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Lower-dose perioperative steroid protocol during endoscopic endonasal pituitary adenoma resection

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ABSTRACT

Background: Perioperative steroid management for pituitary adenoma resections is multifaceted due to possible hypothalamic–pituitary–adrenal (HPA) axis disruption. Although many different strategies have been proposed, there is no standard protocol for prophylaxis of potential hypocortisolemia.

Methods: We performed a retrospective analysis of consecutive endoscopic endonasal pituitary adenoma resections. Before March 2016, patients received ≥100 mg of hydrocortisone intraoperatively followed by 2 mg of dexamethasone immediately postoperatively in most of the patients. Subsequently, patients received only 50 mg of hydrocortisone intraoperatively. A morning cortisol level was checked on postoperative day (POD) 2, and if it was <10 mcg/dL, patients remained on maintenance hydrocortisone. At 6 weeks, serum cortisol was redrawn and low-dose therapy was weaned when indicated.

Results: Of those who received ≥100 mg of hydrocortisone, 8 of 24 (33.3%) were discharged on hydrocortisone compared to 1 of 14 (7.1%) who received 50 mg. 18 of 24 (75%) of ≥100 mg group received dexamethasone on POD 1, and of those, 8 (44.4%) were discharged on hydrocortisone. Of those who received ≥100 mg and were on outpatient steroid therapy initially, 3 of 8 (37.5%) required continuation after 6 weeks compared to none who received 50 mg. There was an association between patient's intraoperative/immediate postoperative steroid use and steroid continuation at discharge.

Conclusion: Through our experience, we hypothesize that ≥100 mg of hydrocortisone intraoperatively followed by postoperative dexamethasone may be overly suppressive in patients with otherwise normally functioning HPA. A 50 mg intraoperative dose alone may be considered to lower rates of unnecessary steroid regimens postoperatively.

Keywords: Adrenal insufficiency, endoscopic endonasal, intraoperative hydrocortisone, pituitary adenoma, steroid replacement therapy, transsphenoidal resection

INTRODUCTION

In the 1950s, after Fraser and Lewis each published reports on mortalities related to intraoperative hemodynamic collapse of patients with chronic steroid use, "stress dose" steroid administration became pervasively implemented during the peri-operative period.[10,19,22] With the pivotal role played by cortisol in both routine metabolism and the systemic adrenergic response, the potentially fatal consequences became apparent when the physiologic demands of surgery go unmet with adequate glucocorticoid support. However, as the adverse effects of perioperative glucocorticoid therapy became clinically evident, such as impaired wound healing and increased infection rate, a diverse range of protocols and recommendations to tailor the application of perioperative steroids have since been published throughout the medical literature and applied in clinical practice.[22]

Pituitary adenoma surgery offers unique challenges to find an optimized cortisol management strategy. As the "master gland," the pituitary serves a crucial role in relaying afferent corticotropin-releasing hormone signals from the hypothalamus, through the hypothalamohypophyseal portal system, to the adrenal glands through adrenocorticotropic hormone (ACTH), first conceptualized by Cushing.[6] Given the fine balance of all pituitary functions, small physical and/or biochemical assaults on the gland can cause a variety of derangements.[6,8,9,14] Adenomas of the anterior pituitary causing mass effect on the gland within the *Sella turcica*, in addition to some having intrinsic hypersecretory properties, can lead to a range of endocrinologic findings from mild and subclinical to severe and life threatening.[1,8,9,14]

Due to the dogmatic attention to perioperative stress dosing of steroids in patients at risk for hypoadrenalism, there has been significant work on the diagnosis of subclinical hypocortisolism in pituitary adenoma patients. However, there is a lack of consensus regarding which tests are regarded as an appropriate workup of subclinical hypocortisolism, with significant clinical limitations to each.[2,7,11-13,15,17,18,21,23,24] In addition, there is a rate of new endocrine dysfunction following an adenoma resection, and thus, postoperative hypocortisolemia evaluations may be routinely implemented to determine a need for supplementation.[11-13,15,17,18,20,21,23,26] Some centers, including ours, have thus adopted a practice of treating all pituitary adenoma patients undergoing resection, with normal morning cortisol levels and without clinical signs of hypocortisolism, using a conservative perioperative hydrocortisone (the pharmacologic analog of cortisol) regimen, followed by postoperative testing, in lieu of a preoperative evaluation.[3,4,25] Additionally, if an iatrogenic injury to the pituitary resulted in profound hypothalamic-pituitary-adrenal (HPA) axis dysregulation, exogenous glucocorticoid would be systemically present in the setting of a universal steroid therapy protocol.[16,21]

While the risks associated with a short course of perioperative hydrocortisone are thought to be minimal, a question arose regarding the potential of transient adrenal suppression in an otherwise normally functioning HPA axis, resulting in an artificially low cortisol on postoperative evaluation. This concern came to light after a significant portion of patients were identified as needing outpatient steroid treatment, but at their 6-week follow-up retesting, no longer required chronic hydrocortisone therapy. We present our findings before and after changing our protocol from 100 mg of intraoperative hydrocortisone dose followed by two doses of postoperative dexamethasone to our new protocol of a single dose of 50 mg of intraoperative hydrocortisone administered during endoscopic endonasal pituitary adenoma resections, with no further steroid replacement therapy being administered postoperatively in patients with clinical and laboratory findings not suggestive of hypocortisolemia.

MATERIALS AND METHODS

Patients/procedure

We retrospectively analyzed consecutive patients over 18 years of age who underwent endoscopic endonasal transsphenoidal surgery for resection of a nonfunctioning sellar lesion over a 49-month period from January 2014 to February 2018. Patients with preoperative steroid use, pituitary apoplexy, preoperative panhypopituitarism, recurrent pituitary adenoma, or a final pathologic diagnosis other than pituitary adenoma were excluded from the study. All surgeries were performed in a technically uniform fashion by a single, dual-surgeon team (senior authors: A.V.G., neurosurgery, and C.R.P., otolaryngology) at either Loyola University Medical Center or Edward Hines, Jr. VA Medical Center. A single dose of intravenous hydrocortisone was administered before induction of anesthesia. Prior to March 2016, a dose of 100 mg of hydrocortisone was administered before induction of anesthesia. Following March 2016, a dose of 50 mg of hydrocortisone was administered. Most patients who received 100 mg of hydrocortisone were also postoperatively given 2-mg dexamethasone twice daily. This was held during the evening of postoperative day (POD) 1, resulting in this subset of patients receiving a total of two doses of dexamethasone postoperatively. Patients who received 50 mg of hydrocortisone and additional dexamethasone by anesthesia for airway management were included in the ≥100 mg group for analysis. Patients were monitored closely for clinical evidence of hypocortisolemia and treated accordingly, as indicated. This study was conducted with approval by the VA and University Hospitals' Institutional Review Board [Figure 1].

Cortisol assessments

A total of three morning serum cortisol (MSC) levels were routinely measured: preoperatively, on POD2 morning, and at 6-week follow-up. If the patients had a post-operative MSC >10 μg/dL and did not have clinical evidence of hypocortisolism when evaluated by an endocrinologist, they

were not given post-operative glucocorticoid replacement. If the POD2 MSC was ≤10 μg/dL, the patient was sent home on steroid replacement therapy (20 and 10 mg of hydrocortisone in the morning and at night, respectively).

Statistical analysis

Patients' baseline demographic and clinical measures were compared by intraoperative hydrocortisone dose, as well as steroid continuation at discharge. Fisher's exact tests were used for all categorical comparisons, while nonparametric Wilcoxon Rank Sum test was employed to assess continuous variables. An alpha error rate of $P \leq 0.05$ was considered to be statistically significant. All statistical analyses were run using SAS 9.4 (Cary, NC).

Survey

A sixteen-question survey was distributed to several US-based academic neurosurgeons who frequently perform endoscopic endonasal skull base surgery to shed light on the current perioperative hydrocortisone management protocols being employed nationally. Respondents were requested to base their answers on their practices regarding endoscopic endonasal resections of pituitary adenomas in patients with no prior history of pituitary adenoma surgery and not on pre-operative steroid replacement therapy. Questions investigated MSC testing, type and dosage of steroid medication used, indications for intra- and post-operative steroid therapy, and whether they had changed their protocol since their training.

RESULTS

Sixty-four patients underwent endoscopic endonasal transsphenoidal surgery for resection of a nonfunctioning sella lesion over the study period. 26 of these patients were excluded from the analysis due to final pathologic diagnosis other than pituitary adenoma ($n = 4$), pituitary apoplexy ($n = 9$), preoperative panhypopituitarism ($n = 1$), preoperative steroid use ($n = 3$), and recurrent pituitary adenoma ($n = 6$). Three patients had a combination of two or more exclusion criteria ($n = 3$). 38 patients were included in the analysis with 24 receiving ≥100 mg hydrocortisone or equivalent steroid and 14 receiving 50 mg. Of those that received ≥100 mg, 18 (75%) received 2 mg dexamethasone twice daily until being held at the night of POD1. Demographic information of the two cohorts is included in Table 1. The two treatment cohorts were found to be evenly balanced across demographic characteristics, comorbidities, volume of tumor, and extent of resection.

All patients had POD2 MSC levels evaluated. A total of 10 patients had POD2 MSC <10 μg/dL (1.1–9.8 μg/dL), and all except one were placed on outpatient steroid replacement therapy per protocol. The patient with a POD2 MSC level of 9.8 μg/dL did not receive outpatient steroids. No other hormone deficiencies occurred.

Preliminary results suggest a marginal association between patients' intraoperative and immediate postoperative steroid use with steroid use at discharge. Patients who received an intraoperative hydrocortisone dose of 50 mg were less likely to require steroids at discharge compared to patients who received ≥100 mg [$P = 0.07$, Table 2]. In addition, a greater proportion of patients who received immediate postoperative steroids were discharged on steroids [$P = 0.01$, Table 2].

Only three patients were continued on steroid replacement following an evaluation by an endocrinologist 6 weeks following surgery. Of those, all three had been operated on before March 2016 and had been given ≥100 mg intraoperatively followed by a short course of dexamethasone [Table 3].

Survey results

A total of nine neurosurgeons responded to our survey. Reported practices were significantly heterogeneous [Table 4]. Regarding first-time pituitary adenoma surgery for patients who have not been on preoperative steroid replacement therapy, two neurosurgeons (22%) routinely administer intraoperative

Table 1: Demographics by intraoperative hydrocortisone dose.

Identifying characteristics	50	≥100	Exact *P*	Total (*n*)
Age (median, IQR)	56.5 (51–72)	65.5 (59.5–68)	0.16	63.5 (55–68)
Sex				
Female	4 (28.6%)	1 (4.2%)	0.052	5 (13.2%)
Male	10 (71.4%)	23 (95.8%)		33 (86.8%)
POD 0 and 1 dexamethasone				
No	14 (100%)	6 (25.0%)	<0.001	20 (52.6%)
Yes	0 (0%)	18 (75.0%)		18 (47.4%)
Obese				
No	8 (57.1%)	13 (54.2%)	0.86	21 (55.3%)
Yes	6 (42.9%)	11 (45.8%)		17 (44.7%)
Pre-operative cortisol levels (median, IQR)	9.0 (8.3–18.2)	12.5 (7.1–16.1)	0.75	12.26 (7.6–17.1)
Post-operative cortisol levels (median, IQR)	14.1 (11.4–17.6)	13.7 (5.5–19.5)	0.60	14.01 (9.8–18.6)
Cortisol levels at 6 weeks (median, IQR)	12.8 (11.5–16.8)	12.4 (9.6–16.7)	0.90	12.58 (9.6–16.8)

Percentages are within parentheses, IQR: Interquartile range, POD: Post-operative day

Table 2: Discharged on steroid replacement.

Identifying characteristics	No discharge steroids	Discharged on steroids	Exact *P*	Total (*n*)
Age (median, IQR)	63 (54–68)	65 (59–68)	0.57	63.5 (55–68)
Sex				
Female	5 (17.2%)	0 (0%)	0.18	5 (13.2%)
Male	24 (82.8%)	9 (100%)		30 (86.8%)
Obese				
No	18 (62.1%)	3 (33.3%)	0.13	21 (55.3%)
Yes	11 (37.9%)	6 (66.7%)		17 (44.7%)
Intraoperative hydrocortisone equivalent dose				
50	13 (44.8%)	1 (11.1%)	0.07	14 (36.8%)
≥100	16 (55.2%)	8 (88.9%)		24 (63.2%)
POD 0 and 1 dexamethasone				
No	19 (65.5%)	1 (11.1%)	0.01	20 (52.6%)
Yes	10 (34.5%)	8 (88.9%)		18 (47.4%)

Percentages are within parentheses, IQR: Interquartile range, POD: Post-operative day

Table 3: Need for long-term steroid replacement.

Steroid protocol	No long-term steroids	Long-term steroids
Intraoperative hydrocortisone equivalent dose		
50 (*n*=14)		
Short-term steroids (*n*=1)	1	0
No short-term steroids (*n*=13)	13	
≥100 (n=24)		
Short-term steroids (*n*=8)	5	3
No short-term steroids (*n*=16)	16	
POD 0 and 1 dexamethasone		
No (*n*=20)		
Short-term steroids (*n*=1)	1	0
No short-term steroids (*n*=19)	19	
Yes (*n*=18)		
Short-term steroids (*n*=8)	5	3
No short-term steroids (*n*=10)	10	

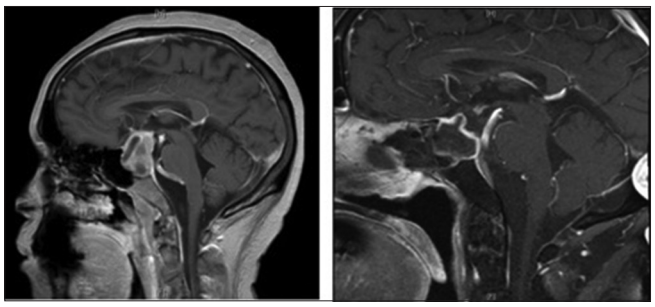

Figure 1: Pre-(left) and post-operation (right) T1-weighted postcontrast sagittal magnetic resonance imaging of a large pituitary adenoma.

steroids, 5 (56%) only use intraoperative steroids if a patient is clinically addisonian, 1 (11%) administers intraoperative steroids for hypocortisolemia, and 1 (11%) does not administer intraoperative steroids. Intraoperative steroids administered include hydrocortisone, dexamethasone, and solu-medrol of varying doses. 8 (89%) check at least a POD1 MSC level. A variety of thresholds for the continuation of steroids and outpatient dosing strategies are reported. 5 (56%) respondents have changed their perioperative steroid management practices since the completion of their training.

DISCUSSION

The management of perioperative steroids for pituitary adenoma surgery remains a clinical challenge given a wide range of potential physiologic scenarios and proposed practices. Such has been demonstrated in our nationwide survey of academic neurosurgeons who routinely utilize endoscopic endonasal skull base techniques. Inder and Hunt and Wentworth *et al.* suggested that patients undergo a ACTH 1-24 (Synacthen) test.[13,24] For those with results in the normal range, they suggest that no pre- or intra-operative steroid is needed, but for those with abnormal tests, they are started on 15–30 mg hydrocortisone daily before surgery, followed by a rapid 2-day hydrocortisone taper started at 50 mg. They then recommend postoperative testing for both the groups. In contrast, De Tommasi *et al.* reported a cohort of asymptomatic patients with MSC <9 μg/dL who inadvertently did not receive intraoperative steroids without complication, thus suggesting that stress-dose steroids may not be necessary in patients lacking symptoms of adrenal insufficiency.[7]

In addition to pre - and post-operative hypoadrenalism treatment, an intraoperative iatrogenic injury to the pituitary or infundibulum is a real, albeit uncommon, surgical complication. Thus, stress-dose steroid administration serves as a prophylactic measure to mediate such complications.[12,23] Multiple large retrospective series have noted new immediate postoperative endocrinologic dysfunction occurring in 3–14% of cases and symptomatic adrenal insufficiency occurring at a rate of about 5%.[5,14,21,23] With this, surgeons may be reluctant to withhold steroid replacement, and our survey results demonstrate this controversy in the present day across the United States.

The use of stress dose steroids and the particular dose are controversial. 100 mg of hydrocortisone was initially used as a

Table 4: Survey results from the US-based academic neurosurgeons who frequently perform endoscopic endonasal skull base surgery regarding perioperative steroid replacement strategies.

Institution	Do you measure a morning cortisol level before pituitary adenoma resection?	Do you routinely administer intraoperative stress dose steroids?	Intraoperative steroid and dose administered	Do you routinely administer post-operative steroids?	Post-operative steroid and dose administered	When do you measure a post-operative morning serum cortisol?	Do you routinely discharge patients on steroids?	What steroid and what dose do you discharge patients home on?	What parameter do you use to prescribe steroids upon discharge?	How long after the operation do you typically have your patients follow-up with endocrinology for repeat morning cortisol levels?	Have you changed your perioperative steroid dosing strategy since your training?	How many years ago did you complete your training?
1	Yes, in all patients	Yes	Dexamethasone, dosed per anesthesia	No	N/A	Morning of POD 1	No	N/A	N/A	1 week	Yes	14
2	Yes, in all patients	No	N/A	No	N/A	Morning of POD 1	No	N/A	N/A	3 weeks	Yes	No response provided
3	Yes, in all patients	Only if the patient is clinically Addisonian	Hydrocortisone 50 mg	Only if the patient is clinically Addisonian	Hydrocortisone, dosed per endocrine	Does not measure	If the patient is clinically Addisonian	Hydrocortisone, dosed per endocrine	Endocrine assessment	N/A	Yes	23
4	Only if the patient is clinically Addisonian	Yes	Hydrocortisone 100 mg	Yes	Hydrocortisone 100 mg TID, tapered off over 2–3 days	On POD 1 if the patient is clinically addisonian	If the patient is clinically Addisonian	Hydrocortisone 20 mg in the am, 10 mg in the pm	Morning cortisol to detect for hypocortisolemia	1–2 weeks	No	18
5	Yes, in all patients	Only if the patient is clinically addisonian	Hydrocortisone 100 mg	Only if the patient is clinically addisonian	Hydrocortisone 50 mg every 8 h, then tapered	POD 1	If the patient is clinically addisonian	Prednisone 20 mg in the am, 10 mg in the pm	If patient is clinically addisonian	1 week	No	6
6	No	Only if the patient is clinically addisonian	Dexamethasone 10 mg	Yes	Hydrocortisone 10 mg daily if not on pre-operative steroids	POD 1 and 5	Yes, all patients	Hydrocortisone 10 mg daily	Hydrocortisone 10 mg daily pending lab results if not on pre-operative steroids. If both POD1 and POD5 morning cortisol levels are greater than 18, steroids are discontinued	3 weeks if steroids required	No	14
7	Yes, in all patients	No, only administered if cortisol is low	Hydrocortisone 50 mg	No	N/A	Every morning of admission	No, administered based on laboratory values	Hydrocortisone 15 mg in the am, 5 mg in the pm	Morning cortisol less than 8	1 week for repeat am cortisol, follow-up with endocrine and neurosurgery at 8 weeks	No	15

(*Contd...*)

Table 4: *(Continued)*

Institution	Do you measure a morning cortisol level before pituitary adenoma resection?	Do you routinely administer intraoperative stress dose steroids?	Intraoperative steroid and dose administered	Do you routinely administer post-operative steroids?	Post-operative steroid and dose administered	When do you measure a post-operative morning serum cortisol?	Do you routinely discharge patients on steroids?	What steroid and what dose do you discharge patients home on?	What parameter do you use to prescribe steroids upon discharge?	How long after the operation do you typically have your patients follow-up with endocrinology for repeat morning cortisol levels?	Have you changed your perioperative steroid dosing strategy since your training?	How many years ago did you complete your training?
8	Yes, in all patients	Only if the patient is clinically addisonian	Hydrocortisone 100 mg	Only if the patient is clinically Addisonian	Hydrocortisone 100 mg every 8 h	POD 1	No, administered based on laboratory values	Hydrocortisone 20 mg in the am, 10 mg in the pm	Morning cortisol less than 10–14, depending on risk and symptoms	2–3 weeks only if on steroids	Yes	10
9	Yes, in all patients	Only if the patient is clinically addisonian	Solumedrol 100 mg	Only if the patient is clinically Addisonian	Hydrocortisone 20 mg every 8 h	POD 1 and 3	No, administered based on laboratory values	Hydrocortisone 20 mg in the am, 10 mg in the pm	Post-operative cortisol <10	6 weeks	Yes	16

POD: Post-operative day

standard stress dose intraoperatively, although this was likely leading to excessive transient adrenal suppression in our patients. It has been estimated that the physiologic cortisol levels in response to surgical stress range from 50 to 150 mg depending on the duration and systemic demands of the procedure.[22] In addition, there is no evidence to support that a supraphysiologic cortisol level is beneficial, and to the contrary, a variety of postoperative complications have been attributed to steroids.[22] Most poignant, Zueger *et al.* reported a retrospective series of nonfunctioning pituitary adenoma patients with preoperative hypoadrenalism noted during initial workup.[27] These patients were stratified into three groups based on the amount of hydrocortisone administered per day, with analysis done for both absolute dosage and weight adjusted. With equivalent clinical characteristics between groups, they found a statistically significant increased mortality at higher dosages.

The retrospective nature of our study and nonrandomized cohorts resulted in some heterogeneity of our defined study groups, but we believe that pragmatic insights can still be drawn from our findings. Furthermore, with the limited sample size and our low surgical complication rate and a decreased need for outpatient steroid supplementations following resection of nonsecretory pituitary adenomas, a single intraoperative 50-mg hydrocortisone dose for preoperatively asymptomatic patients with normal MSC appears to be judicious. Further prospective investigation could provide more insight regarding the effects that a lower-dose intraoperative hydrocortisone strategy could have on the outcomes of patients undergoing pituitary adenoma resection.

CONCLUSION

Currently, a universally accepted protocol has yet to be established for hydrocortisone replacement therapy. A single intraoperative hydrocortisone replacement dose of 50 mg without postoperative steroid replacement therapy for nonaddisonian patients undergoing endoscopic endonasal resection of a pituitary adenoma is a safe and potentially beneficial protocol for perioperative adrenal insufficiency prophylaxis.

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Conflicts of interest

There are no conflicts of interest.

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