ORIGINAL PAPER

Nagoya J. Med. Sci. **76**. 73 ~ 82, 2014

A NOVEL METHOD FOR MANAGING WATER AND ELECTROLYTE BALANCE AFTER TRANSSPHENOIDAL SURGERY: PRELIMINARY STUDY OF MODERATE WATER INTAKE RESTRICTION

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ABSTRACT

Hyponatremia is a common and potentially serious complication of transsphenoidal surgery (TSS). Since September 2009, we have implemented moderate water intake restriction (<2500 mL/day) after TSS in an attempt to prevent this complication. The aim of this study was to investigate the efficacy of a combination of moderate restriction of water intake plus antidiuretic hormone (arginine vasopressin [AVP]) replacement therapy in patients with diabetes insipidus (DI) for reducing the incidence of delayed hyponatremia after TSS. Patients treated from September 2005 to August 2009 were allowed to drink water freely after surgery (the control group), while patients treated from September 2009 to June 2012 were restricted to less than 2500 mL water per day (the water restriction group). To reduce the occurrence of hypernatremia, AVP replacement therapy was provided immediately after the development of DI. We retrospectively analyzed the incidence of hyponatremia, DI, and hypernatremia in patients following TSS. Hyponatremia incidence was significantly lower in the water restriction group (P = 0.017); however, there were no significant differences in DI incidence and hypernatremia incidence between the 2 groups. Under DI control with AVP replacement therapy, the water restriction group showed no significant difference in the daily self-rated thirst level for the patients with and without DI. Moderate water intake restriction in addition to AVP replacement therapy significantly decreases the incidence of hyponatremia without patient discomfort (extreme thirst) and other complications. However, further studies are required to determine the most effective amount of water and the optimal duration of postoperative water restriction.

Key Words: Hyponatremia, Transsphenoidal Surgery, Pituitary Tumor, Syndrome of Inappropriate Secretion of Antidiuretic Hormone, Thirst

INTRODUCTION

Transsphenoidal surgery (TSS) is the first-line treatment for sellar and parasellar lesions, with the exception of some specific anatomical and histopathological conditions. Pituitary adenoma is the most common lesion treated using this approach. This surgery is less invasive and seldom results in serious complications; however, it can be the cause of disturbance in water and electro-

Received: August 13, 2013; accepted: November 18, 2013

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lyte metabolism. Diabetes insipidus (DI) occurs in 10% to 50% of patients after TSS[4, 6, 11, 12, 14], while delayed hyponatremia is reported to occur in 1.8% to 35% of patients around postoperative day[7 9, 11, 13, 16, 19]. Hyponatremia may become symptomatic, and prolonged hyponatremia may be life threatening[5, 9, 21]. It is imperative to minimize risk factors for delayed hyponatremia after transsphenoidal tumor resection, because recent advances in neuroendoscopic techniques are less traumatic to the nasal apparatus, resulting in shorter hospital stays. Hyponatremia following TSS may arise because of deficiency in the supply of adrenocortical hormone, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and/or inappropriate fluid consumption[8, 13, 17]. Although the causes of delayed hyponatremia following TSS are still unclear, some authors attribute this to SIADH and others suggest frequent coincidence with DI[8, 15, 20]. We promote a novel method for managing water and electrolyte balance after TSS. We have previously managed water balance after TSS with free fluid intake and aggressive fluid replacement. In the present study, we adopted moderate restriction of postoperative water intake and reduced fluid replacement while carefully monitoring DI and body weight. We also monitored subjective sensation of thirst, as excessive thirst may hinder treatment compliance. To this end, we created a self-rated thirst level scale and assessed the relationship between thirst and DI in relation to delayed hyponatremia after TSS. The aim of the present study was to investigate the feasibility of moderate restriction of water intake to reduce the occurrence of delayed hyponatremia after TSS.

PATIENTS AND METHODS

Patient Population and Surgical Procedures

In this retrospective study, we collected data from the charts of patients who had sellar and parasellar lesions and underwent purely endoscopic endonasal TSS from September 2005 to June 2012. A single surgeon (TN) performed all surgeries.

Surgeries were performed under general anesthesia, with visualization provided by a 4-mm diameter rigid-lens endoscope. We operated through a unilateral nostril (usually on the right side), using a midline paraseptal approach to access the sphenoid sinus. This approach leaves the contralateral nostril intact and results in reduced postoperative nasal obstruction and less severe postoperative thirst due to oral breathing. The ipsilateral mucosa on the nasal septum was dissected to the level of the anterior wall of the sphenoid sinus. The bony septum was removed to expose the mucosa on the contralateral side. Routine wide-open sphenoidotomy was performed for all patients. Sellar and suprasellar procedures began with internal debulking of the tumor, followed by identification of the tumor capsule. In most cases, capsulectomy with an angled endoscope was possible. After tumor excision, we packed the tumor cavity with abdominal fat to prevent postoperative cerebrospinal fluid leakage. Nasal packing was removed immediately after extubation.

Standard Protocol for Postoperative Management of Water and Electrolyte Balance

In September 2009, we adopted a new protocol for managing water and electrolyte balance after TSS. The core concept of the present study is moderate restriction of water intake and adequate control of DI immediately after surgery.

On the day of surgery and on postoperative day 1, the patients were intravenously administered 1000 mL sugar electrolyte maintenance transfusion solution containing 0.3% NaCl. On postoperative day 2, they were administered 500 mL sugar electrolyte maintenance transfusion solution. Postoperative patients were permitted to drink fluids 3 hours after returning to the ward. Patients without Cushing's disease were intravenously administered 100 mg hydrocortisone on the

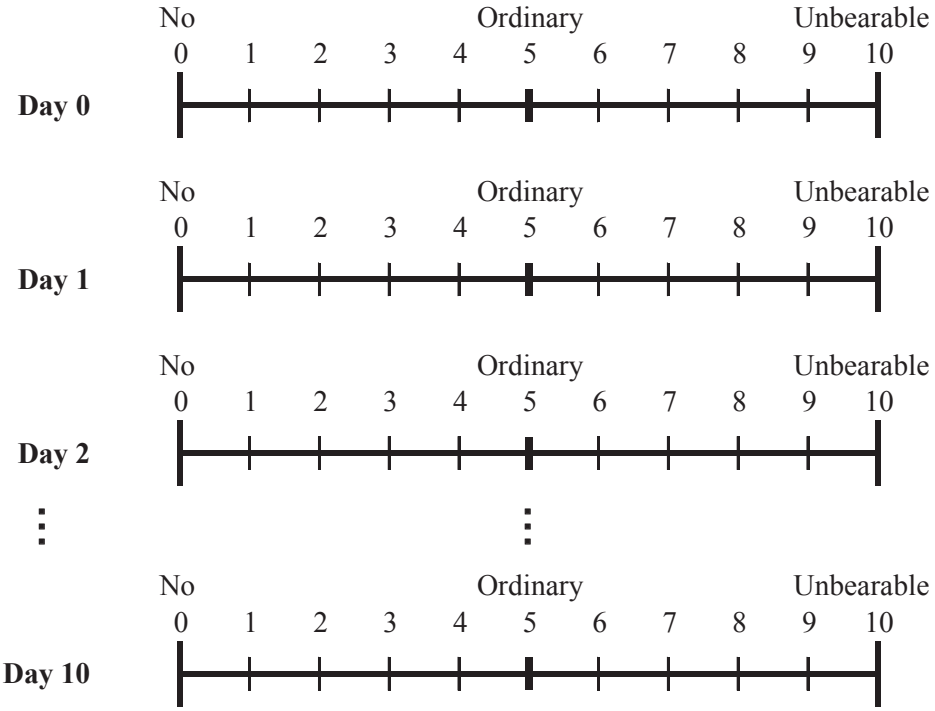

Fig. 1. Thirst Questionnaire. Patients were required to circle a number depicting their own thirst level on this questionnaire each day, from the day of surgery to postoperative day 10.

day of surgery and on postoperative day 1. An additional 100 mg was administered during the surgery. Fifty milligrams of hydrocortisone was administered on postoperative day 2, and 20 mg hydrocortisone was administered orally on postoperative days 3 and 4. For patients with Cushing's disease, cortisol replacement therapy was initiated upon confirmation of adrenal insufficiency.

We prepared a printed form that the patients could use to record their thirst level. We represented thirst on a scale of 0–10, with 0 indicating no thirst and 10 indicating unbearable thirst. The midpoint of the scale (5) represented ordinary thirst (Fig. 1). The patients were instructed to keep the form at their bedside and were required to circle a number on 1 scale for each day.

As a general rule, the patients were permitted to drink no more than 2500 mL water per day from postoperative day 1 to postoperative day 10. Blood tests for serum levels of electrolytes and endocrine function were performed 2 days before surgery and on postoperative days 1, 7, and 10. Hyponatremia was diagnosed if the serum sodium level was less than 135 mEq/L. Hypernatremia was diagnosed if the serum sodium level was greater than 148 mEq/L.

Management of DI

Urine volume was monitored every 2 hours on the day of surgery and on postoperative day 1, and every 8 hours from postoperative day 2 to postoperative day 10. We only observed balanced intake and fluid output on the day of the surgery and on postoperative day 1, because most patients were administered a relatively large volume of fluid during anesthesia. DI was diagnosed if urine volume reached 1000 mL/4 h and urine specific gravity fell below 1.005 on or after postoperative day 2. From postoperative day 2, the patients received intravenous substitution

therapy of vasopressin or were nasally administered deamino-8-D-arginine vasopressin (ddAVP) if they were diagnosed with DI. The target volume of urine output for this treatment was defined as less than 1000 mL/4 h and less than 2500 mL/day. If body weight increased after surgery, administration of antidiuretic hormone (ADH) was discontinued.

Study Design

Patients in puerperium and those with a medical history of hyponatremia were excluded from the study. The remaining patients were categorized into the following 2 groups: control group, patients who were treated from September 2005 to August 2009 and were allowed to drink water freely after surgery; water restriction group, patients who were treated from September 2009 to June 2012 and were subjected to moderate water restriction.

Demographics, tumor type and volume, incidence of hyponatremia, hypernatremia, and DI, operative time, intraoperative blood loss, intraoperative fluid balance, and average daily oral fluid intake between postoperative day 1 and postoperative day 7 or before the day of occurrence of hyponatremia were analyzed.

Preoperative tumor volume was measured using a preoperative magnetic resonance imaging (MRI) scan and was calculated as follows:

Volume (mm^3) = Width (mm) × Height (mm) × Depth (mm) ÷ 2

Statistical Analysis

Statistical analyses were performed with the software package SPSS 19.0 J for Windows (SPSS Inc., IL, USA). Categorical variables were assessed with the Pearson chi-square test, and quantitative variables were compared with unpaired 2-tailed t tests. A P value ≤0.05 was considered statistically significant. Values are expressed as mean ± standard deviation.

RESULTS

A total of 191 patients with sellar lesions were treated using purely endoscopic endonasal TSS during this period. Two patients in puerperium and 4 patients with a medical history of hyponatremia were excluded. The remaining 185 patients were enrolled in the study.

Clinical Characteristics

Clinical characteristics (age, lesion type, and perioperative indices) for the 2 patient groups are summarized in Table 1. The water restriction group included 93 patients and the control group included 92 patients. The mean age was 48.99 ± 14.44 years in the water restriction group and 51.65 ± 15.91 years in the control group (P = 0.271). There were 52 women in the water restriction group and 44 women in the control group (P = 0.216).

There were no statistically significant differences between these 2 groups with respect to clinical characteristics.

Water and Electrolyte Disturbances

Hyponatremia was observed in 5 patients in the water restriction group and 15 patients in the control group; this was a statistically significant difference (P = 0.017, Table 2). Among these patients, symptomatic hyponatremia was observed in only 1 patient in the water restriction group, as opposed to 6 patients in the control group, showing no significant difference (P = 0.052). There were 24 patients with DI and 3 patients with hypernatremia in the water restriction group and 27 patients with DI and 3 patients with hypernatremia in the control group; however,

Table 1 Characteristics of patients treated with endoscopic endonasal TSS. NF, non-functioning pituitary adenoma; GH, growth hormone–secreting pituitary adenoma; PRL, prolactin secreting pituitary adenoma; ACTH, adrenocorticotropic hormone–secreting pituitary adenoma

		Water Restriction	Control	*P*
n		93	92	
Sex				0.271
	Female	52	44	
	Male	41	48	
Age, y		48.99±14.44	51.65 ± 15.86	0.216
Tumor type				0.544
	NF	49	55	
	GH	25	25	
	PRL	9	4	
	ACTH	4	6	
	Craniopharyngioma	3	1	
	Rathke's cleft cyst	2	1	
	meningioma	1	0	
Tumor volume (mm^3)		5426±6944	5571±5427	0.876

Table 2 Incidence of hyponatremia (with or without symptoms), diabetes insipidus (DI), and hypernatremia.

		Water Restriction	Control	*P*
Hyponatremia		5 (5.4%)	15 (16.3%)	0.017
	Symptomatic	1 (1.1%)	6 (6.5%)	0.052
	Asymptomatic	4 (4.3%)	9 (9.8%)	0.145
DI		21 (25.8%)	27 (29.3%)	0.48
Hypernatremia		3 (3.2%)	3 (3.3%)	0.989

there was no statistically significant difference ($P = 0.480$ and $P = 0.989$, respectively; Table 2). There were 24 patients with DI in the water restriction group and 27 patients in the control group, with no significant difference ($P = 0.480$). Three patients in the water restriction group had hypernatremia, with maximum serum sodium levels of 150 mEq/L, 154 mEq/L, and 148 mEq/L respectively, and 3 patients in the control group had maximum serum sodium levels of 158 mEq/L, 148 mEq/L, and 151 mEq/L, respectively.

Isolated hyponatremia, combined DI and hyponatremia, and isolated DI were observed in 3, 2, and 22 patients, respectively, in the water restriction group, and 2, 13, and 14 patients, respectively, in the control group (Table 3). The incidence of both DI and hyponatremia in the same patient was significantly less in the water restriction group than in the control group ($P = 0.003$).

Data on the average daily oral fluid intake of isolated hyponatremia patients, combined DI and hyponatremia patients, and isolated DI patients were available in 3 of 3, 2 of 2, and 19 of 22 patients in the water restriction group, respectively, and 2 of 2, 6 of 13, and 11 of 14

Table 3 Intraoperative and postoperative measurements of water and electrolyte disturbances.
*Average daily oral fluid intake during postoperative day 1 to day 7 or the day before incidence of hyponatremia.

	Water Restriction Group			Control Group		
	Isolated Hyponatremia	Combined DI-Hyponatremia	Isolated DI	Isolated Hyponatremia	DI-Hyponatremia	Isolated DI
n	3 (3.2%)	2 (2.2%)	22 (23.7%)	2 (2.2%)	13 (14.1%)	14 (15.2%)
Sex						
Female	3	2	13	2	4	7
Male	0	0	9	0	9	7
Age, y	44.3 (26–70)	32.0 (28–36)	41.05 (24–62)	53.5 (35–72)	54.3 (19–75)	48.1 (22–77)
Intraoperative data						
Duration, min	208.6±41.4	319.0±190.9	236.1±120.5	122.0 ± 53.7	163.6 ± 30.8	208.5 ± 62.5
Blood loss, mL	30.0±43.6	107.5±65.8	208.7±281.1	15.0 ± 21.2	29.2 ± 24.7	83.2 ± 94.1
Fluid balance, mL	966.7±255.4	1458.0±100.41	1453.7±930.6	1770.0 ± 905.1	1455.7 ± 659.2	1701.2 ± 548.5
Post-operative data						
Oral fluid intake (ml)*	1595.1±754.3	1817.2±807.8	2304.6±640.3	2597.5±1072.9	3034.9±1378.1	3258.2±1946.1

patients in the control group, respectively. The average daily oral fluid intake was 1595.1 ± 754.3 ml, 1817.2 ± 807.8 ml, and 2304.6 ± 640.3 ml in the water restriction group, respectively, and 2597.5 ± 1072.9 ml, 3034.9 ± 1378.1 ml, and 3258.2 ± 1946.1 ml in the control group, respectively (Table 3). Average daily oral fluid intake was greater than 2500 ml in 1 (50%) of 2 isolated hyponatremia patients, 5 (83.3%) of 6 combined DI and hyponatremia patients, and 6 (54.5%) of 11 isolated DI patients in the control group. There were no statistically significant differences between the 2 groups with respect to intraoperative data.

Assessment of Thirst Level

Only 37 of the 93 patients in the water restriction group evaluated their thirst level because the questionnaire was formulated after the treatment protocol had been initiated. These 37 patients included 9 patients with DI and 28 without DI (Fig. 2). There were no statistically significant differences in the thirst levels of patients with and without DI from the day of surgery to postoperative day 10.

Illustrative Case in the Control Group

A 47-year-old woman with a growth hormone-producing pituitary microadenoma detected on MRI underwent purely endoscopic endonasal TSS. Six hours after the surgery, she developed DI, and vasopressin was administered intravenously. On postoperative day 1, intravenous administration of vasopressin was switched to nasal administration of ddAVP, which was continued until postoperative day 4. She was allowed to drink freely and exhibited polyuria and polydipsia. The maximum urine output (9693 mL/day) was observed on postoperative day 4. A subsequent decrease in urine output led to discontinuation of ddAVP administration on postoperative day 5. Despite the alleviation of DI, the patient had been drinking 3000–6000 mL/day from postoperative day 1 to postoperative day 7. She experienced headaches and nausea on postoperative day 8, and blood examination revealed hyponatremia (119 mEq/L) on postoperative day 9. She was kept under water restriction after developing hyponatremia. Her symptoms and serum sodium level improved, and she was discharged from our department on postoperative day 18.

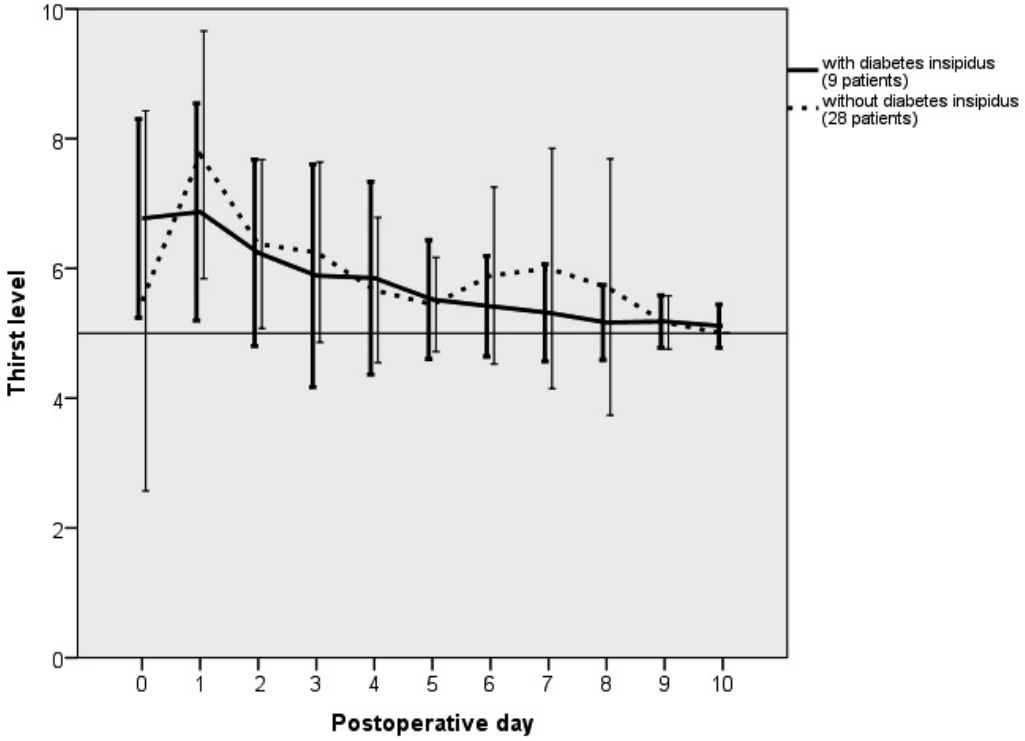

Fig. 2 Changes in the Thirst Level after Transsphenoidal Surgery.

DISCUSSION

Hyponatremia is a common electrolyte disturbance in the neurosurgical population. This complication is attributed to SIADH, cerebral salt wasting (CSW), and adrenal insufficiency[8, 15, 21]. Hyponatremia following TSS has been reported by several authors. The reported incidence of this complication is approximately 30%, and it occurs about 7 days after surgery[3, 7, 11, 16]. Approximately 20% of patients become symptomatic[21]. The symptoms of hyponatremia are variable and include headache, nausea, vomiting, mental status disturbance, seizures, and coma[2, 5, 21]. Therefore, if this complication occurs, patients may require additional treatment and longer hospital stay, even if there are no noticeable problems with the surgery itself. Insufficient or inappropriate treatment for this complication can induce other neurological disturbances, such as seizures, osmotic demyelination syndrome, coma, and even death[5, 15].

The pathophysiology of delayed hyponatremia has been discussed extensively, and the main cause following TSS is believed to be the release of excessive antidiuretic hormone, presumably induced by surgical manipulation of the posterior pituitary gland and pituitary stalk[7, 18, 20]. SIADH treatment is based on restriction of water intake. We evaluated this treatment by implementing moderate water restriction to prevent hyponatremia after TSS. To date, the method for preventing this complication has not been established. To the best of our knowledge, this is the first study to test a possible method for preventing hyponatremia following TSS.

Occurrence of Hyponatremia

We evaluated the usefulness of limiting oral fluid intake to 2500 mL/day from immediately

after TSS to postoperative day 10. Previously identified risk factors for hyponatremia after TSS are older age, female sex, microadenomas, adrenocorticotropic hormone (ACTH)-producing tumors, and the presence of transient DI[7, 10, 13, 16, 17, 21]. Although there were no significant differences in patient demographics or tumor-type distribution between the water restriction group and the control group, moderate water restriction significantly decreased the occurrence of this potentially life-threatening complication. Although there was no significant difference in the occurrence of symptomatic hyponatremia between the 2 groups, the occurrence of symptomatic hyponatremia tended to be quite low, because only 1 patient on water restriction developed symptomatic hyponatremia (1.1%) compared with 6 control patients (6.5%). The incidence of combined DI and hyponatremia was significantly lower in the water restriction group than in the control group. Olson et al. reported that two-thirds of normonatremic patients had dysfunctional arginine vasopressin (AVP) secretion under the water load test at 7 days after TSS, and that 9 of 23 patients actually developed hyponatremia after the water load test[13]. Hence, even normonatremic patients can develop hyponatremia after this surgery[13]. Thus, many patients may be susceptible to hyponatremia following TSS if exposed to excessive volitional fluid consumption. In this study, the average daily oral fluid intake was greater than 2500 mL in 83% of the combined DI and hyponatremia patients in the control group. On the other hand, patients restricted to 2500 mL/day, especially those with DI, demonstrated a significantly reduced occurrence of hyponatremia. As revealed by the illustrative case discussed in the Results section, controlling water and osmotic balance is difficult when patients drink water freely. Patients occasionally drink water excessively after their urine output decreases, which can cause delayed hyponatremia after TSS in patients with DI. The reported incidence of combined DI and hyponatremia in this study is within the range of 4.5%–20%[1, 3, 7, 11, 13, 16, 21]. We speculate that water restriction for patients with DI under antidiuretic hormone replacement therapy stabilizes net changes in body fluid content and facilitates the control of fluid and electrolyte balance. This moderate water restriction regimen has the potential to reduce the incidence of hyponatremia after surgery.

Endoscopic TSS for Sellar Lesions

Sigounas et al. reported that the incidence of DI can be reduced by treating patients with endoscopic surgery instead of microscopic surgery[18]. Given that the main cause of both hyponatremia and DI is abnormal ADH secretion, endoscopic surgery may decrease the rate of postoperative hyponatremia. In this study, all patients underwent purely endoscopic endonasal TSS. The incidence of hyponatremia was 5.4% in the water restriction group and 16.3% in the control group. Recent large studies on delayed hyponatremia reported that hyponatremia occurs in 36.7% of patients treated with microscopic surgery[11]. In comparison, the incidence of hyponatremia observed in the present study was relatively low, even in the control group. Transsphenoidal endoscopic surgery may reduce the incidence of postoperative hyponatremia.

Complications of Moderate Water Restriction after TSS

Dehydration is the most serious potential complication of water restriction, especially in patients with DI. There was no significant difference between the incidence of hypernatremia in the experimental and control groups. We implemented AVP replacement therapy to control the urine output immediately after approaching DI criteria to avoid dehydration. However, 3 patients in the experimental group developed DI. To reduce the incidence of hypernatremia among patients, water restriction therapy should be aborted until DI is brought under control. In our opinion, DI control is important for reducing not only the incidence of hypernatremia, but also the thirst level, which in turn reduces oral fluid intake. Some researchers have reported that ADH replacement therapy during the first 2 postoperative weeks can actually increase the risk for hyponatremia, and

thus, close monitoring of patient body weight and urine output is recommended, especially for patients undergoing ADH replacement therapy[7, 11, 12]. ADH replacement therapy can be safe and can even decrease the incidence of hyponatremia if implemented together with water restriction therapy and can be withdrawn when the patient's body weight increases or when the patient's urine parameters no longer meet the criteria for DI.

Alleviation of Thirst

Our department has implemented various methods to reduce patient thirst. Nasal obstruction after TSS should be avoided, as this tends to increase patient thirst due to oral breathing. As a general rule, a hemilateral nasal approach via the right nostril was chosen to keep the left nostril intact. Nasal packing was not employed after surgery if cerebrospinal fluid leakage was not predicted in the intraoperative period. This provided patients a natural nasal airway via their intact left nostril. If nasal packing was necessary to prevent postoperative cerebrospinal fluid leakage, a breathable space was preserved in the nostril.

The patients appeared to tolerate moderate water restriction if they frequently drank small amounts of water, rather than infrequent large amounts. There was no statistically significant difference in postoperative thirst level between water-restricted patients with DI and those without DI. Unfortunately, thirst level data were not available for all patients, but these findings suggest that thirst was not intolerable under moderate water restriction if the patients' DI was sufficiently controlled.

Limitations

This study revealed that the incidence of hyponatremia in patients treated with water restriction after pituitary surgery was significantly lower than that in patients who drank water freely. While body weight, sex ratio, and tumor type distribution did not differ between groups, these factors were not considered when deciding on the maximum allowable volume; thus, all patients in the water restriction group were limited to 2500 mL/day immediately after surgery. Additional studies are also required to determine the optimal start and stop points for this regimen. This was a retrospective study, and we did not perform systematic daily endocrinological tests or water load tests. Therefore, uptake and excretion of electrolytes and daily changes in endocrine functions were not evaluated. Hence, a multicenter, prospective study including these tests is needed.

CONCLUSION

To our knowledge, this is the first study to test a potential method for preventing hyponatremia following TSS. Although there might be other causes of hyponatremia other than postoperative water excess, for example, adrenal insufficiency, moderate water restriction after pituitary surgery is a potentially effective and safe method to reduce hyponatremia. Indeed, hyponatremia after TSS is a largely preventable complication. Patients should not drink water freely after TSS, even if they are normonatremic and develop DI. The optimal amount and duration of water restriction are still unclear and require larger-scale multicenter trials.

Funding: None

Conflict of Interest: None

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