Use of the histological pseudocapsule in surgery for Cushing disease: rapid postoperative cortisol decline predicting complete tumor resection

Clinical article

STEPHEN J. MONTEITH, M.D., ROBERT M. STARKE, M.D., M.SC., JOHN A. JANE JR., M.D., AND EDWARD H. OLDFIELD, M.D.

Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia

Object. Subnormal postoperative serum cortisol levels indicate successful surgery and predict long-term remission of Cushing disease. Given the short serum half-lives of adrenocorticotropic hormone (ACTH) and cortisol, it is unclear why the decline in cortisol postoperatively is delayed for 18–36 hours. Furthermore, the relevance of the rate of cortisol drop immediately after surgery has not been investigated.

Methods. Patient data were analyzed from a prospectively accrued database. After surgery, cortisol replacement was withheld and serum cortisol measurements were obtained every 6 hours until values of 1.0–2.0 μg/dl or less were reached. The authors selected patients in whom serum cortisol dropped to 2 μg/dl or less after surgery (101 patients). Tumor resection was categorized as follows: 1) complete resection using the histological pseudocapsule as a surgical capsule, 2) complete piecemeal resection, 3) known incomplete resection, and 4) total hypophysectomy.

Results. The median time to reach a cortisol level of less than or equal to 2.0 μg/dl was 9.9, 19.4, 25.3, and 29.5 hours with hypophysectomy, pseudocapsule, incomplete resection, and piecemeal techniques, respectively. Pseudocapsule resection produced a faster decline in cortisol than piecemeal techniques (p = 0.0001), but not as rapid a decline as hypophysectomy (p = 0.033).

Conclusions. Complete resection by other techniques is associated with delayed cortisol decline compared with pseudocapsule surgery, which may represent the product of residual tumor cells and therefore may explain the higher rate of recurrent disease associated with piecemeal techniques. The prompt drop in cortisol after hypophysectomy compared with patients with pseudocapsule surgery suggests that the corticotrophs of the normal gland can secrete ACTH for 10–36 hours after surgery despite prolonged and severe hypercortisolism.


key words • Cushing disease • cortisol • pituitary adenoma • pseudocapsule • pituitary surgery

TRANSPHENOIDAL adenomectomy is the mainstay of management of Cushing disease. The reported rates of remission after pituitary surgery for Cushing disease vary widely from center to center. Previous studies have evaluated the relationship between lowest postoperative serum cortisol levels and the rapidity of immediate postoperative cortisol decline with surgical success. We examine the impact of surgical technique on the rate of decline of postoperative cortisol and assess the basis of the unexplained delay in the hypocortisolism that follows complete resection of an ACTH-secreting tumor. We postulated that 1) the rate of serum cortisol decline immediately after surgery may be related to the resection technique employed by the surgeon and that it may reflect the presence or absence of microscopic residual tumor and, thus, the difference in long-term recurrence rates between surgical techniques for tumor removal, and 2) the delay in the drop in serum cortisol to extremely low levels (a delay that is longer than would be expected based on clearance rates of serum ACTH and cortisol) results from transient continued secretion of ACTH by normal corticotrophs despite their suppression by chronic hypercortisolism and before the occurrence of profound hypocortisolism that begins several hours later.

This article contains some figures that are displayed in color online but in black and white in the print edition.
Methods

Data obtained in all patients with Cushing disease who underwent transsphenoidal pituitary surgery at the University of Virginia were accrued into a prospective database. The University of Virginia Health System provided institutional review board approval of this study. All patients underwent endocrinological investigation at the endocrinology service at the University of Virginia before surgery. Cushing disease was diagnosed based on clinical features and accepted biochemical diagnostic criteria for serum ACTH, serum cortisol, 24-hour urinary free cortisol, dexamethasone suppression testing, and inferior petrosal sinus sampling, when needed. Neuroradiological investigation included pituitary MR imaging using sequences for 1–1.2-mm-thick cuts in all patients. Histopathology was performed including immunohistochemistry for ACTH, growth hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, and thyroid-stimulating hormone. Surgery in all patients was performed by 2 surgeons (J.J. and E.O.). Patients whose lowest serum cortisol level was greater than 2.0 μg/dl in the first 2–3 days after surgery and those requiring more than 1 operation to achieve remission were excluded from the study. The postoperative protocol consisted of measuring serum cortisol levels every 6 hours until a level of less than or equal to 1.0–2.0 μg/dl was achieved. Patients then received cortisol replacement. Toward the end of the series, the protocol was modified to include serial postoperative ACTH values, which were measured at the same time as cortisol levels. Five patients who underwent total hypophysectomy were included in the analysis as a comparison group of patients who had no corticotrophs after surgery. Based on these criteria, 101 patients who underwent surgery between 2005 and 2009 were considered for analysis.

Details of the operative procedure were procured from the operative notes and surgical video recordings. Surgery was performed by either a sublabial microscopic approach or an endoscopic endonasal approach. Utilization of the tumor pseudocapsule as a surgical capsule in the treatment of Cushing disease has been described previously. Early identification of the pseudocapsule was used as the basis for categorizing resection technique, as was the presence of invasion into adjacent structures (dura mater and/or cavernous sinus). Tumor resection was categorized as follows: 1) complete resection in which the histological pseudocapsule was used as an intact surgical capsule, 2) complete resection of contained tumors without using the pseudocapsule as a surgical capsule (that is, “piecemeal” resection of abnormal tissue), 3) known incomplete resection (patients with cavernous sinus involvement in whom at least microscopic residual tumor was evident during surgery), and 4) total hypophysectomy. For consistency, if there were remnants of tumor excised after the bulk of tumor had been resected in a large piece, this was classified as piecemeal resection. Patients who underwent total hypophysectomy were included to serve as a comparison group in whom no corticotrophs were present after surgery.

Calculations of normality were carried out by ladder of powers. Statistical analyses of categorical variables were performed using chi-square and Fisher exact tests, as appropriate. Statistics of mean values were calculated using unpaired Student t-test, both with and without equal variance (the Levene test) as necessary and Wilcoxon rank-sum tests when variables were not normally distributed. Analysis of variance followed by Bonferroni post hoc testing was used to assess mean values among 3 or more groups. Kaplan-Meier analysis was conducted to assess time to lowest cortisol level of less than or equal to 2.0 μg/dl between different surgical techniques. The log-rank test was used to assess differences in fractions of patients with serum cortisol less than 2 μg/dl at various times when sampled at 6-hour intervals in the first 2–3 days after surgery, and Cox regression was used to assess hazard ratios. Probability values of 0.05 or less were considered statistically significant.

Results

One hundred one patients were eligible for study inclusion. The distribution of cases to each category is shown in Fig. 1. Of the 101 patients, 71 (70%) had tumors that were contained within the pituitary gland, 25 (25%) had invasive tumors (extending into adjacent tissue such as the dura and cavernous sinus), and 5 (5%) underwent total hypophysectomy. (In 3 cases the tumor was invading the cav-
Postoperative cortisol in Cushing disease

ernous sinus, the sella, the diaphragm sella, and/or the pituitary gland itself and total hypophysectomy was required for total tumor removal. In 2 cases hypophysectomy was performed during repeat exploration of the pituitary in the face of persistent hypercortisolism after no tumor had been found at the original surgery and a portion of the pituitary had been removed. In these 2 cases no obvious tumor could be identified at repeat surgery, and total hypophysectomy was performed.) All patients had ACTH-secreting adenomas identified on histopathological examination. Of the 71 patients with tumors contained within the gland, 35 underwent complete resection in which the pseudocapsule was used as a histological capsule. All of these tumors were removed in a single piece. Thirty-six patients (36%) underwent a piecemeal but complete resection of tumor contained within the pituitary gland. Of the 25 patients with invasive tumors, 20 (80%) had complete resection of all visible tumor including invaded cavernous sinus/dura. Five (20%) of the patients with invasive disease did not have complete resection (based on intraoperative observation), although their postoperative serum cortisol dropped to below 2.0 μg/dl. Tumors that were confined within the gland ranged from 2 to 15 mm (mean 7.5 mm, median 6 mm) in maximum diameter, except 1 tumor, which was 2.2 cm with a large cystic component.

Median time to reach a cortisol of 2.0 μg/dl or less was 9.9, 19.4, 25.3, and 29.5 hours with hypophysectomy, pseudocapsular complete resection, incomplete resection, and complete resection by other piecemeal techniques, respectively. Figure 2A displays the results of Kaplan-Meier analysis of the time after surgery to reach a serum cortisol level of 2.0 μg/dl or less for the categories of patients. Despite the fact that 25 tumors were invasive, the patients harboring these lesions still achieved biochemical remission. When Kaplan-Meier analysis was performed to compare cases with visible residual invasive tumor (5 patients) and those with invasive lesions in which a complete resection (including diseased cavernous sinus and dura) was achieved (20 patients), there was no statistically significant difference (p = 0.94). There was no statistically significant difference in the median time taken for the cortisol level to reach its nadir for the group of 5 patients with invasive tumors and known incomplete resection compared with the group in which contained tumors were completely resected in a piecemeal fashion (p = 0.79). Pseudocapsular resection produced a faster decline in serum cortisol than other techniques (p = 0.0001) (Fig. 2B). There was no significant difference in tumor size between the individual surgical groups, and there was no statistically significant difference in the results of Kaplan-Meier analysis of the patients with a serum cortisol level lower than 2 μg/dl for adenomas of different size within any of the individual surgical subgroups (including the pseudocapsule resection group), or for the entire series as a whole (p = 0.75).

All 5 patients who underwent total hypophysectomy had an ACTH-staining adenoma identified within the submitted tissue sample. The difference in median time taken for the serum cortisol to reach its nadir in the total-hypophysectomy group compared with the pseudocapsule group was significant (p = 0.033) (Fig. 2D).

Serial postoperative ACTH values were available for 3 patients who underwent adenomectomy in which the pseudocapsular resection technique was used. In each, the pattern of serum cortisol decline followed the pattern of ACTH decline. Note that in Case 1 (Fig. 3), there is an initial rise in serum cortisol before the rapid decline to the subnormal level. The ACTH level mirrors this initial rise before dropping to worst levels. Cases 2 and 3 (Fig. 3) similarly demonstrate curves for the decline of serum cortisol concentration that closely match the slope of the ACTH decline curve.

Discussion

Prognostic Implications

Although patients with postoperative hypocortisolism are less likely to have a recurrence than patients with normal levels of cortisol production, some patients develop recurrent disease despite profound postoperative hypocortisolism (serum cortisol ≤ 2 μg/dl). The current study was precipitated by the observation by one of us (J.J.) that patients whose tumor was resected using the pseudocapsule technique seemed to have a more rapid drop of serum cortisol levels than patients whose tumors were removed with other techniques.

The results of this study demonstrate that patients with Cushing disease whose tumors are contained within the pituitary and whose tumors are removed using the pseudocapsule as a technique have a rapid postoperative decline in serum cortisol production that is more rapid than that seen with other techniques.

Many authors have examined patterns of serum ACTH and cortisol diminishing following transsphenoidal surgery for Cushing disease and have demonstrated lower values in groups of patients whose disease is in remission than in those in whom remission has not been achieved.4 It has also been demonstrated that the mean of the worst early postoperative serum cortisol values is lower in groups of patients without recurrence than in groups with recurrent disease.1,3,19,20 However, some patients with profound hypocortisolism shortly after surgery recur despite serum cortisol that is 2 μg/dl or lower.1,4,19,20 Others have shown that tumors always recur in these patients at the same site as the original tumor,7 indicating that microscopic deposits (not obvious at surgery and not evident on MR imaging) of tumor cells are left behind at the original surgery—deposits that are too small to produce detectable levels of serum cortisol but that are sufficient to produce recurrent tumor growth and recurrent hypercortisolism.

In patients treated with standard resection techniques a biochemical remission is often achieved during the hospital stay. However several studies have demonstrated that while the initial remission rate may be relatively high, remission is not sustainable during a long-term follow-up period.2,16,23 For example, Patil et al.26 described recurrences in 23 of 50 patients with microadenomas who were followed up for more than 5 years. In contrast, a report on the outcome of the adenoma removal technique in which the histological pseudocapsule was used as a surgical capsule, a technique in which a microscopic envelope of compressed normal gland is used as the margin of tumor removal,
demonstrated a high and sustained remission rate (98% at 10 years) in patients with Cushing disease. Although the selection of patients for these 2 studies was not identical (in the series reported by Patil et al. children and patients with macroadenomas were excluded and patients with invasive tumors were included, whereas in the other report patients with invasive tumors were excluded and children and patients with macroadenomas were included), the substantial difference in recurrence rates suggests that the use of the tissue envelope provided by the pseudocapsule may result in a greater likelihood of removal of all peritumoral microscopic tumor involvement with adenomas contained within the pituitary gland (tumors not invading surrounding structures).

We sought to establish if there are differences in early postoperative cortisol dynamics in cases unequivocally defined as in remission (serum cortisol ≤ 2 μg/dl) after surgery that involved different techniques of selective tumor removal.

In our study, the worst cortisol level (< 2 μg/dl) in patients treated with the pseudocapsule technique occurred at a median of 19.4 hours postoperatively compared with 29.5 hours postoperatively in patients treated with other piecemeal surgical techniques. This difference in the rate of serum cortisol decline between the pseudocapsule resection group and the group with complete resection of contained tumors by piecemeal techniques likely represents the product of residual tumor cells at the margin of the tumor. Furthermore, the difference may explain the higher rate of recurrent disease reported with these piecemeal techniques compared
with the pseudocapsule approach. This is supported by the observation that there was no difference in the median time for cortisol to reach its nadir in patients with known incomplete tumor resection and cavernous sinus invasion (25.3 hours) and patients with tumors contained within the pituitary gland removed with piecemeal techniques.

Physiology of Prolonged Suppression of the Hypothalamic-Pituitary-Adrenal Axis by Hypercortisolism

In the setting of prolonged, sustained exposure to hypercortisolism in Cushing disease, corticotropin-releasing hormone secretion from the hypothalamus and ACTH secretion by the corticotrophs of the normal pituitary gland have been suppressed by chronic hypercortisolism and have lost the capacity to regulate cortisol normally. This results in prolonged, but ultimately reversible, hypocortisolism after successful removal of the adenoma causing Cushing disease.10,11,21 Others have shown an unexpected interval of transient continued secretion of ACTH and cortisol in the very early postoperative period after successful surgery for Cushing disease, an interval that seems to be inconsistent with known pharmacokinetics of serum ACTH and cortisol, given that the half-life of ACTH is 10–12 minutes and the half-life of cortisol is approximately 70 minutes.12,22 This has been proposed to arise from normal corticotrophs, or perhaps from residual tumor cells that die over the first hours or days after surgery. We sought to examine this issue for the early postoperative interval by comparing the cortisol dynamics shortly after surgery in patients with Cushing disease and remission after selective adenomectomy (normal corticotrophs still in place) versus total hypophysectomy (no residual corticotrophs).

In patients treated with the pseudocapsule technique, the remaining fully suppressed corticotrophs should be non-functional and the rate of serum cortisol decline should mirror that of the total hypophysectomy patients. Because of the very low recurrence rate with the pseudocapsular resection technique,13 it is reasonable to assume that all tumor cells have been removed at surgery. This is confirmed by the encasement of the densely staining adenoma within an intact pseudocapsule (with compressed reticulin layers) surrounding the tumor.15

In hypophysectomy-treated patients, the rate of cortisol decline following total hypophysectomy was rapid, but was longer than we expected (it took 5–17 hours for serum cortisol to drop to < 2 μg/dl). All patients in this group had an ACTH adenoma identified in the submitted tissue sample. In these patients, all endogenous sources of ACTH have been eliminated. The rate of decline in serum cortisol, therefore, is only a function of the clearance of the residual circulating ACTH at the moment of completing the hypophysectomy. Thus, because of the absence of endogenous sources of ACTH in these patients, they serve as a measure of the pace of serum cortisol decline in the setting of absent ACTH secretion. The delay in reaching a plasma cortisol level of less than 2 μg/dl on first inspection may seem long in relation to the plasma half-lives of ACTH and cortisol. However, we do not know the peak plasma ACTH and cortisol levels reached during surgery, and the manipulation of the tumor and/or gland during surgery can produce a burst of ACTH and cortisol secretion. For instance, Lüdecke14 reported cavernous sinus ACTH levels of 939,049 ± 1,198,974 pg/ml during surgery for Cushing disease, and Czirják and colleagues6 reported peripheral venous ACTH levels of exceeding 200 pg/ml in 5 of 7 patients during surgery for Cushing disease. It has also been known since the work by Liddle's group9 almost 5 decades ago that during surgery the hypothalamic-pituitary-adrenal axis can still respond to stress even under the influence of glucocorticoid suppression. Thus, hypothalamic corticotropin-releasing hormone, produced in response to the stress of surgery, stimulates the ACTH-producing pituitary tumor to secrete high levels of ACTH during surgery, which enters the plasma before the tumor and gland are removed, and the interval to reach cortisol levels of below 2 μg/dl after total hypophysectomy would be prolonged because of the high peak levels of ACTH and cortisol occurring during surgery.5

However, our data demonstrate a significant difference in the rate of decline of the serum cortisol (median
time to reach a level $\leq 2.0$ μg/dl) between patients who underwent pseudocapsule surgery (19.4 hours) and patients who underwent total hypophysectomy (9.9 hours). The lingering measureable serum cortisol in patients who underwent pseudocapsule surgery compared with the prompt drop in patients who underwent hypophysectomy suggests that the corticotrophs of the normal remaining gland are functioning and can secrete ACTH for 10–36 hours after surgery despite having been exposed to prolonged and severe hypercortisolism. In our patients with serial ACTH values monitored postoperatively, the cortisol decline was reflected by the changes in ACTH values (Fig. 3), similar to the observations of Pimentel-Filho et al. This suggests that corticotrophs within the normal pituitary gland, rather than residual tumor cells, continue to secrete functional ACTH in the immediate postoperative period.

Pathological analysis of the pituitary gland in patients with Cushing disease supports this notion (Fig. 4). Not only does the tumor stain for ACTH, but so do the corticotrophs within the normal gland surrounding the tumor, an observation that we have noted consistently in normal anterior lobe removed during surgery for Cushing disease. These cells transiently continue to secrete ACTH for an interval of several hours despite their chronic exposure to severe hypercortisolism. However, the ACTH stored in these normal corticotrophs is limited and rapidly depleted, as profound and lasting hypocortisolism follows after several hours. This suggests that the normal corticotroph cells do not have the capacity to produce or secrete additional ACTH until recovery occurs over the ensuing weeks and months.

Conclusions

Patients with Cushing disease treated by “pseudocapsular” resection have rapid decline in serum cortisol postoperatively. ‘Complete’ resection by other techniques is associated with a more delayed cortisol decline, which may represent the product of residual tumor cells and which may explain the higher rate of recurrent Cushing disease with these other techniques. The prompt drop in cortisol after hypophysectomy compared with patients with “pseudocapsule” surgery suggests that the corticotrophs of the normal gland can secrete ACTH for 10–36 hours after surgery despite exposure to prolonged and severe hypercortisolism and despite the appearance of severe hypocortisolism several hours later.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Monteith, Oldfield. Acquisition of data: Monteith, Starke. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Monteith. Statistical analysis: Starke. Administrative/technical/material support: Monteith. Study supervision: Jane, Oldfield.

References


**Fig. 4.** Photomicrograph demonstrating ACTH immunohistochemistry of an adenoma (right area of the image) and rim of surrounding pituitary (left area of the image) removed from a patient with Cushing disease in whom serum cortisol reached its nadir of less than 1.4 μg/dl and 24-hour urine free cortisol of less than 1.2 μg in the first few days after surgery. The ACTH staining is positive for corticotrophs within the normal gland, indicating storage of ACTH despite exposure to prolonged and severe hypercortisolism. Asterisk indicates the margin of the pituitary gland. Magnification $\times 100$. S. J. Monteith et al.
Postoperative cortisol in Cushing disease


---

Manuscript submitted May 17, 2011. Accepted December 12, 2011. Please include this information when citing this paper; published online January 27, 2012; DOI: 10.3171/2011.12.JNS11886. Address correspondence to: Stephen J. Monteith, M.D., Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908. email: sjm9n@virginia.edu.