

## **Prediction of adrenocortical insufficiency after pituitary adenoma surgery using postoperative basal cortisol levels**

Václav Hána jr.<sup>1</sup>, Jana Ježková<sup>1</sup>, Mikuláš Kosák<sup>1</sup>, Michal Kršek<sup>1</sup>, Josef Marek<sup>1</sup>, David Netuka<sup>2</sup>, Martin Hill<sup>3</sup>, Václav Hána<sup>1</sup>

<sup>1</sup>3rd Department of Internal Medicine, General University Hospital and 1st Faculty of Medicine, Charles University, U Nemocnice 1, Prague 2, 128 08, Czech Republic

<sup>2</sup>Department of Neurosurgery, Central Military Hospital, 1st Faculty of Medicine, Charles University, U Vojenské Nemocnice 1, 162 00, Prague 6, Czech Republic

<sup>3</sup>Steroid Hormone Unit, Institute of Endocrinology, Národní 8/139, 113 94, Prague 1, Czech Republic

### **Corresponding author:**

Václav Hána jr.  
3rd Department of Internal Medicine, General University Hospital and 1st Faculty of Medicine, Charles University, U Nemocnice 1, Prague 2, 128 08, Czech Republic  
Email: vaczech@gmail.com  
Telephone: 00420 224962919  
Fax: 00420 224919780

## Summary

**PURPOSE:** Our aim was to analyze the correlation of early postoperative cortisol levels in patients after transsphenoidal pituitary adenoma surgery compared to the standard dose ACTH test and Insulin tolerance test (ITT) several months later.

**METHODS:** We retrospectively reviewed data from 94 patients operated for pituitary adenoma in years 2009 - 2012. The comparison of day 7 (median) postoperative basal cortisol levels and 3,6 months (median) after pituitary adenoma surgery stimulation test - standard dose 250 µg1-24ACTH test in 83 patients or ITT in 11 patients were performed.

**RESULTS:** All 16 patients with early postoperative cortisol levels >500 nmol/l proved a sufficient response in the stimulation tests. At basal cortisol levels of 370-500 nmol/l the sufficient response was found in 96% (27/28) of patients. In the postoperative basal cortisol levels 200-370 nmol/l we found a preserved corticotroph axis later on in 88% (28/32) of cases. Patients with basal cortisol levels 100-200 nmol/l had a maintained corticotroph axis function in 8/11 cases – 73%.

**CONCLUSIONS:** All patients with an early postoperative basal cortisol level above 500 nmol/l proved in the stimulation tests a preserved corticotroph axis function. The interval 370-500 nmol/l showed a minimal risk of postoperative adrenal insufficiency.

**Keywords:** adrenal insufficiency, hypocorticalism, pituitary adenoma, surgery, ACTH test

## **Introduction**

One of the key procedures in the postoperative care for patients after a pituitary tumor surgery is the decision to continue with glucocorticoid replacement therapy. There have been consistent data showing that patients with basal cortisol levels under 100 nmol/l show up as glucocorticoid insufficient with a need for lifelong glucocorticoid replacement. On the other hand patients with basal cortisol levels above 500 nmol/l (400-500 from different authors) prove in stimulation tests a preserved hypothalamo-pituitary-adrenal (HPA) axis function (Courtney *et al.* 2000)(Klose *et al.* 2005)(Jayasena *et al.* 2009). The remaining group of patients with postoperative cortisol levels between 100 and 400 - 500 nmol/l has to be evaluated.

Many possible tests have been advised to assess the postoperative adrenal function. An Insulin tolerance test (ITT) has long been considered as a gold standard for testing HPA axis function, but a more practical alternative, a short ACTH test is getting more popular for its simplicity, fewer contraindications, price (in countries with a high staff labor price). The ACTH test has also shown a good correlation with the ITT (Stewart *et al.* 1988). There is still a debate about the dose of ACTH used with reasonable arguments for both alternatives - 1 and 250 µg (Agha *et al.* 2006)(Abdu *et al.* 1999)(Tordjman *et al.* 2000). Other tests such as metyrapone or glucagon tests were also tested for the diagnosis of secondary adrenal insufficiency, but do not play a major role in most of the endocrinology departments (Inder and Hunt 2002). Other methods for postoperative HPA axis function evaluation have been suggested such as pre- and postoperative basal cortisol index (Zada *et al.* 2012) or DHEA, DHEA-S levels after a low dose ACTH test (Sayyed Kassem *et al.* 2012).

Concerning the time of definitive testing it has been shown that using the ACTH test, HPA axis can be reliably tested from 1-3months postoperatively (Klose *et al.* 2005)(Inder and Hunt 2002). Up to this time the ITT, metyrapone or glucagon tests are proposed as the test of choice. In some patients due to an early testing a HPA axis recovery in later period could be underestimated (Inder and Hunt 2002).

## **Patients and Methods**

From all patients with pituitary adenomas operated between 1.1.2009 – 31.12.2012 in the Dept. of Neurosurgery, Central Military Hospital, 1st Medical Faculty, Charles University and treated in the 3<sup>rd</sup> Dept. of Internal Medicine, General

University Hospital in Prague medical records were retrospectively analysed. A group of 94 patients (Table 1), where a postoperative HPA axis stimulation test – ACTH test or ITT was performed, was selected and analysed. This group included patients with non-functioning pituitary adenomas, GH producing adenomas, prolactinomas. Very few patients with basal cortisol repeatedly below 100 nmol/l or above 500 nmol/l were included in the analysis, because in these groups the stimulation test is not routinely performed and so we included only several, where we did the stimulation testing. Besides the patients with Cushing disease, also those who were reoperated were excluded.

HPA axis is not routinely preoperatively evaluated by dynamic testing, because pituitary function is expected to be changed by operation and patients are covered during the pituitary surgery and postoperatively with corticosteroids anyway. Only those with very low morning cortisol levels and/or with clinical symptoms of hypocortisolism are preoperatively replaced with hydrocortison without dynamic testing of HPA axis. Under such conditions 9 patients were preoperatively replaced with hydrocortisone. Based on low basal free T4 levels and inappropriately low TSH had preoperatively 22/94 patients secondary hypothyroidism. Secondary hypogonadism (using total testosterone and gonadotropins) was diagnosed preoperatively in 31/49 males; premenopausal women were hypogonadal in 6 out of 15 (evaluation of gonadal axis in postmenopausal women is not accurate). Patients had an adequate replacement with thyroid hormone pre and postoperatively, if necessary. None of the patients received contraceptives or estrogen substitution therapy during the analysed period.

All patients underwent an endonasal endoscopic adenectomy with a standard postoperative hydrocortisone replacement. After the operation a hormonal testing was done including basal cortisol level on day 7 (6, 8; expressed as median with quartiles) at 7 am, with a withdrawal of hydrocortisone replacement at least 13 hours before the blood test was done. In patients with repeated basal cortisol level >500 nmol/l the hydrocortisone treatment was omitted, in the rest the hydrocortisone replacement was continued in a replacement dose 15 - 20 mg/day with an increase during stress and exercise up to the definitive testing a few months later. All subjects were followed in an outpatient department and their adrenocortical function was tested after 3,6 months (64, 220 days; expressed as median with quartiles). For the HPA axis evaluation a standard 250 µg dose ACTH test in 83 patients and ITT in 11 patients was performed.

Using the ACTH test a 250 µg 1-24 ACTH(Synacthen®) was administered intravenously with a 30 and 60 minute plasma cortisol measurement. In the evaluation of sufficiency the higher value of these two was used. In the ITT a dose of 0.1 - 0.2 IU/kg rapid acting insulin was administered intravenously and hypoglycaemia <2,2 mmol/l was reached. 30,60,90

minutes samples were taken. The highest cortisol level was used. In both tests a cortisol cut-off level of 500 nmol/l after stimulation was set as a level for HPA axis sufficiency.

Analytical method used for cortisol measurement was ADVIA Centaur Cortisol assay - a competitive immunoassay using direct chemiluminiscentmethod. Interassay CV =3.07%, intraassay CV=2.89%. Analytical sensitivity = 27.6 nmol/l.

The differences between basal and stimulated cortisol levels for ITT and ACTH tests were evaluated using a repeated measures ANOVA model consisting of subject factor separating inter-individual variability, between-subject Factor test (ITT vs. ACTH test), within-subject factor Stimulation (basal vs. stimulation) and Factor  $\times$  Stimulation interaction. The original data were transformed to attain symmetry and constant variance by a Box-Cox transformation.

## Results

All 16 patients with early postoperative cortisol levels  $>500$  nmol/l proved a sufficient response in the stimulation tests. 78 out of 94 patients had a postoperative basal cortisol levels  $<500$  nmol/l (Fig. 1). From these 78 patients only 13 patients (17%) showed insufficient response ( $<500$  nmol/l) during the stimulation test a few months later. 10 patients were tested by the short ACTH test and 3 patients by ITT.

In the group with basal cortisol levels  $<100$  nmol/l only 2 out of 7 patients had a sufficient HPA axis function after the stimulation (all had ACTH test, with insufficient maximal stimulated cortisol levels 202, 278, 386, 447, 480 nmol/l, respectively).

With basal cortisol levels 100-200 nmol/l a maintained HPA axis function was demonstrated in 8 out of 11 patients – 73% (6/8 in ACTH test and 2/3 in ITT). The insufficient maximal cortisol responses after the stimulation were 190, 366, 469 nmol/l, respectively.

Then a group of patients with basal cortisol levels 200 - 370 nmol/l was selected due to the distribution of the results (Fig. 1). In this cohort 88% of patients had a sufficient HPA axis testing (25/27 tested by ACTH test and 3/5 by the ITT) with insufficient maximal stimulated cortisol values: 354, 435, 454, 479 nmol/l, respectively.

In the group with basal cortisol levels 370-500 nmol/l 27/28 patients - 96% had sufficient response (24/25 in the ACTH test, 3/3 in ITT). The only one patient had a basal cortisol level 494 nmol/l and maximal response of 465 nmol/l (60 minute) in the ACTH test.

From the 9 patients with corticosteroid replacement preoperatively 7 had normal HPA axis function postoperatively and 2 had adrenal insufficiency after the operation. Apart from these, there were 11 patients with newly diagnosed adrenal insufficiency after the operation.

The ANOVA model demonstrated significant differences between basal and stimulated values as expected and significantly higher maximum levels in ACTH test when compared with ITT.

## **Discussion**

In the postoperative period after pituitary surgery an evaluation of pituitary axes plays an important role. The key and potentially life saving is the management of the HPA axis function. From the clinicians' point of view, a basal cortisol level is the earliest and only measure to assess the HPA axis function in the early postoperative period. It has neither high specificity nor sensitivity for the diagnosis of adrenal insufficiency in all patients, but showed a good prognostic value in the marginal groups.

It has been repeatedly noted that basal cortisol levels postoperatively < 80-111 nmol/l are highly indicative of adrenal insufficiency (Courtney *et al.* 2000)(Jayasena *et al.* 2009)(Inder and Hunt 2002)(Karaca *et al.* 2010)(Watts and Tindall 1988). On the other side of scale a sufficient level of basal cortisol permitting a safe withdrawal of hydrocortison substitution showed more variation, 450 nmol/l (Courtney *et al.* 2000)(Inder and Hunt 2002), 400 nmol/l (Klose *et al.* 2005), 392 nmol/l (Jayasena *et al.* 2009). In our conditions the basal cortisol level with 100% specificity for detecting only adrenal insufficient patients is 82 nmol/l, whereas 100% specificity for adrenal sufficiency would be 495 nmol/l. This higher result compared with other publications is distorted by only one patient with basal cortisol 494 nmol/l and stimulated 465 nmol/l. Without this exceptional patient a more statistically powerful cut-off level of basal cortisol would be 370 nmol/l under which stand all the other subjects with adrenal insufficiency and which would be more in agreement with previous

works. In these two groups with highly probable HPA axis insufficiency and sufficiency respectively, no further stimulation tests would technically be necessary in most of these patients. This cannot be applied absolutely, because rarely a delayed adrenal insufficiency was published (Gleeson *et al.* 2003).

The remaining group with uncertain basal cortisol levels needs to have a stimulation test. Some authors divide this group in two subgroups according to the need of permanent glucocorticoid substitution or only stress period glucocorticoid administration up to the definitive HPA axis testing (Courtney *et al.* 2000)(Khan *et al.* 2011). They suggest a safe level for withdrawal of permanent corticosteroid replacement early after surgery when a basal cortisol level is higher than 250, or 276 nmol/l, respectively (Courtney *et al.* 2000)(Khan *et al.* 2011). Using such criteria Khan *et al.* presented in their cohort, that HPA axis insufficiency in the dynamic testing was not uncommon in a group of patients with “sufficient” postoperative day-3 basal cortisol level (11 out of 46 patients). Nevertheless only two of these patients had long term regular cortisol replacement (Khan *et al.* 2011). The subgroup of patients without replacement and finally with proved adrenocortical insufficiency might be from our point of view endangered by hypocortical state in a case of serious stress (infection, trauma, surgery etc.). We prefer to use the glucocorticoid replacement in all of these patients with the aim to minimalise the risk of clinically serious hypocorticalism, but we use lower replacement doses than mentioned in the study of Khan *et al.*, where authors used supraphysiological doses of hydrocortisone 30 mg daily in a significant number of patients (Khan *et al.* 2011). Our clinical experience is that using currently usual replacement doses 15 – 20 mg of hydrocortisone per day, the dosage based on pharmacokinetic studies (Mah *et al.* 2004), does not cause any side effects when used for a short period till the stimulation test.

The ACTH test has shown a good correlation with the ITT (Stewart *et al.* 1988). However, in the postoperative time the ACTH test could underestimate the adrenal insufficiency due to a maintained sensitivity of adrenal cortex to direct adrenal stimulation in the ACTH test shortly after a pituitary insult. Thus the definitive testing should not be done earlier than 1- 3 months postoperatively (Klose *et al.* 2005)(Inder and Hunt 2002). In our study a part of the group had an ITT but from the statistical point of view the group was too small to make a statistically significant conclusion only from the ITT. The majority of the patients had an ACTH test because of its simplicity, low limitations, good accessibility of 1-24ACTH. We used a 250 µg ACTH stimulation test, which is widely accepted and its utility was confirmed in many studies (Agha *et al.* 2006)(Abdu *et al.* 1999)(Tordjman *et al.* 2000). This test avoids the risk of error after an inaccurate dilution, which is stressed by critics of the 1µg ACTH test. We used a cut off level for the ACTH test of 500 nmol/l which is in correlation with other published studies and recommended cut off levels and in our experience reflects the clinical outcome in our

patients. The higher stimulated cortisol levels for ACTH test described by the statistical analysis may be ascribed to the unrandomised selection of patients for each test, where ITT has several limitations as described above.

In conclusion a basal cortisol level measurement reliably predicts a maintained HPA axis function in all patients with cortisol levels above 500 nmol/l allowing a withdrawal of hydrocortisone replacement therapy. In patients with cortisol levels 370 – 500 nmol/l there is a very high probability of maintained HPA axis function. In this group in clinically selected cases the regular continuation of hydrocortisone replacement probably might be used only in stressful situations and the later stimulation testing is necessary. Basal cortisol levels under 370 nmol/l require a hydrocortisone treatment up to the definitive testing a few months later. In patients with basal cortisol under 100 nmol/l postoperatively there is a high probability of adrenal insufficiency subsequently, but in individual cases a restitution of HPA axis can appear.

The experiments comply with the current laws of the country in which they were performed.

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**Table 1** –Group characteristics

	Total	NF	GH	PRL
n	94	61	29	4
Age (years)	53.3±30.2	57.7±28.8	46.2±26.8	36.2±10.6
Men/Women	49/45	31/30	16/13	2/2
Postoperative adrenal insufficiency	13	12	0	1

NF- non-functioning adenoma, GH - growth hormone producing adenoma, PRL – prolactinoma; age shown as mean±2SD

**Figure legends:**

**Fig.1** Postoperative basal cortisol level (median day 7, range 6-8) v.s. peak serum cortisol in the stimulation test (median 3.6 months after surgery); O – ACTH test, ▲ – Insulin tolerance test

**Figure 1**

