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.\textsuperscript{[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.\textsuperscript{[12]}

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.\textsuperscript{[6]} Given the fine balance of all pituitary functions, small physical and/or biochemical assaults on the gland can cause a variety of derangements.\textsuperscript{[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.\textsuperscript{[6,8,9,14]}

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.\textsuperscript{[12,13,15,17,18,21,23,24]} In addition, there is a rate of new endocrine dysfunction following an adenoma resection, and thus, postoperative hypocortisolism evaluations may be routinely implemented to determine the need for supplementation.\textsuperscript{[11-13,15,17,18,20,21,23,24]} 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.\textsuperscript{[3,4,23]} 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.\textsuperscript{[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 technologically 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 transphenoidal 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 transphenoidal 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 transphenoidal 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 \( [P = 0.07, \text{Table 2}] \). In addition, a greater proportion of patients who received immediate postoperative steroids were discharged on steroids \( [P = 0.01, \text{Table 2}] \).

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

| Identifying characteristics | 50 | =100 | Exact P | Total (n) |
|----------------------------|----|------|---------|----------|
| Age (median, IQR)          | 56.5 (51–72) | 65.5 (39.5–68) | 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.
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 mitigate 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

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**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 |

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**Figure 1:** Pre-(left) and post-operation (right) T1-weighted postcontrast sagittal magnetic resonance imaging of a large pituitary adenoma.
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           | N/A                                               | Morning of POD 1                             | No                                            | N/A                                          | N/A                                          | 1 week                                                     | Yes                                                                          | 14                                                                           |
| 2           | Yes, in all patients                                                             | No                                                            | N/A                                          | 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 Addison                     | Hydrocortisone 50 mg                          | Hydrocortisone, dosed per endocrine               | Does not measure                            | If the patient is clinically Addison          | Hydrocortisone, dosed per endocrine             | Endocrine assessment                                      | N/A                                          | Yes                                                                          | 23                                                                           |
| 4           | Only if the patient is clinically Addison                                        | Yes                                                           | Hydrocortisone 100 mg                         | Yes                                               | Hydrocortisone 100 mg TID, tapered off over 2–3 days | If the patient is clinically Addison          | 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 Addison                     | Hydrocortisone 100 mg                         | Only if the patient is clinically Addison         | Hydrocortisone 50 mg every 8 h, then tapered  | If the patient is clinically Addison          | Hydrocortisone 20 mg in the am, 10 mg in the pm | Endocrine assessment                                      | N/A                                          | Yes                                                                          | 6                                                                            |
| 6           | No                                                                               | Only if the patient is clinically Addison                     | Dexamethasone 10 mg                           | Yes                                               | POD 1 and 5                                 | Yes, all patients                             | Hydrocortisone 10 mg daily                        | Morning cortisol less than 8                                 | 3 weeks if steroids required                                               | No                                                                          | 14                                                                           |
| 7           | Yes, in all patients                                                             | No, only administered if cortisol is low                      | Hydrocortisone 50 mg                          | 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...)
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 suplementations 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.

**REFERENCES**

1. Arafa BM. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. J Clin Endocrinol Metab 1986;62:1173-9.

2. Arraee MA. Assessment of postoperative hypocortisolism after pituitary surgery: When and how? World Neurosurg 2013;80:495-7.
3. Auchus RJ, Shewbridge RK, Shepherd MD. Which patients benefit from provocative adrenal testing after transsphenoidal pituitary surgery? Clin Endocrinol (Oxf) 1997;46:21-7.

4. Ausiello JC, Bruce JN, Freda PU. Postoperative assessment of the patient after transsphenoidal pituitary surgery. Pituitary 2008;11:391-401.

5. Cappabianca P, Cavallo LM, Colao A, de Divitiis E. Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. J Neurosurg 2002;97:293-5.

6. Cushing H. The Pituitary Body and its Disorders, Clinical States Produced by Disorders of the Hypophysis Cerebri. Philadelphia, PA, London: J.B. Lippincott Company; 1912.

7. De Tommasi C, Goguen J, Cusimano MD. Transsphenoidal surgery without steroid replacement in patients with morning serum cortisol below 9 μg/dl (250 nmol/l). Acta Neurochir (Wien) 2012;154:1903-15.

8. Ebersold MJ, Quast LM, Laws ER Jr., Scheithauer B, Randall RV. Long-term results in transsphenoidal removal of nonfunctioning pituitary adenomas. J Neurosurg 1986;64:713-9.

9. Fleseriu M, Bodach ME, Tumialan LM, Bonert V, Oyesiku NM, Patil CG, et al. Congress of neurological surgeons systematic review and evidence-based guideline for pretreatment endocrine evaluation of patients with nonfunctioning pituitary adenomas. Neurosurgery 2016;79:E527-9.

10. Fraser CG, Preuss FS, Bigford WD. Adrenal atrophy and irreversible shock associated with cortisone therapy. J Am Med Assoc 1952;149:1542-3.

11. García-Luna PP, Leal-Cerro A, Rocha JL, Trujillo F, Garcia-Pesquera F, Astorga R, et al. Evaluation of the pituitary-adrenal axis before, during and after pituitary adenomectomy. Is perioperative glucocorticoid therapy necessary? Acta Endocrinol (Copenh) 1990;122:83-8.

12. Hout WM, Arafah BM, Salazar R, Selman W. Evaluation of the hypothalamic-pituitary-adrenal axis immediately after pituitary adenomectomy: Is perioperative steroid therapy necessary? J Clin Endocrinol Metab 1998;66:1208-12.

13. Inder WJ, Hunt PJ. Glucocorticoid replacement in pituitary surgery: Guidelines for perioperative assessment and management. J Clin Endocrinol Metab 2002;87:2745-50.

14. Jane JA Jr., Laws ER Jr. The surgical management of pituitary adenomas in a series of 3,093 patients. J Am Coll Surg 2001;193:651-9.

15. Jane JA Jr., Thapar K, Kaptain GJ, Maartens N, Laws ER Jr. Pituitary surgery: Transsphenoidal approach. Neurosurgery 2002;51:435-42.

16. Jayasena CN, Gadhvi KA, Gohel B, Martin NM, Mendoza N, Meeran K, et al. Day 5 morning serum cortisol predicts hypothalamic-pituitary-adrenal function after transsphenoidal surgery for pituitary tumors. Clin Chem 2009;55:972-7.

17. Joseph SP, Ho JT, Dooque MP, Burt MG. Perioperative management of the hypothalamic-pituitary-adrenal axis in patients with pituitary adenomas: An Australasian survey. Intern Med J 2012;42:1120-4.

18. Kristof RA, Wickers M, Haun D, Redel L, Klingmüller D, Schramm J, et al. Peri-operative glucocorticoid replacement therapy in transsphenoidal pituitary adenoma surgery: A prospective controlled study. Acta Neurochir (Wien) 2008;150:329-35.

19. Lewis L, Robinson RF, Yee J, Hacker LA, Eisen G. Fatal adrenal cortical insufficiency precipitated by surgery during prolonged continuous cortisone treatment. Ann Intern Med 1953;39:116-26.

20. Marko NF, Gonugunta VA, Hamrahian AH, Usmani A, Mayberg MR, Weil RJ, et al. Use of morning serum cortisol level after transsphenoidal resection of pituitary adenoma to predict the need for long-term glucocorticoid supplementation. J Neurosurg 2009;111:540-4.

21. Nemergut EC, Dumont AS, Barry UT, Laws ER. Perioperative management of patients undergoing transsphenoidal pituitary surgery. Anesth Analg 2005;101:1170-81.

22. Salem M, Tainsh RE Jr., Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994;219:416-25.

23. Tohti M, Li J, Zhou Y, Hu Y, Yu Z, Ma C, et al. Is peri-operative steroid replacement therapy necessary for the pituitary adenoma treated with surgery? A systematic review and meta analysis. PLoS One 2015;10:e0119621.

24. Wentworth JM, Gao N, Sumithran KP, Maartens NF, Kaye AH, Colman PG, et al. Prospective evaluation of a protocol for reduced glucocorticoid replacement in transsphenoidal pituitary adenomectomy: Prophylactic glucocorticoid replacement is seldom necessary. Clin Endocrinol (Oxf) 2008;69:29-35.

25. Wilson CB, Dempsey LC. Transsphenoidal microsurgical removal of 250 pituitary adenomas. J Neurosurg 1978;48:13-22.

26. Zada G, Tirosh A, Huang AP, Laws ER, Woodmansee WW. The postoperative cortisol stress response following transsphenoidal pituitary surgery: A potential screening method for assessing preserved pituitary function. Pituitary 2013;16:319-25.

27. Zueger T, Kirchner P, Herren C, Fischli S, Zwahlen M, Christ E, et al. Use of morning serum cortisol level after transsphenoidal pituitary adenomectomy: Is peri-operative glucocorticoid replacement therapy necessary for the pituitary adenoma treated with surgery? J Clin Endocrinol Metab 2012;97:E1938-42.