Pituitary-adrenal dynamics after ACTH-secreting pituitary tumor resection in patients receiving no steroids post-operatively

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ABSTRACT. It has recently been suggested that the classical routine of glucocorticoid administration before and after transsphenoidal surgery (TSS) in Cushing's disease (CD) patients may not be necessary, since it is likely that peritumoral normal corticotrophs are not completely suppressed during this period. We compared the dynamics of ACTH and cortisol from a group of CD patients (cured and not cured), receiving no steroids post-operatively, with a control group of acromegalic patients who presented normal hypothalamic-pituitary-adrenal (HPA) axis. Blood samples for ACTH and cortisol determination were obtained immediately before, at the end of surgery and at 4, 8, 12, 16, 24, 48 and 72 h after surgery, in 8 cured CD patients (Group I), 9 not cured CD patients (Group II) and in 7 subjects with acromegaly (Group III) who presented normal HPA axis (control group). The mean ACTH level in Group I was significantly lower than in Group III from 4 to 12 h and lower than in Group II from 8 to 12 h post-operatively. The mean cortisol level in Group I was lower than in Groups II and III from 8 to 72 h after surgery. No difference in mean cortisol level was observed among Groups II and III during the evaluated period. The lowest cortisol value in Group II was 193 nmol/l (at 24 h after surgery) and in Group I patients, after 20 h post-operatively, the highest cortisol level was 165 nmol/l. Although all cured CD patients (Group I) presented serum cortisol level lower than 55 nmol/l until 72 h after surgery, none had significant complications related to adrenal insufficiency. Ours findings are in agreement with recent observations that there is probably no need for glucocorticoid administration until clinical and/or laboratorial data are suggestive of adrenal insufficiency. However, we have also shown that a subphysiological HPA axis response could be observed in cured CD patients after TSS, and a definitive conclusion about glucocorticoid management during and after this procedure could not be made on the ground of the few cases studied in the literature.
(J. Endocrinol. Invest. 28: 502-508, 2005)

INTRODUCTION

A strong activation of the hypothalamic-pituitary-adrenal (HPA) axis and adrenomedullary sympathetic system, with substantial increase in ACTH, cortisol and epinephrine is considered a normal stress response in patients with normal HPA axis submitted to surgery (1). Patients with ACTH-secreting pituitary tumor were thought to have complete suppression of the normal peritumoral corticothrophs by chronic hypercortisolemia. Adrenal insufficiency is frequently seen after pituitary tumor resection for Cushing's disease, (2-6). In many centers, exogenous steroids are administered to patients with CD undergoing transsphenoidal surgery (TSS), to avert adrenal insufficiency (2-4, 7-10). Some authors have emphasized that a supraphysiologic amount of steroids would be needed intra- and post-operatively to avoid the symptoms and signs of Addison's syndrome (10).

Key-words: ACTH, Cushing's disease, transsphenoidal surgery, pituitary tumor.

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Accepted January 3, 2005.

Table 1 - *ACTH levels (pmol/l) before and after transsphenoidal surgery (TSS) in patients with Cushing's disease (CD) who were cured (Group I) after surgery.*

	Surgery		After surgery (h)							
Patient (No.)	Before	At the end	4	8	12	16	20	24	48	72
1	27.7	27.5	10.5	6.6	2.5	2.6	2.9	4.2	2.4	3.1 (*)
2	6.2	42.5	18.9	12.1	6.8	3.5	2.2	2.6	4.2 (*)	2.9 (*)
3	27.1	31.5	27.7	11.0	10.5	8.8	8.8	8.6	4.6 (*)	4.4 (*)
4	23.3	87.6	44.2	3.3	3.5	3.8	3.1	2.9	2.6 (*)	2.2 (*)
5	15.2	7.7	7.9	3.7	2.2	2.2	2.2	2.2	2.2 (*)	2.3 (*)
6	13.0	27.1	2.5	2.2	2.2	2.2	2.2	2.2	2.2 (*)	2.2 (*)
7	11.9	23.1	17.6	14.1	6.7	3.3	2.2	2.2	2.2 (*)	2.2 (*)
8	21.6	8.1	10.6	5.5	4.4	3.3	2.6	2.2	2.2 (*)	2.2 (*)

(*): Oral cortisone acetate administered at least 12 h prior.

On the other hand, Graham et al. (11) have not observed any significant change in ACTH levels during the first hours after tumor resection in patients in whom no exogenous steroid was administered. Recently, we (12) have shown that ACTH levels did not change in the early recovery period (first 5 h) after ACTH-secreting pituitary tumor resection, even in cured patients. We (12) have also shown that mechanical pituitary manipulation was able to release ACTH but probably has not interfered in the maintenance of high ACTH-levels during the early post-operative period. Moreover, high cortisol level approximately 6 h after surgery in cured patients receiving no steroid during TSS was previously described by others (5, 6, 13). These high cortisol levels even in cured CD patients were probably related to high ACTH levels during the first post-operative hours (11-13).

Therefore, the behavior of the human HPA system during and immediately after TSS in patients with ACTH-secreting pituitary tumors may not conform to the specifications of a negative feedback mechanism. Peritumoral normal corticotrophs might not be completely suppressed in patients with CD during the immediate post-operative period (11-13), and it was recently suggested that exogenous steroids may not be necessary for these patients during and immediately after TSS.

In the present study, we compared post-operative ACTH and cortisol levels obtained from patients with CD to those obtained from a control group of acromegalic patients with normal HPA axis who have not received perioperative steroid therapy.

MATERIALS AND METHODS

Twenty-four non-consecutive patients with pituitary tumor were evaluated before and after TSS. High resolution magnetic resonance imaging of the sellar region was obtained in all patients. Seventeen patients had ACTH-secreting pituitary tumor and 7 had GH-secreting pituitary tumor confirmed by histological and immunohystochemical analysis after surgery. All patients had clinical and laboratory data suggestive of CD or acromegaly before surgery. Surgery was performed by the same neurosurgeon (AC) in all patients through the transsphenoidal route. Informed consent was obtained from all patients and the research protocol was approved by the Institutional Review Board.

Eight out of 17 of the studied patients with CD presented remission of the hypercortisolism after TSS (Group I, no.=8, 2 males, age=30±2 yr). One of them had pituitary macroadenoma and 7 had pituitary microadenomas. The remission of hypercortisolism was confirmed by serum cortisol levels <55 nmol/l during the first 72 h and by persistently low 24 h urinary free cortisol excretion and/or suppression of serum cortisol in the overnight 1-mg dexamethasone test during the first 12-24 months, associated to clinical remission. The other 9 CD patients exhibited persistent hypercortisolemia during the postoperative and follow-up periods, and were considered not cured (Group II; no.=9; 2 males; age=32±3 yr). Six of them had pituitary microadenomas and 3 had pituitary macroadenomas.

Group III included 7 patients (age=37±3 yr; 2 males) with acromegaly who presented with normal HPA axis before and after the surgery.

ACTH and cortisol dynamics were studied before and after TSS in all patients. Blood samples for ACTH and cortisol determination were obtained immediately before and at the end of surgery and at 4, 8, 12, 16, 24, 48 and 72 h after surgery. Exogenous glucocorticoid was not administered until laboratory or clinical findings were suggestive of adrenal insufficiency.

Plasma ACTH and serum cortisol levels were measured by automated chemiluminescent enzyme immunoassay kits (IMMULITE, Diagnostic Products Corp., Los Angeles, CA) and the inter-assay

coefficients of variation were 7.4 and 6.9%, respectively. The intra-assay coefficients of variation for ACTH and cortisol were 3.9 and 5.3%, respectively. The ACTH and cortisol reference ranges were 2.2-10.2 pmol/l and 138-690 nmol/l, respectively.
Data were analyzed by the Kruskal-Wallis analysis of variance (ANOVA) analysis (for comparisons between groups), Friedman repeated measure ANOVA on ranks and Kelss-Newman's multiple range test (for analysis after pituitary tumor resection within the same group). Results were reported as mean +/– SE. p-values <0.05 were considered statistically significant.

RESULTS

No statistical difference was observed in mean ACTH level before and at the end of surgery in the 3 groups. In Group III patients, there was a massive ACTH release during the first 4 h after surgery (51±9 pmol/l), followed by rapid decrease until normalization in ACTH level after 16 h (7±1 pmol/l) (Fig. 1). The mean ACTH level in Group I was significantly lower than in Group III from 4 to 12 h and lower than in Group II from 8 to 12 h post-operatively. In Group I patients, a statistically significant decrease in mean ACTH level was observed only 8 h after surgery (7±2 pmol/l) in comparison with the end of surgery (32±9 pmol/l). In Group II patients, a significant reduction in ACTH was observed only 16 h after surgery (11±3 pmol/l) (Fig. 1).
There was no difference in mean cortisol level between the three Groups until 4 h post-operatively. The mean cortisol level in Group I was lower than in Groups II and III from 8 to 72 h after surgery (Fig. 2). In Group III, there was a significant increase in cortisol level up to 4 h after surgery (1214±138 nmol/l) followed by a plateau from 4 to 16 h and a progressive decrease in cortisol levels afterwards. The mean cortisol level at 24, 48 and 72 h was no different from the pre-operative values in these patients (group III). No difference in mean cortisol level was observed between Groups II and III during the evaluated period.
There was no overlap in cortisol level between Groups I and II after 20 h of the end of surgery, since the highest serum cortisol value in Group I measured from 20 up to 72 h post-operatively was 165 nmol/l and no patient from Group II had serum cortisol <193 nmol/l during the evaluated period. After surgery, there was a late reduction in cortisol levels in Group II patients when compared to Group I patients (as occurred with ACTH levels). A statistically significant decrease in mean cortisol level was observed after 8 h in Group I patients (466±133 nmol/l) in comparison to cortisol values immediately at the end of surgery (822±157 nmol/l). In Group II, a significant reduction in mean cortisol level was observed 16 h after surgery (994±301 nmol/l) in comparison to cortisol values at the end of surgery (2070±604 nmol/l).
No Group I patients received exogenous glucocorticoid until 24 h post-operatively, since no signs and/or symptoms of adrenal insufficiency were observed during this period (Table 2). Only three patients presented signs and/or symptoms of adrenal insufficiency (all of them after 24 h post-operatively), although serum cortisol <55 nmol/l was observed between 12 and 24 h in 5 patients and between 24 and 72 h post-operatively in the other 3 patients. Oral cortisone acetate (25 mg b.i.d) was begun between 24 to 72 h post-operatively for all Group I patients. The blood sample for ACTH and cortisol measurement at 48 and 72 h was collected at least 12 h after the latest dose of oral cortisone acetate (Tables 1 and 2).

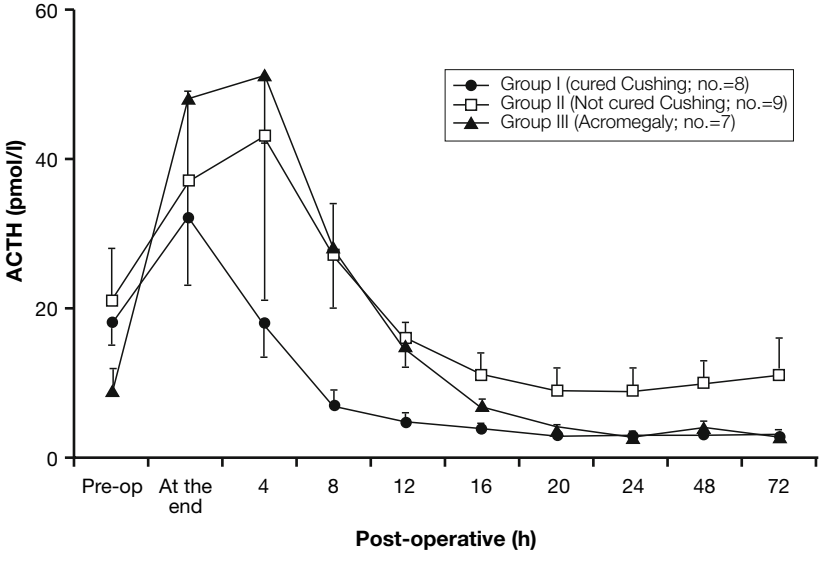

Fig. 1 - *ACTH levels before and after transsphenoidal surgery (TSS) in cured Cushing's disease (CD) patients (Group I) or not cured CD patients (Group II) and in acromegalic patients (Group III).*

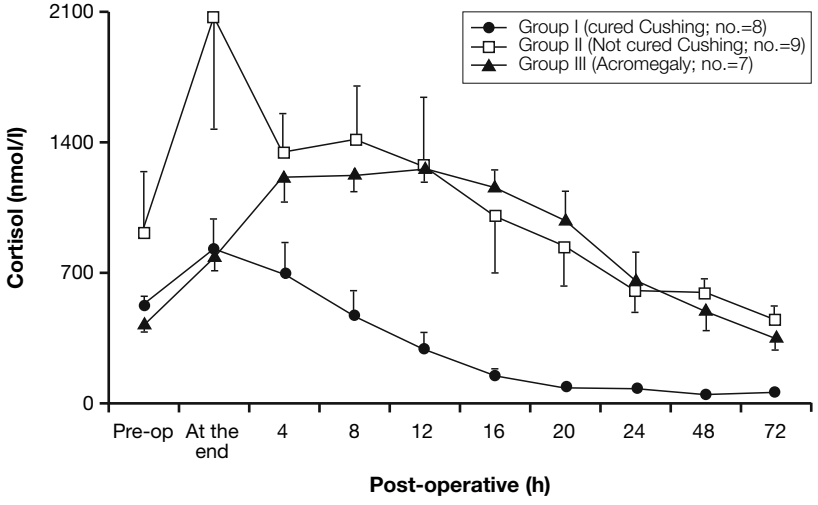

Fig. 2 - *Cortisol levels before and after transsphenoidal surgery (TSS) in cured Cushing's disease (CD) patients (Group I) or not cured CD patients (Group II) and in acromegalic patients (Group III).*

DISCUSSION

Clinical and laboratory evidence of adrenal insufficiency during the immediate post-operative period is an important criterion for the diagnosis of hypercortisolism remission after TSS for CD. Adrenal insufficiency occurs in this setting due to supression of the peritumoral normal corticotrophs induced by chronic hypercortisolism. However, the timing for the development and management of adrenal insufficiency after surgery for CD has been poorly documented. From a biochemical perspective, adrenal insufficiency should be detected immediately after tumor resection has been completed, taking into consideration that ACTH´s half-life is 8-15 min. (14, 15). This rationale led to the practice of administering exogenous steroids to patients with CD undergoing TSS, to avoid adrenal insufficiency (2-4, 7-10). Adrenal insufficiency might be lethal if left untreated (15, 16).

Normal corticotrophs release high amounts of ACTH in response to surgical stress in spite of excess of glucocorticoid administration, suggesting that during stress the behavior of the human HPA axis may not conform to the specifications of a rigid negative feedback mechanism (17, 18). In 1994, Arafah et al. (19) observed that ACTH levels in patients who recovered the pituitary-adrenal function after pituitary macroadenoma resection reached normal values in spite of glucocorticoid administration, suggesting that the use of hydrocortisone does not interfere in the ACTH secretion during stress. In patients with CD undergoing TSS, we (12) have previously observed

Table 2 - *Cortisol levels (nmol/l) before and after transsphenoidal surgery (TSS) in patients with Cushing's disease (CD) who were cured (Group I) after surgery.*

	Surgery		After surgery (h)							
Patient (No.)	Before	At the end	4	8	12	16	20	24	48	72
1	612.5	711.8	615.3	689.7	480.1	220.7	80.0	113.1	71.7	55.2 (*)
2	491.1	1462.3	1407.1	689.7	634.6	331.1	157.3	137.9	68.9 (*)	55.2 (*)
3	477.3	844.2	540.8	386.3	223.5	215.2	165.5	126.9	27.6 (*)	71.7 (*)
4	606.9	1379.5	827.7	499.4	275.9	140.7	110.4	49.7	49.7 (*)	82.8 (*)
5	562.8	297.9	157.3	57.9	11.1	22.1	19.3	8.3	5.5 (*)	35.8 (*)
6	204.2	982.2	579.4	140.7	55.2	35.9	38.6	49.7	33.1 (*)	33.1 (*)
7	692.5	675.9	1211.2	1164.3	549.1	129.7	55.2	63.4	27.6 (*)	27.6 (*)
8	543.5	226.2	165.5	99.3	60.7	55.2	41.4	27.6	27.6 (*)	27.6 (*)

(*) Oral cortisone acetate administered at least 12 h prior.

that even in those patients cured by surgery ACTH level did not decrease during the first 5 h after tumor resection. This occurred even after administration of high doses of glucocorticoids and chronic hypercortisolism, suggesting that peritumoral normal corticotrophs might not be totally suppressed in patients with CD under intense stress (as during surgery).

Graham et al. (11) had studied ACTH clearance after ACTH-secreting pituitary tumor removal without exogenous glucocorticoid administration and shown high ACTH levels during the first 60 min, post-operatively, in patients with CD cured by surgery. Recently, Nasrallah et al. (13) also showed high cortisol and ACTH levels during the first 12 h post-operatively, in patients with CD cured by surgery who did not receive exogenous glucocorticoid. Simmons et al. (5) have studied cortisol dynamics in 27 patients with CD who underwent TSS and suggested that even cured patients may be safely followed-up clinically during post-operative day 1 without corticosteroid supplementation. In the present study, we evaluated ACTH and cortisol dynamics in patients with CD (Groups I and II) and acromegaly (Group III, control group) during the first 72 h post-operatively. By the end of the surgery, ACTH and cortisol levels in all patients were higher than those seen pre-operatively. Mechanical pituitary manipulation and an immediate post-operative stress response might justify the early rise in ACTH and cortisol levels in these patients (12).

Group I (CD in remission) patients had no change in mean ACTH during the first 4 h after surgery, suggesting an ACTH leaking from damaged corticotrophs (normal or tumoral) or that peritumoral normal corticotrophs were not totally suppressed in these patients. Only mechanical pituitary manipulation could not explain the maintenance of high ACTH level during that period since the ACTH's half life is 8-15 min (14, 15). Several substances secreted during surgical stress might induce ACTH release from normal corticotrophs, such as CRH, vasopressin, angiotensin-II, catecholamines and interleukin-1 and 6 (1, 20). Some of these substances could be acting as potent ACTH-releasing factors and might be secreted during the surgical procedure or during the first post-operative hours. However, it is unlikely that these ACTH-releasing factors would have been efficaciously secreted during the development of post-operative adrenal insufficiency, since our data showed no ACTH response from 8 to 72 h after surgery, even when cortisol level was <55 nmol/l. The suppression of residual normal corticotrophs was almost complete by that time. On the other hand, it is not possible to rule out that the ACTH measured during the early recovery period might reflect secretion by surviving tumor cells, which subsequently died (5, 10-12).

In Group III (acromegalic with normal HPA axis) patients, ACTH values were higher than pre-operatively up to 12 h after surgery. In this group, ACTH and cortisol level returned to the pre-operative levels, respectively, 16 and 24 h post-operatively. The same pattern of ACTH and cortisol secretion was observed in Group II (CD not cured) patients. Group I patients presented a reduced cortisol secretion when compared to Groups II and III patients from 8 to 72 h. This decrease in cortisol secretion was probably related to reduced ACTH release observed in these patients. Although there was no statistical difference between Groups I and III at 4 h post-operative evaluation, the cortisol and ACTH curves are clearly different. Thus, our data suggest, for the first time in the literature, that CD patients cured by TSS presents a subphysiological HPA axis response to post-operative stress. It has been previously suggested that after long-term hypercortisolism tissues become adjusted to a higher glucocorticoid concentration, so that a fall towards normal levels would represent a relatively hypoadrenal state (21). Cortisol could raise the vasoconstrictor actions of catecholamines and has an important supportive role in the maintenance of vascular tone, permeability and distribution of total body water within the vascular compartment (22, 23). It was supposed that a subphysiological response of the HPA axis or acute adrenal insufficiency in the early post-operative period could result in hemodynamic abnormalities, such as hypovolemic shock (decreased preload, depressed myocardial contractility, and increased systemic vascular resistance) or hyperdynamic shock (high cardiac output and decreased systemic vascular resistance similar to those seen in septic shock) (16, 24-29). Thus, in a recent review of the literature Inder et al. (9) suggested that all patients with CD should receive per-operative physiologic hydrocortisone therapy. Although in the present study and in others (5, 6, 11, 13) no patient had significant complications related to adrenal insufficiency, all Group I patients presented a subphysiological HPA axis response (or adrenal insufficiency) during the early period of post-operative stress when compared to normal control group (Group III). Our findings suggest that before and during surgical procedure glucocorticoid replacement might not be necessary for CD patients undergoing TSS. In medical centers where it is possible to measure blood cortisol levels with immediate results and patients undergo intensive care, steroid replacement could be avoided during the early (24 h) post-operative period. However, a definitive conclusion that glucocorticoid replacement therapy post-operatively is not necessary for all CD patients undergoing TSS could not be made on the grounds

of the few cases studied in the literature.

Although the mean ACTH level was statistically lower in Group I than in Group II patients by 8 and 12 h post-operatively, there was an overlap in ACTH level between the Groups in all evaluated periods. Thus, our data suggest that plasma ACTH level determination is not enough to adequately distinguish between cured and not cured patients. This is in accordance with previous data, suggesting that intraoperative or immediate post-operative (5 h) ACTH levels were not able to predict cure (11, 12).

Mean cortisol level in Group I was lower than in Group II and there was no overlap in cortisol level between the Groups after 20 h of the end of surgery. In Group I patients, the highest serum cortisol measured from 20 up to 72 h post-operatively was 165 nmol/l (6 μg/dl) and in Group II no patient had serum cortisol lower than 193 nmol/l (7 μg/dl) during the same period.

The diagnosis of hypercortisolism remission in patients with CD could not be accurately established early in most patients receiving exogenous glucocorticoid during the peri-operative period. Our data suggest that CD patients receiving no steroids who presented serum cortisol level ≥165 nmol/l (6 μg/dl) from 20 up to 72 h post-operatively would probably undergo failure.

Moreover, although the present study is in agreement with recent observations that there is no need for glucocorticoid administration during the first 24 h after TSS adenomectomy in CD patients, more data are necessary for a definitive conclusion.

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