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Analysis of the HPA (hypothalamic pituitary adrenal) axis perioperatively in patients who underwent transsphenoidal surgery for pituitary adenomas with a normal preoperative HPA axis

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ABSTRACT

Background: To observe the changes in the HPA axis postoperatively in those patients who underwent trans-sphenoidal excision of the pituitary adenomas with a normal preoperative HPA axis. **Settings and Design:** 61 patients presenting with pituitary adenomas with a preoperative normal HPA axis were chosen and were not given the routine perioperative steroid cover and their serum cortisol levels were assessed after undergoing transsphenoidal surgery with intraoperative preservation of the normal gland.

Methods: Basal early morning (8 am) serum cortisol estimation using a Cortisol ELISA Kit, before and after undergoing transsphenoidal surgery. Synacthen test was used to assess the HPA axis for patients with a preoperative serum cortisol level between 3.6- 16 mcg/dl. Statistical analysis used: SPSS statistical software programme was used for analysis. 'p' value < 0.05 was considered as statistically significant.

Results: The mean serum cortisol levels preoperatively and on the postoperative days 1, 2 and 3 were analysed. The pituitary gland was preserved in all 61 patients intraoperatively. It was found that there was significant difference between the mean preoperative cortisol and mean cortisol on day 1 ($p=0.04$) suggesting a definite cortisol surge in the immediate postoperative period by 55.7%. Post-operatively, 19 patients (31%) required steroids, out of which 16 of them developed hyponatremia, 2 had a low serum cortisol level< 3.6 mcg/dl and 1 developed symptoms of hypocortisolemia, hence given steroids postoperatively.

Conclusion: It was observed that there was a 55.7% surge in serum cortisol in the immediate postoperative period. The true incidence of postoperative hypocortisolemia was 8% (5/61 patients)..

Keywords: Serum cortisol - pituitary adenoma patients - transsphenoidal surgery- Synacthen test

INTRODUCTION

Transsphenoidal surgery for pituitary adenomas is the favoured approach for the surgical management of these tumours. Conventionally glucocorticoids are administered perioperatively to all patients undergoing transsphenoidal pituitary surgery under the presumption that there is a temporary dysfunction of the pituitary gland[1] during surgery.

Hypothalamo pituitary adrenal axis (HPA)

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The main components of the HPA axis are the para-ventricular nucleus of the hypothalamus which contains neuro-endocrine neurons that synthesize and secrete vasopressin and corticotropin-releasing hormone (CRH). The corticotrophin releasing hormone and vasopressin both stimulate the secretion of adrenocorticotropic hormone (ACTH). ACTH in turn acts on the adrenal cortices, which produce the glucocorticoid hormones. The glucocorticoids in turn act on the hypothalamus and pituitary (to suppress CRH and ACTH production) in a negative feedback cycle.[2,3]

Hence in a patient with a pituitary adenoma, there is dysfunction at the level of the pituitary gland with a decreased secretion of the ACTH and a low serum cortisol due to a decreased release from the adrenal gland. In some patients, the adrenal reserve of cortisol is still maintained responding to exogenous ACTH. This is done in a Synacthen test which involves administration of synthetic ACTH intravenously and the serum cortisol assessed one hour later. This test can be done at anytime during the day and helps to identify patients who can still manage to produce an appropriate surge of cortisol during surgery.

In a study by Cozzi et al including 72 patients undergoing transsphenoidal resection of non-functioning pituitary adenomas, 14 patients (19.4%) had hypocortisolemia pre-operatively as defined by an 8am serum cortisol level less than 8 mcg/dl and they were given perioperative steroids.[4] Since a definitive test such as Synacthen or an Insulin tolerance test was not done preoperatively in this study the incidence of preoperative hypocortisolemia might have been underestimated. Hence the requirement of a standard test to identify patients with a normal HPA axis is required. In one of the studies by Oelkers et al[5], 13 out of 57 (22.8%) patients had an abnormal response to the short Synacthen test and 14 of 57(24.56%) patients had an abnormal response using the Insulin hypoglycaemia test.

The Insulin tolerance test was considered the gold standard[6]to assess the HPA axis but the Synacthen test has become popular as it can be done easily on an outpatient basis and is equally reliable.[7,8]The insulin tolerance test carries a risk of hypoglycaemia and requires inpatient observation for the same. It also requires an assessment of the renal function. Though it remains the gold standard to assess the HPA axis, the short Synacthen test is preferred in view of convenience.[8,9]

The Synacthen Test

Patients with 8 am serum cortisol between 3.6-16 mcg/dl underwent a Synacthen test to assess the adequacy of the HPA axis. The Synacthen test involved administration of 1ml (250 mcg) of synthetic ACTH intravenously and serum cortisol was measured one hour following the injection. If the serum cortisol levels increased to greater than 20 mcg/dl, these patients were considered to have a normal HPA axis and did not receive steroid cover during surgery. If the serum cortisol level remianed <20 mcg/dl the HPA axis was considered to be abnormal and the patient received perioperative steroids.

Our experience is that it is possible to identify and preserve the normal adenohypophysis during transsphenoidal pituitary surgery.[10] It is debatable whether perioperative steroid supplementation is required when the preoperative cortisol levels are normal [11,12,13]. It has been noticed that there is an intraoperative surge of serum cortisol levels in those patients with preoperative normal HPA axis, probably an appropriate response to the stress of surgery[14].

If the normal gland is preserved by the surgeon, it may be possible to withhold steroids in patients with a preoperative normal HPA axis. This is supported by studies[10]which show that normal gland is usually compressed to the periphery of the tumor and an intracapsular dissection

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might help preserve normal gland during surgery. Though extra capsular dissection offers a better surgical cure, normal gland is preserved with intracapsular dissection

A prolonged postoperative course of steroids also might suppress the adrenal function that will mask a potential recovery of the HPA axis function and also making the postoperative assessment of the HPA axis difficult in those patients who receive supra-physiological doses of steroids.[15]Recently, trials have shown that reduction in the dose of postoperative steroid supplementation is safe and beneficial.[10]

In this study, we identified those patients with a normal pituitary adrenal axis from preoperative serum cortisol levels and a positive Synacthen test and withheld steroids for these patients perioperatively. These patients were monitored closely in the postoperative period both clinically and with daily serum cortisol and electrolytes estimations for 3 days.

MATERIALS AND METHODS

This was a prospective study that included 61 patients who underwent transsphenoidal surgery for pituitary adenomas between June 2020-December 2021 with age <60 years, posted for surgery in the Dept of Neurosurgery, Govt Dharmapuri Medical College. The HPA axis before surgery was assessed based on the protocol as laid down in the guidelines for perioperative steroid replacement by Inder et al16. Based on this protocol patients with 8 am serum cortisol greater than 16 mcg/dl were considered to have a normal HPA axis and did not receive steroid cover during surgery. All patients with preoperative cortisol levels less than 3.6 mcg/dl were excluded from the study. Patients with a serum cortisol between 3.6-16 mcg/dl underwent a Synacthen test and were not given perioperative steroid cover if their HPA axis was normal as determined by this test (rise in cortisol to more than 20 mcg/dl).

If the surgeon was unable to recognize or preserve the adenohypophysis at surgery the patient was given steroid cover postoperatively irrespective of the preoperative integrity of the HPA axis. For the first 3 days after surgery, a serum 8AM cortisol and twice daily serum sodium estimations were done. Postoperatively, the patients were monitored for symptoms of hypocortisolism in the ICU and ward such as nausea, vomiting and tiredness/lethargy. A random cortisol was done whenever hypocortisolism was clinically suspected. Injection hydrocortisone was given if any serum cortisol value was <3.6 mcg/dl. In addition those patients who complained of nausea, vomiting or tiredness had an immediate serum sodium and a cortisol sample drawn and Injection Hydrocortisone was given immediately. Subsequently if the cortisol levels were normal but the sodium value was < 130 mEq/L, the patient was treated as for hyponatremia without continuing steroids.

RESULT

The mean serum cortisol levels preoperatively and on the postoperative days 1,2 and 3 as well as at follow up are shown in Figure 1. The mean preoperative 8am serum cortisol value was 14.77 mcg/dl with a standard deviation (SD) of 6.72. The mean / SD values for the postoperative cortisol levels on days 1,2 and 3 for all the 61 patients were 23.00 / 13.79, 15.68/ 16.38 and 14.96 / 7.32 mcg/dl respectively. It was found there was significant difference between the mean preoperative cortisol and mean cortisol on day 1 ($p=0.04$) suggesting a definite cortisol surge in the immediate postoperative period by 55.7% compared to the preoperative cortisol. The maximum surge of cortisol noticed among the 61 patients was 111%.

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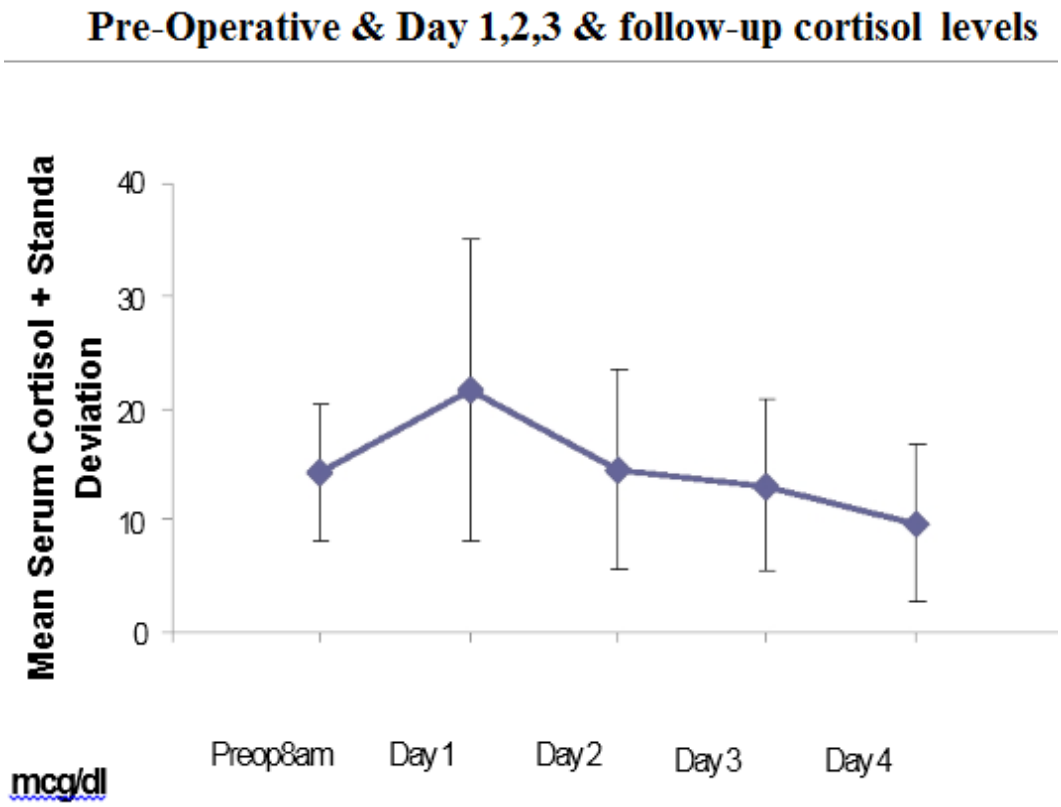

Among the 61 patients, 42 patients (69%) did not have any problem postoperatively and their cortisol levels also remained normal during the first 3 days and were followed up after 3-6 months without steroids. The remaining 19 patients (31%) required steroids. Sixteen of them developed hyponatremia and hence were given steroids. Of the remaining 3 patients, two had a low serum cortisol level, one with a cortisol value 1.88 mcg/dl on day 1 and another with a cortisol value 1.36 mcg/dl on day 2 after surgery and hence were given steroids. One patient developed generalized tiredness and vomiting on Day 3 after surgery with a cortisol level of 9.02 mcg/dl and had no hyponatremia and given steroids. The mean serum cortisol value for the 16 patients who developed hyponatremia (Fig 2) were 19.84, 12.36 and 9.20 mcg/dl respectively on days 1, 2 and 3.

Of the 19 patients who required steroids, 16 patients had developed hyponatremia, 11 patients showed symptoms of hypocortisolemia and 5 patients had a serum cortisol < 3.6 mcg/dl considered as definite hypocortisolemia.

This accounts for the overlap of the number of patients described as a bar graph in Fig2

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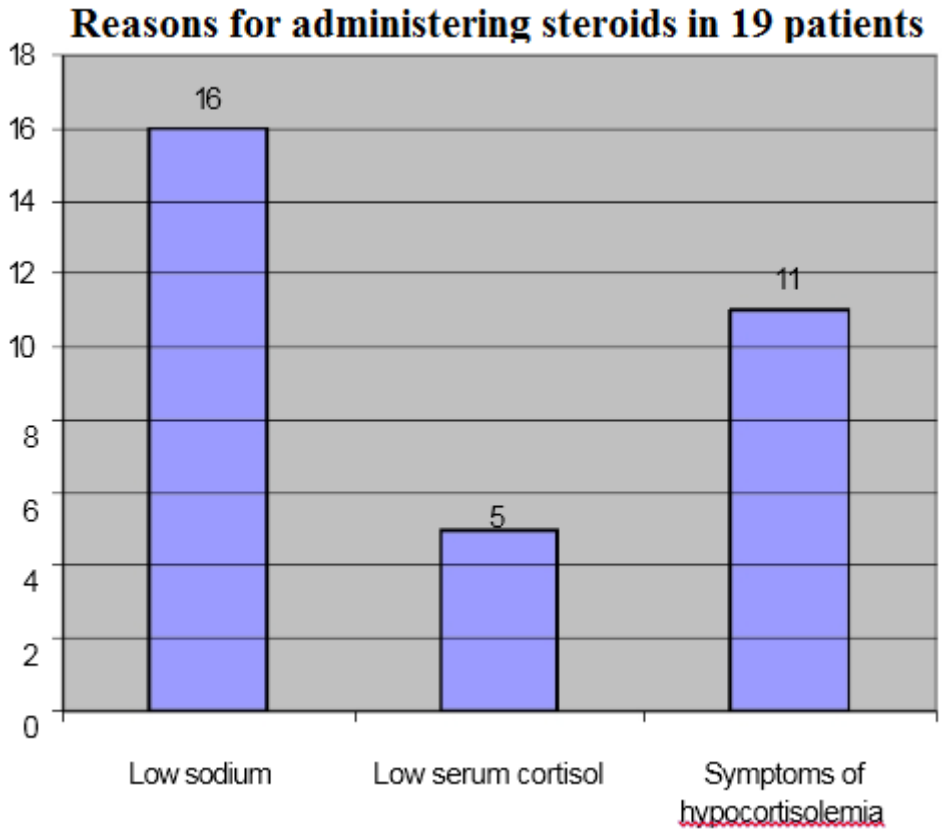

DISCUSSION

The conventional protocol has been to administer high dose steroid cover in the perioperative period for patients undergoing transsphenoidal resection of pituitary adenomas.[1]Udelsman et al[17] had earlier proved that supra-physiological doses of steroids did not offer any significant advantage during the surgical stress in adrenalectomised primates. In a study by Nicholas et al[18] it was shown that a normal immediate postoperative HPA axis would be able to identify patients who will have normal HPA axis function at follow up later. The ability of immediate postoperative cortisol levels >15 mcg/dl (done 60-80 minutes after the surgery) to predict normal HPA axis function in future was assessed by standard analytical methods with a sensitivity of 98% and a positive predictive value of 99%.

In another study, the cortisol level on the morning after surgery in 83 patients undergoing transsphenoidal resection of pituitary adenomas were done and demonstrated that levels ≥ 15 μg/dl are predictive of normal long-term HPA function assessed by a definitive test done 1-3 months later. This estimation of morning cortisol had a sensitivity of 80.5%, specificity of 66.7% and a positive predictive value of 96.9%[19] for assessment of HPA axis on a the long term.

Our findings indicate that 42 out of the 61(69%) patients in whom steroids were withheld perioperatively did not have any problems postoperatively and subsequently at follow up. Nineteen patients required perioperative steroids either due to clinical symptoms,11 patients (58%), hyponatremia, 16 patients (84%) or a serum cortisol<3.6 mcg/dl, 5 patients (26%). (. Five of the 19 patients had definite hypocortisolemia with a cortisol < 3.6 mcg/dl of which 3 developed symptoms and 2 were asymptomatic. 8 other patients had a serum cortisol < 16 mcg/dl but > 3.6 mcg/dl of which 5 patients were symptomatic and also had hyponatremia, 2 had

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hyponatremia alone and one patient had become symptomatic but no hyponatremia. The 2 patients who had a low serum cortisol alone < 3.6 mcg/dl had their tumor size 2cm and 5 cm respectively. Hence the incidence of true hypocortisolemia would include the 5 patients who had a serum cortisol level < 3.6mcg/dl and also the 8 patients who had either developed hyponatremia or clinical features of hypocortisolism with a serum cortisol< 16 mcg/dl. This would amount to a true incidence of 13 patients(21%). Hence the possibilities considered for the hypocortisolemia in these patients postoperatively could be either inadequate preservation of the adenohypophysis or an infarction of the gland postoperatively. The remaining 6 of the 19 patients who had hyponatremia with or without symptoms were able to produce a good cortisol response> 16 mcg/dl and might have benefitted from an evaluation for other causes of hyponatremia as SIADH or a cerebral salt wasting syndrome.

The true incidence of hypocortisolemia from our study was 21% (13 patients) including those who had a definite low serum cortisol<3.6 mcg/dl(5 patients) and those 8 patients with a cortisol<16 mcg/dl but with hyponatremia or became symptomatic. Hence the remaining 6 of 19 patients who required steroids postoperatively with hyponatremia could have been evaluated for other causes and long term steroids prevented.

CONCLUSION

It was observed that there was a 55.7% surge in serum cortisol in the immediate postoperative period. The true incidence of postoperative hypocortisolemia was 8% (5/61 patients).

REFERENCES

1. Clayton RN and Wass JA. “Pituitary Tumor: Recommendations for Service Provision and Guidelines for Management of Patients. Summary of a Consensus Statement of a Working Party from the Endocrinology and Diabetes Committee of the Royal College of Physicians and the Society for Endocrinology in Conjunction with the Research Unit of the Royal College of Physicians.” J R Coll Physicians Lond., 1997. 31(6):628-36
2. Carmel PW. “Surgical Syndromes of the Hypothalamus.” Clin Neurosurg., 27:133-59 1980.
3. Peters LL,, Hoefer MT, and Ben-Jonathan N. “The Posterior Pituitary: Regulation of Anterior Pituitary Prolactin Secretion.” Science., 1981;213(4508):659-61.
4. Cozzi R, Lasio G, Cardia A, Felisati G, Montini M, and Attanasio R. “Perioperative Cortisol Can Predict Hypothalamus-Pituitary-Adrenal Status in Clinically Non-Functioning Pituitary Adenomas.” J Endocrinol Invest., 2009;32(5):460-4
5. Oelkers W. “The Role of High- and Low-Dose Corticotropin Tests in the Diagnosis of Secondary Adrenal Insufficiency.” Eur J Endocrinol, 1998;139(6):567-70
6. Fish HR, Chernow B, and O’Brian JT. “Endocrine and Neurophysiologic Responses of the Pituitary to Insulin-Induced Hypoglycemia: A Review.” Metabolism., 1986;35(8):763-80
7. Stewart PM, Corrie J, Seckl JR, Edwards CR, and Padfield PL. “A Rational Approach for Assessing the Hypothalamo-Pituitary-Adrenal Axis.” Lancet.1988;1(8596):1208-10
8. Grinspoon Sk, and Biller BM. “Clinical Review 62: Laboratory Assessment of Adrenal Insufficiency.” J Clin Endocrinol Metab., 1994;79(4):923-31
9. Tordjman K, Jaffe A, Grazas N, Apter C, and Stern N. “The Role of the Low Dose (1 Microgram) Adrenocorticotropin Test in the Evaluation of Patients with Pituitary Diseases.” J Clin Endocrinol Metab, 1995;80(4):1301-5

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10. Chacko AG, Chacko G, Seshadri MS, and Chandy MJ. "The 'Capsule' of Pituitary Macroadenomas Represents Normal Pituitary Gland: A Histopathological Study." Br J Neurosurg.,2003. 17(3):213-8
11. Lindner G, Funk GC, Schwarz C, Kneidinger N, Kaider A, Schneeweiss B, Kramer L, and Druml W. "Hypernatremia in the Critically Ill Is an Independent Risk Factor for Mortality." Am J Kidney Dis., 2007. 50(6):952-7.
12. Ghaffar A, McGowan B, Tharakan G, Narayan N, Rebecca Cox, and Hatfield E & Meeran K. "Unmasking of Diabetes Insipidus with Steroid Treatment." Endocrine Abstracts, P227-2008.
13. Rajaratnam S, Seshadri MS, Chandy MJ, and Rajshekhar V. "Hydrocortisone Dose and Postoperative Diabetes Insipidus in Patients Undergoing Transsphenoidal Pituitary Surgery: A Prospective Randomized Controlled Study." Br J Neurosurg., 2003. 17(5):437-42
14. García-Luna PP, Leal-Cerro A, Rocha JL, Trujillo F, Garcia-Pesquera F, and Astorga R. "Evaluation of the Pituitary-Adrenal Axis Before, during and after Pituitary Adenomectomy. Is Perioperative Glucocorticoid Therapy Necessary?" Acta Endocrinol (Copenh), 1990. 122(1):83-8
15. Agha A, Liew A, Finucane F, Baker L, O'Kelly P, Tormey W, and Thompson CJ. "Conventional Glucocorticoid Replacement Overtreats Adult Hypopituitary Patients with Partial ACTH Deficiency." Clin Endocrinol (Oxf)., 2004. 60(6):688-93
16. Inder WJ, and Hunt PJ. "Glucocorticoid Replacement in Pituitary Surgery: Guidelines for Perioperative Assessment and Management." J Clin Endocrinol Metab., 2002;87(6):2745-50
17. Jerry V Glowniak, Lyn loriaux D: A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery, 1997; 121(2):123-129.
18. Marko NF, Hamrahian AH, and Weil RJ. "Immediate Postoperative Cortisol Levels Accurately Predict Postoperative Hypothalamic-Pituitary-Adrenal Axis Function after Transsphenoidal Surgery for Pituitary Tumors." Pituitary, 2010;13(3):249-55
19. Marko NF, Gonugunta VA, Hamrahian AH, Usmani A, Mayberg MR, and Weil RJ. "Use of Morning Serum Cortisol Level after Transsphenoidal Resection of Pituitary Adenoma to Predict the Need for Long-Term Glucocorticoid Supplementation." J Neurosurg, 2009;111(3):540-4