Neuroendocrinology Letters Volume 37 No. 3 2016
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

The role of early cortisol level in the assessment of the radicality of resection in central Cushing's disease

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Submitted: 2016-02-24 Accepted: 2016-03-23 Published online: 2016-07-27

Key words: **pituitary adenoma; endoscopic resection; early cortisol level**

Neuroendocrinol Lett 2016; **37**(3):233–238 **PMID:** 27618608 NEL370316A07

Abstract

INTRODUCTION: To increase radicality and avoid surgical complications new treatment options are under investigation. One of the promising possibilities is to assess early morning cortisol levels on the first and second postoperative day.
MATERIAL AND METHODS: We enrolled 34 patients (9 males, 25 females) diagnosed with Cushing's disease. Blood samples to determine cortisol level were taken always at 06:00 and sent to the lab. The samples were taken on the first and second postoperative day. For all patients, standard four-handed, a bi-nostril endoscopic endonasal technique was used. Endocrinological follow-up (6–34 months) was performed using morning cortisol sampling.
RESULTS: In total, 36 patients (88%) were disease-free post-surgery. In the group with early postoperative levels of morning cortisol of less than 463 nmol/L, only 2 of 29 patients (7%) exceeded the final morning level of cortisol at follow-up. In patients with early postoperative cortisol levels between 17 nmol/l and 234 nmol/l all subjects showed normal postoperative cortisol levels.
DISCUSSION: In 30 of 34 patients (88%), the level of cortisol was within normal limits. The prediction importance of early measurement of cortisol is 93% for patients with early postoperative cortisol levels of less than 463 nmol/L. The prediction importance of early measurement of cortisol is 100% for patients with early postoperative cortisol levels from 17 to 234 nmol/L.
CONCLUSION: The monitoring of early morning cortisol levels seems to be an important tool in the management of central Cushing's disease.

ORIGINAL ARTICLE

INTRODUCTION

Cushing disease or pituitary Cushing's syndrome is characterised by the pituitary gland releasing an overproduction of adrenocorticotropic hormone (ACTH) in 1910. The first transsphenoidal resection of pituitary adenoma was performed by Harvey Cushing using the method of sublabial incision (1, 2). The transsphenoidal approach was abandoned by Cushing in 1925 in favour of the transcranial approach to pituitary adenomas. The disease itself was first described in 1932 (Cushing 1932). Lately, the sublabial transsphenoidal approach has be revived through the work of N. Dott and G. Guiot. The first transsphenoidal pituitary surgery in the Central Military Hospital in Czech Republic was performed by E. Černý in 1972. In May 2006, the endoscopic mononostril endoscopic approach was first used as surgical treatment at the our department. Later we started to use the binostril endoscopic endonasal approach. From 2008, all pituitary surgeries are performed using intraoperative MRI suite. On average, 100 surgeries are performed yearly. To increase radicality and avoid surgical complications new treatment options are under investigation. One of the promising possibilities is to assess early morning cortisol levels on the first and second postoperative day.

Currently, the high risk of recidivism is being considered by early morning cortisol levels at 585 nmol/l (Acebes *et al.* 2007) and the measurement of early morning cortisol is generally regarded as a promising marker of the therapeutic effect of surgery and makes the decision about re-operation easier (Esposito *et al.* 2006).

METHODS

Subjects

Thirty-four patients operated between January 2013 and June 2015 were enrolled in the study. The male: female ratio was 9:25. The age of patients was 37 years (range 8–37 years). The average age was 42 years (range 20–69 years) in males and 40 years (range 8–78 years) in females. The size of the tumour was measured with navigation Brainlab software. The size of the tumour varied from 4 mm^3 to 3078 mm^3, with the average size at 443.83 mm^3. If the arbitrary size of the macroadenoma were 523.60 mm^3, most of the tumours in our sample can be considered microadenomas. In our sample, 30 patients underwent surgery for microadenoma and 4 patients for macroadenoma.

Cortisol sampling

Blood samples were always taken at 06>00 and immediately sent to the lab for analysis. The samples were collected on the first and second postoperative day. The only application of hydrocortisone took place in a dose of 100 mg i.v. right before surgery. There was no further application of hydrocortisone. After surgery, the patient was moved to the intensive unit with regular osmolality, glycaemia and mineralogram controls every 6 hours. The amount of urine and urine osmolality were measured every 6 hours. After a second blood cortisone sampling, a standard dosage of Hydrocortisone was started in a dose of 40-30-20-10 mg with the first dose given at 07:00 and the last at 20.00 with a night pause. The dose was gradually reduced and before the transfer of the patient to the Department of Internal Medicine, the dose was set to 20-10-5-0 mg daily.

The reference values for the cortisol blood levels were between 171 and 536 nmol/l. The reference corresponds with unisex cortisol levels for ages ranging from 0 to 100 as set by our laboratory. Here, there is the extinction of morning serum cortisol activity in the true sense of the word. For static processing a direct comparison of levels was performed.

Follow-up for the morning cortisol levels ranged from 6 to 30 months.

Surgical technique

All patients were treated by a standard four-hands endoscopic transsphenoidal technique with the binostril approach. A rigid endoscope with direct 0° optics was used in sellar region Storz (180/4mm). A high definition (HD) camera was employed. A surgical intradural technique was the same as in open surgery. Both blunt and sharp dissection was used. Accidental bleeding was stopped by haemostatic foam, so that the biopsy area could easily be approached. We attempted to identify the pituitary gland using navigation. An area of pituitary gland, as well as of the pituitary tumour is identified on the preoperative MRI and with the use of navigation. 3T MRI was used both pre- and postoperatively. Postoperative MRI was performed one day and 3 months after surgery. Another MRI was performed after 1 year or according to the endocrinological results.

RESULTS

A. Comparison of the postoperative cortisol level with the final cortisol level during follow-up.
   1. Cortisol levels were assessed on the first and second postoperative day. In three patients, the cortisol level was higher compared with the first post-operative day. In all other patients, there was a reduction of the cortisol level on the second day after surgery. In other words, in 91% of the patients the level of cortisol was reduced on second postoperative day. Further statistical analysis was performed using the results from the second postoperative day (Figure 1).
   2. In 30 of the 34 patients (88%), the level of early postoperative cortisol was within normal limits. In 4 patients, the early postoperative cortisol levels were abnormal. In 2 of these 4 patients, the cortisol levels spontaneously corrected and no further treatment was required. Increased level

of cortisol both early postoperatively and after 3 months postoperatively was observed in two of these patients and further medical treatment was needed.

In a long-term follow-up, increased cortisol levels were noted in 4 patients, out of which 2 presented increased cortisol levels in an early postoperative assessment (see above). In 2 patients early postoperative cortisol was normal but increased later on in follow up (Figures 2, 3).

3. Specific situation: in one case, there was elevation of the cortisol level postoperatively. Postoperative MRI showed a small residual adenoma that could not be seen in the intraoperative MRI. On the third postoperative day, a second surgery was performed and subsequent cortisol levels became normal.
4. We divided postoperative morning cortisol levels into two subgroups: patients with early postoperative levels of 463 nmol/L (29 patients) and patients above 463 nmol/l (5 patients). In the group with early postoperative levels of morning cortisol of 463 nmol/L, only 2 of 29 patients (7%) had abnormaly increased morning level of cortisol at follow-up. If the early postoperative morning cortisol levels were above 463 nmol/L, two of 5 patients (40%) exceeded final morning level of cortisol at follow-up. The follow up endocrinological evaluation corresponded with these results. 93% of patients with early postoperative cortisol levels up to 463 nmol/l showed normal cortisol levels in a long term. In patients with early postoperative cortisol levels between 17 nmol/l and 234 nmol/l 100% of subjects showed normal postoperative cortisol levels (Figures 4, 5).

B. Statistical file evaluation

1. We examined the correlation between the early postoperative cortisol levels and the long term morning cortisol levels using Fisher test. The cut off value for the normal early postoperative cortisol value was 536 nmol/l. The results approached the statistical value of significance (p=0.55) (Tables 1, 2).
2. Agreement between early morning cortisol levels and final hormonal levels is evident at the follow-up (Figure 6, Table 3).

C. Complication

The hypocortical crisis did not occurre postoperatively.

DISCUSSION

In 1910, Harvey Cushing performed the first transsphenoidal surgery for pituitary adenoma using sublabial incision (Rosegay 1981; Walker 1982). In 1925, Cushing replaced the transsphenoidal approach with the

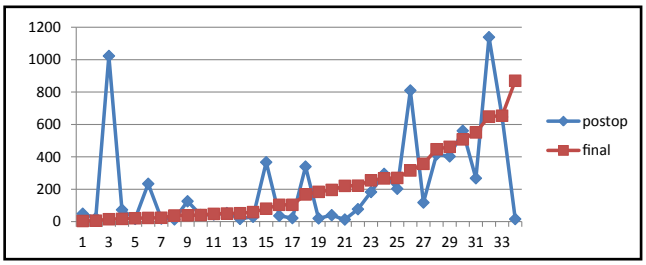

Fig. 1. Agreement between early postoperative cortisol levels and final levels in all patients at the follow/up.

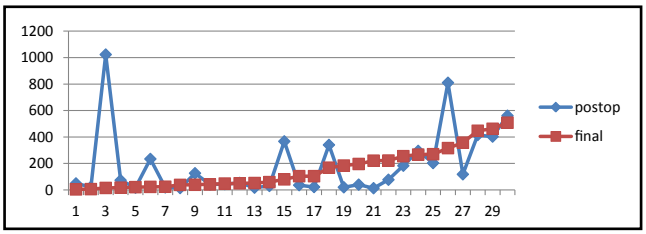

Fig. 2. Agreement between early postoperative cortisol levels and final levels in patients with a sufficient decrease in cortisol levels at follow/up.

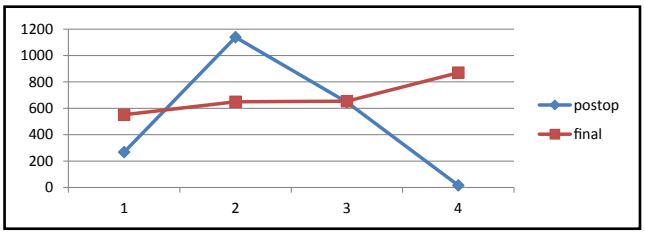

Fig. 3. Disagreement between early postoperative coritsol levels and final levels in patients with an insufficient decrease in cortisol levels at follow-up

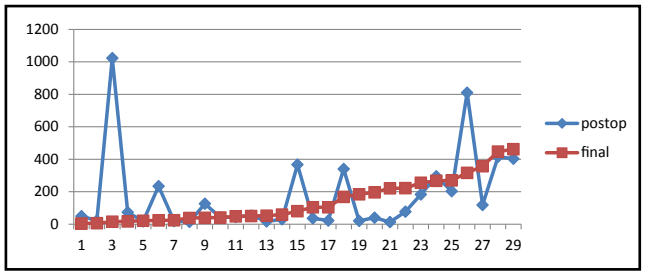

Fig. 4. Agreement between early postoperative cortisol levels of 463 nmol/L and final levels in patients with a sufficient decrease in cortisol levels at follow-up.

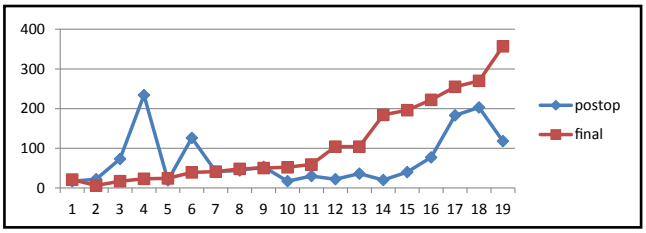

Fig. 5. Agreement between early postoperative cortisol 17–234 nmol/l and final cortisol level.

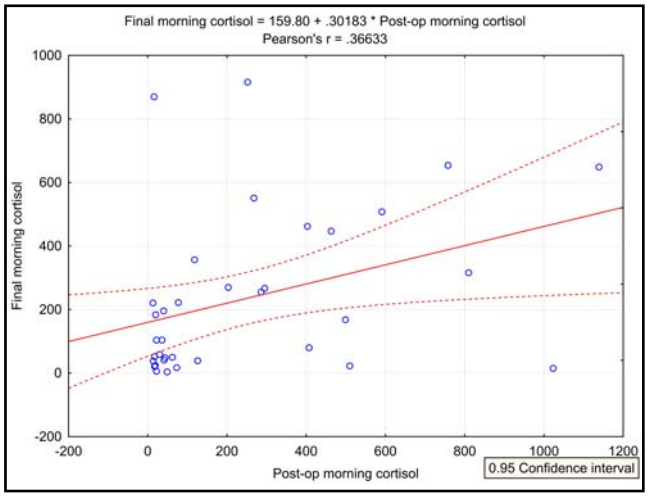

Fig. 6. Agreement between early postoperative cortisol levels and final levels at follow-up.

Tab. 1. Correlation between final morning cortisol activity levels and early postoperative results of hormonal activity in the statistical processing.

Normalisation postop	2-dimensional table: The observed frequency (Data) The frequency of labelled cells> 10		
	Normal Final 0	Normal Final	Line Totals
0	2	2	4
1	2	29	31
Total	4	31	35

Statist.	Statist. : Normal postop(2) × Normal final(2) (Data)		
	Chí-kvadr.	sv	*p*-value
Pearsonův chí-kv.	6.637617	df=1	*p*=0.00998
M-V chí-kvadr.	4.500165	df=1	*p*=0.03389
Yatesův chí-kv.	3.032567	df=1	*p*=0.08161
Fisher exact, 1-page			*p*=0.05567
Fisher exact, 2-page			*p*=0.05567
McNemar chí-kv. (A/D)	21.80645	df=1	*p*=0.00000
McNemar chí-kv. (B/C)	.2500000	df=1	*p*=0.61708

Tab. 2. Correlation.

Variable	Correlation (Data) Marked correlations are significant at $p<0.05$ N=35 (The whole case dropped by CHD)			
	Averages	Stn. deviation	Postop final	Last morning cortisol
Postop final	250.3714	306.0335	1.000000	0.366331
Last morning cortisol	235.3714	252.1508	0.366331	1.000000

Tab. 3. Spearman correlation.

Variable	Spearman's correlation (Data) CHD dropped in pairs Marked correlations are significant in $p<0.05$	
	Postop final	Last morning cortisol
Postop final	1.000000	0.362191
Last morning cortisol	0.362191	1.000000

transcranial approach. The sublabial transsphenoidal approach continued to be used because of the work of N. Dott and G. Guiot. Dott and Guiot not only adopted the transsphenoidal technique but also introduced intraoperative fluoroscopy. In the same period, J Hardy made an important breakthrough in pituitary surgery using an operative microscope, which led to the resurrection of the sublabial approach (Hardy 1971).

The first transsphenoidal pituitary surgery in the Central Military Hospital in Prague was performed by E. Černý in 1972. This technique was later improved by I. Fuks and eventually became a standard procedure (Fusek & Černý 1977). In May 2006, the endoscopic endonasal mononostril approach was introduced in the Neurosurgical Department of the 1st Medical Faculty of Charles University. Since November 2006, the binostril endoscopic endonasal technique was employed (Masopust *et al.* 2008). The arrival of intraoperative magnetic resonance imaging (iMRI) in April 2008 enabled increased radicality in pituitary surgery (Netuka *et al.* 2009; Netuka *et al.* 2011).

There are four basic therapeutic approaches to sellar lesion: observation, neurosurgery, pharmacological therapy and radiosurgery. These four methods can be regarded as complementary. The application of modern surgical techniques leads to increased radicality with fewer complications (Masopust *et al.* 2014).

The extent of radicality is of major importance in accessing the efficacy of any surgical approach. One possible method to assess radicality is early postoperative control of cortisol levels. Interestingly. in patients in whom the first surgery failed, the second resection led to long-term success in only 45% of the patients. It appears that measurement of early morning cortisol levels is a good marker of prediction of the future effect of pituitary surgery and can be viewed as a determining factor for a second surgical intervention (Esposito *et al.* 2006).

In the study, Acebes *et al.* studied the effect of surgery in 44 patients with Cushing disease. The histological examination was evaluated as well. The efficacy of surgery was 89%: early cortisol levels were higher than 585 nmol/L, plasma ACTH was higher than 7.55 nmol/L and no positive histology were strong predictors of the treatment failure. The ACTH level itself increased the probability of the failure from 80 to 97.4% (Acebes *et al.* 2007).

Another study demonstrated treatment efficacy, if there is an association between intrasellar lesions and postoperative cortisol levels lower than 50 nmol/L (Rees *et al.* 2001).

Another study of 103 patients examined examining cortisol levels. The positive predictive value of early postoperative cortisol levels was 100% and the negative predictive value was 60%, assessment of the cortisol levels days 10–12 after surgery proved more effective, but does not allow early reoperation (Costenaro *et al.* 2014).

Karaca *et al.* evaluated the validity of preoperative basal serum cortisol levels measured to predict preoperative adrenal on days 2–6 after surgery. The study was prospectively designed and included 64 patients. The positive predictive value of the ITT performed on the 6th postoperative day was 69.7%, and the negative predictive value in predicting adrenal insufficiency at the 1st postoperative month was 58%. Early postoperative cortisol levels may be used as the first-line test in the assessment of the hypothalamic-pituitary-adrenal axis (Karaca *et al.* 2010).

Not all studies showed the efficacy of the early cortisol levels. The study of Hameed *et al.* in their 52 subjects sample did not show any association between the early morning cortisol level and the time to relapse (Hameed *et al.* 2013).

In a long-term follow-up (median 11 years) study, patients with postoperative cortisol levels below 2 μg/dl showed a recidivism of 9.5% and in patients with cortisol levels from 2–5 μg/dl relapse was 20%. This study showed that even patients with low postoperative cortisol levels require long-term follow-up (Lindsay *et al.* 2011).

There has been studied early postoperative cortisol importance of the need for administration of hydrocortisone in a study in which 139 patients underwent endonasal surgery for pituitary adenomas on the other hand. Cushing disease was excluded. The result was that normal morning cortisol values on the first and second day after surgery reliably predict adequate and safe adrenal function in 98% of the patients. This simple protocol of withholding postoperative glucocorticoids avoids unnecessary steroid exposure and poses minimal risk to the well-informed and closely monitored patient (McLaughlin *et al.* 2013).

The 2009 study confirms previous results and determines the level of 15 μg/dl as safe for preservation of hypothalamo-hypophyseal-adrenal fiction (Marko *et al.* 2009). Better results were demonstrated immediately after surgery by the same author (Marko *et al.* 2010).

The reference values in our study for the cortisol blood levels are between 171 and 536 nmol/L. The reference corresponds with unisex cortisol levels for ages between 0 and 100 as set by our laboratory. In our study, the level of cortisol was within normal limits in 30 of 34 (88%) patients. In 4 patients, the early postoperative cortisol levels were abnormal. In 2 of these 4 patients, the cortisol levels spontaneously corrected and no further treatment was required. Two patients are on hormonal therapy. In a long-term follow-up, the increased cortisol levels were noted in 4 patients, out of which 2 had an increased cortisol level in an early postoperative assessment and in 2 patients the increased cortisol levels were assessed at follow-up.

Examining the postoperative morning cortisol levels in the figure 4, we see that in the group with early postoperative levels of morning cortisol of 463 nmol/L, only 2 (7%) of 29 patients had exceeded the final morning level of cortisol at follow-up. In patients with early postoperative cortisol levels between 17 nmol/l and 234 nmol/l 100% of subjects showed normal postoperative cortisol levels. The prediction importance of early measurement of cortisol is 100% for patients with early postoperative cortisol levels from 17 to 234 nmol/L.

We examined the correlation between the early postoperative cortisol levels and the long term morning cortisol levels using Fisher test. The cut off value for the normal early postoperative cortisol value was 536 nmol/l. The results approached the statistical value of significance (p=0.55).

The total radicality in our sample (e.g., the absence of hormonal hyper-production) reached 88%. In the literature, radicality results of the transsphenoidal surgery in Cushing disease have been found to range 79.5–89% (Acebes *et al.* 2007; Esposito *et al.* 2006). It can be further increased with the use of intraoperative MRI (in our sample, it was increased by 2.5%) (Falbush *et al.* 2005; Nimsky *et al.* 2006; Jones & Ruge 2007; Schwartz *et al.* 2006; Bohinski *et al.* 2001; Alfieri & Jho 2001). Overall radicality can be influenced by the time of follow-up, which in our case ranged from 6 to 30 months. Thus, final radicality can be assumed to be lower. In our sample there were two patients with persisting hypercorticism and two unsuccessfully operated patients were treated with Leksell Gamma knife. In one of these patients, radiosurgery failed and adrenalectomy was performed. The hormonal treatment options not used (Wójcik *et al.* 2015).

In our cohort, postoperative CSF leakage occurred in one patient who underwent revision surgery that included CSF fistula closure and lumbar drainage insertion. The closure can be performed by self lipid tissue, but we prefer the closure by self muscle tissue (Jun & Pinan 2014). One patient with chronic sphenoid sinus infection suffered postoperative meningitis without CSF leakage and was treated with antibiotics, without need for surgical intervention.

Overall, mortality was 0% and morbidity 6% in our cohort. If we include long-term substitution of vasopressin analogue, morbidity reached 12%.

CONCLUSION

The aim of the study was to assess cortisol levels on days 1 and 2 after surgery and to assess their predictive value for endocrinological radicality. The endocrino-

logical remission (e.g., the absence of hormonal hyperproduction) was achieved 88%. In our study, we arrived at a cut-off value of 462 nmol/L to assess endocrinological radicality. The prediction importance of early measurement of cortisol is 100% for patients with early postoperative cortisol levels from 17 to 234 nmol/L. The monitoring of early morning cortisol levels seems to be an important tool in the management of central Cushing disease.

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