

CLINICAL REVIEW: Early Morning Cortisol Levels as a Predictor of Remission After Transsphenoidal Surgery for Cushing's Disease

Felice Esposito, Joshua R. Dusick, Pejman Cohan, Parham Moftakhar, David McArthur, Christina Wang, Ronald S. Swerdloff, and Daniel F. Kelly

Division of Neurosurgery (F.E., J.R.D., P.M., D.M., D.F.K.), Pituitary Tumor and Neuroendocrine Program (F.E., P.C., D.F.K.), and Division of Endocrinology (P.C.), University of California, Los Angeles (UCLA), School of Medicine, Los Angeles, California 90095; Department of Neurological Sciences (F.E.), Division of Neurosurgery, Università degli Studi di Napoli Federico II, 80131 Naples, Italy; UCLA Gonda Diabetes Center (P.C.), Los Angeles, California 90095; and Division of Endocrinology, Metabolism, and Nutrition (C.W., R.S.S.), Harbor-UCLA Medical Center, Torrance, California 90502

Introduction: We describe the use of serum cortisol and ACTH levels on postoperative d 1 and 2 as remission predictors after transsphenoidal surgery for Cushing's disease (CD).

Methods: Morning cortisol and ACTH levels were drawn daily after surgery; glucocorticoids were withheld until evidence of hypocortisolemia. Early remission was defined retrospectively as a subnormal morning cortisol level [≤ 140 nmol/liter (≤ 5 $\mu\text{g}/\text{dl}$)] on postoperative d 1 or 2 and sustained remission as subsequent eucortisolemia.

Results: Of 40 consecutive adults with CD (mean age 39 yr), 80% achieved early remission. Of 39 patients with a minimum follow-up of 14 months (mean 33 months), 31 (79.5%) achieved sustained remission at a mean follow-up of 32 months, including 30 of 31 (97%) with early remission and one of eight (12%) without early remission ($P < 0.0001$). Sustained remission was achieved in 26 of 28 (93%)

patients having their first operation, compared with five of 11 (45%) with a prior unsuccessful operation ($P < 0.001$). For the 32 patients in early remission vs. the eight in nonremission, mean nadir cortisol levels were 57.6 ± 33.0 (2.05 ± 1.2 $\mu\text{g}/\text{dl}$) vs. 631.1 ± 352.2 nmol/liter (22.9 ± 12.8 $\mu\text{g}/\text{dl}$) ($P < 0.0001$), and nadir ACTH levels were 11.9 ± 6.5 vs. 64.1 ± 54.6 ng/liter ($P < 0.001$). Of 31 patients with sustained remission, 100% had subnormal morning cortisol levels, whereas 31% had subnormal ACTH levels ($P < 0.0001$).

Conclusions: Serum morning cortisol levels on postoperative d 1 and 2 without glucocorticoid replacement provide a safe, simple, and reliable measure of early remission for CD and are predictive of sustained remission. This method allows for consideration of a repeat operation during the same hospitalization in patients with persistent hypercortisolemia. (*J Clin Endocrinol Metab* 91: 7–13, 2006)

CUSHING'S DISEASE (CD) IS a relatively rare but debilitating endocrinopathy, the diagnosis and treatment of which remains a formidable challenge. Currently the treatment of choice for CD is transsphenoidal selective adenectomy resulting in long-term remission rates of 64–93%, with the highest success rates in patients harboring well-defined microadenomas and lower rates in those with macroadenomas or with no adenoma visible on magnetic resonance imaging (MRI) (1–19).

A variety of methods have been used to assess early postoperative corticotroph suppression as predictors of long-term remission from CD. Provocative tests include the overnight low-dose dexamethasone suppression test (4, 20) and the CRH stimulation test (21, 22). Nonprovocative tests include early measurement of 24-h urinary free cortisol concentrations and serum cortisol and ACTH levels (11, 15, 18, 19, 23–26). In recent series, most investigators have conducted such tests several days or weeks after operation and have administered postoperative glucocorticoids because of

the theoretical risk of adrenal crisis (4, 11, 16, 22, 27). In this series of patients, we demonstrate the safety and reliability of withholding early postoperative glucocorticoid replacement and assessing early remission with morning serum cortisol levels on postoperative d 1 and 2. Although there have been two recent reports showing the utility early postoperative cortisol levels for early remission of CD, these reports had fewer patients, used somewhat different methodologies, and addressed only the postoperative dynamics of serum cortisol and not ACTH (18, 25).

Patients and Methods

Patient population

All adult patients with CD from the University of California Los Angeles (UCLA) Pituitary Tumor database who had an endonasal transsphenoidal surgery by the senior author (D.F.K.) since September 1998 at UCLA or Harbor-UCLA Medical Centers and who had at least a 1-yr follow-up were identified. Pre- and postoperative serum and urine hormonal values, MRI reports, pathology reports, and clinic notes were reviewed. This retrospective analysis was approved by the UCLA Institutional Review Board.

Diagnosis of CD and pituitary imaging

All patients were diagnosed with CD based on clinical findings and laboratory criteria including loss of diurnal variation in serum cortisol levels, normal or elevated ACTH levels, failure of cortisol suppression after low-dose (1 mg) dexamethasone test, and/or elevated 24-h urinary

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Abbreviations: CD, Cushing's disease; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging.

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free cortisol concentrations. Inferior petrosal sinus sampling (IPSS) before and after administration of CRH was performed in eight patients with ACTH-dependent Cushing's syndrome whose MRIs showed no definitive adenoma; all eight had a central to peripheral ACTH gradient 3 or greater, indicating CD (28). IPSS was not routinely performed in patients who met all the following criteria: 1) ACTH-dependent Cushing's, 2) suppression with high-dose dexamethasone, and 3) a visible adenoma on MRI. Further evaluation included pre- and postoperative determination of serum GH, IGF-I, TSH, free/total T₄, FSH, LH, free and total testosterone (males), estradiol (premenopausal female), and prolactin using standard assays.

All patients underwent high-resolution (1.5 Tesla) spin echo magnetic resonance of the pituitary-hypothalamic region before and after iv administration of gadolinium-¹¹¹In-diethylenetriamine-pentacetic acid. In the last four patients treated in whom no adenoma was detected on conventional MRI, dynamic postgadolinium sellar MRI was performed with spoiled gradient recalled acquisition the steady-state in 1-mm coronal sections.

Surgical technique

As recently described, all patients underwent endonasal transsphenoidal surgery with the operating microscope (9). In patients with visible tumor on preoperative MRI, after a wide sellar dural opening, selective adenectomy was performed in standard fashion. When no tumor was visible on preoperative MRI but IPSS demonstrated a large side-to-side gradient (>1.4), the first incision was made in the paramedian adeno-hypophysis on the side of the high ACTH gradient (29). If no adenomatous tissue was encountered, then contralateral paramedian and midline incisions were made and explored. When both the preoperative MRI and the IPSS failed to indicate adenoma location, the entire gland was explored through two paramedian vertical incisions and a midline incision. If no tumor was found from exploring the gland, then a partial hemihypophysectomy was performed on the side with the higher ACTH gradient from IPSS or the side with more suspicious-appearing tissue based on the pathologists' intraoperative assessment; total hypophysectomy was not performed, even if no tumor was found.

General perioperative management

Prophylactic iv antibiotics (cefazolin) were given for the first 24 h after operation. Pulsatile stockings were placed in the operating room and patients were started on sc heparin twice daily on postoperative d 1. Patients were typically discharged home on d 2 or 3.

Postoperative endocrine management and follow-up

Blood draws for serum cortisol and ACTH were performed daily on postoperative d 1 and 2. Cortisol levels were measured by polyclonal antibody assay on the Elecsys 2010 analyzer (Roche Diagnostic Corp., Indianapolis, IN) and enzyme immunoassay (Diagnostic System Laboratories, Webster, TX) at UCLA and Harbor-UCLA Medical Centers, respectively. The lowest morning cortisol and ACTH levels (drawn between 0600 and 0900 h) on either postoperative d 1 or 2 were recorded [normal morning range: cortisol 220–690 nmol/liter (8–25 μg/dl); ACTH 9–52 ng/liter (9–52 pg/ml)]. These early postoperative nadir values were then used to determine their predictive value for long-term remission. Glucocorticoids (including dexamethasone, which is sometimes given as an antiemetic) were not given in the perioperative period until biochemical evidence of hypocortisolemia was documented and/or until clinical evidence of adrenal insufficiency (*e.g.* nausea, anorexia, headache, arthralgias) was evident.

A patient was deemed to be in early remission if he/she had a subnormal morning cortisol level on either postoperative d 1 or 2, necessitating glucocorticoids replacement. Although in our laboratory a subnormal morning cortisol is a value less than 220 nmol/liter (<8 μg/dl), given that all patients in our cohort who achieved early remission had a cortisol value of 140 nmol/liter or less (≤5 μg/dl), we retrospectively used this cut-off value for early remission in this study. Patients who met these criteria constituted group 1, whereas those who did not constituted group 2.

Subsequent reassessments of corticotroph function and overall pituitary function were performed at a minimum of 3, 6, and 12 months after

surgery. Criteria for sustained remission included need for glucocorticoid replacement for at least 6 months and clinical and biochemical evidence of eucortisolemia [serum cortisol between 220 and 690 nmol/liter (8 to 25 μg/dl)] thereafter. One exception to these criteria was allowed in one patient with recurrent CD treated for several months before surgery with the thiazolidinedione, rosiglitazone, which has been reported to transiently lower ACTH and cortisol (28). She was weaned off glucocorticoids within 3 months after surgery and has remained in remission. All other patients were weaned off glucocorticoids as clinically tolerated and when there was biochemical evidence of a recovered hypothalamic-pituitary-adrenal axis.

Additional biochemical assessments of anterior pituitary function were taken within 3 months of the operation including thyrotroph function and gonadotroph function (including a menstrual history in women). Baseline somatotroph function was assessed using GH and random IGF-I levels; stimulation tests, typically with GHRH-arginine were performed when the IGF-I levels were near or below the lower limit of normal or when two or more other anterior pituitary axes were deficient.

Statistical analysis

Statistical analyses were conducted using a commercially available software packages (SPSS 13.0, SPSS Inc., Chicago, IL; Systat 11.0, Systat, Point Richmond, CA). The postoperative morning nadir of serum cortisol and ACTH were then compared between patients who met criteria for early remission and those who did not meet criteria for early remission using a *t* test. The rate of long-term disease control between patients in early remission *vs.* those without early remission was compared using the Fisher's exact test. The level of significance was set at *P* = 0.05.

Conversion factors

Conversion factors used were: ACTH, 1 pg/ml = 1 ng/liter; cortisol, 1 μg/dl = 27.59 nmol/liter.

Results

Patient cohort

As shown in Table 1, the 40 patients included 37 women and three men, ranging in age from 21 to 70 yr (mean 39 yr); 36 were treated at UCLA Medical Center and four at Harbor-UCLA Medical Center; 11 (27.5%) had a previous transsphenoidal operation and one had prior radiotherapy. Two patients were admitted with end-stage CD associated with sepsis, uncontrolled diabetes, and hypertension (one with bowel perforation); both were initially too unstable for surgery and required prolonged mechanical ventilation and

TABLE 1. Patient demographics

Characteristics	Value
No. of patients	40
Females	37 (93%)
Males	3 (7%)
Age (yr)	21–70 (mean 39)
Tumor size (based on preoperative MR imaging studies)	
Macroadenoma	9 (22.5%)
Visible microadenoma	23 (57.5%)
Nonvisible microadenoma (normal MRI)	8 (20%)
Prior transsphenoidal operation	11 (27.5%)
Day of discharge from hospital ^a	2–9 (median 3)
Follow-up: range (months) ^a	14–65 (mean 33)

^a Does not include one patient who died 3 months after the surgical procedure (total n = 39 patients).

several weeks of adrenolytic therapies including ketoconazole and etomidate (30–33).

Remission rates

Early remission was observed in 32 of 40 patients (80%), including two who had an unsuccessful first operation but a successful reoperation during the same hospital stay within 4 d of the first procedure. These two patients had morning cortisol nadirs of 524.2 nmol/liter (19 $\mu\text{g}/\text{dl}$) and 744.9 nmol/liter (27 $\mu\text{g}/\text{dl}$) within the first 2 d of their first operation; after the reoperation they had morning cortisol nadirs of 140 nmol/liter (5 $\mu\text{g}/\text{dl}$) and 28 nmol/liter (1 $\mu\text{g}/\text{dl}$), respectively. One patient did not have initial subnormal cortisol levels but developed hypocortisolemia 7 d after surgery and has remained in remission for 25 months. Her postoperative d 2 cortisol nadir was 358.7 nmol/liter (13 $\mu\text{g}/\text{dl}$) followed by a postoperative d 7 nadir of 84 nmol/liter (3 $\mu\text{g}/\text{dl}$). Her history suggested mild CD with numerous elevated urinary free cortisols, several normal urinary free cortisols, and normal to mildly elevated ACTH; IPSS with CRH stimulation showed a large central to peripheral gradient. Because of her clinically mild CD, she was not taken for early repeat surgery, given the concern she may have a less abrupt fall than typically seen with more advanced CD. Her immunostaining confirmed an ACTH-staining adenoma.

Follow-up longer than 1 yr (minimum 14 months) was available in 39 of 40 patients because one patient with end-stage CD died 3 months after an uncomplicated operation. As shown in Table 2, in these 39 patients with a mean follow-up of 33 months (range 14–65 months), remission for longer than 12 months was achieved in 32 patients, but one patient had a recurrence 21 months after surgery (recurrence

rate 3.1%). Thus, sustained remission was observed in 31 patients (79.5%), including 21 of 23 (91%) with microadenomas, six of eight (75%) with macroadenomas, and four of eight (50%) with no adenoma visible on pituitary MRI. Sustained remission was achieved in 26 of 28 patients (93%) having their first operation and in five of 11 (45%) with a prior unsuccessful operation ($\chi^2 = 10.883$, $P < 0.001$). Mean follow-up was 34 months in the 26 patients undergoing a first operation and 20 months in the five patients with a prior unsuccessful operation. All 31 patients who achieved sustained remission required glucocorticoid replacement for 6–19 months (mean 10 months) except one who was on rosiglitazone before surgery and was weaned off glucocorticoids 3 months after surgery but remains in remission 18 months after surgery.

Of the seven patients with failed surgery, one had a third operation elsewhere but has persistent CD, and six patients had bilateral adrenalectomies (4), bilateral adrenalectomies and radiotherapy (1), or radiotherapy alone (1).

Timing of early remission

In the 32 patients achieving early remission, the nadir in morning serum cortisol occurred in 15 patients (47%) on postoperative d 1 and 17 (53%) on d 2. The time of surgery (morning *vs.* afternoon) correlated with the postoperative nadir day; of 17 patients with a morning surgery, 11 (65%) had a cortisol nadir on d 1, and six (35%) had a nadir on d 2, and of 15 patients with an afternoon surgery, four (27%) had a cortisol nadir on d 1, and 11 (73%) had a nadir on d 2 ($\chi^2 = 4.360$, $P = 0.042$).

Early remission as a predictor of sustained remission

As shown in Table 3, of the 32 patients in group 1 (early remission), 32 of 32 (100%) had a subnormal morning postoperative cortisol level of 140 nmol/liter or less ($\leq 5 \mu\text{g}/\text{dl}$), and 30 of 31 (97%) have a sustained remission with a mean follow-up of 32 months. Of the eight patients in group 2 in whom morning postoperative serum cortisol was normal or elevated [$>220 \text{ nmol/liter}$ ($>8 \mu\text{g}/\text{dl}$)], only one (12.5%) achieved a sustained remission ($P < 0.001$, compared with group 1). Thus, 97% of patients (30 of 31) who had sustained remission were identified by the early remission criteria based on morning cortisol levels. Patients who did not have early remission (group 2) were more likely to have had no tumor seen on pituitary MRI ($P < 0.05$) and a prior transphenoidal operation ($P < 0.05$).

As shown in Fig. 1, A and B, the mean nadir cortisol for groups 1 and 2 patients was $56.6 \pm 33.0 \text{ nmol/liter}$ *vs.* $631.1 \pm 352.2 \mu\text{g}/\text{d}$ ($2.05 \pm 1.2 \text{ vs. } 22.9 \pm 12.8 \mu\text{g}/\text{dl}$), respectively ($P < 0.001$), and the mean nadir ACTH was $11.9 \pm 6.5 \text{ vs. } 64.1 \pm 54.6 \text{ ng/liter}$ ($11.9 \pm 6.5 \text{ vs. } 64.1 \pm 54.6 \text{ pg/ml}$), respectively ($P < 0.001$). Regarding the relative predictive value of early morning postoperative cortisol levels *vs.* ACTH levels, of the 31 patients who achieved sustained remission (including the one patient with recurrent CD at 21 months after her first operation), 100% had a subnormal cortisol level, whereas only 31% had a subnormal ACTH level ($P < 0.0001$).

TABLE 2. Sustained remission rate by tumor size and primary *vs.* prior operation^a

	Sustained remission rate
Tumor size	
Macroadenoma	6/8 (75%)
Visible microadenoma on MRI ^b	21/23 (91%)
No adenoma visible on MRI ^c	4/8 (50%)
Total (mean follow-up = 33 months)	31/39 (79.5%)
Surgical procedure	
Primary (first-time) transphenoidal operation (mean follow-up for 26 patients in remission = 34 months)	26/28 (93%)
Prior transphenoidal operation (mean follow-up for 5 patients in remission = 20 months)	5/11 (45%)
Total	31/39 (79.5%)

^a One patient with a macroadenoma and early remission, died 3 months after operation and is not included, leaving 39 patients with follow-up data. Of the 31 patients in sustained remission, 42% had follow-up of 1–2 yr, 22% of 2–3 yr, 10% of 3–4 yr, and 26% of greater than 4 yr.

^b One patient without sustained remission in this group had a prior operation.

^c Three patients without sustained remission in this group had a prior operation. One of these three had initial remission but developed recurrent CD 21 months after a second operation (overall recurrence rate = 3.1%); the patient underwent a third operation with a postoperative d 1 morning cortisol nadir of 55 nmol/liter (2 $\mu\text{g}/\text{dl}$) and is again in remission 5 months after the last operation.

TABLE 3. Summary of patients with early remission (group 1) *vs.* non-early remission (group 2)

Characteristics	Group 1 ^a	Group 2
No. of patients	32 (80%)	8 (20%)
Follow-up in months (mean) ^a	15–65 (32)	14–54 (36)
Age (yr)	23–60	21–70
Tumor size (based on pre-op MRIs)		
Macroadenoma	7 (22%)	2 (25%)
Visible microadenoma	21 (65.5%)	2 (25%)
No adenoma visible on MRI ^b	4 (12.5%)	4 (50%)
Prior transsphenoidal operation ^b	6 (19%)	5 (62.5%)
Mean postoperative cortisol nadir ^c	56.6 ± 33.0 nmol/liter (2.05 ± 1.2 µg/dl)	631.1 ± 352.2 µg/dl (22.9 ± 12.8 µg/dl)
Mean postoperative ACTH nadir ^c	11.9 ± 6.5 pg/ml	64.1 ± 54.6 pg/ml
Sustained remission rate ^c	30/31 (97%) ^a	1/8 (12.5%)

^a Of 32 patients in group 1, one died 3 months after the surgical procedure, leaving 31 patients with follow-up data.

^b $P < 0.05$.

^c $P < 0.0001$.

Tumor removal and histopathology

Of the 40 patients, a selective adenectomy was performed in 31 patients (77.5%), and a partial hemihypophysectomy was performed in eight (20%); seven of these eight patients had no visible adenoma seen on preoperative pituitary MRI. Total hypophysectomy and intentional stalk transection was performed in one patient undergoing her third operation in preparation for radiosurgery (Table 2). She had a highly invasive macroadenoma that invaded the clivus and the entirety of the pituitary stalk.

Tissue histopathology yielded the following results in the 40 patients (Table 4): ACTH-positive immunostaining in 29 patients; adenoma confirmed by histopathology but immunostaining not done because of small specimen size in three; and adequate tissue not available for histopathology in seven; no specimen submitted in one. In all eight patients in which histopathology was either not done or submitted, there was tissue suspicious for adenoma visualized during the surgical procedure; six of these eight patients remain in sustained remission.

Postoperative endocrinopathy

One patient (2.5%) with a recurrent invasive macroadenoma had intentional stalk transection and total hypophysectomy with expected permanent diabetes insipidus and anterior pituitary failure (Table 5). Four additional patients (10%), three in group 1 and one in group 2, had transient diabetes insipidus that resolved within 1 wk. No other patients experienced new hypopituitarism, although stimulation testing for GH deficiency was not performed in all patients.

Surgical complications and length of hospital stay

Four patients (10%) had surgical complications. One patient with end-stage CD had an uncomplicated operation and early remission but died 3 months later from multiorgan failure. One patient with a prior operation and a laterally placed residual adenoma extending to the cavernous sinus had a carotid artery injury after the majority of the tumor appeared to have been removed (confirmed by later ACTH-positive immunostaining), necessitating aborting the procedure. She suffered no neurological sequelae, had initial nor-

mal cortisol levels, but subsequently had persistent CD. One patient had a cerebrospinal fluid leak treated by repeat surgery and another had a minor wound breakdown at the fat graft site that resolved with wound care and antibiotics.

The median day of discharge was postoperative d 3 (range 2–9 d); 50% were discharged home on postoperative d 2 and 90% were discharged home by postoperative d 4. Of four patients with stays beyond d 4, two had complications and two had early reoperations during the same hospitalization.

Discussion

Remission rates in recent transsphenoidal series

Over the last several decades, advances in microsurgical technique and accumulated experience by pituitary surgeons have resulted in generally excellent results for patients with CD. Remission rates since 1980 have ranged from 64 to 93% (1, 4–8, 10, 12, 13, 16–18, 23, 26, 34), with the highest rates of 86–98% in patients with MRI-defined noninvasive microadenomas treated with primary transsphenoidal tumor removal (8, 16, 24, 35–39). In this series, although follow-up was relatively short, the overall sustained remission rate was 79.5% and was 91, 75, and 50% for the subgroups of patients with microadenomas, macroadenomas, and those with no adenoma visible on MRI, respectively. Surgical complications in this series were comparable to previous series (40, 41).

Postoperative assessment of corticotroph function

A variety of methods that assess early postoperative remission have been used to predict long-term remission from CD (3). Provocative tests include the overnight low-dose dexamethasone suppression test (4, 20) and the CRH stimulation test (21, 22). Chen *et al.* (4) showed that in 174 patients, a postoperative d 3 morning cortisol level of 8 µg/dl or less after an overnight 1-mg dexamethasone suppression test was predictive of sustained remission in 97% of patients. Nonprovocative tests include early measurement of 24-h urinary free cortisol concentrations and serum cortisol and ACTH levels (11, 15, 18, 19, 23–26). In most series, testing was conducted days or weeks after surgery and postoperative glucocorticoids were given because of the risk of a surgically induced adrenal crisis (4, 6, 19, 26, 35, 42).

Four previous reports assessed the predictive value of

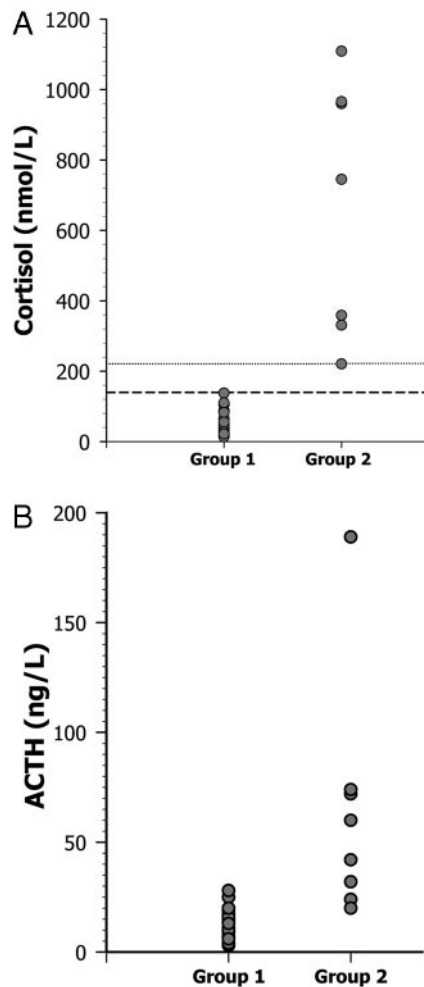


FIG. 1. A, Postoperative cortisol nadir. Scatter plot shows mean values, maximum and minimum values, first and third quartile of the morning postoperative cortisol nadir levels in 32 group 1 (early remission) and eight group 2 (surgical failure) patients ($P < 0.001$). Cortisol levels drawn on the morning of postoperative d 1 and 2. The dotted line shows the normal morning cortisol threshold of 220 nmol/liter (8 $\mu\text{g}/\text{dl}$), and the dashed line shows the highest morning cortisol level in all patients achieving early remission of 140 nmol/liter (5 $\mu\text{g}/\text{dl}$). B, Postoperative ACTH nadir. Scatter plot shows mean values, maximum and minimum values, first and third quartile of the morning postoperative ACTH nadir levels in 32 group 1 (early remission) and eight group 2 (surgical failure) patients ($P < 0.001$). ACTH levels drawn on the morning of postoperative d 1 and 2.

nonmeasurable postoperative cortisol levels using a cut-off value of 50 nmol/liter (1.8 $\mu\text{g}/\text{dl}$) as a criterion for surgical success or failure. However, in all four reports, postoperative

TABLE 4. Histopathological findings

Type of histopathology study	No. of patients	Patients in group 1 (sustained remission)
Histology and immunostaining for ACTH	29	25
Histology alone without immunostaining	3	0
Inadequate tissue for histopathology	7	6
No specimen submitted	1	1
Total	40	32

glucocorticoids were given for a variable period of 24 h to 2 wk, followed by 24 h of steroid cessation followed by morning cortisol measurement (16, 19, 26, 42). In these reports of patients who achieved sustained remission, the percentage of those with morning serum cortisol levels less than 50 nmol/liter (<1.8 $\mu\text{g}/\text{dl}$) in this early postoperative period ranged from 58 to 100%, and the recurrence rate ranged from 0 to 11.5%. These studies indicate an absolute cortisol cut-off criterion of less than 50 nmol/liter (<1.8 $\mu\text{g}/\text{dl}$) is probably too stringent, given a significant minority of patients who achieved remission did not have such low postoperative serum cortisol values. It is also unclear how analogous these studies are to ours, given that postoperative glucocorticoids were given and cortisol values were not obtained until postoperative d 3.

In contrast to these studies, the method of assessing early remission in the present study is similar to that of Simmons *et al.* (18) and Rollin *et al.* (25) in which glucocorticoids were withheld and serial cortisol levels drawn until hypocortisolemia was evident. Similar to our findings, these studies found that subnormal but not necessarily undetectable cortisols within 24–72 h of surgery were highly predictive of sustained remission.

In the report by Simmons *et al.* (18), postoperative cortisol levels were drawn every 6 h for up to 3 d after surgery, with a low serum cortisol cut-off of 10 $\mu\text{g}/\text{dl}$ (275.9 nmol/liter); 21 patients (78%) met this cut-off criterion and 100% of these 21 patients were in remission at a mean follow-up of 27 months. For these 21 patients, the lowest postoperative cortisol levels averaged 5 $\mu\text{g}/\text{dl}$ on postoperative d 1 at noon or 1800 h. In the report by Rollin *et al.* (25), cortisol levels were drawn 6, 12, and 24 h postoperatively. Of 21 patients in remission at a median follow-up of 34 months, serum cortisol levels 24 h after surgery averaged $4.7 \pm 6.8 \mu\text{g}/\text{dl}$ (range 0.5–30 $\mu\text{g}/\text{dl}$) and only nine (43%) had cortisol levels less than 50 nmol/liter (<1.8 $\mu\text{g}/\text{dl}$) (25). In our series, in the 32 patients achieving early remission, the average morning cortisol nadir was $2.05 \pm 1.2 \mu\text{g}/\text{dl}$, which is considerably lower than in the report by Rollin *et al.* (25). However, similar to their report, only 48% of patients with sustained remission in our series had a postoperative d 1 or 2 morning cortisol less than 50 nmol/liter (<1.8 $\mu\text{g}/\text{dl}$). We also noted patients with morning operations tended to reach their nadir on postoperative d 1, whereas those with afternoon operations tended to reach their nadir on d 2. This finding suggests that 18–24 h is needed to allow residual serum cortisol resulting from the adenoma to be biochemically cleared after surgery. The findings from Simmons *et al.* (18) and Rollin *et al.* (25) also support this time line of early remission.

Regarding the absolute cortisol cut-off for establishing early remission, it would appear from our study and those of Simmons *et al.* (18) and Rollin *et al.* (25) that a value of less than 50 nmol/liter (<1.8 $\mu\text{g}/\text{dl}$) is excessively stringent, given that more than 50% of patients in these series had a nadir cortisol above this threshold within 2–3 d of surgery. Although our lower limit of normal morning cortisol was 220 nmol/liter (8 $\mu\text{g}/\text{dl}$), no patients in our series with early remission had a nadir between 140 and 220 nmol/liter (5–8 $\mu\text{g}/\text{dl}$), so the predictive value of this range is uncertain. However, the data from Simmons *et al.* (18) with a cortisol

TABLE 5. Surgical procedure, remission rate, recurrence rate, and new pituitary failure^a

	No. of subjects	Long-term remission ^a	New pituitary failure	Recurrence ^a
Selective adenomectomy	30 (77%)	28/30 (93%)	0/30	1/28 (3.6%)
Partial hemihypophysectomy	8 (20.5%)	4/8 (50%)	0/8	0
Total hypophysectomy	1 (2.5%)	0/1	1/1	N/A
Total	39/39 ^a	32/39 (82%)	1/39 (2.5%)	1/32 (3.1%)

^a Includes only 39 patients with a minimum 1-yr follow-up; one patient had recurrent CD 21 months after the surgical procedure.

cut-off of 10 $\mu\text{g}/\text{dl}$ suggest a higher cut-off between 8 and 10 $\mu\text{g}/\text{dl}$ may still be predictive of sustained remission. Theoretically, a more stringent cortisol cut-off of 140 nmol/liter or less ($\leq 5 \mu\text{g}/\text{dl}$) may be more predictive of long-term remission because it likely indicates a greater degree of normal corticotroph suppression after tumor removal, although this is clearly not 100% predictive, given that we have a 3% recurrence rate at a mean follow-up of 32 months using this criterion. Finally, our results and those from Simmons *et al.* (18) indicate a small percentage of patients (3 and 4.5%, respectively) who achieve sustained remission will not be identified within the first 48–72 postoperative hours. As in our series, patients with relatively mild CD may be more prone to this delayed onset of hypocortisolism.

Regarding the relative predictive value of early ACTH levels, only one third of our patients with early remission had a subnormal ACTH level during this early postoperative period, indicating the absolute ACTH level is a poor predictor of sustained remission.

Clinical practicality of early postoperative serum cortisol assessments

Our study demonstrates several important points. First, although patients with a successful operation without glucocorticoid replacement typically develop symptomatic hypocortisolemia, we have not encountered manifestations of an adrenal crisis in any patient. Because of the careful monitoring of these patients and the relatively brief duration without glucocorticoids, we, like others (18), believe this is a safe practice. Second, using morning cortisol levels is simplistic in that it requires no provocative testing. Third, this method appears to be highly predictive of sustained remission with 97% of patients being identified by the second postoperative day and only a small minority (3%) identified later during the first postoperative week. Fourth, it shows that whereas ACTH levels drop precipitously, they do not consistently decrease into the subnormal range, and there is statistical overlap of ACTH values between patients who achieve sustained remission and those who do not. This finding is of practical significance, given that most hospital laboratories perform cortisol assays on a daily basis but typically send out specimens for ACTH with results available once or twice per week. Using our paradigm in two patients who initially had an unsuccessful first operation, we were able to achieve sustained remission with a second operation within several days of the first operation (34). Finally, this rapid assessment also goes in concert with the current trend of minimally invasive transsphenoidal surgery being practiced at most major pituitary centers. The endonasal microscopic approach we use or the endonasal endoscopic ap-

proach used by others facilitates rapid patient mobilization and discharge home (9, 43).

Conclusions

The results of this series of patient with CD indicate that the assessment of early remission with morning cortisol levels on postoperative d 1 and 2 in the absence of glucocorticoid replacement is a safe, simple, and reliable predictor of sustained remission and allows early discharge from the hospital. Specifically, a morning cortisol level of 140 nmol/liter or less ($\leq 5 \mu\text{g}/\text{dl}$) on postoperative d 1 or 2 appears to predict sustained remission in up to 97% of patients. Given that approximately 50% of patients do not reach their cortisol nadir until postoperative d 2, monitoring morning cortisol levels through the second postoperative morning is recommended. In contrast, early ACTH levels are not as predictive of sustained remission. Further long-term surveillance of this cohort is required to monitor for additional recurrences of CD and determine the long-term reliability of this rapid assessment method using morning cortisol levels.

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Address all correspondence and requests for reprints to: Daniel F. Kelly, M.D., 200 University of Los Angeles California Medical Plaza, Suite 504, Box 718224, Los Angeles, California 90095-7182. E-mail: dkelly@mednet.ucla.edu.

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