidal surgery.

Descriptive Statistics	
Characteristic	
Patients	367
Age	48.5 (range 6-84)
Pediatric	15 (4.1%)
Female	198 (54%)
Operative Time	126 min (range 38-410)
Length of Stay	3.3 (range 1-55)
Pathology	
Pituitary adenoma	75%
Non-functioning	44%
Prolactinoma	13%
ACTH producing	13%
GH producing	4%
Atypical	1%
Rathke cleft cyst	10%
Craniopharyngioma	4%
Meningioma	3%
Metastasis	2%
Esthesioneuroblastoma	1%
Return to Emergency department	52 (14%)
Related to hyponatremia	25 (7%)
Readmission	33 (9%)
Related to hyponatremia	20 (5%)

2.2. Statistical analysis

Univariate analysis of the data was executed using SPSS Statistics for Macintosh (Version 25.0. Armonk, NY: IBM Corp. 2017). Two-tailed *t*-tests were used to identify pre-operative and post-operative, pre-discharge variables associated with delayed hyponatremia. Multivariate analysis of the data was conducted via RStudio (Version 1.1.453, Boston, MA: RStudio, Inc. 2018). To develop a predictive model for risk of developing DSH, a multivariate logistic regression was performed, with DSH occurrence as the dependent variable and the starting pool of independent predictor variables including age, gender, time spent in operating room (OR), length of stay, pre-operative sodium issues, discharge medication, frequency of specific gravity check, episodes of abnormal specific gravity, max tumor size, and surgical procedure performed. The regression model was validated using the Hosmer-Lemeshow Goodness-of-Fit test, with a significant probability value ($p < 0.05$) indicating poor fit between the model's predictions and the data's actual outcome and providing evidence to reject the model. Using data from these analyses, a score was developed as a predictor of delayed symptomatic hyponatremia. The area under the receiver operating characteristic curve (AUC) was calculated for this score with an AUC value of greater than or equal to 0.7 being considered a valid model with good discriminative ability. Equality of the actual DSH rate and the predicted DSH rate was assumed as the null hypothesis for significance testing.

3. Results

3.1. Descriptive statistics

A total of 367 consecutive patients with endoscopic transnasal transsphenoidal surgery for sellar lesions were included in this study (Table 1). The average age was 48.5 years (range 6–84). There were 15 pediatric patients included in this study. Fifty-four percent of patients were female. The average operative time was 126 min and average length of stay was 3.3 days (SD 4.2). The most common pathology was pituitary adenoma (75%). Specifically, these included non-functioning pituitary adenoma (44%), prolactinoma (13%), ACTH producing pituitary adenoma (13%), growth hormone producing pituitary adenoma (4%), and atypical pituitary adenoma (1%). Other pathologies included: rathke cleft cyst (10%), craniopharyngioma (4%), meningioma (3%), metastasis (2%), esthesioneuroblastoma (1%), as well as eosinophilic granuloma, mucoid retention cyst, chondrosarcoma, chordoma, arachnoid cyst, lymphocytic hypophysitis, spindle cell oncocytoma, hyperostosis, and dysgerminoma ($< 1\%$ each). There was no final diagnosis in 1% of patients. The average lesion size was 20 mm (2–90). In each case, special attention was paid to identify and preserve of the normal pituitary gland [9]. Two patients developed post-operative pituitary insufficiency. Both these patients underwent surgery for craniopharyngioma. Discharge medications included: salt tablets in 205 patients (56%), fluid restriction in 25 patients (7%), DDAVP in 55 patients (15%), and fludrocortisone in 10 patients (3%). Ninety-eight percent of patients were discharged to home. The emergency department visit rate was 14.1% and readmission rate was 9%.

3.2. Post-operative delayed symptomatic hyponatremia

The rate of delayed symptomatic hyponatremia was 15% in this series. On average, delayed symptomatic hyponatremia initially began on post-operative day 5.1 (SD 2.9). The hyponatremia was at its worst on post-operative day 7.4 (SD 1.9, range 4–16) (Fig. 1a). There was one

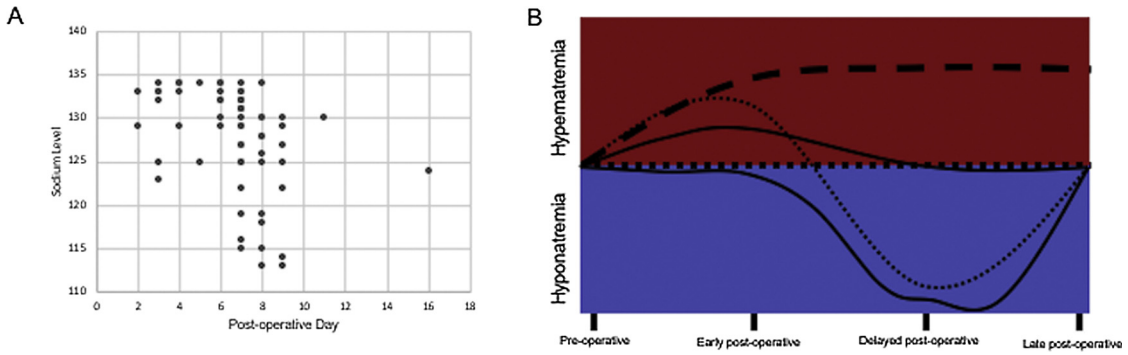

Fig. 1. (A) Delayed (> 3 days) post-operative symptomatic hyponatremia most commonly occurred at post-operative day 7 with an average sodium level of 124. Note, one patient who presented with hyponatremia on post-operative day 43 is not included in this figure. (B) Sodium trends over time fell into one of 5 categories: normal sodium throughout postoperative course (59%) (large dots), permanent DI (3%) (thick dashes), temporary DI followed by no sodium imbalance (23%) (positive solid line), delayed hyponatremia (14%) (negative solid line), and biphasic response (1.3%) (small dots).

patient who never developed hyponatremia in the early post-operative period but developed hyponatremia 43 days after surgery. The average sodium level in patients with delayed hyponatremia was 124.8 (SD 18.1) (Fig. 1a). In regard to patterns of sodium imbalances, 1.3% of patients had a biphasic response (initial polyuria followed by hyponatremia) and 0% of patients had a triphasic response (polyuria – hyponatremia – polyuria) (Fig. 1b). Patients with delayed hyponatremia accounted for 48% of post-operative emergency room visits and 61% of post-operative re-admissions. Of the patients who returned to the hospital for hyponatremia, 83% of patients had a physical exam and laboratory values consistent with SIADH. The other 17% of patients had either hypovolemia or significant salt wasting consistent with cerebral salt wasting syndrome.

3.3. Identification of factors predicting post-operative delayed symptomatic hyponatremia

Independent sample *t*-tests were implemented to identify pre-operative, intra-operative, or pre-discharge post-operative characteristics associated with delayed symptomatic hyponatremia. There was no significant difference in age or whether the patient was in the pediatric population. There was no difference depending on length of the case, the size of the lesion, the length of inpatient stay, or final discharge destination. As discussed above, specific gravity is sent when there is suspicion of DI on basis of elevated urine output. While the number of times specific gravity was ordered did not correlate with delayed symptomatic hyponatremia, patients having an abnormally high specific gravity were less likely to developed delayed symptomatic hyponatremia, although this was not statistically significant. In light of this, we analyzed whether transient post-operative DI, as defined as rising sodium with high urine output and low specific gravity was associated with delayed hyponatremia and found that patients tagged as having transient post-operative DI were significantly less likely to develop post-operative delayed symptomatic hyponatremia ($p = 0.002$). Furthermore, patients who were discharged with desmopressin were also significantly less likely to develop delayed hyponatremia ($p = 0.003$). Female patients were more likely to develop delayed symptomatic hyponatremia ($p = 0.05$). Given the mixture of different pathologies in this study, we independently analyzed rates of delayed hyponatremia with each pathology separately. Patients with craniopharyngioma were significantly less likely to develop delayed hyponatremia ($p < 0.01$), and patients with meningiomas were more likely to develop delayed hyponatremia ($p = 0.027$). All other pathologies had no significant correlation with rates of delayed hyponatremia. Patients who were discharged with a fluid restriction or fludrocortisone were significantly more likely to develop delayed symptomatic hyponatremia ($p = 0.001$, $p = 0.002$).

3.4. Regression modeling and risk stratification for delayed hyponatremia

The final model from the multivariate stepwise logistic regression included sex, discharge medication, and frequency of specific gravity lab testing as predictors of delayed symptomatic hyponatremia and excluded age, time spent in OR, length of stay, preoperative sodium issues, episodes of abnormal specific gravity, maximum tumor size, and tumor pathology from the model. Significant positive predictors of delayed symptomatic hyponatremia were found for discharge orders prescribing fluid restriction ($OR = 12.53$, $p < 0.001$) and fludrocortisone ($OR = 90.66$, $p < 0.001$). Discharge orders prescribing desmopressin was found to be a negative predictor of DSH ($OR = 0.11$) but not significantly ($p = 0.0586$). The remaining identified predictors, female sex ($OR = 1.65$), salt tablets ($OR = 1.35$), and frequency of specific gravity lab testing ($OR = 1.16$/lab test), were all positively associated with delayed symptomatic hyponatremia but not significantly ($p = 0.149$, $p = 511$, $p = 0.111$ respectively). The Hosmer-Lemeshow goodness-of-fit test for the model derived from the stepwise regression reported a p-value of 0.4966.

3.5. Development of risk score for post-operative hyponatremia

Using the factors identified in the above analysis (gender, post-operative DI, discharge medications), we created a score for predicting post-operative hyponatremia (Table 2). We carried out ROC analysis, identifying an area under the curve with of 0.742 and standard error of 0.04 ($p < .001$). This statistically significant analysis identified patients with a score > 0 to have a 82% sensitivity and 62% specificity of developing post-operative hyponatremia.

4. Discussion

Endoscopic transphenoidal surgery is a common treatment option for sellar and suprasellar lesions with one of its largest benefits being its minimally invasive nature and quick recovery period. Most patients at our institution are discharged within 2 days of endoscopic transphenoidal surgery. Classically, the most significant post-operative complication with this surgery has been cerebrospinal fluid leaks, but with

Table 2
A clinical decision tool to identify patients who are at elevated risk for development of delayed symptomatic hyponatremia.

Delayed hyponatremia prediction score	
Attribute	Points
Female Gender	+1
Early post-operative DI	−1
Fluid restriction or fludrocortisone on discharge	+1

increased awareness and techniques for anterior skull base reconstruction including nasoseptal flaps, the rate has dropped considerably. [12] We found that delayed hyponatremia was a more common post-operative issue than post-operative cerebrospinal fluid leak. It was the cause of almost half of all emergency room visits and over half of admissions. This is in concordance with another large study looking at emergency room visits after endoscopic transsphenoidal surgery [15]. Given that these need close monitoring for careful sodium correction, and possibly ICU admission, the cost of this issue is clearly significant. What may now replace post-operative cerebrospinal fluid leak as the most common and costly post-operative clinical issue is delayed symptomatic hyponatremia.

In a series of over 300 consecutive endoscopic transsphenoidal cases, we confirm the incidence and time course of delayed symptomatic hyponatremia. We report a rate of 15%, which is consistent with previous studies [2,3,5–8,10,13,14,16,17,19]. Even more interesting is that our study was completely concordant with the three studies examining the time course of post-operative hyponatremia in which they found that the hyponatremia occurred at or around post-operative day 7 [3,5,6].

The pathophysiology of delayed hyponatremia after transphenoidal surgery is unknown. Most studies suggest the dominant pathophysiology is SIADH while in fewer cases workup suggests cerebral salt wasting syndrome [1]. Our findings upon examination of patients returning with delayed hyponatremia agreed with these findings, were most patients (83%) presented with euvolemic hyponatremia suggestive of SIADH. The classical triphasic response has previously been shown to occur in lower frequency than in animal studies [5]. We report 1.3% of patients with a biphasic response and 0% of patients with a triphasic response. We hypothesize that improved and less aggressive resection of these lesions has led to decreased damage to the hypothalamic-posterior pituitary pathway and decreased incidence of these polyphasic responses. Damage to the posterior pituitary is not common in our study and only find long term hypopituitarism due to disruption of the gland in patients with craniopharyngiomas. We believe delayed symptomatic hyponatremia is a distinct entity from the classically described triphasic response associated with damage to this axis.

In this study we attempt to identify predictors of delayed symptomatic hyponatremia. Using univariate and multivariate analysis, we identify gender, presence of early post-operative DI, and the need for discharge medications statistically significant predictors of hyponatremia. Previous studies have identified female gender as a predictor of hyponatremia as we have in this study [13,19]. A new perspective this study brings to the literature is the analysis of post-operative inpatient data. Patients with early postoperative elevated sodium and polyuria were less likely to develop delayed hyponatremia, as supported by the lack of polyphasic sodium changes in our study group. We found that patients who were discharged on fludrocortisone and/or fluid restriction were more likely to have delayed symptomatic hyponatremia. Because both of these used in the treatment of hyponatremia, we hypothesize that this finding suggests evidence of downtrending sodium on discharge rather than a paradoxical effect of the treatments themselves. Two previous studies saw a correlation between early post-operative hyponatremia and delayed hyponatremia, suggesting that there may be early signs suggesting development of significant hyponatremia [16,18]. We created a statistically robust score than can identify patients who will develop delayed symptomatic hyponatremia. With this data, we have changed our practice to aggressively treat patients at high risk with delayed symptomatic hyponatremia with fluid restriction, salt tablets, and fludrocortisone and follow these patients with post-discharge outpatient sodium checks at least 2 times within the first week after surgery.

The major limitations to this study center around remaining selection bias and improving the predictive ability of our clinical tool. Our case series includes heterogenous lesions with different structural characteristics. Although we attempt to control for selection bias by including lesion size and pathology in our analysis, unaccounted differences may exist. In addition, there may be certain characteristics such as intraoperative manipulation of normal pituitary gland that can help improve the predictive capacity of or clinical tool with addition of more variables. Given the variability among previous studies it is clear that the etiology of postoperative hyponatremia is complicated and multifactorial, but we hope that the robust ability of inpatient variables to predict delayed hyponatremia can help prevent readmissions in the clinical setting.

5. Conclusions

With post-operative hyponatremia being the most common etiology for ED visits and readmissions, we suggest that delayed post-operative hyponatremia is now the most clinically prevalent issue after transsphenoidal surgery for sellar pathology. This hyponatremia occurs in a consistent number of patients at predictable time point after surgery. It is not commonly in a polyphasic pattern, but rather simply delayed hyponatremia. We develop a score to identify patients who should have close follow up with sodium checks as well as prophylactic treatment upon discharge. Further studies should focus the ability of these measures to decrease readmissions as well as to understand the pathophysiology of delayed hyponatremia.

Conflict of interest

None.

Funding

No funding was received for this research.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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