



Original Article

Postoperative day 1 versus postoperative day 5 morning cortisol for predicting an intact hypothalamic-pituitary axis: A cohort analysis

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ABSTRACT

Background: A reliable standard for evaluating postoperative hypothalamic-pituitary-axis (HPA) function following transsphenoidal pituitary surgery (TSS) could reduce hospital stays and unnecessary prolonged steroid therapy. We retrospectively examined the predictive role of morning cortisol levels on long-term HPA function to develop an institutional protocol. Here, we report the results of this analysis, which is the first to report the predictive strength of multiple variables (i.e., timing of measurement and values of serum cortisol cutoffs) within the same cohort.

Methods: A retrospective chart review was performed in 183 patients at a single institution from 2007 to 2012. 67 patients met inclusion criteria. The predictive value of postoperative day (POD) 1 and POD 5 morning cortisol for HPA function as determined by 1 ug cosyntropin stimulation test was evaluated using standard confusion matrix calculations and receiver-operator control curve analysis.

Results: In our cohort, an early POD 5 serum morning cortisol ≥ 15 ug/dl predicted an intact HPA axis with 100% specificity, 51% sensitivity, and a positive predictive value (PPV) of 100%. A POD 1 serum cortisol ≥ 25 ug/dl was needed to achieve a specificity of 100% and PPV of 100% to predict an intact HPA axis with a sensitivity of 30%. A POD 1 serum cortisol ≥ 18 ug/dl predicted an intact HPA axis with 33.3% specificity, PPV of 90.9%, and a sensitivity of 51.3%.

Conclusion: A POD 5 morning cortisol level ≥ 15 ug/dl is an excellent predictor of normal postoperative HPA function in patients undergoing TSS for pituitary adenoma.

Keywords: Hypothalamic-pituitary axis, Postoperative cortisol, Transsphenoidal adenomectomy

INTRODUCTION

Transsphenoidal pituitary surgery (TSS) for pituitary adenomas is a fairly frequent necessity as a treatment modality of pituitary adenomas that are causing visual deficits and threatening vision or are hypersecretory. Hospital stays for this surgery can be brief and often patients can discharge within 24–48 h of the procedure

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which challenges physicians with assessing the hypothalamic-pituitary-adrenal axis (HPA) in a short span of time to avoid prolonging hospital length of stay.

The most commonly performed traditional tests to assess the HPA axis are the low dose (1 µg) or high dose (250 µg) 1 µg cosyntropin stimulation tests (CSTs). However, these tests cannot be performed with any reliability acutely after surgery or any form of pituitary injury because it takes 2–4 weeks for the adrenal glands to atrophy from a lack of ACTH stimulation. The insulin tolerance test is the gold standard test of the HPA axis because it stimulates the entire axis and, therefore, does not require waiting 2–4 weeks to perform. However, it is cumbersome and associated with some risk and, therefore, impractical to perform in the immediate postoperative period.

Due to the limitations of available tests, a variety of methods have been proposed to rapidly assess the HPA axis after surgery; however, there is no current gold standard and pituitary centers use a variety of methods. The critical issue is balancing the adverse effects and risk to patients of prolonged glucocorticoid exposure before definitive CST can be performed versus the potentially catastrophic risk of missing a case of central adrenal insufficiency if the screening test in the postoperative period is inaccurate.

Due to the possibility for a fatal outcome with missed adrenal insufficiency, our institution historically utilized a conservative approach with empiric postoperative glucocorticoid coverage until a definitive assessment was performed 4–6 weeks postsurgery.^[3,7,11,12] However, this resulted in decreased patient satisfaction due to weight gain and other Cushingoid features and exposed patients to increased risk associated with adverse effects from prolonged steroid exposure including difficulty with blood glucose control and gastric ulcers among others.

There are other published protocols involving the utilization of an immediate POD 1 or day 5 cortisol values in the assessment of the HPA axis but none assessing multiple time points and cutoff values in a single population.^[6,11–13] Our study evaluated the ability of POD 1 and POD 5 (outpatient) morning cortisol levels to correctly predict long-term HPA function as assessed by the low-dose CST, and the results are the basis of our current protocol for postoperative management, which has greatly improved patient satisfaction.

MATERIALS AND METHODS

We reviewed data from all patients who underwent endoscopic transsphenoidal surgery for pituitary adenoma at the University of Alabama at Birmingham between August 2007 and March 2012. This resulted in a total of 183 patients. Patients taking long-term exogenous steroids or who underwent TSS for Cushing's disease or pituitary apoplexy or who received stress dose corticosteroids perioperative or postoperative due to nasal flap were excluded from the study. A total of 67 patients met inclusion criteria.

All patients in our cohort group received 0.5 mg of dexamethasone in the operating room before start endoscopic transsphenoidal pituitary adenectomy. A 0800 am serum cortisol level was drawn on POD 1. Regardless of the 0800 am serum cortisol, patients were started on hydrocortisone (HC) 10 mg once a day. A serum cortisol was checked again as an outpatient at 0800 on POD 5. Patients were instructed to hold their dose of HC until after this laboratory was drawn on POD 5. If both POD 1 and POD 5 0800 am cortisol were ≥ 18 µg/dl, then HC was discontinued. If either POD 1 or POD 5 0800 am cortisol was < 18 µg/dl, then HC was continued. The patients who were continued on HC were scheduled for follow-up approximately 4 weeks postoperatively for a low-dose (1 µg) CST. Before the CST, HC was tapered from 10 mg/day to 5 mg/day and then held on the day of CST. During the CST, serum total cortisol levels were assayed at baseline and 30 min postinjection. Patients who had a serum cortisol ≥ 18 µg/dl at 30 min postinjection were deemed to have an adequate and sufficient response and were taken off of HC. This management algorithm is outlined in Figure 1.

The ability of POD 1 and POD 5 cortisol to predict HPA function was determined using standard confusion matrix calculations and receiver-operator control curve analysis. Analyses were performed using both a serum cortisol ≥ 18 µg/dl and ≥ 15 µg/dl.

RESULTS

Twenty-one of the 67 patients who met inclusion criteria had a POD 1 and POD 5 0800 am cortisol ≥ 18 µg/dL and, therefore, did not continue HC after the results from POD 5 were received. Forty-six patients had either POD 1 or POD 5 or both 0800 am cortisol < 18 µg/dL. One patient did not follow-up at our institution. Two of the 46 patients with a POD 1 < 18 µg/dL but POD 5 0800 am cortisol ≥ 18 µg/dL and were not continued on HC.

Forty-three patients were continued on HC and had a CST after approximately 4 weeks. Forty patients passed the CST and three patients had a serum cortisol < 18 µg/dl at 30 min postinjection. These three patients were continued on long-term HC [Figure 1]. All patients with POD 5 cortisol ≥ 18 µg/dL and all patients with a POD 5 cortisol ≥ 15 µg/dL went onto pass their CST [Tables 1 and 2]. Twenty-one of 23 patients with a POD 1 cortisol ≥ 18 µg/dL passed their CST [Table 3]. The results of POD 1, POD 5, and 30 minutes postinjection for the CST in the three patients continued on long-term HC are provided [Figure 2].

In our cohort, an early POD 5 serum morning cortisol ≥ 15 µg/dl predicted an intact HPA axis with 100% specificity, 51% sensitivity, and positive predictive value (PPV) of 100%. POD 5 serum morning cortisol ≥ 18 µg/dl also predicted an intact HPA axis with 100% specificity and PPV. A POD 1 serum cortisol ≥ 25 µg/dl was needed to achieve a specificity and PPV of 100% with a sensitivity of 30%. A POD 1 serum cortisol ≥ 18 µg/dl predicted an intact HPA axis with only 33.3% specificity, PPV of 90.9%, and a sensitivity of 51.3%. A POD 1 cortisol ≥ 15 µg/dl predicted an intact HPA axis

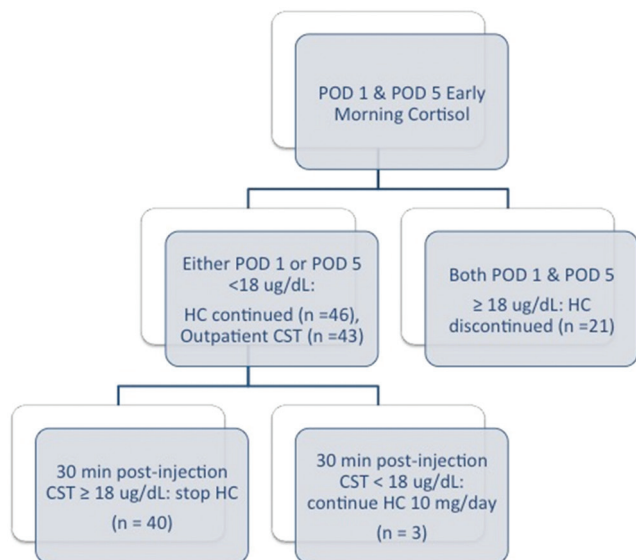


Figure 1: Algorithm showing management strategy based on postoperative cortisol levels. HC: Hydrocortisone, CST: 1 ug cosyntropin stimulation test.

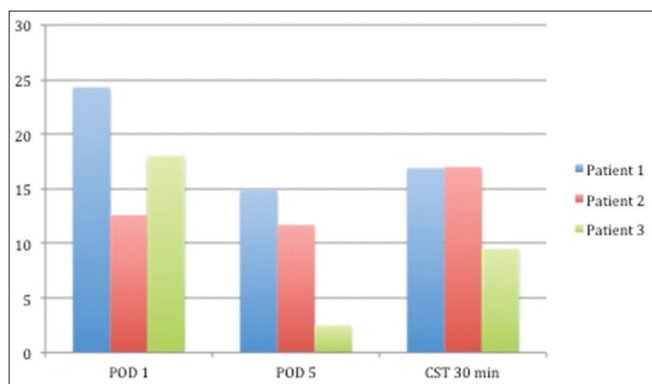


Figure 2: Results of postoperative day 1 and 5 morning serum cortisol and CST in patients who failed CST and were continued on long-term hydrocortisone. CST: 1 ug cosyntropin stimulation test.

with 69.2% sensitivity, 33.3% specificity, and 93.1% PPV. These data are presented in Table 4.

DISCUSSION

Physicians are faced with balancing the risk of unnecessary exposure to glucocorticoids compared to the potentially fatal risk of missing a case of central adrenal insufficiency when deciding to continue patients on glucocorticoid treatment postoperatively. A reliable standard for evaluating HPA function in the immediate postoperative period would enable clinicians to choose treatment strategies that minimize the risk to individual patients. However, there is no current gold standard for assessing the function of the HPA axis in the immediate postoperative period. Our study aimed to assess the utility of POD 1 and POD 5 serum cortisol measurements for this purpose.

Table 1: POD 5 0800 cortisol.

0800 Cortisol lab result	Failed CST	Passed CST	Total subjects
POD 5 cortisol <18 ug/dl (failed)	3	30	33
POD 5 cortisol ≥18 ug/dl (passed)	0	10	10
-All-	3	40	43

POD: Postoperative day, CST: 1 ug cosyntropin stimulation test

Table 2: POD 5 0800 cortisol.

0800 Cortisol lab result	Failed CST	Passed CST	Total subjects
POD 5 cortisol <15 ug/dl (Failed)	3	19	22
POD 5 cortisol ≥15 ug/dl (Passed)	0	21	21
-All-	3	40	43

POD: Postoperative day, CST: 1 ug cosyntropin stimulation test

Table 3: POD 1 0800 cortisol.

0800 Cortisol lab result	Failed cort stim	Passed cort stim	Total subjects
POD 1 0800 cortisol <18 ug/dl (Failed)	1	19	20
POD 1 0800 cortisol ≥18 ug/dl (Passed)	2	21	23
-All-	3	40	43

POD: Postoperative day, CST: 1 ug cosyntropin stimulation test

The gold standard for assessing HPA function is the insulin tolerance test. However, adverse side effects (e.g., myocardial ischemia, seizures, and arrhythmias) make this test undesirable in many patient populations including postoperative and elderly patients.^[1,3,6,11,12] Low-dose (1 µg) CST performed in a delayed fashion 4–6 weeks postoperatively has been established as a definitive test of HPA function.^[4,6,8,9,12] Low-dose CST has been reported to be more sensitive but less specific for identifying adrenal insufficiency when compared to standard dose CST (250 µg).^[8,9,12]

A variety of protocols have been proposed to assess function in the early postoperative period, but controversy persists in key aspects of each protocol.^[1,3,4,7,10-13] This includes both cutoff values and the timing of testing using morning serum cortisol. In general, it is agreed that there is a lower limit for a morning serum cortisol value that correlates with adrenal insufficiency as well as an upper limit indicating a functional HPA. There is also agreement that the values in the range between these cutoff values generally need additional dynamic testing and should be continued on replacement glucocorticoids in the interim. However, there is no agreement on the exact values that should be used as cutoffs.

Proposed morning serum cortisol cutoff values indicative of intact HPA function range from >8 µg/dL to >18 µg/dL.^[1-8,11-15] A value of >15 µg/dL has been used in recent studies of the predictive value of early postoperative measurements.^[11,12] A

Table 4: Predictive values of morning serum cortisol values for passing CST.

Value Calculated	POD 1≥15 ug/dl	POD 1≥18 ug/dl	POD 1≥25 ug/dl	POD 5≥15 ug/dl	POD 5≥18 ug/dl
Sensitivity (%)	69.2	51.3	30	51	25.6
Specificity (%)	33.3	33.3	100	100	100
PPV (%)	93.1	90.9	100	100	100

PPV: Positive predictive value, POD: Postoperative day, CST: 1 ug cosyntropin stimulation test

value of >18 µg/dL is commonly accepted as correlating with an intact HPA when evaluating the response to CST but has also been used when interpreting morning serum cortisol.^[1,5,8,14,15] In our study, we evaluated cutoff values for morning serum cortisol of 15 and 18 µg/dL for consistency with recently assessed cutoff values in similar patient settings^[11,12] and what has previously been established as a cutoff value in a variety of patient settings that reflect a more conservative approach.^[1,5,8,14,15]

In respect to the timing of morning serum cortisol measurements, earlier literature supports using values on POD 3–7^[2,3,6] while more recent studies have evaluated measurements in the early postoperative period, from POD 0 to –2.^[9,11,12] Manuylova *et al.* recently reported 67% concordance between POD 1 and POD 6 in their series.^[10]

Our study aimed to address both areas of key controversy by assessing multiple cutoff values at time points of both POD 1 and 5. We used the low-dose cosyntropin stimulation after 4–6 weeks for definitive testing. In doing so, this is the first study to report results for multiple variables in regard to timing and cutoff values within the same study cohort allowing for direct comparisons.

We found that POD 5 values (both >18 and >15 ug/dl) were better predictors of a functional HPA with a specificity and PPV of 100%. Furthermore, two of 23 patients (8.7%) with a POD 1 cortisol ≥18 ug/dl ultimately failed the CST, which calls into question the safety of using this time point to make treatment decisions and suggests that early POD 1 measurements are less reliable indicators of an intact HPA than POD 5 measurements. This is consistent with the results reported by Manuylova *et al.* In their series, 9 of 32 (28%) patients with an initial POD 1 cortisol ≥14 ug/dl went onto have POD 6 cortisol <14 ug/dl.^[10] Their protocol was similar to ours in that all patients received intraoperative steroid coverage. However, clinical evaluation used a single cutoff value for serum cortisol (14 ug/dl) and CST was not consistently performed in their series.

This contrasts with the findings of earlier studies. Marko *et al.* reported POD 1 serum cortisol levels >15 ug/dL corresponding to an intact HPA with 80.5% sensitivity, 66.7% specificity, and 96.9% PPV.^[11] In a subsequent prospective study, they found that immediate POD 0 serum cortisol values >15 ug/dL indicated an intact HPA with 98% sensitivity, 97% specificity, and 99% PPV.^[12] Our POD 1 data for serum cortisol >15 ug/dL do not demonstrate as strong of a predictive value (69.2% sensitivity, 33.3% specificity, and 93.1% PPV). Their patient population in both studies had a known normal preoperative HPA and did not receive intraoperative steroids. The use of intraoperative coverage

could contribute to the difference in our findings underscoring the need for interpretation only in the appropriate context.

Jayasena *et al.* also used intraoperative coverage although preoperative function was unknown in their population.^[7] They found that POD 5 cortisol >14 predicts normal CST with 100% sensitivity, 46.1% specificity, and 76.6% PPV.^[7] Courtney *et al.* evaluated patients at 1 week postoperatively and compared morning serum cortisol with results of ITT at 4–6 weeks later. They report serum cortisol >16 ug/dL as a definite indicator of normal HPA function.^[3] These studies support our finding that POD 5 measurements are appropriate predictors of HPA function.

Our findings are limited by our small sample size, which is similar to other reported studies. In addition, it is difficult to compare our findings to other studies that use dissimilar protocols, specifically with respect to intraoperative steroid coverage. All patients included in our study received 0.5 mg dexamethasone intraoperatively and it is possible that these patients represent a unique subset compared to patients with known normal function who do not receive intraoperative steroid coverage. We feel it is unlikely that the intraoperative steroid dose administered (0.5 mg dexamethasone) altered the utility of POD 1 versus POD 5 morning cortisol values but recommend that future studies take this into consideration and address this potential limitation through the use of uniform protocols and subset analysis to further delineate if these two groups are truly distinct. A large multicenter study with uniform protocols is needed to address the limitations identified in our study.

CONCLUSION

Given the potentially serious consequences of failing to recognize patients with an impaired HPA, screening tests with 100% PPV should be used when deciding which patients require replacement steroids. In our cohort, 8.7% of patients with POD 1 cortisol >18 ug/dl failed CST while POD 5 cortisol >15 and 18 ug/dl predicted a functional HPA with 100% specificity and PPV. A POD 5 morning cortisol level ≥15 ug/dl is an excellent predictor of normal postoperative HPA function.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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