

## Neuroendocrinology and Pituitary NEUROENDOCRINOLOGY AND PITUITARY CLINICAL ADVANCES

### *Early Moderate Fluid Restriction and the Risk of Delayed Hyponatremia Following Transsphenoidal Surgery*

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**Background:** The most common cause for readmission after transsphenoidal surgery (TSS) is hyponatremia (hypoNa). Delayed hypoNa, defined as hypoNa occurring 3 to 14 days post TSS, occurs in up to 35% of patients and, if severe, can be life-threatening. We conducted a preliminary prospective study comparing two approaches of postoperative fluid management and hypothesized that patients treated with early postoperative fluid restriction would have decreased rates of delayed hypoNa.

**Methods:** Patients scheduled for TSS were randomly assigned to the control (CON, n=65) or fluid restriction group (Total FR (EXP 1 + EXP 2), n=57). Patients with chronic kidney disease stage III or greater, diabetes insipidus, chronic hyponatremia, or untreated adrenal insufficiency or hypothyroidism were excluded. All patients were started on postoperative weight-based intravenous fluids until postoperative day (POD) 1 and allowed to drink freely. Patients in the EXP 1 group (n=39) were fluid restricted to 1.8 liters/day (2 liters/day if weight > 100 kg) from POD 3 through POD 14. The fluid restriction was changed to 1 liter/day (1.2 liters/day if weight > 100 kg) (EXP 2, n=18) during the study due to interim analysis suggesting a trend toward a reduction in the incidence of hypoNa with fluid restriction. Patients in the CON group were instructed to drink ad lib. Serum sodium (Na) levels were checked every 8 hours in the hospital and on POD 3, 7, 10, and 14. Average and nadir Na between POD 3 and POD 14, incidence of mild (130-134 mEq/L), moderate (125-129 mEq/L), and severe (< 125 mEq/L) hypoNa, and readmission for hypoNa were evaluated. Mann-Whitney U test, Fischer's exact test, Pearson's chi-square, and T-test were used for statistical analysis.

**Results:** Nadir Na was lower in CON compared to EXP 2 (135.1 ± 5.8 vs 138.4 ± 2.8, p=0.024). There was a trend toward a decreased incidence of hypoNa in EXP 2 (11%) compared to CON (30%) (p=0.133). Although there was no significant difference in the incidence of hypoNa (p=0.323) between CON and the EXP 1 and EXP 2 groups combined (Total FR), there was a trend toward a lower nadir Na (135.1 ± 5.8 vs 137 ± 4.6, p=0.082) and average Na (138.8 ± 3.1 vs 139.8 ± 2.5, p=0.140) in CON versus Total FR group, respectively. There was no statistically significant difference in average Na or incidence of hypoNa in CON compared to EXP 1. The incidence of mild, moderate, and severe hyponatremia was similar among groups, except in EXP 2 which had a lower, although not statistically significant, incidence of severe hyponatremia (0% vs 7.7%) and readmission for hyponatremia (5.6% vs 17.5%) compared to CON. There was no difference in the incidence of acute kidney injury or hypernatremia between groups.

**Conclusion:** Preliminary results suggest early moderate fluid restriction after TSS may reduce the incidence of delayed hyponatremia as compared to mild or no fluid restriction. Further analysis with more participants is needed.

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### *Efficacy, Efficiency and Security of Urea Treatment in the Syndrome of Inappropriate Antidiuretic Hormone Secretion*

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**Introduction:** In the present times, several strategies have been proposed for the treatment of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Urea has demonstrated to be an effective treatment but its use has not been extended. Our work analyzes our experience with urea in the treatment of SIADH. **Material and Methods:** Observational retrospective analysis of 39 patients with SIADH in which urea has been used in our hospital with pre- and post-analysis of plasmatic sodium concentrations. **Results:** We included 39 patients with SIADH with a mean age of 76.4 ± 15.8 years. The plasma sodium nadir was 120.0 ± 5.1 mmol/L and at the initiation of treatment 125.2 ± 4.1 mmol/L. Total time of treatment was 2.42 ± 3.86 months being the treatment still active in 4 patients. We observed an improvement of sodium in all patients with a mean sodium at the end of treatment of 134.3 ± 5.0 mmol/L being this value statistically significant compared to the initial sodium (p<0.01). As a matter of fact we found significant differences at one week of treatment (p<0.01), keeping sodium stable levels around 135 mmol/L during the treatment period. The treatment was stopped in 3 cases (7.7 %) by the patient, one for mild digestive symptomatology and two for limited palatability. Of them two were treated with tolvaptan and the other did not need any further treatment. There were no adverse events in the rest of the patients. From the economic perspective and considering the duration of treatment, if we compare this to the cost of tolvaptan during the same period and the same number of patients, there was a reduction of cost of 87.9 % in comparison with treatment with tolvaptan. **Conclusions:** In our experience urea has shown to be a safe and cost effective option in the treatment of hyponatremia caused by SIADH showing improvement in sodium levels from the first week of treatment in all patients. We think it should be considered a valid therapeutic option.

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### *Endocrine Dysfunction in Covid-19*

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**Introduction:** Evidence pertaining to new-onset endocrine dysfunction in patients with COVID-19 is currently limited and extrapolated from prior SARS epidemics. Further, identifying whether the quantum of this dysfunction is associated with the severity of disease in patients with COVID-19 is unknown. We aimed to comprehensively explore the prevalence, nature and degree of endocrine dysfunction stratified based on disease severity at a dedicated COVID care centre.

**Patients and Methods:** Consecutive patients enrolled at PGIMER Chandigarh, were stratified on the basis of disease severity as: group I (moderate to severe disease including oxygen saturation <94% on room air or those with comorbidities) and group II (mild disease, with oxygen saturation >94% and without comorbidities). Hypothalamo-pituitary-adrenal, thyroid, gonadal axes and lactotroph function were evaluated. Inflammatory and cell-injury markers were also analysed.

**Results:** Patients in group I had higher prevalence of hypocortisolism (38.5 vs 6.8%,  $p=0.012$ ), lower ACTH (16.3 vs 32.1pg/ml,  $p=0.234$ ) and DHEAS (86.29 vs 117.8µg/dl,  $p=0.086$ ) as compared to group II. Low T3 syndrome was a universal finding, irrespective of disease severity. Sick euthyroid syndrome (apart from low T3 syndrome) (80.9 vs 73.1%,  $p=0.046$ ) and atypical thyroiditis (low T3, high T4, low or normal TSH) (14.3 vs 2.4%,  $p=0.046$ ) were more frequent in group I than group II. Male hypogonadism was also more prevalent in group I (75.6% vs 20.6%,  $p=0.006$ ) than group II, with higher prevalence of both secondary (56.8 vs 15.3%,  $p=0.006$ ) and primary (18.8 vs 5.3%,  $p=0.006$ ) hypogonadism. Hyperprolactinemia was observed in 42.4% patients, without significant difference between both groups.

**Conclusion:** COVID-19 can involve multiple endocrine organs and axes, with a greater prevalence and degree of endocrine dysfunction in those with more severe disease. Involvement of multiple axes, particularly at hypothalamo-pituitary level suggests the possibility of hypophysitis as an underlying etiology. We also observed less characterised findings like atypical thyroiditis and normal DHEAS despite secondary hypocortisolism. Follow-up surveillance of these patients at periodic intervals and estimation of anti-pituitary antibodies could be considered to elucidate viral cytopathic effect or inflammation as the major underlying mechanism of endocrine dysfunction.

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#### Gonadotropin-Releasing Hormone Agonist Induced Pituitary Apoplexy

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**Background:** Gonadotropin-releasing hormone agonists (GnRHa), used in the treatment of prostate cancer (PC) and for reproductive purposes in women, have been implicated as the cause of pituitary apoplexy (PA), a potentially life-threatening condition. The pathophysiology of PA after GnRHa has not been completely elucidated. Proposed mechanisms include a stimulatory effect of GnRHa on pituitary adenoma cell metabolism, causing mismatched blood supply prompting hemorrhage or infarction. Prior documentation of PA associated with GnRHa has been scarce and limited to case reports.

**Methods:** This is a detailed clinical case series of GnRH-induced PA from a single institution, obtained by a Research Patient Data Repository query. Clinical characteristics of the patients including demographics, detailed history, time interval between GnRHa and PA, physical exam, biochemical data, pituitary imaging and pathology were reviewed.

**Results:** Seven cases were identified between 1990-2020; six men (aged 55 – 83 years) receiving treatment for PC and one woman (aged 22 years) receiving GnRHa for oocyte donation. All patients presented with headache; four within 48 hours of, one >1 month after, and one 5 months after, receiving GnRHa. One patient had insufficient data on time between GnRHa and PA. Most patients (86%) presented with nausea and vomiting. Other symptoms included ophthalmoplegia (43%), visual field defects (17%), and altered consciousness (29%). All patients had sellar masses and/or evidence of hemorrhage on MRI. Five patients underwent pituitary surgery while the others were managed medically. Of those who underwent surgical resection, 80% had positive histopathological staining for gonadotropins. Five patients with reliable hypothalamic-pituitary-adrenal (HPA) axis testing had impairment of this axis after PA; 40% recovered adrenal function. Central hypothyroidism occurred in 60% of whom 66% recovered. Hyponatremia occurred in 43%.

**Conclusions:** Patients with gonadotrope-secreting adenomas may develop PA in response to GnRHa, more frequently in elderly men who are receiving GnRHa treatment for PC. This may be due to older age and higher prevalence of GnRHa use in this group. However, as demonstrated here and in prior case reports, women are not exonerated from this complication. Headache and adrenal insufficiency are typically present. HPA axis recovers in a subset. While most patients present <48 hours after GnRHa treatment, delayed presentations may occur. Therefore, a history of prior GnRHa exposure should be ascertained in patients presenting with PA. While the incidence of PA after GnRHa is low, this case series and prior case reports suggest that this serious potential complication should be recognized prior to treatment, especially in patients with known pituitary macroadenomas.

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