The Management And Outcome of Hyponatraemia Following Transsphenoidal Surgery: A Retrospective Observational Study

Ziad Hussein (ziad.hussein1@nhs.net)
University College London Division of Medicine https://orcid.org/0000-0002-9129-853X
Ploutarchos Tzoulis
University College London Division of Medicine
Hani J Marcus
National Hospital for Neurology and Neurosurgery
Joan Grieve
National Hospital for Neurology and Neurosurgery
Neil Dorward
National Hospital for Neurology and Neurosurgery
Pierre Marc Bouloux
University College London Division of Medicine
Stephanie E Baldeweg
University College London Division of Medicine

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Abstract

Purpose:

Hyponatraemia is a common complication following transsphenoidal surgery. However, there is sparse data on its optimal management and impact on clinical outcomes. The aim of this study was to evaluate the management and outcome of hyponatraemia following transsphenoidal surgery.

Methods:

A prospectively maintained database was searched over a 4-year period between January 2016 and December 2019, to identify all patients undergoing transsphenoidal surgery. A retrospective case-note review was performed to extract data on hyponatraemia management and outcome.

Results:

Hyponatraemia occurred in 162 patients (162/670; 24.2%) with a median age of 56 years. Female gender and younger age were associated with hyponatraemia, with mean nadir sodium being 128.6 mmol/L on postoperative day 7. Hyponatraemic patients had longer hospital stay than normonatraemic group with nadir sodium being inversely associated with length of stay ($p < 0.001$). In patients with serum sodium ≤132 mmol/L, syndrome of inappropriate antidiuretic hormone secretion (SIADH) was the commonest cause (80/111; 72%). Among 76 patients treated with fluid restriction as a monotherapy, 25 patients (25/76; 32.9%) did not achieve a rise in sodium after three days of treatment. Readmission with hyponatraemia occurred in 11 cases (11/162; 6.8%) at a median interval of 9 days after operation.

Conclusion:

Hyponatraemia is a relatively common occurrence following transsphenoidal surgery, is associated with longer hospital stay and risk of readmission, and the effectiveness of fluid restriction is limited. These findings highlight the need for further studies to better identify and treat high-risk patients, including the use of AVP receptor antagonists.

Introduction

Postoperative hyponatraemia, defined as serum sodium value less than 135 mmol/L within 30 days of surgery, is a frequent complication following transsphenoidal surgery for pituitary adenoma, with a reported incidence of 16 – 23%[1–5]. The most common aetiology is syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a consequence of surgical manipulation of the neurohypophysis and hypothalamus[4,6,7]. Other causes include cerebral salt wasting syndrome (CSWS), hypocortisolism due to adrenocorticotropic hormone (ACTH) deficiency, severe hypothyroidism, overzealous desmopressin (DDAVP) administration, and hypotonic fluid infusion[4,8]. The optimal therapeutic strategy for postoperative hyponatraemia differs according to its cause. Fluid restriction remains the mainstay of treatment in SIADH, fluid and sodium replenishment are the treatment of choice in CSWS, and glucocorticoid and thyroxine replacement are required for adrenal and thyroid deficiency, respectively.

Despite recent initiatives in the United States and the United Kingdom[9,10], hyponatraemia remains the leading cause of unplanned hospital readmissions within 30 days of transsphenoidal surgery for pituitary tumours[10–12]. To this end, the aim of this study was to evaluate the management and outcome of hyponatraemia following transsphenoidal surgery.

Methods

Study design and population

A retrospective case control study design was adopted, and the study was registered and approved by the local Clinical Governance Committee. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was used in the preparation of this section of the manuscript[13].

A prospectively maintained database was searched over a 4-year period between 1st January 2016 and 31st December 2019, to identify all patients undergoing transsphenoidal surgery that were found to have serum sodium less than 135 mmol/L during their hospitalisation. The study was conducted at the National Hospital for Neurology and Neurosurgery, which performs the highest volume of pituitary operations in the United Kingdom.. Operations were performed by three experienced neurosurgeons using either an operating microscope (JG) or endoscope (HJM and NLD).

Data collection

Demographic, clinical, laboratory, and radiological data were obtained from each patient's medical records. Pituitary adenomas were classified according to their size and endocrine activity. The pre-operative adenoma size was determined using magnetic resonance imaging (MRI) and Computed Tomography (CT), with pituitary microadenoma being defined as an adenoma with a diameter less than 1 cm and pituitary macroadenoma as an adenoma with a diameter equal or more than 1 cm. The diagnosis of functioning and non-functioning pituitary adenomas was based on standard endocrine assessment and histological analysis of the resected tumours. Histological diagnosis of other sellar and parasellar lesions was also recorded.

All patients underwent measurement of anterior pituitary hormones prior to surgery and on the second post-operative day. Patients noted to have secondary adrenal insufficiency and/or hypothyroidism were treated with replacement therapy. Hypocortisolism was defined as early morning serum cortisol less than 350 nmol/L and secondary hypothyroidism was defined as free T4 level less than 12 pmol/L (reference range 12-22 pmol/L).

Serum sodium was recorded at baseline preoperatively and during the first week postoperatively. Hyponatraemia in this study was classified into mild (serum sodium level between 130-134 mmol/L), moderate (serum sodium level between 125–129 mmol/L), and severe hyponatraemia (serum sodium level less than 125 mmol/L)[14]. Nadir sodium is the lowest sodium level measured at any point within 30 days following transsphenoidal surgery. In our institution, serum sodium of 132 mmol/L is considered clinically meaningful and prompts management. Therefore, data on the management and outcome of hyponatraemia were extracted for those who developed serum sodium ≤132 mmol/L following surgery. Renal function, serum osmolality, urine osmolality and sodium, serum cortisol and thyroid function were also recorded. The diagnosis of SIADH was made in those who met the diagnostic criteria of clinical euvolaemia, measured serum osmolality <275 mOsm/kg, urine osmolality >100 mOsm/kg and urine sodium >30 mmol/L, as well as normal adrenocortical and thyroid function, without recent administration of diuretics[14]. Data on treatment, and serum sodium level post treatment initiation were recorded. Data on short-term outcomes, including intensive care unit admission and length of hospital stay, as well as on readmission rate were collected.

Statistical analysis

Basic data were evaluated using descriptive statistics. Mean and standard deviation (SD) were used to describe continuous variables. Median and interquartile range (IQR) were used to describe data not normally distributed. Chi square test was used to compare categorical variables including the trend in postoperative sodium level. Linear regression analysis was used to evaluate the relationship of nadir sodium with patient’s age, gender and length of stay. Statistical significance was defined as p-value <0.05. Statistical analysis was performed using GRAPHPAD PRISM 8 software.

Results

Baseline characteristics and risk factors for hyponatraemia in all patients with serum sodium level <135 mmol/L

Among 670 patients who underwent transsphenoidal surgery over 4 years, 162 patients (162/670; 24.2%) developed hyponatraemia (serum sodium <135 mmol/L) postoperatively. Mild hyponatraemia occurred in 90 patients (90/670; 13.4%), 38 patients had moderate hyponatraemia (38/670; 5.7%), and severe hyponatraemia was recorded in 34 patients (34/670; 5.1%).

Patients’ characteristics, tumour histology and surgical approach are shown in Table 1. The median age for hyponatraemic patients was 56 years (IQR 44-68). Younger age was associated with hyponatraemia ($p = 0.043$). On average, the value of nadir sodium increased by 0.05 mmol/L for each year increase of age ($F(1,159) = 4.18$, $p = .043$, $R^2 = 0.03$) (Figure 1).

There was no difference in the incidence of hyponatraemia observed between males and females ($p = 0.4$). However, female gender was significantly associated with lower nadir level (mean sodium = 124.8 mmol/L) than with male gender (mean sodium = 133 mmol/L) ($p < 0.001$).

There was no significant difference in the frequency of hyponatraemia between patients with microadenoma and those with macroadenoma ($p = 0.6$) (Table 1). The frequency of hyponatraemia was similar in patients with pituitary macroadenoma with and without optic nerve ($p = 0.7$). In addition, there was no difference in the frequency of hyponatraemia between patients with functioning and non-functioning adenomas ($p = 0.5$). With respect to the neurosurgical technique, the occurrence rate of hyponatraemia was similar between microscopic and endoscopic transsphenoidal surgeries ($p = 0.4$).

Incidence, time course, and severity of hyponatraemia in all patients with sodium <135 mmol/L

Prior to surgery, ten patients (10/156; 6.4%) had pre-existing hyponatraemia with a level of 132.2 (± 3.5) mmol/L. The median time for serum sodium to decrease below 135 mmol/L was 4 days (IQR 1-6) after tumour resection. The mean (± SD) nadir sodium level for all patients was 128.6 (± 5.2) mmol/L and the median timepoint to exhibit nadir sodium was postoperative day 7 (IQR 2-8). Nadir sodium according to hyponatraemia severity is showed in table 2. Nadir sodium varied according to the aetiology. In SIADH, nadir level was 125.1 (± 5) mmol/L with a median time of onset of 8 days (IQR 6-9 days). In patients with adrenal insufficiency, lowest sodium concentration was 130 (± 2.4) mmol/L, occurring after a median time period of one day (IQR 1-5). In patients with DDAVP overreplacement, nadir sodium was 127 (± 4.4) mmol/L with a median duration of 7 days (IQR 3-9) postoperatively.

We examined the trend of hyponatraemia according to the severity during the first postoperative week. Mild hyponatraemia was more common in the early postoperative period, mostly on day 1 ($p = 0.0001$), while severe hyponatraemia started from day two and evolved in a delayed pattern most commonly on day 7 ($p = 0.0001$) (Supplementary Figure). Mean serum sodium during the first seven days following transsphenoidal surgery according to hyponatraemia severity is shown in Figure 2.

Investigations and aetiology for patients with serum sodium ≤132 mmol/L

One hundred and eleven patients had serum sodium levels of 132 mmol/L and below. The commonest cause was SIADH (80/111; 72%), followed by adrenal insufficiency (9/111; 8.1%), overzealous treatment of diabetes insipidus with DDAVP (6/111; 5.4%), and hypotonic hyponatraemia due to hypotonic fluid administration (3/111; 2.7%). There were no documented cases of CSWS. No clear diagnosis was documented in 13 patients (13/111; 11.7%).

All patients had early morning cortisol checked 48 hours postoperatively. In patients with a new onset of secondary adrenal insufficiency, mean morning cortisol was 138.7 (± 84) nmol/L. Thyroid status was assessed in all patients pre-operatively and postoperatively with mean free T4 level of 18 (± 5) pmol/L (reference range 12-22 pmol/L). Notably, 11 patients had low free T4 level prior to surgery which was treated appropriately with levothyroxine replacement.

Treatment of hyponatraemia in patients with serum sodium ≤132 mmol/L

Fluid restriction was imposed on 84 patients of those with serum sodium ≤132 mmol/L; this includes 80 patients with SIADH, 3 patients with fluid overload and 1 patient on desmopressin therapy.

For patients with SIADH, 72 (72/80; 87.8%) had fluid restriction as a monotherapy. Of those, 60 patients had fluid restriction between 500 and 1000 ml daily, 8 patients reduced fluid intake to 1500 ml daily and 4 patients were asked to drink to thirst.

Fluid restriction as a monotherapy achieved a mean increase in serum sodium of 3.3 mmol/L over a 3-day period. Notably, 23 patients (23/72; 31.9%) did not achieve any increase in sodium levels during the first three days of fluid restriction, four patients (4/72; 5.5 %) had a mean sodium increase of 1-2 mmol/L, 8 patients (8/72; 11.1%) had 3-4 mmol/L sodium increase and 37 patients (37/72; 51.3%) had sodium increment of ≥5 mmol/L during the first three days of fluid restriction. The median time to achieve an increase in serum sodium of ≥5 mmol/L was 3 days (IQR 2-6 days) and to achieve normal sodium concentration was 4 days (IQR 2-6). Figure 3. demonstrates sodium levels at baseline and after starting fluid restriction in those received fluid restriction only.

Second-line treatment for SIADH was administered in a total of 8 patients; with hypertonic saline 1.8% being used in 5 patients (5/84; 5.9%), hypertonic saline 2.7% in 1 patient (1/84; 1.1%), *sodium*chloride *tablets in 1 patient* (1/84; 1.1%)*, and tolvaptan at a dose of 7.5mg in one patient* (1/84; 1.1%). The patient who was treated with 2.7% hypertonic saline and the second one who received tolvaptan developed sodium overly rapid correction by more than 10 mmol/L over the first 24 hours.

Patients diagnosed with new onset of secondary adrenal insufficiency (number = 9) received glucocorticoid replacement and achieved a mean sodium increase of 8 mmol/L in the first 3 days post therapy. Patients with DDAVP over replacement (number = 6) were treated by dose down titration, leading to a mean sodium increase of 8 mmol/L during the first 3 days of therapy. No patients were treated with urea or demeclocycline.

Outcome for all patients with hyponatraemia <135 mmol/L

The mean serum sodium level on discharge for the full cohort was 137.3 (± 4.2) mmol/L. For the full cohort (number = 162), hyponatraemia was corrected in 4 days (IQR 2-6 days) and the length of hospital admission was longer for patients with hyponatraemia (median = 8 days [IQR 5-14]) than the patients who remained normonatraemic throughout hospitalisation (median = 5 days [IQR 4-7]) ($p < 0.001$). Lower nadir sodium was significantly associated with longer inpatient stay. On average, one mmol/L reduction in sodium concentration resulted in an increase of inpatient stay by 0.39 days ($F(1,154) = 14.39$, $p < .001$, $R^2 = 0.09$) (Figure 4).

Seven patients out of 162 (7/162; 4.3%) were admitted to the intensive care unit with a median stay of 3 days (IQR 2-4). One patient had a seizure secondary to severe hyponatraemia. No patients developed permanent neurological morbidities and there was no associated mortality.

Among 162 patients who developed hyponatraemia, a subset of eleven patients (11/162; 6.7%) had normal sodium levels during initial hospitalisation; however, they were readmitted post discharge with hyponatraemia during the first 30 days of surgery. Those patients were discharged after a median length of initial hospital stay of 4 days (IQR 4-6). Six patients (6/11; 54.5%) were men and five (5/11; 45.5%). The median time of readmission from surgery was 9 days (IQR 7-10). All patients had severe hyponatraemia due to SIADH with a mean sodium level of 120.1 (± 4.4) mmol/L. Among the 11 patients who were readmitted, 8 patients (8/11; 72.7%) were treated with fluid restriction, two (2/11; 18.1%) were treated with both fluid restriction and 1.8% hypertonic saline in the intensive care unit, and one (1/11; 9%) patient was treated with a combination of fluid restriction and 2.7% hypertonic saline. The median duration to regain normal sodium levels was 4 days (IQR 3-6) and median duration to hospital discharge was 5.5 days (IQR 3-10).

Discussion

Principal findings

This is a real-world study of 670 patients who underwent transsphenoidal surgery in the largest pituitary neurosurgical centre in the United Kingdom. We report the following principal findings: (1) the prevalence of post-operative hyponatraemia was 24.2%; (2) female gender and young age were associated with hyponatraemia; (3) tumour size, optic nerve compression, functional status of pituitary adenomas and surgical technique were not predictors for the development of postoperative hyponatraemia; (4) hyponatraemia was mainly due to SIADH, with day 4 being the median time of onset of hyponatraemia and nadir sodium being reported around seven days postoperatively; (5) fluid restriction was used as the treatment strategy in the majority of SIADH patients and was often ineffective in correcting hyponatraemia, leading to prolonged hospitalisation; 6) hyponatraemia was not associated with any long term neurological sequalae or mortality.

Comparison with other studies

This study reports a prevalence of post-operative hyponatraemia at 24.2%, in agreement with 16-23% frequency reported in other studies[4,15–18]. This series identified two factors associated with postoperative hyponatraemia, female gender and younger age. According to Barber and Zada *et al.*[4,19], female gender, but not age was a risk factor for developing hyponatraemia, while Rajaratnam *et al.*[20] documented that males had a higher risk of hyponatraemia. The novel finding in this cohort is that the incidence of hyponatraemia increased with younger age. This contrasts with the findings of Hussain *et al.*[21] and Tomita *et al.*[5] who reported a link of older age with hyponatraemia, while other reports have not found an association between age and hyponatraemia[3,4,19]. In this cohort, tumour size, optic nerve compression, functional status of pituitary adenomas and surgical technique (microscopic versus endoscopic) were not shown to increase the risk of developing hyponatraemia in contrast to other studies[9,22,23].

In line with other studies, we confirmed SIADH as the leading cause of hyponatraemia following transsphenoidal surgery. Disturbance of fluid balance and sodium concentration resulting from dysregulated secretion of arginine vasopressin from the neurohypophysis during surgical manipulation has been reported to cause antidiuresis and subsequent hypoosmotic hyponatraemia[24–26]. Interestingly, we did not report a single case of CSWS. Our data contradicted the finding by Barber *et al.*[4] that 24% of hyponatraemic patients post- pituitary surgery had CSWS.

Fluid restriction is the standard first line therapy for the management of SIADH but with controversial efficacy. Fluid restriction is known for its limited effectiveness in treating SIADH, irrespective of its aetiology[4,27,28]. This study showed that one third of patients did not respond to therapy within the first three days of treatment, while responders required a median time period of 4 days to restore normal sodium. On reviewing the data from the International Hyponatraemia Registry, Verbalis *et al.*[28] observed that 52% of patients treated with fluid restriction as a monotherapy did not achieve sodium correction of ≥5 mmol/L. Vasopressin receptor antagonists have been used for the treatment of SIADH since 2008 with much higher effectiveness in sodium correction than fluid restriction[28,30]. However, concerns were raised of their unpredictable effect and the risk of overly rapid sodium correction and subsequent deleterious outcome[28,31,32]. A recent study by Kleindienst *et al.*[17], the only one comparing tolvaptan versus fluid restriction in the treatment of SIADH following pituitary surgery, reported that small doses of tolvaptan (7.5mg) were more effective than fluid restriction in the treatment of SIADH, but resulted in overly rapid correction of serum sodium in a significant percentage of cases, without shortening the duration of hospitalisation.

We demonstrated a significant association between hyponatraemia and duration of hospital stay with an increase of 4 days in the duration of hospital stay of hyponatraemic patients compared to those with normal sodium. In addition, the severity of biochemical hyponatraemia was related to the length of hospital stay. Tomita *et al.*[5] also reported longer hospital stay in those underwent endoscopic surgery for pituitary adenoma only. We reported this outcome for all sellar and parasellar pathologies.

Unplanned hospital admissions following transsphenoidal surgery are associated with significant clinical and financial implications[33]. Hyponatraemia has been reported as the commonest cause of unplanned readmission following transsphenoidal surgery for pituitary tumours[11,18]. There is sparse data about the aetiology and predictive factors for rehospitalisation with hyponatraemia[34]. A potential strategy to decrease readmissions due to hyponatraemia would include routine assessment of serum sodium levels in all patients 5-7 days after operation, allowing early identification of hyponatraemia and prompt initiation of fluid restriction on outpatient basis [reference 9, crogh et al]. An alternative pathway to lower readmission rate is to limit fluid intake in all patients post discharge [35,36]. However, to date there is no general consensus in respect to the best strategy to identify patients at risk and manage delayed hyponatraemia post discharge. This highlights the need to educate patients about the risk of developing delayed hyponatraemia following transsphenoidal surgery and the importance of measuring serum sodium on days 7-9 after surgery.

Strengths and weaknesses

The main strength of this study is that it assessed the incidence, management and clinical outcome of hyponatraemia following transsphenoidal surgery in a large cohort of patients. In addition, we reported a detailed impact of different degrees of hyponatraemia on several patient specific clinical outcomes as well as the effectiveness of treatment in those patients which many other studies did not analyse.

This study was based on a retrospective review of medical records and clinical practice, making it subject to limitations of retrospective reports, such as selection bias and incomplete data. Another limitation is the lack of data regarding patient comorbidities and postoperative complications which can be an important confounder contributing to extended in-hospital stay.

Conclusion

This study has shown that hyponatraemia, a common complication post transsphenoidal surgery, is associated with prolonged hospital admission and is a common cause of readmission. The limited effectiveness of the current treatment of SIADH highlights the need for prospective studies, evaluating the effectiveness and safety of other therapies for SIADH in this context. Apart from determining the success rate in timely correction of hyponatraemia, these studies should explore the impact of other strategies on outcomes, such as patient's symptomatology, length of hospital stay, and readmission rate. In particular, the potential role of tolvaptan, a V2-specific arginine vasopressin receptor antagonist which is the only medication approved by the regulatory authorities in Europe and the US for the treatment of SIADH, warrants further exploration in these patients.

Declarations

Funding Statement

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Conflict of Interest Statement and Author Declaration

All authors have completed conflict of interest statement.

Data Availability Statement

The data that support the findings of this study are openly available at

https://figshare.com/s/455d5b30d05ab9fd520d

Ethics approval

The study was registered and approved by the local Clinical Governance Committee.

Corresponding author

Dr Ziad Hussein MBChB, MRCP

Department of Endocrinology, University College London Hospital, London, UK

Department of Medicine, University College London, London, UK

Mobile: 07722429743

E-mail: ziad.hussein1@nhs.net

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Tables

Table 1
The incidence of hyponatraemia according to patients' characteristics, pituitary tumour size, presence of optic nerve compression, tumour pathology, and surgical technique. FPA: Functioning Pituitary Adenoma; NFPA: Non-Functioning Pituitary Adenoma.

	Hyponatraemia (< 135 mmol/L)	**Normal sodium**	**Total**	**P value**
Gender				
Male	77 (22.9%)	259	336	P = 0.4
Female	85 (25.4%)	249	334	
Pituitary tumour size				
Microadenoma	15 (20.2%)	59	74	P = 0.6
Macroadenoma	109 (23.1%)	363	472	
Macroadenoma without optic nerve compression	28 (22%)	99	127	P = 0.7
Macroadenoma with optic nerve compression	81 (23.5%)	264	345	
Tumour histology				
Gonadotroph Adenoma	64 (24.3%)	199	263	
Cushing's disease	15 (24.3%)	53	68	
Acromegaly	14 (16.6%)	70	84	
Craniopharyngioma	11 (39.2%)	17	28	
Null cell adenoma	11 (22.4%)	38	49	
Prolactinoma	7 (35%)	13	20	
Plurihormonal adenoma	4 (26.6%)	15	19	
Silent corticotroph adenoma	5 (16.1%)	26	31	
Rathke's cyst	5 (20%)	20	25	
Meningioma	6 (23.1%)	20	26	
Pituitary metastasis	2 (20%)	8	10	
Pituitary inflammation	1 (11.1%)	8	9	
FPA	36 (20.9%)	136	172	P = 0.5

	Hyponatraemia (< 135 mmol/L)	Normal sodium	Total	P value
NFPA	87 (23.2%)	287	374	
Surgical Technique				
Microscopic surgery	107 (25.2%)	316	423	P = 0.4
Endoscopic surgery	55 (22.2%)	192	247	

Table 2

The diagnostic work-up of hyponatraemia for patients with serum sodium ≤ 132 mmol/L caused by syndrome of inappropriate antidiuretic hormone secretion. Results are expressed in mean levels and standard deviation (SD).

	Mean level (± SD)
Nadir serum sodium (135–145 mmol/L)	125.1 (± 5)
Urea (1.7–8.3 mmol/L)	4.6 (± 1.7)
Serum Creatinine (66–112 umol/L)	63 (± 21)
Serum Osmolality (285–295 mOsm/kg)	265 (± 13)
Urinary Osmolality (300–900 mOsm/kg)	508 (± 223)
Urinary Sodium (mOsm/kg)	80 (± 50)

Table 3

The timing and impact of hyponatraemia according to severity on regaining normal sodium level and inpatient hospital stay. IQR: Interquartile range; SD: Standard Deviation; Na: sodium.

	Mild hyponatraemia	Moderate hyponatraemia	Severe hyponatraemia
Mean nadir Na (SD)	132.5 (± 1.4)	127 (± 1.2)	120 (± 3.3)
Median time to exhibit nadir Na post TSS (IQR)	3.5 days (1–8)	7 days (2–8)	8 days (7–9)
Median time to achieve normal Na post hyponatraemia therapy (IQR)	2 days (1–3)	4 days (2–6)	6 days (4–9)
Median hospital stay (IQR)	7 days (5–10)	12 days (7–16)	11 days (7–16)

Figures

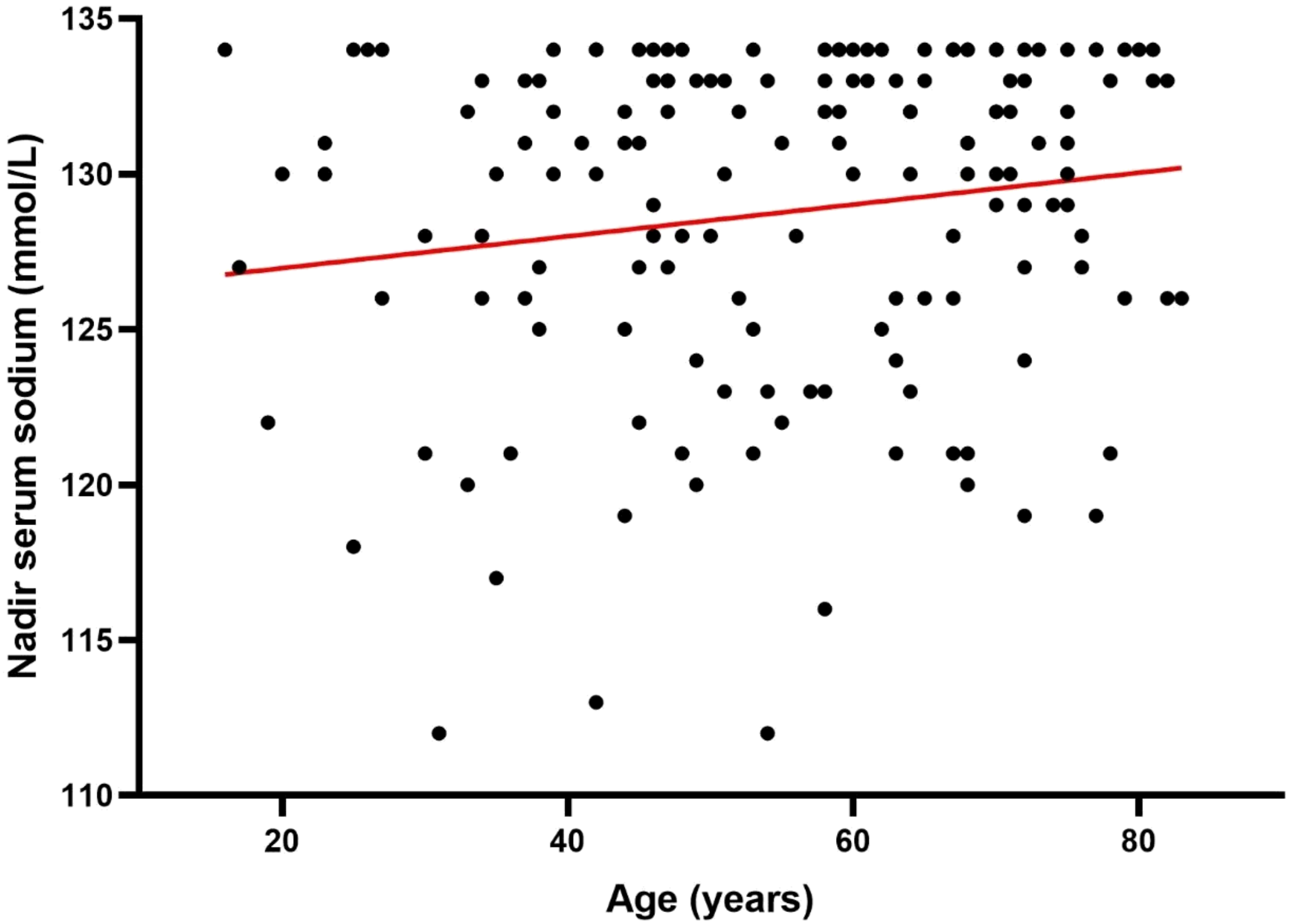
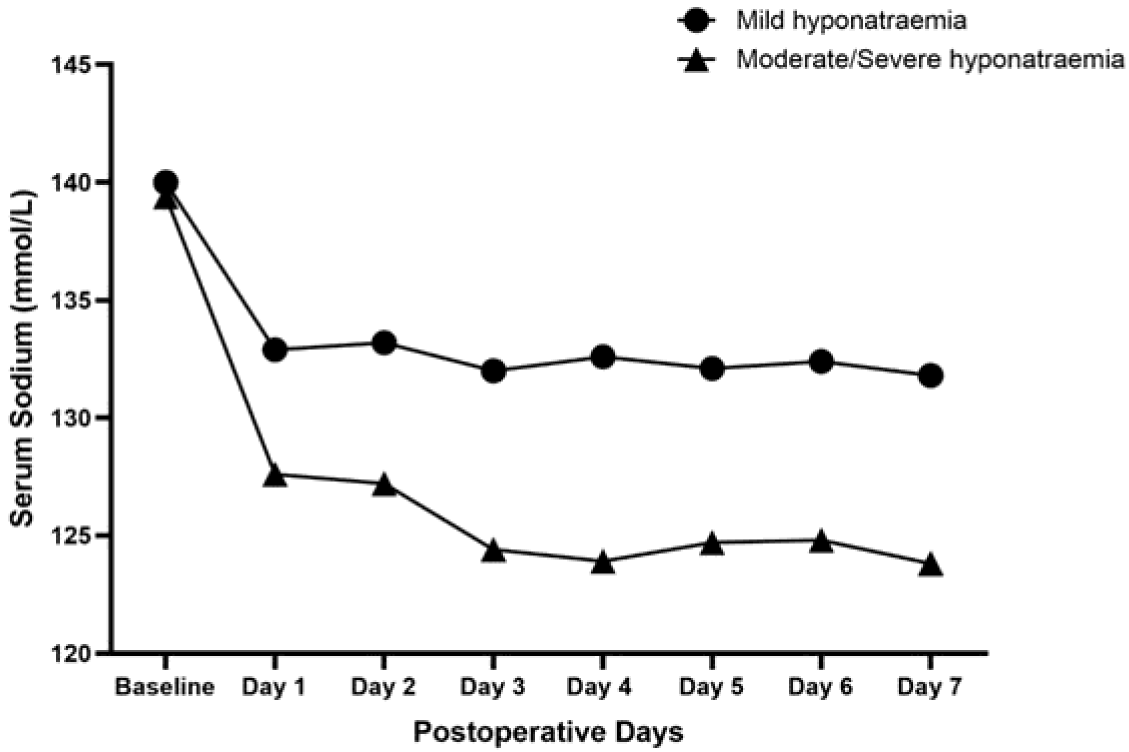


Figure 1

Linear regression analysis of age and nadir serum sodium. X axis represents patients’ age in years and Y axis represents nadir serum sodium (mmol/L). Individual sodium levels plotted as dark circles.



Number at risk								
Normal sodium	152	95	131	129	105	74	48	32
Mild hyponatraemia	9	55	18	15	19	24	31	32
Moderate & severe hyponatraemia	1	8	10	9	8	13	25	34
Total	162	158	159	153	132	111	104	98

Figure 2

Mean serum sodium during the first seven days following transsphenoidal surgery according to hyponatraemia severity. Sodium levels in mild hyponatraemia are expressed in black circles, in moderate and severe hyponatraemia in black triangles.

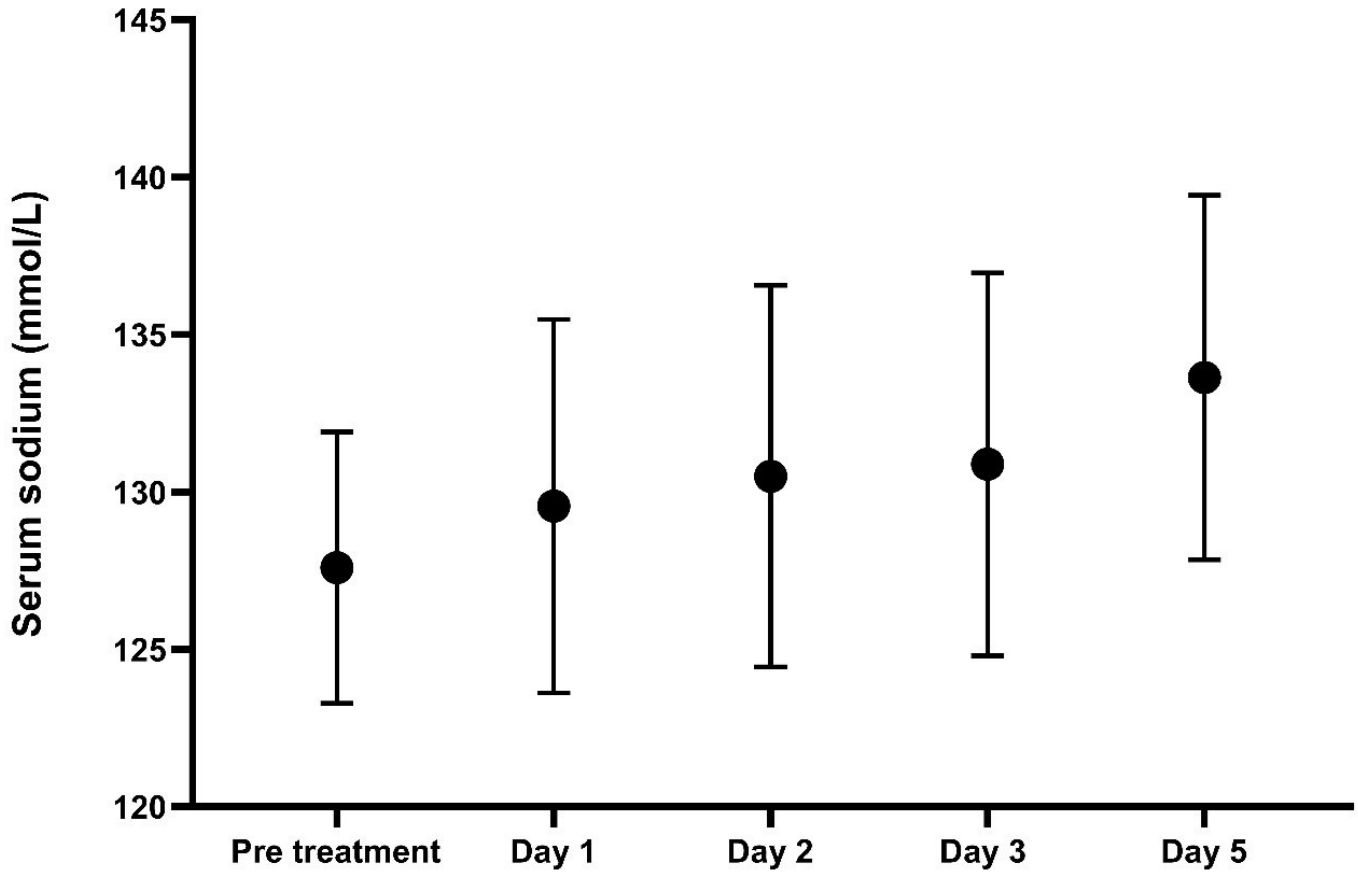


Figure 3

Serum Sodium concentration after starting fluid restriction. Sodium levels are expressed as mean and standard deviation. The black squares represent levels for those were treated with fluid restriction.

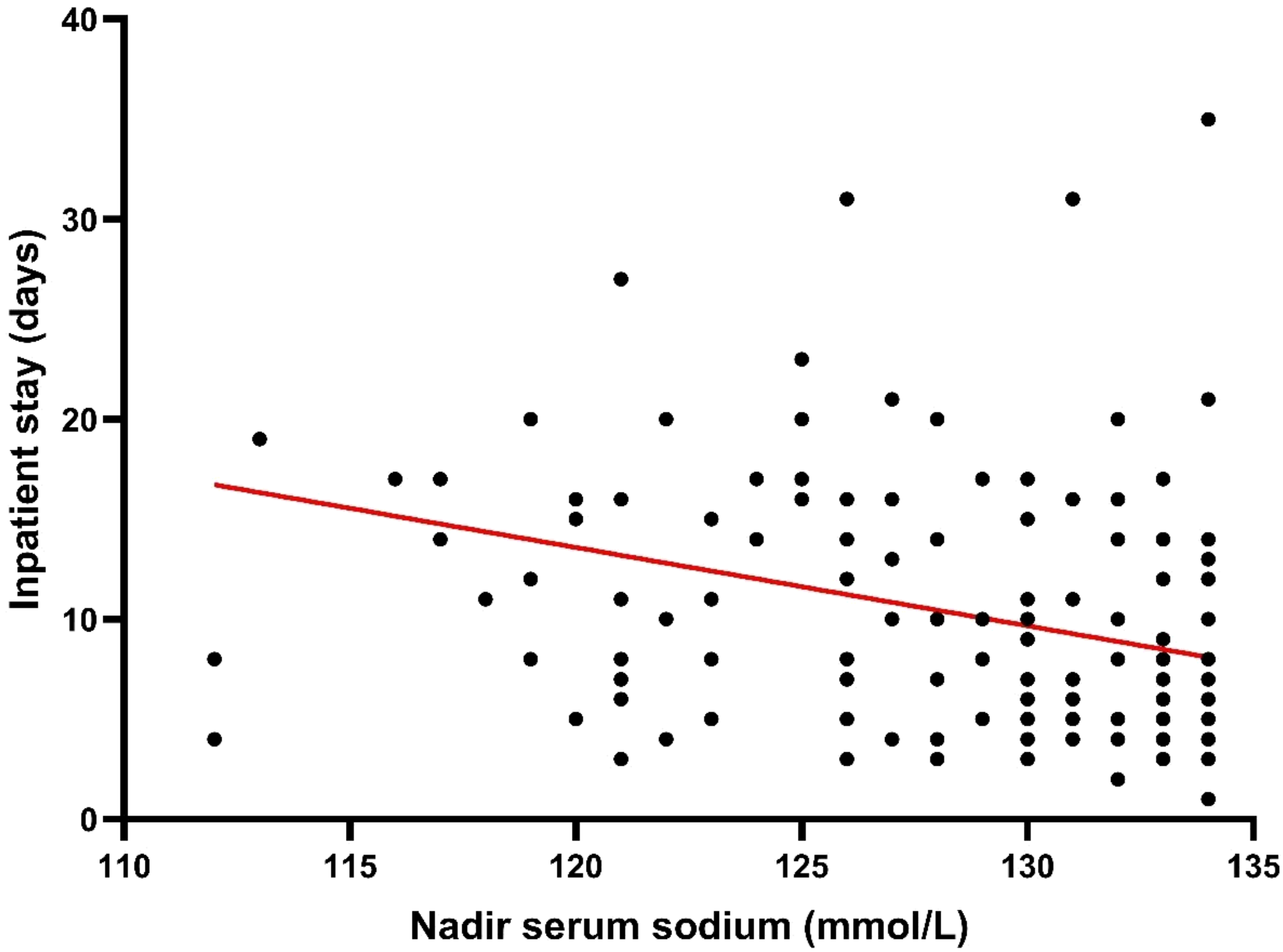


Figure 4

The relationship between mean nadir serum sodium (mmol/L) and in-hospital length of stay in days. Mean levels are expressed as black circles.

Supplementary Files

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- Supplemantaryfigure.docx