Review Article

SALT & WATER BALANCE FOLLOWING PITUITARY SURGERY

Paul Grant\\, Ben Whitelaw\\, Sinan Barazi\\ & Simon Aylwin

1. Department of Endocrinology, Kings College Hospital, Denmark Hill, London, UK
2. Department of Neurosurgery, Kings College Hospital, Denmark Hill, London, UK

[drpaul.grant@doctors.org.uk](mailto:drpaul.grant@doctors.org.uk)

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ABSTRACT

Neurosurgical insults to the pituitary gland have the potential to precipitate a disparate group of electrolyte disorders in both the short and long term. The normally robust production of anti-diuretic hormone (ADH) from the posterior pituitary can be disrupted in the post surgical period and can present with a variety of salt and water disturbances. Shared care between neurosurgeons and endocrinologists is perhaps the best practice approach to investigation and management using agreed protocols. This review article covers the pathophysiology of salt and water balance relating to pituitary surgery and uses this as a guide to inform the clinical scenarios which may range from diabetes insipidus, to cerebral salt wasting to the syndrome of inappropriate ADH hormone secretion and looks at the latest evidence on the subject as well as new treatments.
Introduction

Neurosurgery represents a significant insult to the pituitary gland and has the potential to precipitate a variety of fluid and electrolyte disturbances. It is important to be aware of the incidence, spectrum of clinical manifestations and their course to allow us to optimally manage patients in the peri-operative period.

Our clinical experience suggests that salt and water balance is frequently abnormal post operatively and signifies dysregulation of the usual control mechanisms. A recent audit of sodium levels in our own hospital – a large tertiary centre - illustrates the wide distribution of results in our patients in the initial post-operative period, (see figure 1). Only 35% of patients appear to be within the normal reference range for sodium following neurosurgery.

Figure 1. Day 1 post operative sodium level distribution in a population of 100 pituitary surgery patients (previously unpublished audit data).

This distribution of sodium levels is markedly different from the normal population reference range, so the suggestion is that electrolyte disturbance following pituitary surgery is commonly outside the normal range. Whilst these changes may be transient and most trans-sphenoidal pituitary surgery is accomplished without complication, assessment is required postoperatively for a set of disorders that are specific to this type of surgery. Monitoring for water imbalances, which are due to deficiency or excess of anti-diuretic hormone (ADH) is achieved by continuous assessment of fluid input and output, serum electrolyte measurements and osmolalities of urine and plasma when appropriate (1). In one series of neurosurgical patients, SIADH was found to occur in up to 62% of patients with hyponatraemia (2). The spectrum of clinical manifestations which affect sodium and fluid status after neurosurgery...
include hypovolaemic hyponatraemia (26.7%), drug associated (16.6%), cerebral salt wasting (CSWS) (4.8%), dilutional hyponatraemia secondary to IV fluids (3.7%) and mixed SIADH/CSWS (2.7%). The other relevant issue is that such patients tend to have a significantly longer hospital stay (median 19 days) than normonatraemic patients (median 12 days). Given the pressure on neurosurgical beds and the frequency of such complications, should endocrinologists be getting more involved and take over these patients immediately post operatively?

Shared care between neurosurgeons and endocrinologists has been suggested as the best practice approach to investigation and management using agreed protocols. This review article covers the pathophysiology of salt and water balance relating to pituitary surgery and uses this as a guide to inform the clinical scenarios which may range from diabetes insipidus, to cerebral salt wasting to the syndrome of inappropriate ADH hormone secretion and looks at the latest evidence on the subject, including the introduction of V2 receptor antagonists into clinical practice.

Methods


Hypothalamic and Pituitary Control of Salt and Water

Vasopressin is synthesised in the supraoptic and paraventricular nuclei of the hypothalamus. It is transported to the posterior pituitary where it is stored. The secretion of vasopressin is regulated by two physiological variables: osmolality and circulating volume. In the euvolaemic state it is plasma osmolality which determines vasopressin release. Osmoreceptors (in this part of the brain) have direct access to the circulation through fenestrations in the blood brain barrier. Vasopressin secretion is suppressed when the plasma osmolality is less than 284 mosm/kg. When plasma osmolality rises, above this level, vasopressin secretion increases in a linear fashion (3).
The main physiological effect of vasopressin is to regulate water re-absorption in the distal tubule. Vasopressin binds to V2 receptors, stimulating the expression of aquaporin 2 water channels on the apical surface of renal collecting ducts. This allows re-absorption of water, utilising the osmotic gradient in the renal medulla, giving rise to an anti-diuresis (4). Nausea and pain can stimulate vasopressin release as well as a fall in circulating volume or blood pressure - this mechanism is highly sensitive to even small changes (less than 10%) in circulating volume and can occur even if extracellular volume seems normal and with a normal eGFR. Therefore under euvoaemic or hypervolaemic conditions vasopressin release is determined by plasma osmolality. Thirst itself is signalled and regulated by osmoreceptors in the hypothalamus and in normal physiological circumstances there is a linear relationship between thirst and vasopressin release, as shown in the graph below (figure 2).

**Figure 2.** Graph to show relationship between plasma (A) and urine (B) osmolality and plasma AVP concentration (5). *(Reproduced with permission from Robertson Gl, Berl T. Water Metabolism. In Brenner BM, Rector FC Jr, eds. The Kidney. Philadelphia, PA: WB Saunders; 1986:392)*

Surgery on or near the pituitary can affect the regulated secretion of vasopressin. This can occur through damage to the hypothalamus, pituitary stalk or posterior pituitary. Inadequate Hydrocortisone replacement therapy and anticonvulsant agent therapy may also potentially increase the risk of life threatening hyponatraemia in the course of Desmopressin (DDAVP) treatment. Normally the thirst mechanism is unaffected by surgery but adipsia / hypodipsia is a rare complication of hypothalamic damage. Therefore, appropriate management, in order to avoid disabling electrolyte disturbances, requires a good grasp of the relevant pathophysiology.

The classical tri-phasic pattern of endogenous vasopressin secretion, first described by Fisher & Ingram in 1936 (6) constitutes; an initial phase of symptomatic diabetes insipidus occurring within 24 hours of surgery with polyuria; a second phase of inappropriate vasopressin secretion potentially causing hyponatraemia and a third phase with a return to diabetes insipidus – occurring up to 2 weeks later – is often complicated by cerebral salt wasting and thirst disorders. This process reflects: initial interruption of vasopressin release,
followed by unregulated release of pre-synthesized vasopressin and finally permanent diabetes insipidus due to the absence of vasopressin. The frequency of the triphasic response is about 1% and similarly a biphasic response (transient polyuria, followed by hyponatraemia, then resolution) has a frequency of 3% (7). In the triphasic response: first phase will typically lasts 5-7 days and the second phase can last 2-14 days (8).

**Spectrum of Clinical Disorders**

In one prospective, observational study of 57 patients, Kristof et al (9) found that postoperative water and electrolyte disturbance occurred in as many as 75% of their patients, with 38% as isolated diabetes insipidus (DI). The DI group was interesting in that the maximum of medians of diuresis (5.75 litres/24 hours) occurred on postoperative day 2. Only 8.7% of the patients however had to be treated with Desmopressin because of DI persisting for 3 months or longer.

Of the patients with hyponatraemia (21%) the nadir of medians was 132 mmol/l and this occurred as late as postoperative day 9. Those with a sodium level below 130mmol/l irrespective of symptomatology (42.8%) were treated with transient fluid intake restriction. Generally the occurrence of postoperative water and electrolyte disturbances was linked to the intraoperative manipulation of the neurohypophysis, increased thirst and decreased urine osmolality correlated significantly with DI (p=0.001, p=0.02 and 0.023 respectively). They concluded that the pattern of DI development generally began on the first postoperative day, was transient and resolved in the majority of cases within 10 days. In only a relatively few cases does it persist and require exogenous ADH analogue therapy. Hyponatraemia as a consequence of pituitary surgery usually occurs at the end of the first postoperative week and resolves in most cases within 5 days. Very few patients appeared to need treatment other than fluid intake restriction to avoid serious complications.

Deficiency in vasopressin leads to diabetes Insipidus with a raised osmolality, whereas excess vasopressin can lead to hyponatraemia. These disorders can be viewed as opposite ends of the same spectrum, but interestingly both can occur sequentially in the same patient (figure 3).  

Figure 3. Schematic representation of the spectrum of ADH/ Vasopressin behaviour
Many patients have something wrong with their salt and water balance post operatively, when does this become clinically apparent? The answer is when then the changes are at the extremes of the spectrum.

The underlying pituitary disease state may also have an effect on post operative surgical outcomes. In the case of craniopharyngiomas for example, Ghirardello et al (10) reported that DI occurred in over 70% of patients following surgery. Hensen et al performed a risk analysis which showed that patients with Cushing’s disease had a fourfold higher risk of polyuria than patients with Acromegaly and a 2.8 fold higher risk for postoperative hyponatraemia (6). Younger age, male sex and intrasellar expansion were found to be associated with a higher risk of hypotonic polyuria, but this was not considered to be clinically relevant (10, 11).

Cranial Diabetes Insipidus

Cranial or Hypothalamic diabetes Insipidus (DI) is the commonest disorder of salt and water balance post–pituitary surgery, occurring in 18-38% of cases (depending on the series) resulting from vasopressin deficiency (6,8,9,10). It is characterised by 3 features;

- Persistence of an inappropriately dilute urine in the presence of strong osmotic or non-osmotic stimuli for ADH secretion.
- Absence of intrinsic renal disease.
- Rise in the urine osmolality after the administration of ADH.

The diagnosis is based on the clinical picture, together with a demonstration of hyperosmolar serum and inappropriately dilute urine (see summary Box 1).

BOX 1.
The onset of diabetes insipidus is typically within the first 24 hours post-operatively (12). However it can be as late as day 11 post-op (9). It is usually transient and thought to be due to a minor injury to the posterior pituitary inhibiting vasopressin release (13). Half of all cases will resolve within a week (11). There is variation in clinical practice as to the treatment of transient DI with desmopressin. Some authorities recommend withholding treatment initially and only instituting it in cases of severe DI or when the condition persists beyond day 3 (9). One series reported that less than 2% of patients needed DDAVP after 10 days post-op (14). Ultimately, permanent diabetes insipidus complicates only 0-3% of cases of pituitary surgery (9, 15, 16).

**Predisposing factors:** Functioning pituitary adenomas and surgery in younger patients are predictive of DI (10, 11). The extent of intra-operative manipulation of the posterior pituitary is known to foreground the development of DI (9, 16). Similarly an intra-operative CSF leak predicts both transient and permanent DI (11).

**Hyponatraemia**

Hyponatraemia is less common, but well described, following transsphenoidal surgery for pituitary tumours. Its frequency ranges between 1.8 – 35% (2, 8, 9, 16). Of these patients 16.7 – 56.0% who were symptomatic indicated a mean serum sodium level of 120.5-123.5 mEq/l. Hyponatraemia can occur early or as an isolated late event (16, 17). It can also occur after an episode of DI as part of a biphasic or triphasic response.

The prevalence of post-operative hyponatraemia is up to 30% of patients during the first 10 days (6, 8). The pathophysiology is thought to relate predominantly to damage to the posterior pituitary, giving rise to unregulated secretion of vasopressin, but other factors including secretion of natriuretic peptides and level of fluid and sodium intake are also thought to be involved (5, 6). Early post operative hyponatraemia may be caused, in part, by stress, pain & nausea which lead to increased secretion of vasopressin (7, 9, 16).
In one large study from Japan, Kinoshita and colleagues (18), examined 88 consecutively operated patients who were managed using a uniform treatment protocol. Post operative hyponatraemia occurred in 30.7% of patients from post op day 4 to day 7. Emergence of hyponatraemic symptoms depended on the severity of post operative hyponatraemia and the degree of post-TSS serum sodium reduction.

In their prospective series of 57 patients, Kristof et al showed that the median day of hyponatraemia occurrence was day 6 post-op with remission occurring median day 10. The hyponatraemia was mild with a median nadir sodium 132 mmol/l (9). Half of the hyponatraemic patients described mild symptoms including headache, fatigue, nausea. One third of these patients were treated with fluid restriction.

Causes of hyponatraemia are given in box 2 below.

**BOX 2.**

**Predisposing factors:** Hyponatraemia is more common following surgery for ACTH secreting adenomas (19). Hensen et al demonstrated that patients with Cushing’s disease have the largest odds ratio for developing polyuria and hyponatraemia. Patients risk of having such complications is three times higher than those with Prolactinoma, four times higher than those with Acromegaly and 2-8 times higher than patients with non-functioning pituitary tumours.

There are a couple of postulated mechanisms for this, firstly there is likely to have been pre-existing hypertension due to the mineralocorticoid effects of cortisol (cortisol overwhelms the 11 beta-HSD enzyme protecting the mineralocorticoid receptor from cortisol). Cortisol may also increase angiotensinogen levels and there is the possibility of adrenal / mineralocorticoid suppression as a consequence of the Cushing’s which induces a state of hyporeninaemic hypoaldosteronism – which would predispose to fluid and electrolyte disturbance.

**A Pathway to Assessment**

Whilst most transsphenoidal pituitary surgery is accomplished without complication, monitoring is required post operatively for a set of disorders that are specific to this type of procedure. Early diagnosis and treatment are important to prevent potential adverse effects on the central nervous system. Post-operative assessments are tailored to the early and later post-operative periods (1,2).
Detection of electrolyte and fluid imbalance is achieved by regular monitoring of fluid status, osmolalities and daily electrolyte level checking. Diabetes insipidus is characterised by hypernatraemia and polyuria – excessive volumes of dilute urine, and this can be exacerbated in patients with impaired thirst or reduced mobility. Most patients are able to maintain normo-volaemia through an adequate fluid intake but desmopressin therapy is required for some.

SIADH, tends to peak around the 7th post operative day presents with hyponatraemia and can be severe and symptomatic.

Several authors recommend daily sodium measurements while patients remain an inpatient and recommend sodium is re-checked, probably as an outpatient 7 to 9 days post-operatively. (3, 8, 15, 20).

**Figure 4. Protocol for suspected Diabetes Insipidus**

Desmopressin is the drug of choice for acute and chronic DI. Its onset of action is fast and it works for up to 12 hours, promoting anti-diuresis and a reduction in urine output. Electrolyte and osmolality monitoring at regular intervals is important to aid re-evaluation, re-dosing and to avoid hypernatraemia. As a safety measure, to avoid fluid overload, subsequent doses of Desmopressin should be given when polyuria recurs but prior to the re-development of the hyperosmolar state (21).

The ‘as required’ usage of Desmopressin allows the normalisation of urine output to demonstrate itself, which occurs as endogenous ADH release returns. With regards to hyponatraemia post pituitary surgery, this may be as a component of the triphasic pattern or a consequence of Desmopressin use. It was shown in one large study of patients that 8.4% developed low sodium levels at some time up to day 10 post-operatively and 2.1% developed symptomatic hyponatraemia (9). It is therefore especially important to suspend Desmopressin treatment until the serum sodium level returns to the normal range. Failure to allow this correction can lead to catastrophic cerebral oedema (22).
Assessment of Hyponatraemia

Patients with hyponatraemia are usually asymptomatic. Symptoms may not occur until the serum sodium falls below 125 mmol/l. Common manifestations are neurological, the consequence of swelling of brain cells secondary to intracellular movement of water. Patients may develop nausea, headache, lethargy, confusion, coma or respiratory arrest.

Making an accurate diagnosis between the many causes of hyponatraemia (Box 2), especially between SIADH and CSWS, is important because the treatments differ greatly between the conditions. The clinical presentation of both syndromes is identical and the differential diagnosis can be difficult. The determination of the patient’s volume / fluid status is essential for the diagnosis. The SIADH is a volume expanded condition (Box 3), whereas CSWS is a volume contracted state that involves renal loss of sodium.

FIGURE 5. Diagnostic flowchart for post pituitary surgery hyponatraemia

A recent conference on ‘red flags’ in medicine (23) highlighted the fact that hydration status, especially in the elderly can be difficult to determine. Axillary dehydration for example has been shown to be a significant, sensitive marker of global dehydration and should be specifically assessed. Several methods can be used to detect the volaemic state, over and above clinical examination, when there is difficulty, for example the frusemide test (24). This involves an infusion of 20mg of IV frusemide, which normalises serum sodium levels in patients with SIADH, but not in CSW, in which patients will remain hyponatraemic.

Treatment for patients with SIADH is fluid restriction and treatment for patients with CSWS is generally salt and water replacement (25). Practical management recommendations for hyponatraemia often relies heavily on expert opinion because there is a paucity of class I evidence available in the literature (26).

Pharmacological treatment of water and electrolyte disorders
A patient with diabetes insipidus and an intact thirst mechanism and free access to fluids can keep themselves adequately hydrated. For this reason some authorities advocate not treating DI in the first 2 weeks post operatively. (8, 27). However this can be disruptive and unpleasant for patients. DI may be treated with DDAVP (Desmopressin), usually 1mcg s/c. This dose will last about 12 hours and repeat doses can be given once polyuria recurs. DDAVP replacement should be handled carefully in the first 2 post-operative weeks. Too liberal use of DDAVP can promote hyponatraemia. (7, 11).

For SIADH, free water restriction (which needs to be as tight as 750mls per day) is maintained until the underlying cause of the disorder is corrected. Administration of normal saline is not appropriate therapy because the sodium may be rapidly excreted while the water is retained which will exacerbate the hyponatraemia. An adjunct to water restriction in some circumstances is Demeclocycline in a dosage of 600 to 1200mg per day. This induces nephrogenic DI and therefore helps to correct the hyponatraemia; this can be useful in patients where free water restriction is difficult and is most useful in the setting of chronic hyponatraemia (its main indication for use is in the setting of advanced malignancy). Demeclocycline has a slow onset of action (7-14 days) which usually makes it unsuitable for hospital usage (28).

In the context of SIADH which has not responded to initial fluid restriction for 48 hours, there is potential for the use of Tolvaptan, this is a first in class agent, which acts as a selective, competitive antagonist at the V2 receptor site for which it has greater affinity than native AVP. It is recognised to increase the excretion of excess fluid when taken orally and this then helps to increase the rate of normalisation of sodium to safer physiological levels, importantly without having an adverse effect on renal function. It has recently been licensed for the specific indication of hyponatraemia secondary to SIADH and it is usually started at a dose of 15mg per day and this can be increased to a maximum of 60mg once per day, as tolerated to achieve the desired level of serum sodium. During titration, patients should be monitored regularly for serum sodium and volume status.

There is increasing evidence for its use in clinical practice. In patients with SIADH, Tolvaptan significantly increased the percentage of patients with normal sodium levels (p<0.001), it improved mental component scores on the SF-12 health survey (p<0.024) and reduced the need for fluid restriction compared with placebo (p<0.03) (28). There is also a
corresponding increase in the rate of normalisation of sodium levels, which has the benefit of reducing length of hospital admission, which may be especially important on neurosurgical units (27, 29, 30, 31).

**Discussion**

Patients undergoing pituitary surgery represent a heterogeneous population each with unique clinical, biochemical, radiologic, pathological and neurological considerations. The postoperative management of patients often occurs in the context of a dynamic state of the hypothalamic-pituitary-end organ axis. Diabetes insipidus and hyponatraemia are both known to occur post-pituitary surgery but there is now new data to show that they are both very common and may affect up to 75% of cases (9). Consequently, a significant component of postoperative care of these patients focuses on vigilant screening and observation for neuroendocrinological disturbances such as varying degrees of hypopituitarism and disorders of water balance (32). Failure to secrete / ability to regulate vasopressin, results in diabetes insipidus. Excessive unregulated secretion of vasopressin, leads to hyponatraemia and syndrome of inappropriate anti-diuretic hormone (SIADH) – failure to downregulate ADH release. Disturbances in osmoregulation resulting in polyuria and perturbations of serum sodium are of high prevalence and need observation in the peri-operative period – especially in patients with Cushing’s disease (10, 11).

We have explored a systematic approach to monitoring with reference to clear protocols and clinical assessment and suggest that this is the best way of screening for such disorders and allow early detection and treatment to restore the normal balance and aid recovery.

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**Figure 3.** Schematic representation of the spectrum of ADH/Vasopressin behaviour

*Many patients have something wrong with their salt and water balance post operatively, when does this become clinically apparent? The answer is when then the changes are at the extremes of the spectrum.*

**Figure 4.** Protocol for suspected Diabetes Insipidus

**FIGURE 5.** Diagnostic flowchart for post pituitary surgery hyponatraemia
Figure 3. Schematic representation of the spectrum of vasopressin behaviour.

- Risk of symptomatic diabetes insipidus
- Risk of symptomatic hyponatraemia

ADH Secretion
Figure 4. Protocol for suspected Diabetes Insipidus

POLYURIA
ie. >200mls / hr for 2 consecutive hours if catheterised.
800mls over 4 hours if not catheterised.

Check urgent;
U&E, Plasma and Urine osmolality

Is Na > 140 mmol/l
Or
Plasma osmolality > 285 mosmol/kg

NO
YES

Dilute plasma

Appropriate diuresis

Appropriate natriuresis

Review patient in 12 hours. If polyuria repeat investigations

DIABETES INSIPIDUS

1mcg DDAVP s/c

NO
YES

Access to oral fluids / drinking sufficiently?

NO
YES

Oral + IV dextrosaline to = output

Patient to drink to thirst
HYPONATRAEMIA (Post pituitary surgery)

Ensure normal renal and liver function in all patients. Rule out Glucocorticoid and thyroid deficiency

HYPOVOLAEMIA
Exclude:
Volume depletion, Hypodipsia, Diuretics, Use of Mannitol

Check Urine Na
If > 20 mmol/l then Cerebral salt wasting is likely diagnosis

EUVOLAEMIA
Check Plasma Osmolality
> 270 mOsm
< 270 mOsm

Check Urine Na
Mineralocorticoid deficiency
Salt losing nephropathy

HYPERVOLAEMIA
Check Plasma Osmolality
< 270 mOsm
> 270 mOsm

Check Urine Na
Excess water; Polydipsia
Urine Osmolality >100 mOsm

SIADH
Urine Osmolality >100 mOsm

Ensure normal renal and liver function in all patients.
Rule out Glucocorticoid and thyroid deficiency

Salt losing nephropathy

Excess water; Polydipsia
Overzealous IV fluids or DDAVP
**BOX 1. Diagnosis of postoperative DI**

Rule out osmotic diuresis or fluid overload.

**Clinical signs & symptoms;**
- Polyuria > 3 – 18l/day
- Polydispisa, with fluid craving

**Laboratory;**
- Dilute urine, urine osmolality < 200 mosm/kg
- Normal or increased serum osmolality
- Increased serum sodium > 140 mmol/l with continued diuresis of hypotonic urine
**BOX 2. Causes of post operative hyponatraemia**

- Renal or liver dysfunction
- Pseudohyponatraemia
- Untreated thyroid or gluco-corticoid deficiency
- Dehydration (which may be exacerbated by diuretic use or Mannitol)
- Cerebral salt wasting
- Excessive IV fluids or PO fluid intake
- SIADH or excess DDAVP
- Co-existent congestive cardiac failure