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Predictors of Delayed Hyponatraemia After Surgery for Pituitary Tumour

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ABSTRACT

Delayed hyponatraemia(DH) is a common complication following trans-sphenoidal surgery(TSS) for pituitary tumour. We evaluated the prevalence of DH following TSS, and assessed the factors associated with DH, including early post-operative diabetes insipidus(EPDI). This retrospective study included 100 TSS for pituitary tumours in 98 patients, over a period of 26 months. Subjects were divided into two groups: those who developed hyponatraemia and those who did not develop hyponatraemia, during post-operative days 4 to 14. The clinical characteristics and peri-operative parameters were compared between the two groups, to identify factors predicting DH. The mean age of the patients was 42.0 ± 13.6 years, 58 (59 %) were females and 61 (61 %) had functional tumours. Thirty-six patients(36 %) developed DH following TSS of whom majority(58 %) were diagnosed on post-operative days 7 and 8; only 8/36 (22 %) were symptomatic. Syndrome of inappropriate antidiuretic hormone secretion(SIADH) was found to be the most common aetiology of DH. On logistic regression analysis, intra-operative cerebrospinal fluid(CSF) leak (OR 5.0; 95 % CI 1.9–13.8; p = 0.002), EPDI (OR 3.4; 95 % CI 1.3–9.2; p = 0.015) and peri-operative steroid use (OR 3.6; 95 % CI 1.3–9.8; p = 0.014) were found to be significantly associated with DH. In conclusion, EPDI, intra-operative CSF leak and peri-operative steroid use were significant predictors of DH. EPDI predicts moderate to severe hyponatraemia with 80 % specificity but has low sensitivity(47 %). As most patients have asymptomatic hyponatraemia, serum sodium measurement on POD 7 to 10 would be helpful to identify DH in patients at increased risk.

Introduction

Delayed hyponatraemia (DH) is a well-known complication following trans-sphenoidal pituitary surgery (TSS), varying in incidence from 9–35 % and occurs between postoperative day (POD) four to 14, but more commonly occurs on POD seven to ten [1–8]. Despite the relatively common occurrence of DH following pituitary surgery, the pathogenesis and the aetiology of the same disorder is not well understood. DH may also occur as part of the triple phase response or as an isolated second phase of the triphasic response following complete or partial damage to the hypothalamico-neurohypophyseal tracts. Common causes cited for this condition are the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypocortisolemia, depletional or rarely secondary to cerebral salt wasting. Although gender, age, tumour size, pre-operative hypopituitarism, Cushing's disease, and surgical and post-operative complications have been found to be associated with DH in several studies, there is lack of consistency in the observations [1–7, 9–12]. The delayed nature of occurrence is of particular concern, as most patients are discharged between the 3rd and 5th postoperative day and hyponatremia may warrant a readmission [13]. The

identification of factors that predict DH in individual patients may facilitate early detection and appropriate treatment. Therefore, we evaluated the prevalence of DH following TSS, and assessed the factors that were associated with DH, including early post-operative diabetes insipidus (EPDI).

Patients and Methods

Participants

In this retrospective study, we accessed data from the hospital electronic data base pertaining to 136 patients, ≥ 15 years of age, who underwent endoscopic trans-nasal TSS for pituitary adenomas between 1st November 2017 to 31st December 2019. We excluded 38 patients who were either operated trans-cranially or for whom data was incomplete. Particular attention was paid to the presence of post-operative fluid intake and output measurements in the in-patient charts for at least five days, and serum sodium measurements on POD 1 to 3 and 7 to 10. Finally, 100 TSS for pituitary tumours in 98 patients were analysed. Clinical characteristics, biochemical and hormonal profile, imaging features, pre-operative and peri-operative hormonal replacement, operative details, intra and post-operative complications, and duration of hospitalisation were recorded. The study was approved by the institutional review board and ethics committee [IRB Min. No. 13522 (Retro) dated: 28.10.2020].

Peri-operative protocol

Peri-operative hydrocortisone was only administered to patients with an 8 AM serum cortisol < 100 nmol/l or post-ACTH (Acton prolongatum- injectable long-acting porcine sequence ACTH 1–39) stimulation cortisol < 496 nmol/l. Those patients with a basal 8 AM serum cortisol ≥ 440 nmol/l and those with an intact hypothalamo-pituitary-adrenal (HPA) axis were not given glucocorticoids peri-operatively. The serum cortisol levels were measured on the first three post-operative days for those patients as per our protocol to check for post-operative hypocortisolism [14]. Patients with Cushing's disease did not receive peri-operative glucocorticoid cover; their serum cortisol was monitored every morning at 8 AM for three consecutive days following surgery and whenever they had hypocortisolaemic symptoms, to assess for remission. All patients were operated via an endoscopic endonasal approach. In the event of an intraoperative cerebrospinal fluid (CSF) leak, we repaired the sella with fat or a nasoseptal graft depending on the size of the defect and placed a lumbar subarachnoid catheter for post-operative CSF drainage for a maximum duration of five days. All patients had serum sodium measurements at least once daily for the first three POD, between POD 7 to 10, and in the interim period (POD 4 to 6) if they had symptoms of hyponatraemia. Patients with polyuria were evaluated with serum sodium and corresponding urine specific gravity measurements. EPDI was defined as diabetes insipidus occurring within the first three post-operative days as per the following criteria [15] suggested by Sterl et al. – urine output ≥ 6 litres per day or ≥ 300 ml/h for ≥ 3 consecutive hours and a corresponding urine specific gravity ≤ 1.003 or serum sodium ≥ 145 mmol/l. Those who developed EPDI were treated with vasopressin infusion or oral desmopressin as required, the dose of which was titrated based on the fluid balance and serum sodium measurements at least twice daily. Permanent diabetes insipidus (DI) was defined as the persistence of DI up to at least three months after surgery.

Hyponatraemia was defined as a serum sodium level of < 135 mmol/l with a sub-classification of mild, moderate, or severe at serum sodium levels of 130–134 mmol/l, 125–129 mmol/l and < 125 mmol/l, respectively [16]. Patients with hyponatraemia who had a low urine spot sodium (< 20 mmol/l) were classified as depletional hyponatraemia. SIADH was diagnosed by the presence of hyponatremia, an euvolemic intravascular volume status, with a urine spot sodium of > 20 mmol/l [17]. Prolonged hospitalisation was defined as a post-operative hospital stay more than five days in patients without a lumbar CSF drain and more than seven days in patients with a lumbar CSF drain. Readmissions to hospital for delayed hyponatraemia were also recorded.

Statistical methods

The data was analysed using SPSS version 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Continuous variables such as age, the number of days of hospitalisation, and serum sodium levels were reported using mean ± SD; categorical variables were reported as frequencies and percentages. Clinical features such as gender, age, tumour characteristics and, intra and post-operative complications were compared between patients with and those without DH using the chi-square test. Urine output in the hyponatraemic and normonatraemic groups were compared by independent samples 't' test. Univariate and multivariate logistic regression analysis were used to assess the independent effects of various risk factors on the incidence of DH.

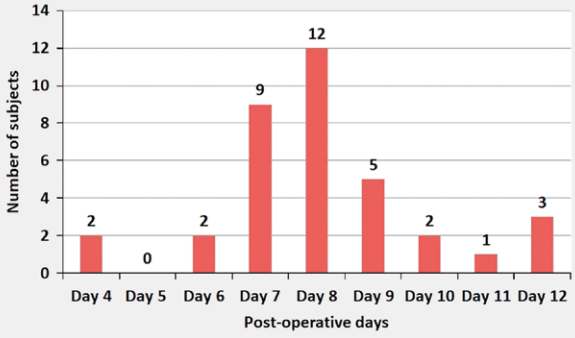
Results

Ninety-eight patients underwent 100 trans-sphenoidal surgeries leading to 100 post-operative assessments over the study period. The clinical characteristics of the patients, their surgical and post-operative details are summarised in ▶ **Table 1**. The mean age of the patients was 42.0 ± 13.6 years with a female predominance (59 %). Among the 98 patients who underwent 100 pituitary surgeries, 20 were microadenomas and 80 were macroadenomas; 61 were functioning tumours. Thirty patients (30 %) developed EPDI, two patients (2 %) had post-operative secondary hypocortisolaemia within a week following pituitary surgery and 36 (36 %) had DH between POD 5 to 12. Only eight patients (8 %) had symptomatic hyponatraemia; the most common symptom being tiredness. The serum sodium levels of the patients with DH had remained stable up to POD 3 and then, subsequently decreased to nadir levels around POD 7–9 (▶ **Fig. 1,2**). The mean nadir sodium level of patients who developed hyponatraemia (n = 36) was 127.4 ± 5.5 mmol/l (range: 112 to 134 mmol/l) as compared to 138.3 ± 2.5 mmol/l in those who had persistently normal serum sodium levels. Twenty patients (55.6 %) had SIADH and two (5.6 %) had depletional hyponatraemia. Among the two patients with post-operative hypocortisolaemia, one developed delayed hyponatraemia due to SIADH on POD 8 after receiving six days of glucocorticoid replacement. The remaining 14 patients had mild to moderate hyponatraemia, which had resolved within 48 hours by fluid restriction

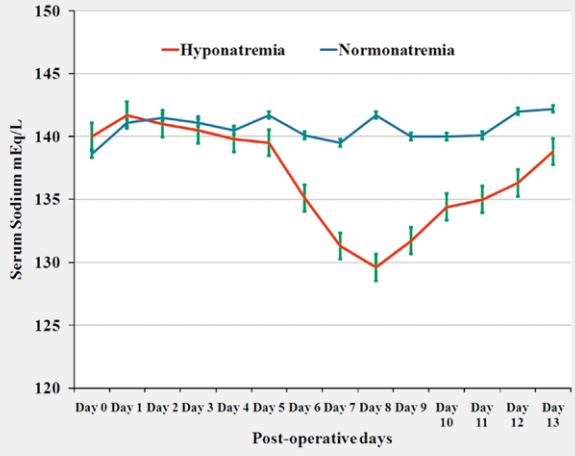
▶ **Table 1** Clinical characteristics, surgical and post-operative details of the subjects.

Parameter	Total n = 100
Age (years) (mean ± SD) n = 98	42.0 ± 13.6
Gender n (%) n = 98	
Male	40 (40.8)
Female	58 (59.2)
Tumour size n (%)	
Macroadenoma	80 (80)
Microadenoma	20 (20)
Tumour grade n (%)	
Invasive	35 (35)
Non-invasive	65 (65)
Hardy's grade A/B/C/D	41/13/11/2
Hardy's A&E/B&E/C&E/D&E	5/10/15/3
Functional status of the pituitary tumours n (%)	
Acromegaly	38 (38)
Cushing's disease	21 (21)
Prolactinoma	2 (2)
Non-functioning	39 (39)
Co-morbidity n (%)	61 (61)
Diabetes mellitus	12 (12)
Hypertension	19 (19)
Diabetes mellitus + Hypertension	24 (24)
Others	8 (8)
Anterior pituitary hormone deficiency n (%)	
Central hypothyroidism	31 (31)
Central hypogonadism	39 (39)
Central hypocortisolaemia	25 (25)
≥ 2 Pituitary hormone deficits	28 (28)
Re-operative TSS n (%)	2 (2)
Early post-operative DI (EPDI) n (%)	30 (30)
Permanent DI (PDI) n (%)	3 (3)
Hyponatraemia n (%)	36 (36)
Mild	15 (15)
Moderate	10 (10)
Severe	11 (11)
Symptomatic hyponatraemia n (%)	8 (8)
Nadir serum sodium level (mmol/l) (mean ± SD)	
Hyponatraemia group	127.4 ± 5.5
Normonatraemia group	138.3 ± 2.5
Aetiology of hyponatraemia n (%) n = 36	
SIADH	20 (55.6)
Depletional	2 (5.6)
Unknown#	14 (38.8)
Number of days of hospitalization (mean ± SD)	6.6 ± 3.5
Re-admission/prolonged hospitalisation for hyponatraemia n (%) n = 36	
Yes	18 (50)
No	18 (50)

Mild to moderate hyponatraemia which resolved within 48 hours by fluid restriction.



▶ **Fig. 1** Time of occurrence of delayed hyponatraemia in the patients.



▶ **Fig. 2** Line graph displaying the serum sodium levels during the post-operative period after TSS in the two groups: hyponatraemia (red) and normonatraemia (blue).

on an outpatient basis and were not evaluated in detail for the aetiology. Patients with DH were advised fluid restriction to < 1.5 litres per day, along with extra oral salt intake (8 to 12 g/day). Those on oral glucocorticoid replacement were given intravenous hydrocortisone injections – 100 to 200 mg per day in four divided doses, until the correction of hyponatraemia. Two patients who did not respond to the initial measures were administered intravenous 3 % sodium chloride at the rate of 25 to 30 ml/h for 48–72 hours. Two patients were administered tolvaptan – one patient received a 7.5 mg single dose which led to correction of hyponatraemia; however, the other patient required tolvaptan for three months. The mean duration of time to normalisation of the serum sodium level was 3.8 ± 2.5 days. As expected, subjects with DH had prolonged hospital stay compared to subjects with normal serum sodium (7.9 ± 3.6 vs. 5.9 ± 3.3 days; p = 0.01) (▶ **Table 2**). Twelve patients required a prolonged hospital stay and six patients required re-admission to the inpatient service for hyponatraemia (▶ **Table 1**).

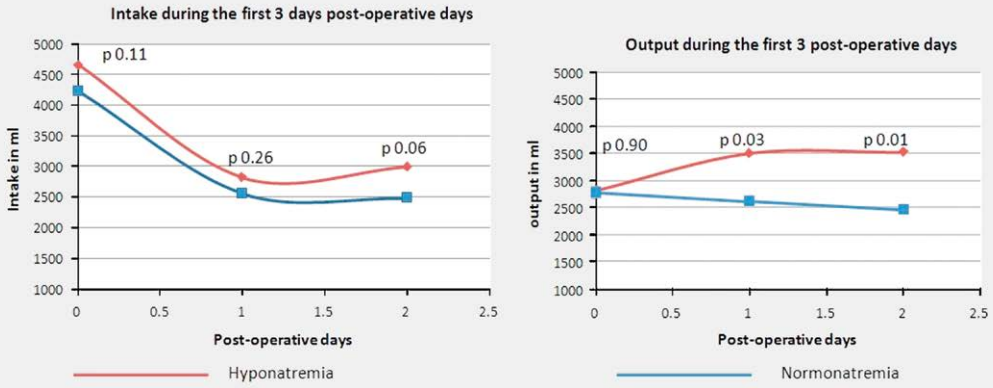
We compared the clinical, surgical details and post-operative parameters between patients with DH and those with normonatraemia to identify potential predictors of DH. We found that hyponatraemia was significantly more common in those patients who were given peri-operative glucocorticoids (p = 0.04), those with an intra-operative CSF leak requiring a lumbar subarachnoid drain for CSF drainage (p = 0.002) and among patients who had EPDI (p = 0.007) (▶ **Table 2**). Among the 30 patients with an EPDI, 17 (47.2 %) developed DH. Patients with DH had a significantly higher cumulative urine output during the POD 0–2 when compared to those patients who remained normonatraemic despite comparable fluid intake (▶ **Fig. 3**) (cumulative output on first three POD 10 014 ml vs. 8056 ml, p = 0.001).

By univariate logistic regression analysis, we found that intra-operative CSF leak (odds ratio, 4.3; 95 % CI 1.8–10.7; p = 0.002), EPDI (odds ratio, 3.5; 95 % CI 1.4–8.6; p = 0.006) and peri-operative glucocorticoid usage (odds ratio, 2.6; 95 % CI 1.1–6.3; p = 0.03) were significantly associated with DH. Further, on multivariate logistic regression analysis, the same parameters emerged as significant predictors of DH. However, when we looked at the factors predicting moderate to severe hyponatraemia, using multivariate logistic regression, only EPDI emerged as a significant risk factor (▶ **Table 3**). EPDI predicted DH with a sensitivity of 47 %, specificity of 80 %, positive predictive value (PPV) of 57 % and negative predictive value (NPV) of 73 %.

▶ **Table 2** Comparison of clinical characteristics, surgical and post-operative details between the two groups – hyponatraemia and normonatraemia.

Parameters	Total n = 100	Hypo-natraemia n = 36	Normo-natraemia n = 64	p-Value
Age n (%)				
≤ 50 years	73 (73)	25 (69.4)	48 (75)	0.65
> 50 years	27 (27)	11 (30.6)	16 (25)	
Functional status of tumour n (%)				
Functional	61 (61)	20 (55.5)	41 (64.1)	0.52
Non-functional	39 (39)	16 (44.5)	23 (35.9)	
Tumour size n (%)				
Microadenoma	20 (20)	7 (19.4)	13 (20.3)	1
Macroadenoma	80 (80)	29 (80.6)	51 (79.7)	
Lumbar subarachnoid drainage n (%)				
Yes	30 (30)	18 (50)	12 (18.8)	**0.002**
No	70 (70)	18 (50)	52 (81.2)	
Peri-operative glucocorticoid use n (%)				
Yes	31 (31)	16 (44.4)	15 (23.4)	**0.04**
No	69 (69)	20 (55.6)	49 (76.6)	
Pre-operative thyroxine supplementation n (%)				
Yes	38 (38)	18 (50)	20 (31.2)	0.09
No	62 (62)	18 (50)	44 (68.8)	
Post-operative hypocortisolaemia n (%) (n = 48) *				
	n = 48	n = 13	n = 35	0.48
Yes	2 (4.2)	1 (7.7)	1 (2.9)	
No	46 (95.8)	12 (92.3)	34 (97.1)	
Early post-operative DI n (%)				
Yes	30 (30)	17 (47.2)	13 (20.3)	**0.007**
No	70 (70)	19 (52.8)	51 (79.7)	
Number of days of hospitalisation (mean ± SD)				
	6.6 ± 3.5	7.9 ± 3.6	5.9 ± 3.3	**0.01**
With lumbar drain	9.5 ± 4.8	9.8 ± 3.5	8.5 ± 6.3	0.53
Without lumbar drain	5.6 ± 2.3	6.3 ± 3	5.4 ± 2	0.22

* Excluding those with Cushing's disease and those who received peri-operative steroid cover.



▶ **Fig. 3** Intake output of patients with hyponatraemia (red) and normonatraemia (blue) during post-operative day 0 to 2.

▶ **Table 3** Multivariate logistic regression analysis: Factors predicting delayed hyponatraemia.

Parameter	Odds ratio	95 % CI	p-Value
Factors predicting delayed hyponatraemia (mild, moderate, & severe)			
CSF leak	5.0	1.9–13.8	**0.002**
Early PDI	3.4	1.3–9.2	**0.015**
Peri-operative glucocorticoid use	3.6	1.3–9.8	**0.014**
Factors predicting moderate to severe hyponatraemia			
CSF leak	2.7	1–7.3	0.05
Early PDI	4.5	1.6–12.4	**0.003**
Peri-operative glucocorticoid use	2.5	0.9–6.8	0.06

Discussion

Delayed hyponatraemia following TSS

In this retrospective study, we found that DH occurred in 36 % of patients following TSS for pituitary tumours between POD 4 to 11, a higher incidence when compared with other studies reporting hyponatraemia in 9 to 35 % of patients [1, 2, 4–10]. It is likely that our strict protocol of testing all patients post-operatively between days 7 to 10, detected asymptomatic and mildly symptomatic cases of DH, which would have gone unreported if not tested. Sixty one percent of the subjects had co-morbidities; the high proportion with co-morbidity is probably due to a larger proportion of functioning tumours (61 %) in our cohort. We included cases operated under a single neurosurgery unit which manages all the functioning pituitary tumors in our centre.

Aetiology of DH

The aetiology of DH has been well documented in patients undergoing TSS for pituitary lesions. The most common cause being SIADH, likely related to intra-operative trauma to the neurohypophysis with unregulated antidiuretic hormone (ADH) release without overt features of diabetes insipidus as seen in some experimental studies [3, 12]. In our study, twenty patients (55.6 %) with DH had SIADH, characterised by an euvolemic state, elevated urine spot sodium and response to fluid restriction. Depletional hyponatraemia was noted in two (5.6 %) patients. However, the aetiology could not be determined in the majority of patients with mild to moderate hyponatraemia. We speculate that SIADH was the likely cause as their serum sodium subsequently normalised with fluid restriction within 48 hours.

Predictors of DH

The identification of factors predicting DH is important for guiding postoperative management and avoiding serious complications. Although several studies have been published in this regard, there is no consensus regarding the risk factors underlying DH. Male gender, advanced age (> 50 years), pituitary macroadenoma, Cushing's disease, pre-operative hypopituitarism, CSF leak, decline in serum sodium in the early post-operative period and EPDI, have all been identified as risk factors in different studies [1–7, 9–11]. We found that EPDI, lumbar CSF drainage for intra-operative CSF leak and peri-operative glucocorticoid usage were significant predictors of DH. Intra-operative CSF leak has been reported to be associated with 2.5 times higher risk of DH [1]. We hypothesise that since patients with an intra-operative CSF leak are generally placed on a lumbar subarachnoid drain in the postoperative phase, considerable sodium depletion may occur over a few days as CSF contains as much as 147 mmol/l (3.4×10^{-3} kg/l) of sodium [18]. We found that peri-operative use of glucocorticoids was associated with an increased risk of DH. Most centres use routine peri-operative glucocorticoids for patients undergoing pituitary surgery. Pre-operative hypopituitarism was reported as a risk factor for DH in a large series by Jahangiri et al. [19], while a recent study by Winograd et al. [20] has shown that pre-operative and intra-operative glucocorticoid usage for those without preoperative hypoco-

rtisolaemia was associated with a lower risk of DH. It has been shown quite clearly by Rajaratnam et al. that higher doses of parenteral glucocorticoids administered peri-operatively suppress ADH release and contribute towards the higher incidence of DI following TSS for pituitary tumours [21]. It has not been studied, as to whether this EPDI, which is unmasked by glucocorticoids, could increase the risk of DH.

Early postoperative diabetes insipidus and delayed hyponatraemia

The patterns of water and electrolyte disturbances, following pituitary surgery can be categorised as periods of polyuria or hyponatraemia, which are attributable to an abnormally low or abnormally high secretion of ADH respectively. These derangements may not always escalate to the level of clinically defined central DI or SIADH requiring treatment. Zada et al. [6] also have reported a higher incidence of DH in patients with EPDI; 48 % of patients who had EPDI developed DH when compared to 26 % without EPDI. Six profiles of polyuria or hyponatraemia have been reported following TSS for pituitary adenomas by Hensen et al. [22]: brief or sustained polyuria, immediate or delayed hyponatraemia, and biphasic or triphasic DI. It has been postulated that the pattern of derangement depends on the extent of damage to the hypothalamico-neurohypophyseal tracts during pituitary surgery – brief polyuria, isolated DH and biphasic DI being associated with partial damage to the infundibulum. Amongst such patients, there is sufficient AVP function to prevent the occurrence of the first and third phases of the triphasic response (DI); however, there appears to be enough damaged tissue to produce the uncontrolled release of ADH characteristic of the second phase, leading to an isolated second phase as reported by Ultmann et al. [12]. The same has been tested and demonstrated using a mathematical model, HumMod by Blair et al. [23]. We found that those patients who developed DH had a significantly higher urine output on the day of surgery (POD 0) and post-operative days 1 and 2 when compared to those patients who remained normonatraemic (▶ **Fig. 3**), suggesting a possible association between the neuro-hypophyseal tract damage and DH.

Fluid restriction after pituitary surgery

A simple cost-effective strategy has been shown to reduce the incidence of post-operative DH. Matsuyama et al. [7], in a retrospective analysis of 207 patients who underwent TSS for pituitary adenomas or Rathke's cleft cyst clearly documented the benefit of fluid restriction for prevention of SIADH (51 % without fluid restriction vs. 13 % with fluid restriction, $p < 0.005$). Several studies have reported the benefits of varying degrees of fluid restriction ranging from 1 to 2.5 litres in the post-operative period and reported decrease in the incidence of hyponatraemia due to SIADH [7, 19].

Prolonged post-operative hospitalisation

After TSS, there was a significant prolongation of hospital stay in those with hyponatraemia compared to those without (7.8 ± 3.6 vs 5.9 ± 3.3 days; $p = 0.01$). Bohl et al. [13] retrospectively reviewed patients who underwent TSS for pituitary lesions and identified DH as the primary cause of re-admission at around POD 8. In our cohort, there were six re-admissions for delayed hyponatraemia. Daily serum sodium measurements following pituitary surgery in our patients could have led to an early diagnosis of hyponatraemia, which was often asymptomatic but had led to a prolonged hospital stay for the treatment of hyponatraemia. On the other hand, patients who are otherwise well, are likely to be discharged early by 3 to 4 days after surgery. The standard protocol of an out-patient clinic follow-up of these patients between POD 7 to 10 with serum sodium measurements would pick-up hyponatraemia in a proportion of patients leading to readmissions. Therefore, more appropriate risk stratification of patients who are more likely to develop delayed hyponatraemia, could facilitate early discharge of patients at a lower risk from the inpatient service.

Limitations of the study

In view of the retrospective nature of the study, the accurate details of fluid intake and output were not available for some patients, who thereby had to be excluded from the analysis. Although, CSF leak was found to be a risk factor for DH, the volume of CSF drained was not recorded, nor was the sodium level in this fluid measured; this measurement may have helped us calculate the quantum of sodium lost in the drained CSF. Larger prospective studies with meticulous monitoring of fluid balance, serum sodium and urinary osmolality or specific gravity in the post-operative period would help in better understanding of the aetiology and risk factors for DH in patients undergoing trans-sphenoidal pituitary surgery.

Conclusion

DH is a common complication following TSS that may lead to prolonged hospitalisation or readmission following discharge. EPDI, intra-operative CSF leak, and peri-operative glucocorticoid use were significant risk factors for DH. As SIADH is the major aetiology of DH, whether fluid restriction after the 4th post-operative day prevents DH needs further prospective evaluation.

Conflict of Interest

The authors declare that they have no conflict of interest.

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