Early Morning Cortisol Levels as Predictors of Short-Term and Long-Term Adrenal Function After Endonasal Transsphenoidal Surgery for Pituitary Adenomas and Rathke’s Cleft Cysts

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OBJECTIVE: Patients undergoing pituitary adenoma or Rathke cleft cyst (RCC) removal are often administered perioperative glucocorticoids regardless of lesion size and preoperative adrenocorticotropic hormone/cortisol levels. To minimize unnecessary glucocorticoid therapy, we describe a protocol in which patients with normal preoperative serum cortisol and adrenocorticotropic hormone levels are given glucocorticoids only if postoperative day 1 or 2 (POD1 or POD2) cortisol levels decrease below normal.

METHODS: A total of 207 consecutive patients undergoing endonasal surgery for an adenoma or RCC were considered for study. Of these, 68 patients with preoperative adrenal insufficiency or Cushing disease were excluded. Glucocorticoids were withheld unless POD1 or POD2 cortisol values were below normal (≤4 μg/dL). Subsequent adrenal status was assessed through follow-up biochemical and clinical evaluations.

RESULTS: The 139 patients included 119 with macroadenomas, 14 microadenomas, and 6 RCCs (follow-up, 3–41 months; median, 10 months). Nine patients (6.5%), all with macroadenomas (mean diameter, 26 ± 10 mm) had low POD1 or POD2 cortisol values and received glucocorticoids; of these, five patients were weaned off within 3–28 weeks of surgery. Overall, 12 of 139 patients (8.6%) were treated for early (n=9) or delayed (n=3) adrenal insufficiency but only 5 patients (3.6%) remain on glucocorticoid replacement. No patient experienced an adrenal crisis. Using morning POD1 or POD2 cortisol values >4 μg/dL as a measure of adequate hypothalamic-pituitary-adrenal axis function, yields a sensitivity of 96%, a specificity of 57%, and a positive predictive value of 98%.

CONCLUSIONS: In patients with normal preoperative cortisol levels undergoing endonasal removal of a pituitary adenoma or RCC, normal morning cortisol values on POD1 and POD2 reliably predicts adequate and safe adrenal function in 98% of patients. This simple protocol of withholding postoperative glucocorticoids avoids unnecessary steroid exposure and poses minimal risk to the well-informed closely monitored patient.

INTRODUCTION

New anterior pituitary failure is a well-known potential consequence of pituitary surgery, ranging from 2%–22% (1, 4, 7, 8, 14, 27, 34). Specifically, de novo long-term adrenal insufficiency after endonasal removal of pituitary adenomas or Rathke cleft cysts (RCC) generally occurs in ≤5% of patients and is more common in adenomas more than 2 cm in size (14). Postoperative adrenal insufficiency typically presents with symptoms of fatigue, loss of appetite, nausea, vomiting, arthralgias, and, in some instances, hypotension (24).

Although it is considered standard of care to administer perioperative glucocorticoids to patients with documented adrenal insufficiency undergoing pituitary surgery, the need for perioperative glucocorticoids in patients with normal preoperative cortisol and adrenocorticotropic hormone (ACTH) levels is more controversial. To avoid potential complications of postoperative adrenal insufficiency, many centers routinely administer perioperative glucocorticoid therapy to patients, regardless of tumor size and preoperative pituitary-adrenal function. However, this practice likely results in unnecessary treatment of some patients with normal hypothalamic-pituitary-adrenal (HPA) axis function and exposes them to potential complications of exogenous glucocorticoids including hyperglycemia, bone loss, hypertension, mood changes, and weight gain (29–32, 35). Other centers withhold glucocorticoids in patients with normal preoperative adrenal function depending on early postoperative cortisol levels, and typically use a postoperative morning cortisol threshold lower than 8–15 μg/dL to initiate treatment (12, 19, 23–25, 33).
In an effort to minimize unnecessary glucocorticoid therapy, we describe a protocol in which patients with normal preoperative serum cortisol and ACTH levels are given glucocorticoids only if postoperative day 1 (POD1) or 2 (POD2) cortisol levels decrease below normal. In this report, we analyze 139 patients who, during a 41-month period, underwent endonasal transsphenoidal removal of a pituitary adenoma or RCC.

METHODS

All consecutive patients who underwent an endonasal transsphenoidal removal of a pituitary adenoma or drainage of a RCC between July 2007 and December 2010 were considered for this study. Procedures were all performed by the senior author (D.F.K.) at Saint John’s Health Center. Medical records were reviewed to document preoperative and postoperative hormonal status, pathology reports, magnetic resonance imaging (MRI) characteristics, operative notes, and clinic follow-up notes from the patient's neurosurgeon and endocrinologist. Overall, a total of 207 patients were identified from the database; 68 of these patients were excluded from this analysis as they had preoperative adrenal insufficiency or Cushing disease. This retrospective study of patient data was approved by Saint John’s Health Center’s Institutional Review Board.

Preoperative, Perioperative, and Postoperative Hormonal Assessment

The majority of preoperative and postoperative endocrine assessments for this patient cohort were performed at outside laboratories. Although not all patients had identical evaluations, the following preoperative and postoperative tests (at least 3 months after surgery) were used for assessing the different hormonal axes: morning plasma ACTH and serum cortisol, thyroid-stimulating hormone (TSH), total thyroxine (T4) or free T4, luteinizing hormone, follicle-stimulating hormone, prolactin, growth hormone (GH), and insulin-like growth factor 1. Results were therefore interpreted as normal or abnormal based on each laboratory’s reference range. Secondary hypothyroidism was diagnosed if the patient had the combination of either a low free T4/low TSH or a low free T4/normal TSH. Hypogonadism in women was diagnosed if amenorrhea and/or infertility were present and if gonadotropins were low or low normal in the setting of low estradiol levels. Secondary hypogonadism was diagnosed if the patient had low serum testosterone (or low estradiol) in the context of either normal or low gonadotropin levels. GH deficiency was based on low age- and sex-adjusted insulin-like growth factor 1 and in some instances by gonadotropin-releasing hormone arginine or the insulin tolerance test (ITT). Any patient who had three other anterior hormonal axis deficiencies (corticotrop, thyrotrop, and gonadotrop) was categorized as being GH deficient, whether in the preoperative or postoperative state. Posterior pituitary function was assessed based on urine specific gravity, serum sodium, and urine output. Patients were diagnosed with postoperative diabetes insipidus (DI) if urine specific gravity was ≤1.005 and urine volume was >200 mL/h for at least 3 consecutive hours.

The corticotrop axis evaluation included morning plasma ACTH and serum cortisol levels. The normal reference range for the morning plasma ACTH (quantiative chemiluminescent immunoassay performed on the Immulite 2000 Analyzer [Siemens Healthcare Diagnostics Inc., Tarrytown, New York, USA]) is 6–58 pg/mL. The normal reference range for AM serum cortisol is 3.7–19 μg/dL and PM (after 5 PM) serum cortisol is 2.9–17.3 μg/dL (chemiluminescent microparticle immunoassay performed on the Architect i2000 Systems [Abbott Diagnostics, Abbott Park, Illinois, USA]). In patients with subnormal serum cortisol levels and/or those with clinically suspected adrenal insufficiency, a dynamic testing of the hypothalamic-pituitary axis was often performed with a Cortrosyn stimulation (Amphastar Pharmaceuticals, Rancho Cucamonga, California, USA) or metyrapone test. Patients with Cushing disease or adrenal insufficiency were excluded from this analysis.

Perioperative Evaluation of Adrenal Axis and Need for Glucocorticoid Replacement

For patients with normal preoperative serum cortisol levels, no glucocorticoids were given preoperatively or intraoperatively. Morning (5–7 AM) serum cortisol and ACTH levels were drawn on POD1 and POD2, and the need for cortisol replacement was based on the AM cortisol value results, which were typically available within 2–3 hours of the blood draw. Glucocorticoids were withheld unless POD1 or POD2 morning cortisol values were below normal (≤4 μg/dL). Patients who maintained normal cortisol levels in the postoperative setting with no symptoms suggestive of adrenal insufficiency (i.e., nausea, vomiting, dizziness, malaise, hypotension, and tachycardia) were discharged home without glucocorticoids. In a small subset of patients with low normal cortisol values and questionable symptoms of adrenal insufficiency, a repeat afternoon serum cortisol value was obtained. If levels were below normal at that time, glucocorticoid replacement was initiated. Patients with morning POD1 or POD2 cortisol levels ≤4 μg/dL were typically given a single dose of intravenous hydrocortisone (25–50 mg intravenously) and then converted to oral hydrocortisone (25 mg) the day after diagnosis of adrenal insufficiency. Patients are discharged with an order of prednisone 10 mg daily for the first week after surgery, then are typically reduced to 5 mg in the AM and 2.5 mg in the PM or 5 mg daily if tolerated by the patient.

At the time of discharge, typically on POD2, written and verbal instructions specifically regarding symptoms of adrenal insufficiency were given to all patients and they were reminded to call the office if such symptoms occurred. All patients had their first postoperative clinic visit within 7–14 days after surgery. Subsequent adrenal status was assessed through routine clinical evaluations and biochemical follow-up typically within 3–6 weeks of surgery and then at least within 6 months, although provocative adrenal function testing was not routinely used. These evaluations were typically done through our clinic or with the patient’s endocrinologist. For patients who required glucocorticoid replacement in the initial postoperative period or in a delayed fashion, the decision to discontinue glucocorticoids was deferred to their treating endocrinologist. Although provocative testing was not standardized, recovery of function was typically documented using either a Cortrosyn stimulation or metyrapone test.

Statistical Analysis

Statistical analyses were performed with the Prism 5.0 GraphPad Software (La Jolla, California, USA). The Mann-Whitney test was used to compare the distribution between two groups. Age of patients and tumor diameters between groups were compared using, respectively, a t-test and
a Mann-Whitney test. Percentages of patients between groups were compared using Fisher’s exact test. A P value of < 0.05 was considered significant.

**Surgical Technique of Adenoma and Rathke Cleft Cyst Removal**

As previously described (13), a direct endonasal approach to the sellar region was performed. Operations done from July 2007 to April 2010 were performed using an endoscope-assisted microsurgical approach. Since April 2010, pituitary adenomas were removed using either an endoscope-assisted approach or a fully endoscopic approach. Regardless of the approach, relevant to this report is the recognition of normal gland location. In almost all cases of pituitary adenomas, the normal pituitary gland is easily identified on preoperative sellar MRI as an enhancing rim of tissue adjacent to the hypoenhancing adenoma. In most cases of RCCs, the cyst is posterior to the anteriorly displaced anterior pituitary gland. In all patients a selective adenomectomy was attempted with the additional goal of preserving normal pituitary gland. In most patients, a tumor resection using the tumor pseudocapsule was performed to help maximize tumor removal and minimize chances of gland damage (14, 20, 28). For larger tumors, compressed pituitary gland is most often found lining the superior, superolateral, or lateral edges of the tumor. Attenuated and severely compressed normal gland that is draped over the anterior aspect of the tumor and that limits exposure to the tumor is often sacrificed by sharply cutting it to create a wider window into the tumor and to limit overt manipulation of more viable gland closer to the infundibulum.

For typical intrasellar RCCs with the cyst located behind the anterior lobe, removal involves an approach through the anterior gland by a low midline vertical incision (11). Through this small corridor, the cyst contents are removed with suction, curettes, and irrigation; no attempt is made to vigorously strip the cyst wall off of the normal gland.

In all cases, inspection of the sellar resection cavity under endoscopic visualization is performed to evaluate for completeness of tumor removal or cyst drainage and to assess for intraoperative cerebrospinal fluid leaks. Full-strength (3%) hydrogen peroxide is irrigated directly into the sellar surgical bed for several minutes to aid in hemostasis and for its tumoricidal effect (14). Hydrogen peroxide is used for almost all adenomas unless there was a large surgical defect in the diaphragma sellae.

**RESULTS**

**Study Cohort**

After excluding patients with Cushing disease or preoperative adrenal insufficiency who received perioperative glucocorticoids, 139 patients were analyzed including 63 women and 76 men, with a median age of 50 years (range, 17–88 years). The cohort included 119 patients with macroadenomas, 14 with microadenomas, and 6 with RCCs. Of those with a macroadenoma, 92 underwent a first time adenomectomy and 27 had a repeat surgery for recurrent or residual tumor. Among all pituitary adenomas (n = 133), 59 were endocrine-active adenomas, including all 14 microadenomas and 45 macroadenomas (35 prolactinomas, 21 GH-secreting adenomas, and 3 thyrotropinomas).

**Occurrence of Postoperative Hypocortisolemia**

Nine (6.5%) of 139 patients had subnormal cortisol values documented (2 patients on POD1 and 7 patients on POD2) (Table 1). POD1 and POD2 morning cortisol values in these nine patients averaged 7.5 μg/dL (range, 1–22.5 μg/dL) and 2.4 μg/dL (range, 1–4.4 μg/dL), respectively (Figure 1). None of these patients developed the electrolyte abnormalities (hypokaliemia/hypocalcemia) that could be found in the context of adrenal insufficiency. Of these nine patients, three had low POD1 cortisol values, Patient 2 had a low normal POD1 cortisol value and symptoms of adrenal insufficiency with a repeat low POD1 afternoon serum cortisol of 1.7 μg/dL and was administered glucocorticoids. Patient 8 had a low morning POD1 cortisol value and was immediately started on steroids. Patient 9 had a low morning POD1 cortisol level (1 μg/dL) but no symptoms of adrenal insufficiency. It was thought that his adrenal axis would rapidly recover given his normal preoperative cortisol value (10.4 μg/dL), the uneventful resection of a small macroadenoma, and the normal-appearing gland and infundibulum on his postoperative day 1 MRI. However, on POD2 his cortisol level remained at 1 μg/dL and he was then started on glucocorticoids, although he had no symptoms of adrenal insufficiency. The remaining six patients with low POD2 morning cortisol values were all started on glucocorticoids including one symptomatic patient with a borderline low value of 4.4 μg/dL. She was tapered off prednisone within 1 month of surgery and remains off glucocorticoids 2 years after surgery.

All nine patients with low POD1 or POD2 cortisol had macroadenomas (average tumor diameter, 26.1 ± 10 mm) and seven patients had at least one preoperative anterior pituitary hormonal axis deficiency (Table 1). None of the six patients with a RCC had low POD1 or POD2 cortisol value (mean cyst diameter, 12.5 ± 4 mm).

In comparing the nine patients with POD1 or POD2 hypocortisolemia with the 130 patients without early hypocortisolemia, POD1 cortisol values were lower on POD1 (7.5 μg/dL vs. 19.1 μg/dL; P = 0.013) and on POD2 (2.4 μg/dL vs. 11.6 μg/dL; P < 0.0001).

Of the nine patients with early postoperative hypocortisolemia given glucocorticoid replacement, five were weaned off within 3–28 weeks of surgery (Table 1). The mean size of macroadenomas in patients who were tapered off glucocorticoids versus those who not was 25 mm versus 27.5 mm (Mann-Whitney test. P = 0.22).

Among the 130 patients with normal POD1 and POD2 morning cortisol level, only 3 patients (2.3%) were subsequently placed on glucocorticoids within 12 months of surgery; all with macroadenomas ranging in size from 16–30 mm. The POD1 and POD2 cortisol values of these three patients ranged from 3.7–32 μg/dL. The patient with a 3.7 μg/dL value on POD1 had a value of 4.1 μg/dL on POD2 and remained asymptomatic. Of these 3 patients, 2 were weaned off steroids by their endocrinologist after being treated for 5 and 10 months, respectively.

Median follow-up of patients included in this study was 10 months (range, 3–41 months). Overall, 12 of 139 (8.6%) patients were treated for early or delayed adrenal insufficiency, but at last follow-up only 5 (3.6%) remain on glucocorticoid replacement. No patient experienced a delayed adrenal crisis throughout their follow-up.

Using a cutoff of >4 μg/dL as a measure of normal HPA function and including all 12 patients who required early or delayed glucocorticoid replacement, sensitivity of this test was 96%, specificity was 78%, and positive predictive value was 98%. 
Risk Factors for Postoperative Hypocortisolemia

In comparing the 9 patients with early hypocortisolemia to the 130 without early hypocortisolemia, mean maximal tumor or cyst diameter was 26.1 mm versus 20.4 mm (Mann-Whitney test, \( P = 0.13 \)); mean age was 56 years versus 50 years, respectively (\( t \)-test, \( P = 0.28 \)); and 2 of 9 patients (22.2%) versus 25 of 130 patients (19.2%) were undergoing reoperations (Fisher’s exact test, \( P = 0.69 \)).

### DISCUSSION

#### Summary of Findings

In this study of 139 consecutive patients with normal preoperative adrenal function who had endonasal removal of a pituitary adenoma or a RCC, 6.5% patients, all with macroadenomas, had subnormal POD1 or POD2 morning cortisol values and received glucocorticoid replacement on POD1 in two patients and on POD2 in seven patients. Of these nine patients, five were weaned off steroids within 3–28 weeks of surgery. In 130 patients with normal POD1 and POD2 morning cortisol values, only 3 (2.4%) subsequently required glucocorticoid replacement and of these patients, 2 patients were weaned off glucocorticoids. In both groups, the average cortisol values were higher on POD1 than on POD2, likely reflecting the impact of gland manipulation and surgical stress immediately after surgery. Overall, none of the 139 patients experienced an adrenal crisis in early or subsequent follow-up, and only 5 patients (3.6%) remain on glucocorticoids at last follow-up. No patient developed electrolyte abnormalities that could be found in the context of adrenal insufficiency. In fact it...
would have been unusual for such patients to develop electrolyte imbalance related to their adrenal insufficiency as the renin-angiotensin-aldosterone axis is not disrupted in secondary adrenal insufficiency.

**Long-Term Pituitary Dysfunction After Pituitary Surgery**

The risk of new long-term anterior pituitary failure after pituitary adenoma surgery has ranged from 2%—22% (1, 4, 7, 8, 14, 27, 34) and permanent DI is typically 3% or less, varying from 0.4%—15% (1, 5, 6, 8, 10, 14, 16, 17, 26). We previously reported on 444 patients who underwent transsphenoidal adenomectomy and noted that new hypopituitarism occurred in 5% of patients. On multivariate analysis, larger tumor size was the only predictor of new hypopituitarism (14). Average tumor diameter in patients who developed new hypopituitarism was 28 mm versus 20 mm in those that did not (14).

The risk of new long-term postoperative adrenal insufficiency was found to be 2% in the overall study population and 4% in patients with endocrine-inactive adenomas, similar to the long-term rate of adrenal insufficiency of 3.6% we report in the present series. In patients undergoing RCC removal or drainage, the rate of new long-term hypopituitarism has ranged from 4%—30% (3, 11, 22). In our recent report in a series of 50 patients with RCC, new anterior or posterior pituitary gland dysfunction occurred in 4 (8%) patients, but new adrenal insufficiency occurred in none (11). Therefore, the occurrence of new hypopituitarism, and specifically new adrenal axis dysfunction, is uncommon, especially when efforts are made to minimize pituitary gland manipulation and traction during adenoma removal or drainage of a RCC (11, 14).

**Implications of Hypocortisolemia and Inadequate Supplementation**

Although the risk of long-term adrenal insufficiency after adenoma or RCC removal is quite low, particularly in smaller tumors, some centers administer prophylactic perioperative glucocorticoid therapy to all patients undergoing adenoma or RCC removal, regardless of tumor or cyst size and even if preoperative ACTH/cortisol levels are normal. Although this is a safe practice from the standpoint of avoiding potential symptomatic adrenal insufficiency, which may manifest in the early postoperative period as malaise, postural hypotension, poor stress response, and electrolyte disturbances, glucocorticoid therapy, particularly if prolonged can lead to known adverse effects such as Cushingoid body habitus, metabolic disturbances of glucose intolerance, hypertension, protein catabolism, and osteoporosis (29—32, 33). On the other hand, identifying patients with hypocortisolemia is important and requires appropriate supplementation of glucocorticoids. Appropriateness of supplementation remains an area of discussion as there is no clear consensus on the optimum glucocorticoid supplementation dose (2). Assessing patients’ postoperative pituitary function, especially the corticotroph axis is most critical in the early postoperative period during the first 7—10 days after surgery.

**Provocative Postoperative Assessment of the HPA Axis in Patients With Pituitary Lesions**

In addition to symptoms and signs, numerous dynamic tests (i.e., Cortrosyn stimulation test, metyrapone test, and ITT) have been developed to assist in the evaluation of the HPA axis after surgery. However, at present, there is no consensus as to which test should be used, or when is the optimal time to perform the test. Watts and Tindall (33) studied the corticotrophin reserve in 35 patients undergoing pituitary surgery. Glucocorticoids were administered 1—2 days postoperatively and a 6 AM cortisol level was assessed 24 hours after discontinuation of steroids. A cortisol level of 9 μg/dl (250 nM) or more was predictive of a normal axis, based on an ITT performed 5—7 days postoperatively. Postoperative adrenal insufficiency was documented in 22% of patients (8/35) by using the ITT—all had cortisol levels of 3 μg/dl (80 nM) or less. Permanent adrenal insufficiency occurred in only three patients. The investigators propose that a transient or partial adrenal insufficiency may occur in the early postoperative setting, remaining subclinical and asymptomatic in most patients (33).

**Nonprovocative Assessment of Postoperative Morning Cortisol Levels**

More than 2 decades ago, Hout et al. (18) documented that 97.5% (81/83) of patients with pituitary adenomas with normal preoperative HPA function had no postoperative clinical or biochemical signs of adrenal insufficiency, defined as morning serum cortisol <5 μg/dl (138 nmol/L). They proposed that multiple levels should be drawn to assess the axis rather than a single value. They recommended close clinical observation in the initial postoperative period with multiple morning serum cortisol levels (POD1 to POD6) to reliably predict the integrity of the HPA axis and obviate the need for perioperative steroids and further delayed testing (15).

More recently, many centers withhold perioperative steroids depending on the early postoperative cortisol levels, using morning cortisol level thresholds between 8 and 15 μg/dl (25). Cozzi et al. (3) assessed 8 AM serum cortisol levels preoperatively and on POD2 and compared these results to peak cortisol after low dose ACTH at 6 weeks after surgery. In their series, a cortisol level of >8 μg/dl on POD2 was considered as normal and corroborated with results of low dose ACTH test. Hypocortisolism was detected on POD2 in 10.3% of patients. In this series (9), no relation was found between the occurrence of hypocortisolism and age, preoperative tumor size, occurrence of DI, or extent of tumor resection.

Marko et al. (24) recently reported that an immediate postoperative cortisol level >15 μg/dl within 60—180 minutes after surgery is a sensitive and accurate predictor of normal postoperative HPA axis function with a sensitivity of 98% and accuracy of 97%, with a positive predictive value of 99%. In their series on 100 patients undergoing transsphenoidal pituitary adenoma resection, they found 6.7% of patients who had levels <15 μg/dl and started on steroids (range, 5.2—14.4 μg/dl). These patients passed their postoperative Cortrosyn stimulation test and were subsequently weaned off steroids. In a related study (23), the investigators noted that only 1.6% of patients who had an early PO morning cortisol level >15 μg/dl had demonstrable evidence of HPA dysfunction requiring steroid replacement. In our series, using a cutoff of >4 μg/dl as a measure of normal HPA function, sensitivity was 96%, specificity was 57%, and positive predictive value was 98%. The potential advantage of the present protocol with testing on POD1 and POD2 may be that it allows the wide fluctuations in serum cortisol often seen in the first few hours after surgery to resolve and therefore may give a more accurate baseline assessment of serum cortisol closer to the
time of patient discharge. The impact of gland manipulation, surgical trauma, and general anesthesia may all impact postoperative cortisol levels in the first few hours after surgery leading to wide fluctuations. Also the relatively wide time window of 60–360 minutes after surgery used in the Marko protocol may be another source of cortisol variability. Given that most patients undergoing pituitary surgery remain in hospital for 2 days after surgery, there appears to be no disadvantage to delaying cortisol measurements to get a more accurate HPA function assessment closer to patient discharge.

A detailed review of the literature demonstrates conflicting opinions regarding what constitutes a safe morning plasma cortisol level. After transsphenoidal pituitary surgery, obviously, the higher the cortisol level cutoff, the lower the risk of adrenal insufficiency. The upper cutoff used in various studies has ranged from 8–23 μg/dL (21, 23, 24). The lower cutoff for the normal range has varied from 3–4 μg/dL (21). In addition to the individual tailored cutoff values, the timing of assessment has varied significantly. Although most previous studies have recommended POD 3–7, more recent studies have recognized the validity of earlier evaluations on POD1 and POD2 (23, 24).

Practical Utility of POD1 and POD2 Cortisol Levels After Transsphenoidal Surgery

Despite the variations in timing and cutoff levels, the early postoperative AM serum cortisol level after transsphenoidal surgery appears to provide a safe and efficient means of assessing adrenal function. In the present study, a lower cutoff value of 4 μg/dL on POD1/POD2 reliably predicted adequate and safe function in the majority of patients. This simple nonproven test is rapidly performed and allows evaluation of the HPA axis before discharge. It eliminates the need for glucocorticoid administration in a large subset of patients who might otherwise be treated unnecessarily with glucocorticoids.

Several practical points are important to remember in using this clinical protocol. First, in the majority of patients, cortisol levels trend downward from POD1 to POD2, therefore it is essential to monitor patients on both days after surgery. This downward trend is not surprising as the HPA response to surgical stress is expected to decline as more time elapses from surgery. In our series, the decision to treat 7 of 9 patients with glucocorticoids was based on POD1 morning cortisol levels. Although many patients after endonasal pituitary surgery could otherwise go home on POD1, adrenal function monitoring is a strong rationale to keep all patients in the hospital for at least 2 days after adenoma or RCC surgery. Close observation by the surgical team and nursing staff is also important as some patients may manifest symptoms of adrenal insufficiency during the day and it is reasonable to repeat an afternoon cortisol level in a patient whose morning level was in the low normal range. Second, patients who appear most at risk for early de novo adrenal insufficiency include those with macroadenomas, those with at least one preoperative anterior pituitary hormonal deficiency, and possibly older patients. Such individuals should be carefully monitored. For patients with multiple risk factors (i.e., 3-cm macroadenoma in a 70-year-old man with hypogonadism), it may be reasonable to consider perioperative glucocorticoids. Patients most at risk for early adrenal insufficiency include those with macroadenomas developed postoperative adrenal insufficiency, the reflexive practice to give glucocorticoids to this subgroup could likely be abandoned in the majority of such patients.

CONCLUSION

Normal morning cortisol values on POD1 and POD2 after endonasal removal of a pituitary adenoma or RCC appear to reliably predict adequate and safe adrenal function in 98% of patients. Given that cortisol levels trend down from POD1 to POD2 in most patients after endonasal surgery for an adenoma or RCC, assessing morning cortisol levels for the first 2 postoperative days should be routine for patients not given perioperative glucocorticoids. Patients most at risk for early adrenal insufficiency appear to be those with macroadenomas and with at least one pre-existing pituitary hormonal deficiency. This simple protocol avoids unnecessary perioperative glucocorticoid therapy and poses minimal risk to the well-informed closely monitored patient.

REFERENCES