Rational use of glucocorticoid during pituitary surgery – A pilot study

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Background & objectives: The conventionally used perioperative glucocorticoid replacement protocol in patients with pituitary tumours is far from optimal. In this study we evaluated the validity of a modified protocol for perioperative glucocorticoid replacement in non-functioning pituitary macroadenomas.

Methods: A total of 24 consecutive patients with non functioning pituitary macroadenomas were included in this interventional study. Patients with a pre-operative 0800 h cortisol of ≥350 nmol/l (≥12.6 µg/dl) did not receive glucocorticoid replacement during perioperative (d-2-d+) period, while those with ≤100 nmol/l (≤3.6 µg/dl) received glucocorticoid replacement. Those patients with 0800 h cortisol value between 100-349 nmol/l (3.6-12.6 µg/dl) required them to undergo an insulin induced hypoglycaemia (IIH). In response to IIH, patients with a peak cortisol of <550 nmol/l (<19.8 µg/dl) received glucocorticoid replacement. Post-operatively, patients on day 3 with 0800 h cortisol of ≤100 nmol/l (≤3.6 µg/dl) received hydrocortisone 10 mg/m² per day; those between >100-449 nmol/l (>3.6-16 µg/dl) received hydrocortisone replacement only if they had symptoms of adrenal insufficiency (AI) or during stress; while patients with ≥450 nmol/l (≥16.0 µg/dl) did not receive any glucocorticoid replacement. Retesting was done at 12 wk in 23 subjects based on the algorithm.

Results: Pre-operatively, 8 (35%) patients were hypocortisolic and received glucocorticoid supplementation, thereby sparing 15 (65%) subjects from glucocorticoid replacement. On d₁ of surgery, 13 (57%) patients were hypocortisolic, but only 6 with serum cortisol of ≤100 nmol/l (≤3.6 µg/dl), had symptoms and were substituted with glucocorticoid. Remaining seven patients, with serum cortisol between >100-349 nmol/l (>3.6-12.6 µg/dl), were asymptomatic and advised glucocorticoid support only during stress but none required. Overall, 17 (74%) patients were spared from unnecessary glucocorticoid support. At 12 wk, 13 (57%) patients were hypocortisolic and only 6 either with serum cortisol level of ≤100 nmol/l (≤3.6 µg/dl) or symptomatic for AI received glucocorticoids. Post-operative complications including diabetes insipidus and CSF leak remarkably decreased.

Interpretation & conclusions: The protocol used was safe and spared unnecessary use of glucocorticoids peri- and post-operatively. However, more number of patients are to be studied to substantiate the validity of this protocol.

Key words Glucocorticoids - nonfunctioning pituitary tumour - pituitary surgery
Non-functioning pituitary adenomas (NFPA) are the most prevalent pituitary macroadenomas comprising about 50-60 per cent of pituitary tumours\(^1,2\). Hypopituitarism in NFPA is considered to be due to compression and destruction of the normal pituitary gland by the expanding mass and focal necrosis due to compression of the portal circulation\(^3\). Amongst the pituitary hormones affected, adrenocorticotropic hormone (ACTH) and thyrotrophic hormone (TSH) deficiency is of great concern and requires optimal replacement therapy prior to and during surgery. Patients who have hypopituitarism pre-operatively may even resume normal pituitary functions including cortisol secretion within 4 h after uncomplicated pituitary adenomectomy, indicating that hypopituitarism in this setting is reversible and largely due to compression of portal vessels\(^4,6\).

Patients undergoing surgical resection for NFPA are frequently given empiric peri- and post-operative glucocorticoid replacement. Most of these traditional replacement schedules markedly overtreat patients. There is no consensus about what is the best replacement glucocorticoid dose, although the majority use hydrocortisone at a dose of 300-400 mg/day in divided doses for initial 2-3 days and later with hydrocortisone 20 mg/m\(^2\) or more extending for a variable period and sometimes up to 12 wk post-operatively\(^7,8\). Normal endogenous cortisol production is only about 10 mg/day\(^9\) suggesting such doses represent over-replacement for many patients, which may have potential adverse effects. The use of such substitution therapy with high doses of glucocorticoids causes hypothalamo-pituitary-adrenal (HPA) axis suppression of these patients, who might otherwise recover their function. As the replacement doses are not ‘physiological’, there remains a real danger of overtreating with potential adverse effects on bone, glucose metabolism, cardiovascular disease, quality of life and mortality\(^7\). We therefore undertook this study to define, validate and recommend a protocol for perioperative glucocorticoid replacement therapy in patients with NFPA.

**Material & Methods**

This prospective interventional study comprised 24 consecutive patients of NFPA admitted at the Postgraduate Institute of Medical Education and Research, Chandigarh, between July 2004 to January 2005. Clinical, biochemical investigations, management, and outcome data were recorded for all patients.

Patients with a pre-operative (0800 h) cortisol of \(\geq 350 \text{ nmol/l} \ (\geq 12.6 \mu g/dl)\) were considered eucortisolic and did not receive any glucocorticoid replacement while those with 0800 h cortisol of \(\leq 100 \text{ nmol/l} \ (\leq 3.6 \mu g/dl)\) received replacement during pre- and day of surgery till second post-operative day (d\(_{0-2}\)). A 0800 h cortisol level of \(>100-349 \text{ nmol/l} \ (>3.6-12.6 \mu g/dl)\) required the patients to undergo an insulin induced hypoglycaemia (IIH). In response to IIH, patients with a value of \(<550 \text{nmol/l} \ (<19.8 \mu g/dl)\) received glucocorticoid replacement therapy. The replacement schedule of hydrocortisone was as: Day 0, 4 mg/h infusion at 0600 h; Day 1, 25 mg 8 h i.v; Day 2, 25 mg i.v. at 0800 h only. On day 3, 0800 h cortisol was estimated in all patients. In patients already on replacement therapy it was estimated after stopping hydrocortisone for 24 h. The algorithm used for steroid replacement is shown in Fig. 1.

**Assessment of HPA-axis:** Insulin induced hypoglycaemia (IIH) was performed pre- and post-operatively at 12 wk post-operatively under supervision,
wherever indicated as per protocol. After an overnight fast, the patient was weighed and an intravenous cannula was inserted into one of the cubital veins at 0800 h. A basal sample was collected and short acting human insulin 0.1 IU/kg body weight (Human Actrapid, NovoNordisk India Private Ltd., Bangalore, India) was given as an intravenous bolus at 0900 h. An adequate hypoglycaemia during an IIH was defined as blood glucose of less than 2.2 mmol/l (40 mg/dl) accompanied by symptoms and signs of hypoglycaemia. Blood samples for cortisol were taken at 0, 30, 60, 90 and 120 min. The blood sample at the point of hypoglycaemia was regarded as the 30 min sample. Capillary glucose was measured by glucose oxidase method by a glucometer. (One Touch, Lifescan, Johnson and Johnson, USA). Cortisol reserve was considered adequate if the serum cortisol increased to ≥550 nmol/l (≥19.8 μg/dl) or more, following hypoglycaemia.

**Anterior pituitary hormones:** Anterior pituitary evaluation was carried out pre-operatively at baseline and at 12 wk post-operatively for all patients. Plasma cortisol was measured using an in-house radioimmunoassay (RIA). The sensitivity of assay was 5 nmol/l with an intra- and interassay coefficient of variation of < 8.5 and <5.7 per cent respectively. T₃ and T₄ were estimated by RIA and TSH by immunoradiometric assay (IRMA) kit supplied by Board of Radiation and Isotope Technology (BRIT, Mumbai, India). LH, estradiol and testosterone were estimated by RIA, while FSH and PRL by IRMA (Radim Pomezia-Rome, Italy).

The following criteria were used to define pituitary hormone deficiency or excess. Secondary hypothyroidism was diagnosed with a T₄ level of <55 ng/ml and low or normal TSH (0.17-4.05 μIU/ml). In males, hypogonadism was defined as serum testosterone level (<9 nmol/l); in pre-menopausal women with serum 17β estradiol levels (<117 pmol/l) with low or normal gonadotropins (<5 IU/l), while in post-menopausal women low or inappropriately normal gonadotropins for age were considered diagnostic. Prolactin levels >15 ng/ml in men and >25 ng/ml in women were considered to be elevated.

**Neuroradiological studies:** This included MRI of hypothalamo-pituitary area at baseline and at 12 wk. Tumour dimensions and presence of any parasellar or suprasellar extension were noted. Tumour volume was calculated by formula of ellipsoid [(volume = saggital x coronal x axial diameters) π /6].

**Post-operative complications:** These included hyponatraemia (serum sodium <130 mEq/l), hyperglycaemia (venous plasma glucose ≥200 mg/dl), cerebrospinal fluid leak and diabetes insipidus (DI). A urine output of 300 ml/h for more than 3 h, urine specific gravity of less than 1005, serum sodium of >140 meq/l and serum osmolality of ≥290 mOsm/kg were taken as criteria for diagnosing diabetes insipidus.

**Surgery:** All patients underwent surgery through transnasal transphenoidal (TSS) approach, by a single surgeon (KKM).

**Statistics:** Statistical analysis was performed using the statistical package for the social sciences (SPSS) for Windows, release 10 (SPSS Inc., Chicago, IL). In descriptive statistics, arithmetic mean, medians, SDs, and SEMs values were evaluated. Results were expressed as mean ± SD unless otherwise specified. A P value of < 0.05 was considered significant. Pearson’s and Spearman’s correlation coefficients were calculated to find out the r values between the quantitative variables.

**Ethics:** The Institute Ethical committee approved the study. A written informed consent was obtained from all the subjects.

**Results**

The study included 24 patients of NFPA (14 men and 10 women) with age range of 26-58 yr. The mean duration of symptoms was 17.3±12.6 months with the range of 1-48 months. The most common symptoms and signs were diminution of vision (100%), headache (74%), optic atrophy (61%) and visual field defects (57%). Atypical presentation included hyponatraemic encephalopathy (1) and stroke (1). The mean tumour volume was 15,000±9,000 mm³. Pre-operatively, 8 patients had hypothyroidism and 10 hypogonadal and were treated with optimal hormone replacement therapy. Post-operatively, 10 patients were hypogonadal and 4 were hypothyroid requiring replacement of respective hormones. Serum prolactin was normal in all patients (14.47 ± 7.81 ng/l/ml). At three month of the study hormonal data and imaging were available in 23 out of 24 patients, as one patient died of undefined cause on d27 of the surgery at home.

Pre-operatively 15 out of 23 (65%) patients were euocortisolic and had a 0800 h serum cortisol of ≥350 nmol/l (≥12.6 μg/dl). Of the remaining 8 patients, 4 had 0800 h serum cortisol between >100-349 nmol/l (3.6 - 12.6 μg/dl) and serum cortisol in these patients did not rise to ≥550 nmol/l (≥19.8 μg/dl) after IIH.
Remaining four patients had 0800 h serum cortisol of 
$\leq$100 nmol/l ($\leq$3.6 µg/dl) and all these eight patients 
who were hypocortisolic received glucocorticoid 
replacement during the surgery. Therefore, 15 (65%) 
out of 23 patients were spared from receiving 
unnecessary glucocorticoid replacement.

On d1 post-operatively, 0800 h serum cortisol levels 
were reassessed and a value of $\geq$450 nmol/l ($\geq$16.2 µg/ 
dl) was defined as eucortisolaemia. Overall 10 patients 
were eucortisolic and 13 were hypocortisolic on d1 of 
the surgery. Of the 15 patients who were eucortisolic 
pre-operatively, seven became hypocortisolic, while 8 
who were hypocortisolic pre-operatively, six continued 
to remain hypocortisolic and 2 of them became 
eucortisolic. Therefore, on d1 in total 13 out 23 were 
hypocortisolic. Interestingly, of these 13 patients who 
were hypocortisolic, only six had symptoms and signs 
of adrenocortical insufficiency and all these 6 patients had a 0800 h serum cortisol of $\leq$100 nmol/l ($\leq$3.6 µg/dl) 
and received glucocorticoid replacement. While 
remaining 7 patients in hypocortisolic group, who had 
serum cortisol between $>$100-449 nmol/l ($>$3.6-16 µg/dl) 
were asymptomatic and given glucocorticoid support 
only with appearance of symptoms or during stress. 
However, none of them required glucocorticoid support 
during their hospital stay and subsequent follow up up to 12 wk. Therefore, 17 (74%) patients were spared from 
receiving glucocorticoid support till 12th wk.

At 12 wk post-operatively, 10 patients were 
eucortisolic and 13 were hypocortisolic. However, one 
patient each from eucortisolic and hypocortisolic group 
became hypocortisolic and eucortisolic respectively. Of 
these 13 patients who were hypocortisolic, 5 had a serum 
cortisol level of $\leq$100 nmol/l ($\leq$3.6 µg/dl), irrespective 
of symptoms of adrenal insufficiency received 
received glucocorticoid support. The remaining 8 patients had a 
serum cortisol between $>$100-349 nmol/l ($>$3.6-12.6 µg/dl) 
and were subjected to IIH and none of them qualified 
$\geq$550 nmol/l ($\geq$19.8 µg/dl) test. Only one of these 8 
patients had symptoms of adrenal insufficiency and 
received glucocorticoid support, while remaining seven 
patients were advised glucocorticoid support only 
during stress. Overall, 17 (74%) patients were spared from 
unnecessary glucocorticoid support. A strong 
correlation was observed between d1 and 12th wk 0800 h 
cortisol levels ($r$, 0.74; $P < 0.01$) and d1 cortisol levels 
predicted the integrity of HPA axis at 12 wk. Outcome 
analysis of these patients are shown in Fig. 2.

Post-operative complications included 
cerebrospinal fluid (CSF) leak in 9 patients (39%),

cerebrospinal fluid (CSF) leak in 9 patients (39%),

transient diabetes insipidus in 6 (26%), hyperglycaemia 
3 (13%) and hyponatraemia in one (4%). No patient 
developed permanent DI, meningitis, and new onset 
visual deterioration.

Discussion

The treatment strategy of NFPA is aimed at excision 
of the tumour and preservation of residual pituitary 
functions. In the present study, with a defined protocol 
pre-, peri- ($d_0$-$d_2$) and post-operatively (12 wk) 65, 74 
and 74 per cent patients respectively were saved from 
unnecessary glucocorticoid replacement. This also 
translated into lesser rate of post-operative 
complications including diabetes insipidus, 
hyponatraemia and hyperglycaemia.

Several authors$^{14,15}$ observed that in patients with 
intact pre-operative HPA-axis and in whom selective 
adnectomy is possible, peri-operative 
glucocorticoid replacement is not necessary. In fact, it 
is well accepted that a morning cortisol of more than 
350 nmol/l (12.6 µg/dl) is predictive of a peak cortisol 
response of more than 550 nmol/l (19.8 µg/dl) in 
response to IIH in majority of the patients$^8$. On the 
contrary, patients with a 0800 h cortisol of $< 100$ nmol/ 
l ($<3.6$ µg/dl) will invariably fail to pass the IIH and
will require glucocorticoid replacement. However, patients with 0800 h cortisol between >100 and <350 nmol/l (>3.6-12.6 µg/dl) will need an HPA-axis evaluation and possible replacement as required depending upon the cortisol response. In this study, pre-operatively 4 patients and post-operatively at 12th wk 8 patients had a 0800 h cortisol between 100-349 nmol/l (3.6-12.6 µg/dl) and none could qualify the IIH supporting the validity of 0800 h cortisol of ≥350 nmol/l (> 12.6 µg/dl) as a predictor of adequacy of adrenocortical reserve. We preferred assessment of adrenocortical reserve in response to IIH rather than with low dose (1µg) synacthene test, as IIH is a 'gold standard' and best correlates with surgical stress and none of our patients had any complications related to it. However, low dose (1µg) synacthene test is convenient but yet to be validated in large cohort of patients. Using this approach, we observed that pre-and peri-operatively only 8 (34.8%) patients required glucocorticoid supplementation.

Post-operatively glucocorticoid replacement is based on the levels of 0800 h cortisol on day 1-7. The measurement should be done on d1-3 in patients not treated with glucocorticoid per-operatively and d 6-7 in those treated with glucocorticoids for initial 48 h. Therefore, multiple sampling for cortisol measurement may be more predictive of adrenocortical reserve. Watts et al reported a basal cortisol of <80 nmol/l, (2.8 µg/dl), 3 to 4 days after pituitary surgery as indicative of ACTH deficiency. Courtney et al observed that in the immediate post-operative state, patients with 0800 h cortisol of ≥450 nmol/l (≥16 µg/dl) have an extremely low risk of adrenal insufficiency with no need of retesting. This higher post-operative cut-off level of 450 nmol/l (16 µg/dl) defines an intact HPA axis (compared to preoperative cut-off of >350 nmol/l (>12.6 µg/dl) and is likely due to increased post-operative stress. However, patients with cortisol levels between >100 and <450 nmol/l (<3.6-16 µg/dl) are likely to be ACTH deficient and should be treated if symptoms of adrenal insufficiency appear or during stress until definitive testing of the HPA-axis is performed. Using this approach, post-operatively at day 3, we noted that only 6 (26%) patients required steroid supplementation and all had symptoms of adrenal insufficiency with a serum cortisol of ≤100 nmol/l (≤3.6 µg/dl). However, 7 patients who were eucortisolic pre-operatively and became hypocortisolic post-operatively, but could not be diagnosed hypocortisolic as sample for cortisol measurement was taken on d1. Therefore, those who do not receive glucocorticoid pre-operatively should be assessed on d3 post-operatively. At 12th wk, only 6 patients received glucocorticoid therapy, sparing 17 (74%) patients from unnecessary glucocorticoid replacement.

It has been observed by others as well as by us that there is a poor correlation between symptoms and signs of adrenal insufficiency and circulating cortisol levels. In our study, out of 8 patients who had serum cortisol of ≤ 100 nmol/l, only 5 had symptoms of adrenal insufficiency, while among 5 patients with cortisol levels between >100-349 nmol/l (>3.6-16 µg/dl), only one was symptomatic. A strong correlation (r, 0.74; P <0.001) was observed between d3 and 12th wk 0800h cortisol thereby, indicating that d3, 0800 h cortisol levels predict the subsequent integrity of HPA-axis. We also correlated the pre- and post-operative cortisol status with age, sex, duration of symptoms and percentage tumour volume reduction. There was no significant contribution by any of these parameters. However, patients who had relatively longer duration of symptoms and larger tumour volume were pre-operatively hypocortisolic. It is possible that their hypocortisolic state is related to prolonged compression and irreversible damage to the corticotrophs.

A variety of complications have been reported after transsphenoidal surgery (TSS). The prevalence of transient DI after TSS in various studies was reported as 10-66 per cent and permanent DI 0.4-15 per cent. CSF leak has been reported in 14 percent of patients with macroadenoma and it has been correlated with DI in patients undergoing transsphenoidal surgery. Transient DI was seen in 26 per cent of our patients, and half of them had concurrent CSF leak. This is reasonably acceptable with such a large tumour volume (15000 ± 9000 mm³). In one study, the incidence of DI was 52 per cent with conventional hydrocortisone doses, and with low dose protocol it decreased to 24 per cent, thereby decreasing the incidence by 46 per cent. The relatively low prevalence of DI in our study is probably explicited by the judicious use of steroid supplementation. One patient had hyponatraemia which is similar to a previous study. None of the patients developed permanent DI, meningitis or septal perforation. Our observations confirm previously published work by Rajarathnam et al who had shown that patients with normal pre-operative cortisol values mount a normal cortisol response intra-operatively during transsphenoidal pituitary surgery and have lesser complications.

We conclude that the protocol used for steroid replacement in this study was safe and effective. Day 3
morning cortisol predicts the subsequent integrity of HPA axis. However, more number of patients with a control group and postoperatively frequent sampling for cortisol is required to substantiate the validity of this protocol.

References


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