Early Basal Cortisol Level as a Predictor of Hypothalamic-Pituitary-Adrenal (HPA) Axis Function After Pituitary Tumor Surgery

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Source / Izvornik: **Experimental and Clinical Endocrinology & Diabetes, 2020, 128, 709 - 714**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1055/a-0885-1568

Title: EARLY BASAL CORTISOL LEVEL AS A PREDICTOR OF HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS FUNCTION AFTER PITUITARY TUMOR SURGERY

Short running title: BASAL CORTISOL AS A PREDICTOR OF HPA-AXIS

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Abstract

PURPOSE: The purpose of this study was to evaluate the clinical relevance of the early postoperative basal cortisol level in assessing the postoperative hypothalamic-pituitary-adrenal (HPA) axis function after pituitary tumor surgery.

METHODS: We performed a prospective observational study that enrolled 83 patients operated for pituitary adenoma or other sellar lesions at the University Hospital Center Zagreb between December 2013 and April 2017 (44 nonfunctioning pituitary adenomas, 28 somatotropinomas, 5 craniopharyngiomas, 2 prolactinomas resistant to medical therapy and 4 other lesions - Rathke's cleft cyst, arachnoid cyst, chondroma and gangliocytoma). Exclusion criteria were Cushing's disease, chronic therapy with glucocorticoids prior to surgery and preoperative adrenal insufficiency. Early postoperative basal cortisol levels (measured on the second postoperative day) and the Synacthen stimulation test (performed 3 months after the surgery with the peak cortisol level of >500 nmol/L considered as a normal response) were analyzed to assess HPA axis function during follow-up.

RESULTS: ROC analysis showed a cut-off of the basal cortisol level of ≥300 nmol/L measured on the second postoperative day to predict normal postoperative HPA axis function with the sensitivity of 92.31%, specificity of 87.14 % and positive predictive value of 57.14 %.

CONCLUSION: The basal cortisol level on the second postoperative day is a valuable tool to predict integrity of the HPA axis after pituitary tumor surgery. Our data suggest that the cortisol level of ≥300 nmol/L accurately predicts adrenal sufficiency and that in these patients glucocorticoid therapy can be withdrawn.

Keywords: hypocortisolism, glucocorticoid replacement, transsphenoidal, transcranial surgery

Introduction

Secondary adrenal insufficiency (AI) is a well-known complication after hypothalamic-pituitary surgery with the prevalence ranging from less than 10% to up to 90% after craniopharyngioma surgery [1-7]. Historically, many centers have routinely administered postoperative glucocorticoid therapy to avoid potential complications of AI. This practice might result in unnecessary treatment of some patients with the normal HPA axis function.

The HPA axis integrity can be assessed using different tests. The gold standard in the assessment is the insulin tolerance test (ITT), but this method may be inconvenient to perform due to potential danger of hypoglycaemia [8-9]. Furthermore, standard-dose and low-dose Synacthen tests (LST) are unreliable and should not be used in the early postoperative period as they depend on the secondary adrenal atrophy that takes at least 3-4 weeks to develop following ACTH deficiency [7, 10-12]. Other dynamic tests for HPA axis evaluation like metyrapone, glucagone and CRH tests are not well standardized in the early postoperative setting [11, 13-15]. This is why, based on numerous studies, the measurement of basal cortisol as a marker of the HPA axis function in the immediate postoperative period is recommended [1-3, 10-11, 15-30].

There are many factors influencing the variability in the serum cortisol threshold to predict AI such as the incidence of postoperative AI in each center, expertise of the team taking care of the patient after surgery, extent of the surgery, postoperative course, cortisol assay differences as well as individual variability in the stress reaction of the HPA axis [3, 8, 10, 18, 31-34].

It is widely accepted that standard maintenance of glucocorticoids is necessary in patients with the morning cortisol concentration of <100 nmol/L in the early postoperative period since they are at high risk of AI [16, 30]. Furthermore, it has been suggested by some investigators that it is safe to withhold routine glucocorticoid replacement in patients with postoperative morning serum cortisol of >250 nmol/L until provocative testing of the HPA axis is performed [3, 10, 21]. However, other investigators have suggested that adrenal sufficiency is predicted by postoperative morning serum cortisol thresholds of as much as >400 nmol/L [1-2, 11, 16, 22, 28-29].

The aim of this study was to investigate the reliability of the basal cortisol concentration on the second postoperative day in predicting AI as well as to determine the cortisol cut-off value to predict normal HPA axis function.

Patients and Methods

This single-center, prospective, observational study enrolled 83 patients operated for pituitary adenoma or other sellar lesions at the University Hospital Center Zagreb between December 2013 and April 2017. Exclusion criteria were Cushing's disease, chronic therapy with glucocorticoids prior to surgery and preoperative AI.

The morning serum cortisol level was measured on the second day after pituitary surgery. All the patients received hydrocortisone 100 mg intravenously (before anesthesia induction) prior to surgery, 50 mg 6 hours after the surgery, and again 100 mg on the morning of the first postoperative day. Hydrocortisone replacement was stopped 24 hours before the measurement of serum cortisol.

Patients with early morning cortisol of <250 nmol/L were assumed to have secondary AI and they continued with glucocorticoid replacement (hydrocortisone 10 mg AM and 5 mg midafternoon) until dynamic testing of the integrity of the HPA axis was carried out. Glucocorticoid replacement was discontinued if the morning cortisol was of ≥250 nmol/L. The retesting of the HPA axis with LST was performed in all the patients three months after the pituitary surgery.

LST was performed by administering 1 ug Synacthen intravenously. Synacthen 250 ug (Novartis) was diluted in the sterile 0.9 % saline solution to a concentration of 1 ug/ml and injected immediately. Samples for serum cortisol were obtained at 20 and 30 minutes following injection. A peak cortisol of 500 nmol/L was considered a sufficient cortisol response to indicate an intact HPA axis. Serum cortisol was measured by electrochemiluminescence immunoassay (Roche).

Function of other pituitary axes was evaluated before and 3 months after pituitary surgery. Secondary hypogonadism in males was diagnosed if the patient had low testosterone in the context of either normal or low gonadotrophin levels. Females with amenorrhea and/or infertility and low or low normal gonadotrophins as well as postmenopausal women with inappropriate levels of FSH and LH were considered to have secondary hypogonadism. Secondary hypothyroidism was diagnosed in the presence of a low free T4 alongside with low/normal TSH. GH secretion was evaluated by ITT and IGF-1 measurement, but only in minority of patients in whom GH replacement treatment was considered. Diabetes insipidus was diagnosed by serum sodium >143 mmol/L and serum osmolality >300 mOsm/kg in combination with urine output >3 L/day and urine osmolality <300 mOsm/kg.

Statistical analysis was conducted using SPSS 21.0 (SPSS, Chicago, IL, USA), and $p<0.05$ was considered to be significant. The data were analyzed by descriptive statistics. Quantitative results are presented as the median (range, minimum-maximum). The Wilcoxon signed rank tests were performed for paired nonparametric data, and the Mann-Whitney U test for independent nonparametric data. Multiple logistic regression analysis was used to identify possible predictors of AI. Receiver operating characteristic (ROC) curves were used to determine diagnostic accuracy, sensitivity and specificity.

McNemar's test was used for the comparison of proportions for paired samples and Fisher's exact test was applied for independent samples.

Results

The study group comprised 83 patients (median age 58 years, range 22-82), of which 35 (42.2%) were males and 48 (57.8%) were females. There were 44 nonfunctioning adenomas (53%), 28 somatotropinomas (33.7%), 2 prolactinomas resistant to medical therapy (2.4%), 5 craniopharyngiomas (6%), and 4 other sellar lesions (4.8%) - Rathke's cleft cyst, arachnoid cyst, chondroma and gangliocytoma. Among the 83 patients, 73 (88%) had sellar lesions ≥10 mm, and 10 (12%) had lesions <10 mm. Concerning the surgical approach, 77 patients (92.8%) were operated transsphenoidally and 6 patients (7.2%) were operated transcranially. Among the 6 transcranially operated patients, three had pituitary macroadenomas and three had craniopharyngiomas. Data on preoperative and postoperative pituitary axes deficiencies are presented in Table 1.

Relationships between tumor/patients' clinical characteristics, early postoperative cortisol levels and the prevalence of AI three months after the surgery are shown in Table 2. Patients with sellar lesions smaller than 10 mm in diameter had significantly higher basal postoperative cortisol levels in comparison to the patients with lesions larger than 10 mm ($p=0.007$). None of the patients with lesions <10 mm had AI three months after the pituitary surgery. The incidence of AI after the surgery was significantly higher in patients with craniopharyngiomas ($p=0.026$), after the transcranial surgery ($p=0.046$), and in patients with postoperative diabetes insipidus ($p=0.007$). The Mann-Whitney-U test showed significantly lower early postoperative basal cortisol levels in older patients ($p<0.001$). However, using a multivariate model we found no relation between the analysed variables (age of the patient, tumor size and type, type of surgery, development of postoperative diabetes insipidus) and the presence of AI.

In 20 out of 83 studied patients (24.1%), early basal postoperative cortisol levels were <250 nmol/L and, according to the study protocol, replacement therapy with hydrocortisone was applied. Of these 20 patients, 11 did not pass the postoperative LST three months after the surgery and were diagnosed with secondary AI. The other 9 patients passed the testing and hydrocortisone replacement therapy was discontinued. Of the remaining 63 patients (75.9%) with basal cortisol levels of ≥250 nmol/L, only two patients (2.4%) ultimately failed the postoperative testing and required glucocorticoid supplementation. Their respective basal cortisol levels on the second postoperative day were 283 and 398 nmol/L. Figure 1 presents a graph illustrating each single basal cortisol value on the second day after surgery and its counterpart, the peak cortisol level during a LST three months after the surgery. Altogether, three months after the surgery, 13 out of 83 patients (15.7%) were diagnosed with AI and were put on chronic glucocorticoid replacement.

The sensitivity, specificity, positive and negative predictive values of the second postoperative day basal cortisol levels were calculated to predict AI for various cortisol cut-off values (Table 3). Receiver operating curve (ROC) analysis showed the area under the curve was 0.952 (95% confidence interval 0.898-1.0) (Figure 2). The best combination of sensitivity and specificity was found for the cortisol cut-off level of ≥ 300 nmol/L (sensitivity 92.31%, specificity 87.14 %, PPV 57.14%, NPV 98.39%). Using a multivariate model we found that the early postoperative basal cortisol of <300 nmol/L was associated with significantly higher incidence of AI (p<0.001, OR 0.013, 95% CI 0.001-0.151). In order to reach the sensitivity of 100% we should increase the cut-off to ≥400 nmol/L (specificity 68.57 %, PPV 37.14%, NPV 100%). In contrast, the cortisol cut-off level of ≥250 nmol/L that we used according to the study protocol was associated with sensitivity of 84.62 % and specificity of 87.14 % (PPV 55.0%, NPV 96.83 %) (Table 3).

Discussion

Accurate prediction of HPA axis function after pituitary tumor surgery is very important for proper postoperative management of patients. Many studies of cortisol secretion during the first week following the surgery showed that early morning cortisol levels predict long-term HPA axis function [1, 10-11, 15-29]. In our study, by using the cortisol cut-off level of ≥300 nmol/L we would have misdiagnosed only one patient with AI (sensitivity 92.31 % and specificity 87.14%). By increasing the cortisol cut-off level to ≥400 nmol/L, all patients with AI would be granted replacement therapy (sensitivity 100%). However, that would come at the expense of another 13 patients unnecessarily treated with hydrocortisone (specificity 68.57 %). Other studies which used various cortisol cut-off levels, ranging from 250 to 450 nmol/L, demonstrated similar accuracy of early basal postoperative cortisol level to predict AI with sensitivities of 47-98% [1, 10-11, 18-19, 22, 25, 28-29].

A meta-analysis by Tohti et al. indicated that early postoperative morning serum cortisol levels of less than 60 nmol/L predicted adrenal insufficiency, whereas cortisol higher than 270 nmol/L disclosed normal HPA axis integrity with 94% sensitivity and 100% specificity [30]. However, the study did not provide sufficient data for patients with early postoperative cortisol in the range between 60 and 270 nmol/L [30]. In our study, 17 patients had the postoperative cortisol level between 60-270 nmol/L, among which 8 patients (47%) were ultimately shown to have AI.

There are many risk factors for the development of postoperative AI. According to previous studies, incidence of postoperative AI was found to be higher in patients with larger tumors, those having at least one preoperative anterior pituitary hormonal deficiency, those who were operated by less experienced surgeons, as well as in elderly patients [22, 26, 34]. In our study, we found a relatively high frequency of postoperative AI (13/83 patients, 15.7%) in comparison to other studies, probably reflecting the specificity of our study population regarding tumor size, tumor type and type of surgery.

A considerable proportion of our patients had tumors >10 mm in diameter (88%). In addition, due to their suprasellar localization, six tumours were operated transcranially. Furthermore, the majority of other studies encompassed only the patients in whom the transsphenoidal surgical approach was applied [2-3, 10-11, 17-26, 29], whereas very few studies, including ours, also involved patients with craniopharyngiomas who are known to have higher incidence of postoperative hypopituitarism [27-28, 35].

McLaughlin et al. suggested that there was no need for hydrocortisone replacement in patients with microadenomas because none of the patients with microadenoma in their study group developed postoperative AI [26]. Our results support the above mentioned findings, as each of our patients with microadenoma (10/10) had normal HPA axis function after pituitary surgery. Furthermore, our patients with microadenoma had significantly higher early basal postoperative cortisol levels in comparison to the patients with macroadenoma. In contrast, some authors reported no significant differences in the mean postoperative morning serum cortisol levels between patients with micro- and macroadenoma [2].

In our study group, the transcranial surgical approach, craniopharyngioma and postoperative diabetes insipidus were associated with higher incidence of AI in the univariate analysis. However, after adjusting for age, tumor type and size, type of surgery and development of postoperative diabetes insipidus there was no difference in the incidence of AI. The multivariate analysis confirmed only the early postoperative cortisol level of <300 nmol/L as an independent predictive factor of AI.

Differences in the administration of pre- and postoperative hydrocortisone coverage could be a possible explanation for the variance in the postoperative cortisol levels and for different cortisol cut-offs reported by other authors. Auchus et al. suggested that exogenous glucocorticoids administered perioperatively might cause suppression of the HPA axis [18]. In our study, a relatively high amount of hydrocortisone was regularly administered within the perioperative period (250 mg over two days in total). Nevertheless, a similar replacement protocol was reported by others [18, 31-32]. Although being discontinued for at least 24 hours before blood sampling for basal serum cortisol, this dosage might have had an impact on the reported concentrations. This reflected a relatively high proportion of patients who were considered to have AI during the initial postoperative evaluation, but were found to be healthy following subsequent dynamic testing (9/20 patients). Notwithstanding, Manuylova et al. showed that morning cortisol levels after transsphenoidal surgery for pituitary adenoma accurately predict HPA axis function irrespective of the administration of single perioperative dexamethasone dose of 4 mg [36]. However, another recent study showed that, in contrast to a single dose, multiple perioperative doses of dexamethasone suppress HPA axis during postoperative period [37]. Furthermore, Karaca et al. suggested that a time period of 24h is possibly not long enough for the clearance of exogenous hydrocortisone, which could account for falsely elevated cortisol levels in the early postoperative period

[15]. Accordingly, current guidelines suggest performing biochemical testing for the HPA axis at least 18-24 h after the last hydrocortisone dose or longer for synthetic glucocorticoids [7].

The retesting of the HPA axis in our study was performed with LST three months after the pituitary surgery. A meta-analysis by Ospina et al. demonstrated that both, LST and standard-dose Synacthen tests, have moderate accuracy, primarily due to relatively low sensitivity [38-39]. Anyway, current guidelines suggest using Synacthen tests for the evaluation of HPA axis taking into account the test limitations [7, 38-40].

Finally, assay differences may contribute to variability in cortisol cut-offs as suggested in the literature [3, 8, 10, 18-19, 40]. Accordingly, the cortisol cut-offs that we recommended are only valid for the immunoassay used in our study.

In summary, we conclude that the second postoperative day morning cortisol is a valuable tool to predict the integrity of the HPA axis after pituitary surgery. Early postoperative cortisol level has been found as an independent prognostic factor of AI. Our data suggest that the cortisol level of $\geq$300 nmol/L accurately predicts adrenal sufficiency, so in these patients glucocorticoid replacement can be withdrawn.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Legends of tables and figures

Table 1. Characteristics of 83 patients included in the study

Table 2. Relationship between tumor/ patient's clinical characteristics, an early postoperative basal cortisol level and adrenal insufficiency 3 months after the surgery

Table 3. Diagnostic sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for day 2 morning serum cortisol cut-off concentrations with respect to detection of adrenal insufficiency as defined by low-dose Synacthen test (LST)

Figure 1. Serum basal cortisol concentrations 2nd day after surgery and peak serum cortisol concentrations during a low-dose Synacthen test (LST) three months after surgery

Figure 2. ROC curve for detecting adrenal insufficiency with day 2 postoperative serum cortisol (blue line), shown with reference line (green). Area under the curve is 0.952 (95% CI 0.898-1)

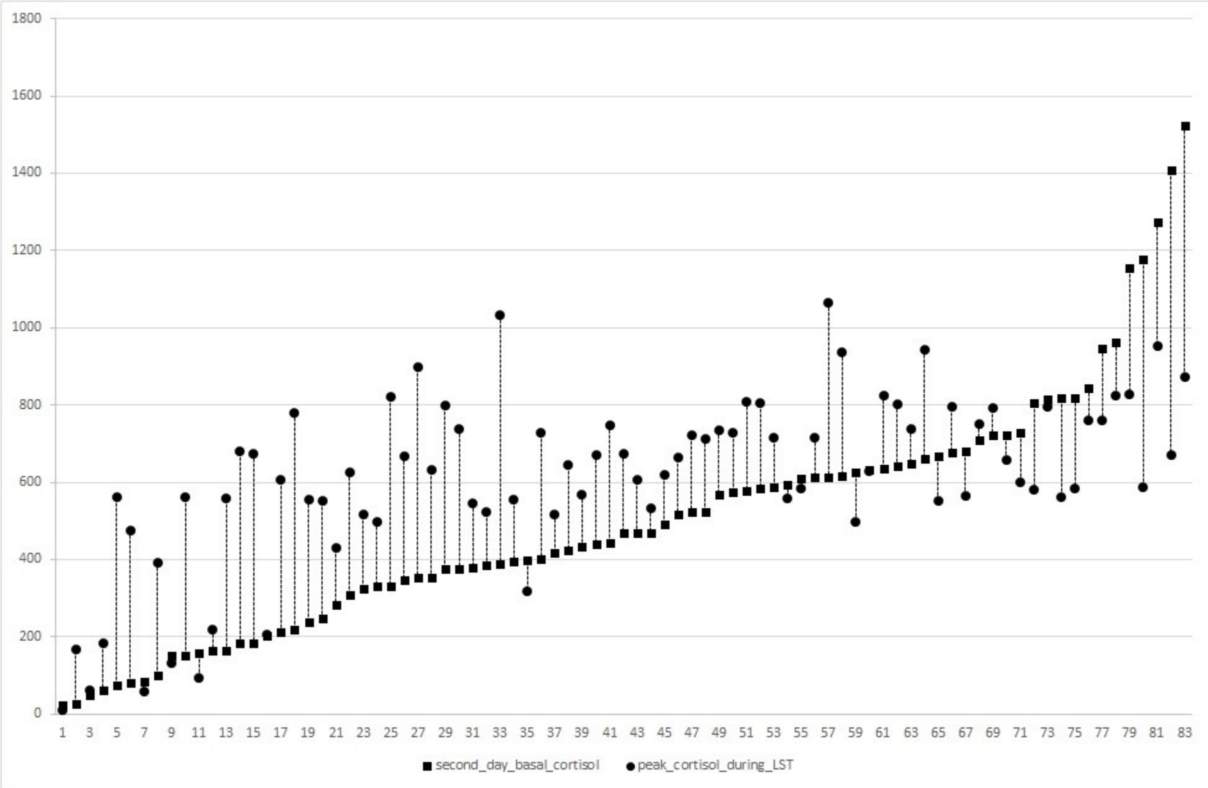

Figure 1.

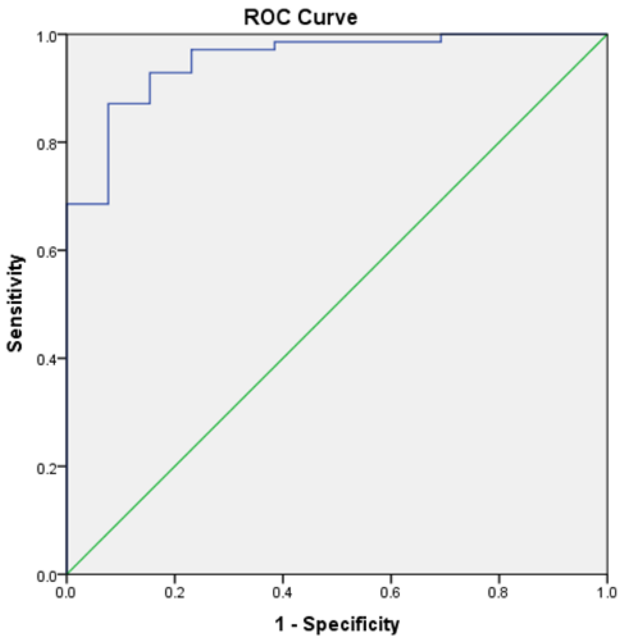

Figure 2.

Table 1.

Age (years, median, range)		58 (22-82)
Sex (male/female)		35(42.2%)/48(57.8%)
Pathohistological diagnosis (n,%)	Nonfunctioning adenoma	44 (53%)
	Somatotropinoma	28 (33.7%)
	Craniopharyngioma	5 (6%)
	Prolactinoma	2 (2.4%)
	Other lesions - Rathke's cleft cyst, arachnoidal cyst, chondroma, gangliocytoma	1,1,1,1 (4.8%)
MRI tumor/lesion diameter (n,%): ≥10 mm / <10 mm		73 (88%)/10 (12%)
Surgical approach (n,%): transsphenoidal/ transcranial		77 (92.8%)/6 (7.2%)
Preoperative/postoperative hormone deficiency (n,%)*:	ACTH	0 (0%)/13 (15.7%)
	LH-FSH	41(49.4%)/40(48.2%)
	TSH	15(18.1%)/27(32.5%)
Postoperative diabetes insipidus (n,%)		6 (7.2%)
Residual tumor after pituitary surgery (n,%)		46 (55.4%)

*GH evaluation was not done in all patients and data are not presented

Table 2.

	Number of patients	Early postoperative basal cortisol (median(range))	Significance	AI 3 months after the surgery (N)	Significance
Sellar tumors/lesions <10 mm vs Tumors/lesions≥10mm	10 73	637 (417-1407) 423(24-1524)	P=0.007	0 13	NS
Craniopharyngioma vs Other tumors/lesions	5 78	163 (24-1524) 470(26-1407)	NS	3 10	p=0.026
Transcranial vs Transphenoidal surgery	6 77	288 (24-1524) 470(50-1407)	NS	3 10	p=0.046
Postoperative diabetes insipidus (DI) vs without DI*	6 74	230.5 (24-1524) 470(50-1407)	NS	3 8	p=0.007

*Patients with transitory DI excluded from analysis

Table 3.

Detection of adrenal insufficiency	250 nmol/L day 2 serum cortisol cutoff	300 nmol/L day 2 serum cortisol cutoff	400 nmol/L day 2 serum cortisol cutoff
Sensitivity (95% CI)	84.62 (54.55 - 98.08)	92.31 (63.97 - 99.81)	100.00 (75.29 - 100.00)
Specificity (95% CI)	87.14 (76.99 - 93.95)	87.14 (76.99 - 93.95)	68.57 (56.37 - 79.15)
Positive predictive value (PPV, (95% CI))	55.00 (38.89 - 70.12)	57.14 (41.53 – 71.45)	37.14 (29.48 - 45.51)
Negative predictive value (NPV, (95% CI))	96.83 (89.47 - 99.09)	98.39 (90.25 – 99.75)	100.00

*Data are presented as %