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The postoperative cortisol stress response following transsphenoidal pituitary surgery: A potential screening method for assessing preserved pituitary function

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Abstract

Purpose—The ability to reliably identify patients with new hypocortisolemia acutely following pituitary surgery is critical. We aimed to quantify the postoperative cortisol stress response following selective transsphenoidal adenomectomy, as a marker for postoperative preservation of functional pituitary gland.

Methods—Records of 208 patients undergoing transsphenoidal operations for pituitary lesions were reviewed. Patients with Cushing's Disease, preoperative adrenal insufficiency, and those receiving intraoperative steroids were excluded. To quantify the postoperative stress response, the Δ cortisol index was defined as the postoperative day (POD) 1 morning cortisol minus the preoperative morning cortisol level. The incidence of new hypocortisolemia requiring glucocorticoid replacement upon hospital discharge was also recorded.

Results—Fifty-two patients met inclusion criteria. The mean preoperative, POD1, and POD2 cortisol levels were 16.5, 29.2, and 21.8 μg/dL, respectively. Morning fasting cortisol levels on POD1 ranged from 4.2-73.0 μg/dL. The Δ cortisol index ranged from −19.0 to +56.2 (mean +12.7 μg/dL). Five patients (9.6%) developed new hypocortisolemia on POD 1-3 requiring glucocorticoid replacement; only one required long-term replacement. The mean Δ cortisol in patients requiring postoperative glucocorticoids was −2.8 μg/dL, compared with +14.4 μg/dL in patients without evidence of adrenal insufficiency (p=0.005). Of the 32 patients (61.5%) with a Δcortisol >25 μg/dL, none developed postoperative adrenal insufficiency.

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Conclusions—The postoperative cortisol stress response, as quantified by the Δ cortisol index, holds potential as a novel and complimentary screening method to predict preservation of normal pituitary function and acute development of new ACTH deficiency following transsphenoidal pituitary surgery.

Graphical Abstract

Precis:

The authors determined that the magnitude of the cortisol stress response following transsphenoidal pituitary surgery may be a reliable and novel indicator of intact pituitary and cortisol axis function.

Keywords

Pituitary neoplasm; transsphenoidal; cortisol; hypopituitarism; hormone replacement; stress response; surgery

Introduction

Following transsphenoidal operations for resection of pituitary adenomas and other sellar lesions, new deficiency of the hypothalamic-pituitary-adrenal (HPA) axis has generally been reported in less than 10% of patients with previously normal cortisol production.[1-6] Because of the crucial physiological role that cortisol plays, especially in the context of stressful events, close monitoring of the HPA axis is imperative in the early postoperative period following transsphenoidal surgery.[7] In the past, some practitioners have avoided the potential problems associated with postoperative ACTH deficiency by empirically administering glucocorticoid replacement to all patients undergoing transsphenoidal pituitary operations.[8] Other studies, however, have demonstrated that empiric administration of glucocorticoids to all patients undergoing pituitary surgery is unnecessary, and that many will maintain or even demonstrate normalization of anterior pituitary function following selective adenomectomy.[1,9-11] Theoretically then, if adequate functional pituitary gland is preserved during selective adenomectomy, no routine corticosteroid administration would be required.

In patients who have normal pituitary function and a functional HPA axis, there is a characteristic ACTH and cortisol stress response that has been demonstrated to occur over the course of 24-36 hours following any surgical procedure.[12-15,7,1] For example, the serum cortisol level in patients within 24 hours following abdominal surgery has been determined to be, on average, up to 15 μg/dL higher than baseline levels, and may be sustained for up to 48 hours following the operation.[15] In patients who maintain normal HPA axis function and a cortisol stress response during the course of a transsphenoidal pituitary operation, the postoperative elevation in cortisol is accompanied by transiently increased serum levels of ACTH.[3] We aimed to determine whether the magnitude of this cortisol stress response could serve as a useful indicator of normally functioning pituitary gland that has been preserved during surgery.

In this retrospective analysis of pre- and post-operative morning cortisol levels, we propose that patients retaining sufficient functional pituitary gland, and therefore, corticotroph function, throughout the course of a transsphenoidal pituitary tumor operation would mount an appropriate post-operative cortisol stress response, and that the relative change in patients' pre- and post-operative morning cortisol levels (Δ cortisol index) may serve as a novel and complimentary technique for providing an individualized assessment of the integrity of the HPA axis.

Materials and Methods

Study Population

This report is a single-center, retrospective study consisting of 208 patients who underwent transsphenoidal operations for pituitary adenomas and other sellar lesions at Brigham and Women's Hospital (Boston, MA) between April 2008-April 2010. All transsphenoidal operations were performed by one senior surgeon (ERL). Approval from the institutional review board (IRB) was obtained.

Data Collection

The medical records of all 208 patients who underwent transsphenoidal operations for resection of pituitary/sellar lesions were retrospectively reviewed. Preoperative clinic notes and laboratory values were reviewed to assess for laboratory evidence of HPA axis dysfunction or use of glucocorticoid medications prior to surgery. Intraoperative anesthesia and medical administration records were reviewed to confirm the absence of glucocorticoid administration during the procedure. Postoperative clinical notes, laboratory data, drug administration records, and discharge medication lists were reviewed to assess for the development of hypocortisolemia or administration of steroids following surgery. Finally, follow-up clinic notes, laboratory data, long-term requirement for hormone replacement, and results of dynamic testing of the HPA axis (when available) were entered into a comprehensive database.

Inclusion and Exclusion Criteria

Of the 208 patients who underwent transsphenoidal operations, 15 (7%) had documented preoperative laboratory evidence of Cushing's Disease, and were excluded from the study. One hundred thirty-nine patients (67%) had received intraoperative steroids for a variety of reasons, including preoperative HPA axis dysfunction (the majority), or concern for: cerebral edema, visual loss, airway edema, nausea/vomiting, minimal residual gland visualized, or other empiric treatment, and were thus excluded from the analysis. Two additional patients received empiric postoperative steroid replacement based on clinical symptoms alone, without documented laboratory evidence of hypocortisolemia, and were excluded from the study.

The remaining 52 patients (25%) had no evidence of preoperative HPA axis dysfunction, and did not receive intraoperative or perioperative steroid replacement unless they developed documented postoperative hypocortisolemia. In all 52 patients, preoperative and

postoperative day 1 morning cortisol levels were available for analysis. These patients formed the basis for the current study analysis.

Preoperative evaluation of HPA axis

Routine preoperative endocrine evaluation at our institution in patients with any pituitary pathology consists of a fasting serum morning cortisol, ACTH, TSH, free T4, prolactin, GH, IGFI, and appropriate sex hormones (LH/FSH, estrogen, or free testosterone), obtained within one week of (usually the day prior to) the operation. Patients with evidence of preoperative hypoadrenalism (morning cortisol less than 5 μg/dL) are treated with glucocorticoid replacement (typically hydrocortisone 20mg in the morning and 10 mg in the evening) until the time of surgery. Patients with questionable preoperative hypocortisolemia (morning cortisol level of 5-10 μg/dL) typically undergo Cosyntropin stimulation testing if time permits, or are given replacement corticosteroids during surgery, as determined by our endocrinologist colleague. All blood samples for cortisol were assayed at the Brigham and Women's core laboratory by an automatic analyzer (Roche Cobas E601).

Postoperative monitoring and replacement of cortisol axis

Patients with normal preoperative cortisol levels not receiving intraoperative steroids are monitored with morning fasting cortisol levels on postoperative days 1, 2, and 3. Our institutional preference is that if laboratory evidence suggestive of new hypocortisolemia is detected (defined **at our institution** as a morning fasting cortisol of less than 10 μg/dL), patients are evaluated clinically, and are usually replaced with intravenous or oral stress doses and subsequent tapering regimens of hydrocortisone. In some asymptomatic patients with a postoperative day 1 morning cortisol level of 8-10 μg/dL, a clinical decision may be made to monitor the patient and await the following morning's cortisol level. The majority of patients are discharged home on postoperative day 2 or 3. Those discharged without glucocorticoid replacement typically undergo additional routine laboratory evaluation for morning sodium and cortisol levels on postoperative day 6 or 7, and again at 6 weeks postoperatively.

The requirement for provocative testing of the HPA axis is determined based on the morning fasting cortisol level off glucocorticoid replacement. In patients on glucocorticoid replacement, evening doses the day prior and the morning dose on the day of the test are withheld until the blood sample has been obtained. All patients with any question of cortisol deficiency on a morning cortisol level (typically a morning cortisol of 5-10 μg/dL) are maintained on glucocorticoids until appropriate dynamic stimulation testing (usually a Cosyntropin stimulation test) can be performed to formally assess HPA axis function.

Key outcome measures and Statistical Analysis

For each patient, the Δ cortisol was calculated as the postoperative day 1 morning cortisol level minus the preoperative morning cortisol level. In this study, we defined new early postoperative HPA axis dysfunction/hypocortisolemia as a morning postoperative cortisol value less than 10 μg/dL on postoperative days 1, 2, or 3 (short term). The proportion of patients requiring new glucocorticoid replacement therapy (short term, at the time of hospital discharge, and long term at most recent follow-up) was also calculated for each

group. Resolution of HPA axis dysfunction/hypocortisolemia was defined by either a fasting morning serum cortisol level greater than 10 μg/dL off glucocorticoid replacement or a normal Cosyntropin stimulation test performed at a follow up appointment six weeks after the operation.

Statistical analysis was performed using SPSS (IBM SPSS statistics, version 18, 2010). The proportion of hypocortisolemia (both at hospital discharge and at six weeks follow-up) in the various groups was compared using a Fisher's exact test. The mean values of serum cortisol and the Δ cortisol index among various groups were compared using a two-tailed t-test. Statistical significance was defined as a p-value <0.05. For any given test and threshold, sensitivity was defined as the number of patients developing hypocortisolemia divided by the sum of these patients and patients with a false negative result that also developed hypocortisolemia. Similarly, specificity was defined as the number of patients not developing hypocortisolemia and with a negative test result (true negatives) divided by the sum of these patients and those with a positive test result that did not develop hypocortisolemia (false positives). Receiver Operator Characteristics (ROC) were calculated to evaluate the sensitivity and specificity of Δ cortisol index levels as potential predictor of post operative hypocortisolemia.

Results

Patient Demographics

Patient demographics and indications for surgery in the 52 included are **described below**. The mean age was 44 years (range 18-75 years). There were 33 women (63%) and 19 men (37%). The indications for surgery were as follows: Nonfunctional adenoma (13 patients, 25%), GH-adenoma (13 patients, 25%), Prolactinoma (10 patients, 19%), Rathke Cleft Cyst (10 patients, 19%), Silent-ACTH adenoma (2 patients, 4%), and other lesions (4 patients, 8%). Cushing's Disease was ruled out in both patients with Silent-ACTH adenomas. Other lesions included one patient each with: arachnoid cyst, lactotroph hyperplasia, TSH-adenoma, and nondiagnostic tissue.

Preoperative and postoperative morning cortisol levels and the Δ cortisol index as a marker for the cortisol stress response

Preoperative morning cortisol levels ranged from 10.3 to 30.4 μg/dL (mean ± SD 16.5 ± 4.7 μg/dL). Morning fasting cortisol levels obtained on POD1 ranged from 4.2 to 73.0 μg/dL (mean ±SD 29.2 ± 13.8 μg/dL) (***Figure 1***). In 32 patients (61.5%), the POD1 morning cortisol levels exceeded 25 μg/dL. Morning fasting cortisol levels obtained on postoperative day 2 ranged from 5.3 to 47.0 μg/dL (mean ± SD 21.8 ± 9.0 μg/dL). The Δ cortisol (postoperative day 1 morning cortisol minus preoperative morning cortisol) ranged from −19.0 to +56.2 (mean ± SD +12.7 ± 13.5 μg/dL).

Incidence of early hypoadrenalism

Five patients (9.6%) had early postoperative hypocortisolemia (defined as a fasting morning cortisol < 10 μg/dL) resulting in initiation of glucocorticoid replacement therapy at the time of hospital discharge. The mean preoperative morning cortisol in patients given early

cortisol replacement was 14.2 μg/dL, compared with 16.7 μg/dL in the patients not given early steroids (p=0.26) (Table 1). The mean postoperative day 1 cortisol level in these 5 patients was 11.4 μg/dL, compared with 31.1 μg/dL in patients not developing HPA axis dysfunction (p=0.0017, two-tailed t-test). The mean ± SD of Δ cortisol index in patients given early cortisol replacement was −2.8 ± 6.0 μg/dL, compared with +14.4 ± 13.0 μg/dL in patients not discharged on steroids (p=0.005, two-tailed t-test).

Three of the 5 patients developing early hypocortisolemia did so on postoperative day 1, **developed symptoms consistent with hypoadrenalism,** and were immediately given replacement steroids (cortisol levels 4.2, 6.4, and 9.5 μg/dL). In the other two patients, postoperative day 1 cortisol levels of 19.3 and 17.5 μg/dL were measured, and subsequent hypocortisolemia developed on postoperative day 2 or 3. In one of these patients, a 71-year-old man with a nonfunctioning adenoma, the preoperative morning cortisol was 18.1 μg/dL, and a postoperative day 1 morning cortisol was 19.3 μg/dL (Δ cortisol of +1.2). He developed hypocortisolemia (cortisol level 5.3 μg/dL) on postoperative day 2 and was discharged home on maintenance doses of hydrocortisone. In another patient, a 73-year-old man with a GH-adenoma, the preoperative cortisol was 12.1 μg/dL, and a postoperative day 1 cortisol was 17.5 μg/dL (Δ cortisol of +5.4). He developed hypocortisolemia on postoperative day 3 (cortisol 8.5 μg/dL), and was discharged home on hydrocortisone replacement.

Incidence of hypocortisolemia at follow-up

Of the 48 patients discharged home without steroid replacement, none developed new hypoadrenalism per evaluation at a six-week follow-up appointment. Of the 5 patients discharged on cortisol replacement medications, at most recent follow-up only 1 (2%) required cortisol replacement for greater than 6 weeks following the operation. Three of the other patients had an intact six-week postoperative Cosyntropin stimulation test, and were asymptomatic off medications. One patient had a morning fasting cortisol of 14.4 μg/dL measured with her previous evening hydrocortisone dose withheld one week following the operation, and hydrocortisone was discontinued with no new symptoms. The one patient with a persistent cortisol replacement requirement had a Δ cortisol index of +1.2. Two women in the analysis group were taking oral estrogen replacement, and one had a low delta cortisol level but did not require cortisol replacement.

The Δ cortisol index as a predictor of hypocortisolemia

The area under the ROC curve was 0.893 (95% CI 0.7899 to 0.9973, P=0.004). The Δ cortisol index of +6 μg/dL as a threshold for predicting early postoperative hypocortisolemia and the need for hormone replacement resulted in a sensitivity of 100% (95% CI 47.8-100%) and specificity of 72.4% (95%CI 71.7-93.8%). Of the 18 patients with a Δ cortisol index less than +6 μg/dL (mean Δ cortisol of −2.0 μg/dL), 5 (28%) required early cortisol replacement therapy. None of the 34 patients with a Δ cortisol index of greater than +6 μg/dL (mean +20.5 μg/dL) required treatment with steroids postoperatively (p value =0.0033, Fisher's exact test). Only 1 such patient (2%) developed permanent hypocortisolemia requiring long-term replacement; thus we were not able to assess the predictive value of the Δ cortisol index for long-term HPA axis dysfunction in this study.

As a comparison with our previous patient data, the criterion of a postoperative day 1 morning cortisol level of <15 μg/dL offered a sensitivity of 60%, a specificity of 89%, a positive predictive value of 38%, and negative predictive value of 95% for predicting perioperative ACTH deficiency. (Table 2) Postoperative day 1 cortisol levels and the Δ cortisol values of the entire study population are depicted in *Figure* **2**, with suggested threshold levels for predicting hypocortisolemia based on each of these parameters.

Discussion

The presence of a normal physiological cortisol stress response to surgical resection of a pituitary tumor may serve as a useful screening method for determining the presence postoperatively of adequate amounts of normally functioning pituitary gland. The ability to mount a sufficient stress response in the face of any physically or emotionally stressful event, such as surgery, may be a useful measure of residual pituitary and corticotroph function in patients without Cushing's Disease and normal preoperative HPA axis function. In a similar fashion, dynamic testing of the HPA axis relies on controlled stimulation of the pituitary corticotrophs in order to assess ACTH secretion. It has been well documented that serum cortisol increases substantially following surgical procedures, with non-stimulated cortisol levels typically documented in the 20-30 μg/dL range following a wide variety of elective surgical procedures.[14,12,16] Sixty-five percent of the patients in the current study had postoperative cortisol levels greater than 25 μg/dL, and 35% had levels greater than 35 μg/dL. Although the majority of patients who undergo pituitary operations with normal preoperative and postoperative HPA axis function are able to mount an appropriate stress response (mean Δ cortisol of +14.4), patients that developed new hypocortisolemia requiring replacement therapy had a mean Δ cortisol of −2.2 (p=0.005).

New HPA axis deficiency requiring glucocorticoid replacement therapy has typically been reported to occur in fewer than 10% of previously normal patients following transsphenoidal pituitary surgery.[2,1,4,3,6,5] Many of these patients demonstrate early, transient ACTH deficiency following pituitary surgery, prompting temporary cortisol replacement medication, and are subsequently found to have normalization of HPA axis function with delayed stimulation testing.[4] Although provocative stimulation testing is the gold standard test for diagnosing longstanding HPA axis deficiency, there is currently no reliable or accepted authoratative test used to screen for new HPA axis deficiency in the short term following transsphenoidal adenomectomy. Strategies for perioperative assessment and replacement of the HPA axis vary considerably from institution to institution, with no universally established consensus in place for practitioners to follow. For example, preoperative assessment may be performed using fasting morning cortisol levels or one of several provocative tests of the HPA axis.[17,18,9] During surgery, intravenous glucocorticoids may be administered empirically to all patients, but many institutions base this decision on preoperative HPA axis function. Finally, there is no universally accepted method regarding the timing, assessment, and replacement strategy of the HPA axis in the post-operative period for patients with normal preoperative HPA axis function.[9,8,19,4] Previous studies have demonstrated that postoperative day 1 or 2 morning cortisol levels may be used to predict the likelihood of HPA axis dysfunction, recommending 15-16 μg/dL as a threshold above which patients are unlikely to develop subsequent cortisol deficiency.

[9,6,11] Although the use of a threshold postoperative cortisol level certainly provides some benefit as a screening tool for hypocortisolemia, it may not entirely account for the individualized HPA axis dynamics that occur in each patient before, during, and after a transsphenoidal operation. Because patients undergoing transsphenoidal operations for pituitary tumors are frequently discharged home as early as postoperative day 2, an early screening method for deciding which patients can be safely discharged home with or without steroid coverage until future assessment is possible would be of great clinical use.

The gold standard tests for assessment of the HPA axis are provocative studies, including the Cosyntropin stimulation test (CST), insulin tolerance test, and metyrapone test. It has been determined, however, that dynamic HPA axis testing may not be accurate within the immediate postoperative period.[20,21,7] Some studies have attempted to correlate morning serum cortisol levels with the results of dynamic HPA axis testing, and suggested various ranges of morning cortisol levels that may be used to assess for hypoadrenalism with some assurance.[17] Based on these studies, cortisol levels <3-4 μg/dL have been reported as minimum values, below which patients are likely to have adrenal insufficiency; Maximal values of morning cortisol levels ranging from 7-16 μg/dL have been reported, above which patients are extremely likely to have normal HPA function.[4,17,9] In patients with morning cortisol levels in the intermediate range, empiric glucocorticoid coverage has been recommended until delayed provocative HPA axis testing can be performed.[9]

Based on correlations between a morning fasting cortisol level and various provocative HPA axis tests, previous studies have defined threshold levels of morning cortisol levels that, in lieu of immediate postoperative dynamic stimulation testing, may serve as predictive markers for short- and long-term hypocortisolemia. The recommended timing of checking morning cortisol levels following selective adenomectomy, however, has varied from postoperative day 1 to 7, or even later in some studies.[1,9,19,4,11] In 2009, Marko et al reported their findings in a series of 83 patients undergoing pituitary surgery, in which all patients had morning cortisol levels assessed on postoperative day 1 (or 2 if intraoperative steroid were administered).[6] The authors reported that a threshold morning cortisol level of 15 μg/dL offered a sensitivity of 80.5%, specificity of 66.7%, and PPV of 96.9% in the ability to detect delayed hypocortisolemia, as compared to delayed dynamic testing. Although the results of this study are insightful, they may not account for a patient's preserved (or compromised) ability to mount a sufficient stress response following a surgical procedure and manipulation, injury to, or resection of the previously normal gland. Perhaps more importantly, some patients in the Marko study with a postoperative day 1 cortisol >15 μg/dL were discharged home without subsequent cortisol assessment until their follow-up CST, and developed HPA axis deficiency. Of the 5 patients in our series who went on to develop symptomatic HPA axis dysfunction, two had cortisol levels greater than 15 μg/dL on postoperative day 1, then subsequently dropped below a level of 10 μg/dL. However, in both of these patients, the Δ cortisol index was low (+1.2 and +5.4).

One of the limitations of the current study is the retrospective design with a relatively small number of patients and single cortisol measurements for many patients; A larger, prospective study would be ideal to confirm the true diagnostic benefit of the Δ cortisol index in predicting new HPA axis deficiency. Similarly, the small number of patients that developed

early hypocortisolemia make the overall usefulness of this method more difficult to interpret. This study is also limited in that delayed dynamic HPA axis testing, which is the gold standard test for evaluation of cortisol secretion, was not assessed in all patients. Delayed testing of morning cortisol levels was performed on all patients, however, and above a certain level (10 μg/dL at our institution) may obviate the requirement for stimulation testing of the HPA axis.[9] It is therefore our practice to perform dynamic HPA axis testing on patients with a delayed morning cortisol level between 5-10 μg/dL. In the current study, 3 of the 5 patients who were discharged home on hydrocortisone replacement were determined to have normal long-term HPA axis function with subsequent Cosyntropin stimulation testing. Therefore, although it is possible that the Δ cortisol index is overly sensitive in detecting HPA axis deficiency, as a screening test this would be preferable to having too low a sensitivity. Finally, the Δ cortisol index may be more useful for predicting short-term HPA axis deficiency and screening for patients who should be discharged home on steroids, rather than predicting long term HPA axis deficiency, which is better measured by stimulation testing for appropriate confirmation.

Conclusions

In patients with normal preoperative HPA axis function undergoing transsphenoidal operations for pituitary lesions, complimentary use of the Δ cortisol index as a marker of an intact cortisol stress response from preserved residual pituitary gland may serve as a novel, individualized, and sensitive screening method to identify patients at risk for developing hypocortisolemia. The ability to accurately screen for patients at risk for new ACTH deficiency shortly after transsphenoidal operations is critical, and no consensus or authoritative test for doing so currently exists for practitioners involved in the routine perioperative care of such patients. Additional prospective studies would be helpful to confirm the fact that the Δ cortisol index is an accurate predictor of HPA axis dysfunction.

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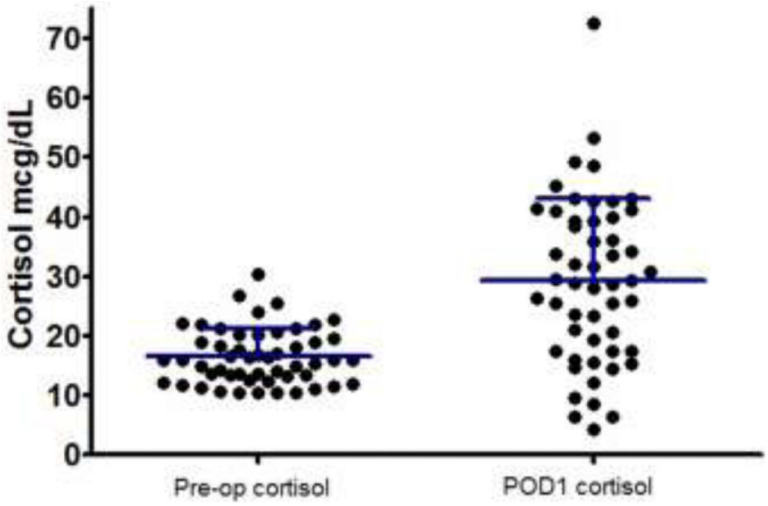

Figure 1.

Distribution of cortisol levels before and on post-operative day 1 following transsphenoidal pituitary surgery. Cortisol levels were measured at 8AM in the fasting condition on both days. The black dots indicate the cortisol levels of the 52 patients included in the study. The blue bars correspond to the mean + SD of preoperative and POD1 cortisol levels.

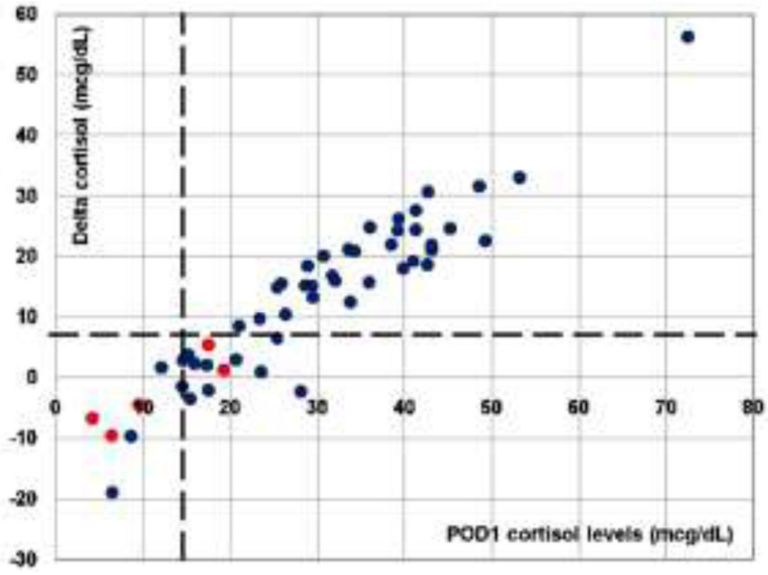

Figure 2.

Suggested threshold for prediction of postoperative hypocortisolemia. All 52 patients included in the study are plotted based on their postoperative day 1 cortisol level and the Δ cortisol index. The red dots indicate patients who developed cortisol deficiency requiring glucocorticoid replacement therapy at hospital discharge.

Table 1

Mean preoperative morning, POD1 morning, and Δ Cortisol Index in 52 patients undergoing transsphenoidal pituitary operations for sellar lesions.

	All Patients	Patients requiring glucocorticoid replacement at hospital discharge	Patients not requiring postoperative glucocorticoid at hospital discharge	p-value
Number of patients	52	5	47	-
Mean preoperative Cortisol level (μg/dL)	16.5	14.2	16.7	0.26
Mean POD1 Cortisol level (μg/dL)	29.2	11.4	31.1	0.0017
Mean Δ Cortisol Index	+12.7	−2.8	+14.4	0.005

Table 2

Comparison of using a postoperative day 1 threshold cortisol level of less than 15 μg/dL versus Δ cortisol index less than +6 μg/dL or less than +1.5 μg/dL to predict the requirement for short-term glucocorticoid replacement.

Test	Sensitivity	Specificity
POD1 cortisol level < 15 μg/dL	60%	89%
A Cortisol index less than +6.0 μg/dL	100%	74%
A Cortisol index less than +1.5 μg/dL	80%	85%