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ORIGINAL ARTICLE - PITUITARIES

Sevoflurane anesthesia rather than propofol anesthesia is associated with 3-month postoperative hypocortisolism in patients undergoing endoscopic transsphenoidal surgery for non-functional pituitary adenoma with preoperative normal hypothalamic–pituitary–adrenal axis

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Abstract

Purpose The effects of anesthetic technique on intermediate-term postoperative adrenocorticotropic hormone (ACTH) functional outcomes have not been fully determined in non-functioning pituitary adenoma (NFPA) patients. Postoperative hypocortisolism is potentially life-threatening and requires steroid replacement after pituitary surgery. The present study determined whether sevoflurane anesthesia was predictive of 3-month postoperative hypocortisolism in NFPA patients with preoperative normal hypothalamic–pituitary–adrenal (HPA) axis.

Methods Demographics, preoperative pituitary hormone status, intraoperative data, and tumor characteristics were retrospectively collected from 429 NFPA patients, who had preoperative normal HPA axis and underwent endoscopic transsphenoidal surgery. Patients were divided into two groups based on intraoperative anesthetic technique: sevoflurane-based inhalation anesthesia group ($n=74$) and propofol-based intravenous anesthesia group ($n=355$). After propensity score matching, 73 patients were selected in each group and the incidence of 3-month postoperative hypocortisolism (primary outcome measure) was compared between the two groups.

Results The incidence of 3-month postoperative hypocortisolism was higher in the sevoflurane anesthesia group than the propofol anesthesia group before ($n=20$[27.0%] vs. $n=49$[13.8%], $P=0.008$) and after ($n=20$ [27.4%] vs. $n=5$ [6.8%], $P=0.002$) propensity score matching, respectively. Sevoflurane anesthetic use (odds ratio [95% CI] 5.37[1.80–15.98], $P=0.003$) and postoperative steroid administration (2.89 [1.06–7.92], $P=0.039$) were predictors of 3-month postoperative hypocortisolism.

Conclusion In patients with preoperative normal HPA axis undergoing endoscopic transsphenoidal surgery for NFPA, sevoflurane anesthesia and postoperative steroid administration were associated with the development of 3-month postoperative hypocortisolism. A large-scale prospective study is needed to confirm the negative association between sevoflurane anesthesia and postoperative ACTH functional outcome.

Keywords Hypocortisolism · Hypothalamic–pituitary–adrenal axis · Non-functioning pituitary adenoma · Endoscopic transsphenoidal surgery

Introduction

Nonfunctioning pituitary adenoma (NFPA) is a benign tumor of the pituitary gland characterized by a lack of excessive secretion of pituitary hormones [6]. Endoscopic transsphenoidal pituitary surgery has been established as the treatment for pituitary adenoma, and is associated with a high gross total resection rate and low complication rate due to improved visualization [8, 15]. However, manipulation

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of the pituitary gland and neuroendocrine stress response can affect postoperative pituitary hormonal status in NFPA patients undergoing endoscopic transsphenoidal surgery [2, 38].

Postoperative hypocortisolism is a common complication of endoscopic transsphenoidal surgery in NFPA patients [3]. Hypocortisolism patients exhibit symptoms such as profound fatigue, weight loss, postural hypotension, and muscle and abdominal pain [24]. Regarding health-related quality of life, general health and vitality are reduced in hypocortisolism patients [13, 21]. Furthermore, hypocortisolism is a potentially serious clinical condition because hypocortisolism patients have an approximately 50% increased risk of adrenal crisis, which leads to hypotension, shock, and even death [31]. In addition, patients with hypocortisolism require steroid replacement, which is associated with various complications such as weight gain, glucose intolerance, and osteoporotic fracture [27]. Therefore, identifying risk factors for postoperative hypocortisolism after transsphenoidal surgery in NFPA patients is of clinical importance. In previous studies, 13–20% of NFPA patients with preoperative normal hypothalamic–pituitary–adrenal (HPA) axis newly developed hypocortisolism after surgery [15, 25]. Although the tumor size, preoperative urinary-free cortisol level, and morning serum cortisol level on postoperative day 2 were identified as predictors of postoperative hypocortisolism in patients with pituitary/peripituitary tumors in a few previous studies [20, 29], there is a lack of evidence regarding predictors of postoperative hypocortisolism in NFPA patients undergoing endoscopic transsphenoidal surgery, especially those with preoperative normal HPA axis.

Anesthetic technique affects perioperative neuroendocrine stress hormones, such as serum ACTH and cortisol, by modulating the neuroendocrine stress response and sympathetic tone. In previous studies, when the effects of inhalation and intravenous anesthesia on perioperative neuroendocrine stress hormones were compared in various surgical patients, the former was associated with higher intraoperative and early postoperative ACTH and cortisol levels [18, 22, 38]. Regarding the effects of anesthetics on intermediate-term postoperative neuroendocrine functional outcome, only one previous study conducted by Dr. Oh and co-workers showed no differences in 3-month postoperative neuroendocrine functional outcomes between inhalation and intravenous anesthetic techniques in NFPA patients. [25]. However, their study included inhomogeneous subjects with respect to preoperative HPA status. In other words, both patients with preoperative normal HPA axis and those with preoperative hypocortisolism were included in their study. In clinical practice, clinicians have an interest in newly developed postoperative hypocortisolism rather than persisting postoperative hypocortisolism in NFPA surgical patients. Therefore, the effects of inhalation and intravenous anesthetics on intermediate-term postoperative ACTH functional outcome are needed to be reinvestigated in NFPA patients with preoperative normal HPA axis.

In this retrospective study, we determined whether the sevoflurane-based inhalation anesthesia was predictive of 3-month postoperative hypocortisolism in patients undergoing endoscopic transsphenoidal surgery for NFPA with preoperative normal HPA axis.

Methods

Subjects

This retrospective single-center study was conducted on adult NFPA patients with preoperative normal HPA axis who underwent tumor removal surgery via the endoscopic transsphenoidal approach at Seoul National University Hospital, between March 2010 and December 2020. Sixty-three patients included in our previous study were again included, in which we investigated a difference in the neuroendocrine stress response between sevoflurane anesthesia and propofol anesthesia in patients undergoing endoscopic transsphenoidal tumor removal surgery between May 2017 and 2018 [38]. Patients with missing laboratory data on serum ACTH or cortisol were excluded from the study. Prior to data collection, this study was approved by the Institutional Review Board of Seoul National University Hospital (number: H-2110–126-1264, date: 27 Oct 2021). The requirement for written informed consent was waived because this was a retrospective study.

Data collection

Demographic data (age, sex, body mass index), American Society of Anesthesiologists physical status, comorbidities, previous treatment history (surgery, gamma-knife surgery, radiotherapy), laboratory data (preoperative and postoperative serum levels of pituitary hormones), oncologic data (tumor size, immunohistochemical staining, cavernous sinus invasion, optic chiasm compression), surgical data (duration and degree of resection), anesthetic data (duration of sevoflurane-based inhalation anesthesia and propofol-based intravenous anesthesia, total time of mean blood pressure [*MBP*] < 65 mmHg, total area under *MBP* < 65 mmHg, time-weighted average of *MBP* < 65 mmHg [total area under *MBP* < 65 mmHg/anesthetic time], and intraoperative arterial partial pressure of oxygen and carbon dioxide), postoperative complications (diabetes insipidus [DI], hyponatremia, infection, cerebrospinal fluid leakage, hemorrhage, and hydrocephalus), and postoperative steroid administration were respectively collected from electronic medical records. Pituitary hormones, such as ACTH and cortisol, were measured within 1 month preoperatively and at 3 months postoperatively.

Propensity score matching

Patients were divided into two groups based upon intraoperative anesthetic technique: inhalational and intravenous anesthesia group. Propensity scores were matched with a ratio of 1:1 to exclude the effects of confounders, which differed significantly between the sevoflurane-based inhalational and propofol-based intravenous anesthesia group, on 3-month postoperative hypocortisolism.

Anesthetic management

The main anesthetic agent was chosen at the discretion of attending anesthesiologists without special considerations. In all patients, target-controlled infusion of remifentanil was used during anesthetic maintenance. All patients were mechanically ventilated and managed to maintain arterial oxygen tension ≥ 100 mmHg and arterial carbon dioxide tension of 36–44 mmHg. Also, all patients were subjected to invasive blood pressure monitoring and fluids and vasoactive drugs were administrated to maintain mean arterial pressure within ± 20% of preoperative value. Intravenous fentanyl 100 µg was administrated for pain control at the end of surgery. Most patients were taken immediate postoperative brain CT and transferred to the neurointensive care unit without emergence and extubation. There was no difference in patient management in the intensive care unit or postoperative recovery unit between sevoflurane-based inhalation anesthesia group and propofol-based intravenous group.

Perioperative steroid management

Among the patients, 84% of the patients received 100 mg intravenous hydrocortisone in the morning and 50 mg intravenous hydrocortisone twice postoperatively on the day of surgery. On postoperative days 1 and 2, 50 and 25 mg of intravenous hydrocortisone, respectively, were administered twice daily. Postoperative morning cortisol levels were measured on postoperative days 2, 7, and 14 and postoperative 1 month, respectively. Oral hydrocortisone was prescribed to patients with morning cortisol < 8 µg/dL in each blood test. Postoperative hyponatremia was assessed on postoperative days 7 and 14, respectively. Oral hydrocortisone was given to patients with postoperative hyponatremia.

Definition and outcome

Hypocortisolism was defined as serum cortisol < 18 µg/dL in the insulin-induced hypoglycemia test, peak cortisol < 18 µg/dL in the short ACTH test, morning cortisol < 8 µg/dL, or random cortisol < 5 µg/dL with a low to normal serum ACTH level.

The primary outcome was the incidence of 3-month postoperative hypocortisolism.

Sample size calculation

In two previous studies of NFPA patients with preoperative normal HPA axis undergoing endoscopic transsphenoidal tumor removal surgery, the incidence of 3-month postoperative hypocortisolism was approximately 20% [15, 19]. To reproduce this proportion with a 99% confidence interval (CI) and margin of error of 0.05, at least 425 patients were required for this study.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). Categorical variables are presented as the number of patients (proportions) and continuous variables as the mean (standard deviation) or median (interquartile range). The chi-squared test or Fisher's exact test was used to compare categorical variables. For continuous variables, the Shapiro–Wilk test was first used to determine the normality of the data distribution, and Student's *t*-test and the Mann–Whitney *U* test were used to compare normally distributed and skewed variables, respectively. Variables with a P value < 0.075 in univariate logistic regression analysis, and well-known factors for postoperative hypocortisolism were included in the multivariate logistic regression to identify risk factors for postoperative hypocortisolism. A P value < 0.05 was considered statistically significant.

Results

A total of 432 NFPA patients with preoperative normal HPA axis underwent endoscopic transsphenoidal tumor removal surgery during the study period; 3 patients were excluded due to missing data for preoperative ACTH or cortisol level. Ultimately, 429 patients were included in the data analysis.

The demographic and perioperative data are summarized in Table 1. A total of 74 and 355 patients received intraoperative sevoflurane-based inhalational and propofol-based intravenous anesthesia, respectively. Six variables (age, preoperative steroid administration, tumor volume, immunohistochemical staining, optic chiasm compression, and cavernous sinus invasion) were matched with a ratio of 1:1 in the two groups using propensity score matching. After checking that there was no variable showing a significant imbalance between two groups ($P = 0.695$ in overall balance test), 73 patients were chosen in each group and included in

Table 1 Comparisons of demographic and perioperative data between two anesthetic techniques

	Before propensity score matching			After propensity score matching		
	Sevoflurane anesthesia (n=74)	Propofol anesthesia (n=355)	P value	Sevoflurane anesthesia (n=73)	Propofol anesthesia (n=73)	P value
Age (years)	53.5 (41.0–63.5)	57.0 (46.0–68.0)	0.072	54.0 (41.0–66.0)	52.0 (42.0–64.5)	0.917
≥65	20 (27.0%)	113 (31.8%)	0.500	20 (27.4%)	18 (24.7%)	0.850
Male sex	28 (37.8%)	160 (45.1%)	0.312	27 (37.0%)	33 (45.2%)	0.400
Body mass index (kg/m^2)	24.7 (22.8–27.7)	25.3 (23.0–27.7)	0.509	24.7 (22.8–27.8)	24.5 (22.4–27.1)	0.479
≥25	33 (44.6%)	191 (53.8%)	0.189	33 (45.2%)	33 (45.2%)	1.000
ASA PS class			0.018			0.986
1	41 (55.4%)	133 (37.5%)		40 (54.8%)	41 (56.2%)	
2	31 (41.9%)	207 (58.3%)		31 (42.5%)	30 (41.1%)	
3	2 (2.7%)	15 (4.2%)		2 (2.7%)	2 (2.7^)	
Comorbidities						
Hypertension	18 (24.3%)	86 (24.2%)	1.000	18 (24.7%)	10 (13.7%)	0.141
Diabetes mellitus	7 (9.5%)	36 (10.1%)	1.000	7 (9.6%)	4 (5.5%)	0.531
Dyslipidemia	15 (20.3%)	56 (15.8%)	0.439	15 (20.5%)	9 (12.3%)	0.264
Cardiac	4 (5.4%)	20 (5.6%)	1.000	4 (5.5%)	3 (4.1%)	1.000
Cerebrovascular	1 (1.4%)	4 (1.1%)	1.000	1 (1.4%)	0 (0.0%)	1.000
Malignancy	2 (2.7%)	17 (4.8%)	0.549	2 (2.7%)	5 (6.8%)	0.442
Musculoskeletal	6 (8.1%)	28 (7.9%)	1.000	6 (8.2%)	3 (4.1%)	0.494
Preoperative steroid administration	71 (95.9%)	290 (81.7%)	0.004	70 (95.9%)	69 (94.5%)	1.000
Preoperative hormone levels						
ACTH (pg/mL)	29.5 (20.0–51.9)	36.8 (23.6–54.9)	0.100	29.0 (19.9–52.0)	38.0 (24.6–49.8)	0.159
Cortisol (μg/dL)	10.5 (7.6–15.2)	10.7 (7.3–15.5)	0.895	10.7 (7.5–15.3)	10.5 (5.7–15.3)	0.609
Preoperative hormone deficiency						
TSH	7 (9.5%)	43 (12.1%)	0.654	7 (9.6%)	10 (13.7%)	0.606
GH	28 (37.8%)	134 (37.7%)	1.000	28 (38.4%)	27 (37.0%)	1.000
Gonadotropin	51 (68.9%)	208 (58.6%)	0.128	50 (68.5%)	47 (64.4%)	0.726
Previous treatment history*	12 (16.2%)	66 (18.6%)	0.752	12 (16.4%)	13 (17.8%)	1.000
Tumor characteristics						
Volume (cm^3)	8.3 (4.5–14.2)	6.9 (4.3–10.8)	0.164	8.2 (4.4–13.8)	6.8 (4.5–10.8)	0.391
Immunohistochemical staining						
ACTH	8 (10.8%)	66 (18.6%)	0.149	8 (11.0%)	9 (12.3%)	1.000
FSH	11 (14.9%)	98 (27.6%)	0.032	11 (15.1%)	18 (24.7%)	0.213
GH	2 (2.7%)	8 (2.3%)	0.685	2 (2.7%)	2 (2.7%)	1.000
LH	0 (0.0%)	2 (0.6%)	1.000	0 (0.0%)	0 (0.0%)	NA
Prolactin	16 (21.6%)	64 (18.0%)	0.577	15 (20.5%)	13 (17.8%)	0.834
TSH	5 (6.8%)	26 (7.3%)	1.000	4 (5.5%)	5 (6.8%)	1.000
Null cell	41 (55.4%)	143 (40.3%)	0.024	41 (56.2%)	36 (49.3%)	0.507
Optic chiasm compression	66 (89.2%)	264 (74.4%)	0.009	65 (89.0%)	65 (89.0%)	1.000
Cavernous sinus invasion**	50 (67.6%)	183 (51.5%)	0.017	49 (67.1%)	41 (56.2%)	0.233
Surgery						
In the morning	59 (79.7%)	263 (74.1%)	0.382	59 (80.8%)	55 (75.3%)	0.548
Duration (min)	100.0 (75.0–130.0)	100.0 (75.0–139.0)	0.770	100.0 (75.0–130.0)	100.0 (80.0–133.0)	0.708
Degree of resection			0.247			0.360
Grossly total resection	51 (68.9%)	273 (76.9%)	0.192	51 (69.9%)	56 (76.7%)	0.454
Subtotal resection	22 (29.7%)	81 (22.8%)	0.264	21 (28.8%)	17 (23.3%)	0.572
Partial resection	1 (1.4%)	1 (0.3%)	0.316	1 (1.4%)	0 (0.0%)	1.000
Anesthetic time (min)	160.0 (135.0–196.3)	165.0 (135.0–205.0)	0.664	160.0 (135.0–192.5)	165.0 (137.5–207.5)	0.405

Table 1 (continued)

	Before propensity score matching			After propensity score matching		
	Sevoflurane anesthesia ($n=74$)	Propofol anesthesia ($n=355$)	*P* value	Sevoflurane anesthesia ($n=73$)	Propofol anesthesia ($n=73$)	*P* value
Total time of intraoperative *MBP* < 65 mmHg (min)	18.5 (6.3–37.5)	12.0 (3.0–28.0)	0.040	18.5 (6.3–37.5)	10.0 (2.0–21.5)	0.014
Total area under intraoperative *MBP* < 65 mmHg (mmHg*min)	48.0 (7.3–114.0)	26.0 (1.5–92.0)	0.038	48.0 (7.3–114.0)	14.0 (0.0–89.3)	0.021
Time-weighted average of intraoperative *MBP* < 65 mmHg (mmHg)	0.16 (0.02–0.62)	0.14 (0.00–0.53)	0.503	0.17 (0.03–0.63)	0.08 (0.00–0.51)	0.205
Intraoperative mean PO_2	198.0 (137.6–254.5)	184.0 (144.0–223.6)	0.131	197.8 (137.6–254.3)	190.3 (163.9–245.8)	0.959
Intraoperative mean PCO_2	37.0 (34.8–40.0)	37.6 (35.1–40.0)	0.558	37.0 (35.1–40.0)	37.6 (34.7–39.0)	0.779
Timing of study			0.057			0.050
First trimester (Mar 2010–Oct 2013)	20 (27.0%)	127 (35.8%)		19 (26.0%)	31 (42.5%)	
Second trimester (Nov 2013–May 2017)	34 (45.9%)	112 (31.5%)		34 (46.6%)	21 (28.8%)	
Third trimester (Jun 2017–Dec 2020)	20 (27.0%)	116 (32.7%)		20 (27.4%)	21 (28.8%)	
Postoperative complication						
Overall DI	18 (24.3%)	106 (29.9%)	0.415	18 (24.7%)	24 (32.9%)	0.361
Transient DI	9 (12.2%)	81 (22.8%)	0.059	9 (12.3%)	20 (27.4%)	0.038
Permanent DI	9 (12.2%)	25 (7.0%)	0.213	9 (12.3%)	4 (5.5%)	0.245
Hyponatremia	17 (23.0%)	56 (15.8%)	0.184	17 (23.3%)	11 (15.1%)	0.293
Infection	2 (2.7%)	20 (5.6%)	0.395	2 (2.7%)	4 (5.5%)	0.681
CSF leakage	2 (2.7%)	13 (3.7%)	1.000	2 (2.7%)	2 (2.7%)	1.000
Hemorrhage	1 (1.4%)	8 (2.3%)	1.000	1 (1.4%)	3 (4.1%)	0.620
Hydrocephalus	2 (2.7%)	2 (0.6%)	0.139	2 (2.7%)	0 (0.0%)	0.497
Postoperative steroid administration	21 (28.4%)	89 (25.1%)	0.655	21 (28.8%)	14 (19.2%)	0.245

ASA PS, American Society of Anesthesiologists Physical Status; *ACTH*, adrenocorticotropic hormone; *TSH*, thyroid stimulating hormone; *GH*, growth hormone; *FSH*, follicle stimulating hormone; *LH*, luteinizing hormone; PO_2, arterial oxygen partial pressure; PCO_2, arterial carbon dioxide partial pressure; *DI*, diabetes insipidus; *CSF*, cerebrospinal fluid. *Previous history of surgery; gamma-knife surgery or radiotherapy. **Knosp grade ≥ 3

data analysis. After propensity score matching, there were no significant differences in demographics, oncologic and perioperative data between the sevoflurane-based inhalation and propofol-based intravenous anesthesia group.

Three-month postoperative hypocortisolism was observed in 69 (16.1%) and 25 (17.1%) patients before and after propensity score matching, respectively. The sevoflurane group had a higher incidence of postoperative hypocortisolism before ($n=20$ [27.0%] vs. $n=49$ [13.8%], $P=0.008$) and after ($n=20$ [27.4%] vs. $n=5$ [6.8%], $P=0.002$) propensity score matching, respectively.

Patients with postoperative hypocortisolism had a lower portion of patients with body mass index (BMI) ≥ 25 ($n=6$ [24.0%] vs. $n=60$ [49.6%], $P=0.034$) and higher proportion of musculoskeletal disease ($n=4$ [16.0%] vs. $n=5$ [4.1%], $P=0.047$), compared with those with postoperative normal HPA axis Table 2. In addition, patients with postoperative hypocortisolism had a larger tumor volume (12.0 [6.0–16.0] vs. 6.8 [4.4–10.8] cm^3, $P=0.019$) and longer surgical duration (120.0 [92.5–159.5] vs. 95.0 [75.0–130.0] min, $P=0.044$). Also, patients with postoperative hypocortisolism had a higher proportion of postoperative permanent DI (5 [20.0%] vs. 8 [6.6%], $P=0.048$) and postoperative steroid administration (11 [44.0%] vs. 24 [19.8%], $P=0.020$) than those with postoperative normal HPA axis.

The results of univariate and multivariate logistic regression analyses are shown in Table 3. The sevoflurane-based inhalation anesthetic technique (5.37 [1.80–15.98], $P=0.003$) and postoperative steroid administration (2.89 [1.06–7.92], $P=0.039$) were significant predictors of postoperative hypocortisolism.

Table 2 Comparisons of demographic and perioperative data between patients with 3-month postoperative hypocortisolism and those with 3-month postoperative normal hypothalamic–pituitary–adrenal (HPA) axis

	Before propensity score matching			After propensity score matching		
	Postoperative hypocortisolism (n = 69)	Postoperative normal HPA axis (n = 360)	P value	Postoperative hypocortisolism (n = 25)	Postoperative normal HPA axis (n = 121)	P value
Age (years)	62.0 (51.5–70.0)	55.0 (45.0–66.0)	0.004	58.0 (50.5–69.0)	52.0 (40.0–64.0)	0.057
≥ 65	31 (44.9%)	102 (28.3%)	0.010	10 (40.0%)	28 (23.1%)	0.134
Male sex	34 (49.3%)	154 (42.8%)	0.388	14 (56.0%)	46 (38.0%)	0.150
Body mass index (kg/m^2)	25.3 (23.1–27.9)	25.1 (22.9–25.1)	0.506	23.6 (22.6–25.1)	24.9 (22.9–28.2)	0.053
≥ 25	38 (55.1%)	186 (51.7%)	0.699	6 (24.0%)	60 (49.6%)	0.034
ASA PS class			0.146			0.443
1	21 (30.4%)	153 (42.5%)		11 (44.0%)	70 (57.9%)	
2	44 (63.8%)	194 (53.9%)		13 (52.0%)	48 (39.7%)	
3	4 (5.8%)	13 (3.6%)		1 (4.0%)	3 (2.5%)	
Comorbidities						
Hypertension	22 (31.9%)	82 (22.8%)	0.143	5 (20.0%)	23 (19.0%)	1.000
Diabetes mellitus	10 (14.5%)	33 (9.2%)	0.258	2 (8.0%)	9 (7.4%)	1.000
Dyslipidemia	14 (20.3%)	57 (15.8%)	0.462	5 (20.0%)	19 (15.7%)	0.817
Cardiac	8 (11.6%)	16 (4.4%)	0.039	2 (8.0%)	5 (4.1%)	0.343
Cerebrovascular	2 (2.9%)	3 (0.8%)	0.184	1 (4.0%)	0 (0.0%)	0.171
Malignancy	4 (5.8%)	15 (4.2%)	0.527	1 (4.0%)	6 (5.0%)	1.000
Musculoskeletal	13 (18.8%)	21 (5.8%)	0.001	4 (16.0%)	5 (4.1%)	0.047
Preoperative steroid administration	61 (88.4%)	300 (83.3%)	0.381	25 (100.0%)	114 (94.2%)	0.604
Preoperative hormone levels						
ACTH (pg/mL)	35.0 (21.7–54.2)	36.8 (23.2–54.2)	0.494	34.0 (22.0–52.0)	36.8 (22.9–51.1)	0.919
Cortisol (μg/dL)	9.4 (5.8–13.3)	11.1 (7.6–15.7)	0.003	8.8 (6.7–13.3)	10.7 (7.1–15.5)	0.249
Preoperative hormone deficiency						
TSH	13 (18.8%)	37 (10.3%)	0.068	4 (16.0%)	13 (10.7%)	0.494
GH	25 (36.2%)	137 (38.1%)	0.880	9 (36.0%)	46 (38.0%)	1.000
Gonadotropin	49 (71.0%)	210 (58.3%)	0.066	15 (60.0%)	82 (67.8%)	0.606
Previous treatment history*	18 (26.1%)	60 (16.7%)	0.091	7 (28.0%)	18 (14.9%)	0.143
Tumor characteristics						
Volume (cm^3)	9.0 (5.8–14.7)	6.7 (4.2–10.7)	0.004	12.0 (6.0–16.0)	6.8 (4.4–10.8)	0.019
Immunohistochemical staining						
ACTH	8 (11.6%)	66 (18.3%)	0.237	1 (4.0%)	16 (13.2%)	0.307
FSH	19 (27.5%)	90 (25.0%)	0.770	4 (16.0%)	25 (20.7%)	0.785
GH	4 (5.8%)	6 (1.7%)	0.060	1 (4.0%)	3 (2.5%)	0.532
LH	1 (1.4%)	1 (0.3%)	0.296	0 (0.0%)	0 (0.0%)	NA
Prolactin	13 (18.8%)	67 (18.6%)	1.000	6 (24.0%)	22 (18.2%)	0.577
TSH	5 (7.2%)	26 (7.2%)	1.000	1 (4.0%)	8 (6.6%)	1.000
Null cell	30 (43.5%)	154 (42.8%)	1.000	12 (48.0%)	57 (47.1%)	1.000
Optic chiasm compression	60 (87.0%)	270 (75.0%)	0.045	23 (92.0%)	107 (88.4%)	1.000
Cavernous sinus invasion**	36 (52.2%)	197 (54.7%)	0.797	18 (72.0%)	72 (59.5%)	0.345
Surgery						
In the morning	41 (59.4%)	227 (63.1%)	0.663	17 (68.0%)	97 (80.2%)	0.283
Duration (min)	120.0 (89.5–157.5)	96.5 (75.0–130.0)	0.001	120.0 (92.5–159.5)	95.0 (75.0–130.0)	0.044
Degree of resection			0.296			0.069
Grossly total resection	48 (69.6%)	276 (76.7%)	0.270	15 (60.0%)	92 (76.0%)	0.161

Table 2 (continued)

	Before propensity score matching			After propensity score matching		
	Postoperative hypocortisolism (n = 69)	Postoperative normal HPA axis (n = 360)	P value	Postoperative hypocortisolism (n = 25)	Postoperative normal HPA axis (n = 121)	P value
Subtotal resection	20 (29.0%)	83 (23.1%)	0.367	9 (36.0%)	29 (24.0%)	0.318
Partial resection	1 (1.4%)	1 (0.3%)	0.296	1 (4.0%)	0 (0.0%)	0.171
Anesthesia						0.708
Duration (min)	180.0 (145.0–245.0)	160.0 (135.0–200.0)	0.001	175.0 (145.0–232.5)	160.0 (135.0–197.0)	0.038
Anesthetic technique			0.008			0.002
Sevoflurane anesthesia	20 (29.0%)	54 (15.0%)		20 (80.0%)	53 (43.8%)	
Propofol anesthesia	49 (71.0%)	305 (85.0%)		5 (20.0%)	68 (56.2%)	
Total time of intraoperative *MBP* < 65 mmHg (min)	18.0 (2.8–27.5)	12.0 (4.0–30.0)	0.811	21.0 (5.0–27.0)	13.0 (4.5–29.5)	0.491
Total area under intraoperative *MBP* < 65 mmHg (mmHg*min)	20.0 (0.8–94.5)	29.0 (5.0–99.0)	0.583	20.0 (7.0–96.0)	27.0 (4.5–106.0)	0.977
Time–weighted average of intraoperative *MBP* < 65 mmHg (mmHg)	0.09 (0.00–0.55)	0.17 (0.01–0.54)	0.412	0.12 (0.02–0.55)	0.13 (0.00–0.59)	0.836
Intraoperative mean PO_2	184.8 (133.3–217.1)	185.5 (144.8–235.8)	0.273	201.0 (134.8–249.9)	192.3 (160.1–250.5)	0.518
Intraoperative mean PCO_2	38.0 (35.8–40.0)	37.3 (35.0–40.0)	0.252	38.0 (35.5–39.9)	37.0 (34.5–39.5)	0.310
Timing of study			0.099			0.458
First trimester (Mar 2010–Oct 2013)	30 (43.5%)	117 (32.5%)		11 (44.0%)	39 (32.2%)	
Second trimester (Nov 2013–May 2017)	24 (34.8%)	122 (33.9%)		9 (36.0%)	46 (38.0%)	
Third trimester (Jun 2017–Dec 2020)	15 (21.7%)	121 (33.6%)		5 (20.0%0	36 (29.8%)	
Postoperative ACTH level (pg/mL)	22.0 (10.8–40.6)	36.0 (23.4–54.5)	< 0.001	27.4 (10.7–49.5)	31.6 (20.4–52.1)	0.334
Postoperative complication						
Overall DI	24 (34.8%)	100 (27.8%)	0.303	8 (32.0%)	34 (28.1%)	0.881
Transient DI	14 (20.3%)	76 (21.1%)	1.000	3 (12.0%)	26 (21.5%)	0.410
Permanent DI	10 (14.5%)	24 (6.7%)	0.050	5 (20.0%)	8 (6.6%)	0.048
Hyponatremia	14 (20.3%)	59 (16.4%)	0.539	6 (24.0%)	22 (18.2%)	0.577
Infection	6 (8.7%)	16 (4.4%)	0.143	2 (8.0%)	4 (3.3%)	0.273
CSF leakage	5 (7.2%)	10 (2.8%)	0.076	1 (4.0%)	3 (2.5%)	0.532
Hemorrhage	3 (4.3%)	6 (1.7%)	0.163	1 (4.0%)	3 (2.5%)	0.532
Hydrocephalus	2 (2.9%)	2 (0.6%)	0.123	1 (4.0%)	1 (0.8%)	0.314
Postoperative steroid administration	30 (43.5%)	80 (22.2%)	< 0.001	11 (44.0%)	24 (19.8%)	0.020

ASA PS, American Society of Anesthesiologists Physical Status; *ACTH*, adrenocorticotropic hormone; *TSH*, thyroid stimulating hormone; *GH*, growth hormone; *FSH*, follicle stimulating hormone; *LH*, luteinizing hormone; PO_2, arterial oxygen partial pressure; PCO_2, arterial carbon dioxide partial pressure; *DI*, diabetes insipidus; *CSF*, cerebrospinal fluid. *Previous history of surgery; gamma-knife surgery or radiotherapy. **Knosp grade ≥ 3

Discussion

Postoperative hypocortisolism in patients undergoing transsphenoidal surgery for NFPA is a major concern for both neurosurgeons and neuroanesthesiologists. Postoperative hypocortisolism is a potentially life-threatening condition associated with significantly increased mortality and poor quality of life in NFPA patients [9, 26]. Thus, identification

Table 3 Predictive factors for 3-month postoperative hypocortisolism in patients undergoing endoscopic transsphenoidal surgery for non-functional pituitary adenomas with preoperative normal hypothalamic–pituitary–adrenal axis

	Before propensity matching						After propensity matching					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (years)	1.03	1.01–1.05	0.005	1.03	1.01–1.05	0.004	1.03	1.00–1.06	0.088			
Body mass index (kg/m^2)							0.88	0.76–1.01	0.059	0.87	0.75–1.00	0.052
Cardiovascular disease	2.82	1.16–6.88	0.023									
Musculoskeletal disease	3.75	1.78–7.91	0.001	3.11	1.40–6.89	0.005	4.42	1.10–17.82	0.037			
Preoperative cortisol level (μg/dL)	1.00	1.00–1.00	0.512									
Tumor volume (cm^3)	1.00	1.00–1.00	0.020				1.00	1.00–1.00	0.052			
Optic chiasm compression	2.22	1.06–4.66	0.034									
Surgery duration (min)	1.01	1.00–1.01	0.001	1.01	1.00–1.01	0.001	1.01	1.00–1.02	0.026	1.01	1.00–1.02	0.066
Gross total resection							0.47	0.19–1.17	0.104			
Sevoflurane anesthesia	2.31	1.28–4.19	0.006	2.69	1.41–5.13	0.003	5.13	1.81–14.57	0.002	5.37	1.80–15.98	0.003
Postoperative ACTH level (pg/mL)	1.00	1.00–1.00	0.800									
Postoperative permanent DI	2.37	1.08–5.22	0.032				3.53	1.05–11.89	0.042			
Postoperative steroid administration	2.69	1.57–4.61	< 0.001	2.81	1.59–4.96	< 0.001	3.18	1.28–7.87	0.013	2.89	1.06–7.92	0.039

OR, odds ratio; *CI*, confidence interval; *ACTH*, adrenocorticotropic hormone; *DI*, diabetes insipidus. Before propensity score matching, in multivariate analysis with the forward stepwise conditional method, cardiovascular disease, tumor volume, optic chiasm compression, and postoperative permanent DI were adjusted. Nagelkerke R^2 statistic = 0.180 and Hosmer and Lemeshow goodness of fit test was not significant at 5% ($P = 0.426$) in step 5

After propensity score matching, in multivariate analysis with the forward stepwise conditional method, musculoskeletal disease, tumor volume, and postoperative permanent DI were adjusted. Nagelkerke R^2 statistic = 0.260 and Hosmer and Lemeshow goodness of fit test was not significant at 5% ($P = 0.445$) in step 4 of predictive factors for 3-month postoperative hypocortisolism is clinically relevant in NFPA patients undergoing endoscopic transsphenoidal surgery with preoperative normal HPA axis.

The present study showed that the sevoflurane anesthetic technique was a significant predictor of 3-month postoperative hypocortisolism in NFPA patients with preoperative normal HPA axis. Sevoflurane anesthesia had a 5.4-fold higher incidence of postoperative hypocortisolism than propofol anesthesia. By contrast, patients who received propofol anesthesia more frequently suffered from postoperative permanent diabetes insipidus (DI). Postoperative permanent DI is known to be associated with irreversible hypothalamus and/or pituitary stalk injuries during surgery [5]. Thus, postoperative permanent DI can be associated with postoperative hypocortisolism. Indeed, our result showed that postoperative permanent DI was significantly associated with postoperative hypocortisolism in univariate logistic regression analysis, although it was not significant in multivariate analysis. Taken together, our findings suggest that propofol seems to have a significant protective effect on long-term steroid dependency. Unfortunately, we were not able to explain the exact pathophysiological mechanism on this finding that the functional outcomes of ACTH at 3 months postoperatively differed between the two different anesthetic techniques. In part, this finding can be explained by the difference in anti-inflammatory and antioxidant properties between propofol and sevoflurane. In a previous study, propofol had greater anti-inflammatory effects than sevoflurane in patients undergoing craniotomy [23]. Propofol exerts anti-inflammatory effects by upregulating annexin A1 (a regulatory protein of pro-inflammatory mediators) and inhibiting the release of inflammatory factors [28, 36]. Greater susceptibility to inflammation is associated with impaired HPA axis function at the pituitary gland level [35, 41]. The anti-inflammatory effects of propofol might contribute to preservation of the function of the HPA axis, leading to a lower rate of 3-month postoperative hypocortisolism in intravenous anesthesia group patients. In addition, propofol, compared with sevoflurane, has greater or similar antioxidant effects [12, 14, 17]. In a previous experimental study, antioxidant-induced activation of the HPA axis via downregulation of glucocorticoid receptors in the pituitary gland was reported [30]. Thus, the antioxidant effects of propofol might reduce the incidence of 3-month postoperative hypocortisolism by activating the HPA axis.

In a previous study, no significant difference in pituitary hormonal outcomes at 3 months postoperatively in NFPA patients was observed between sevoflurane-based inhalation and propofol-based intravenous anesthetic techniques [25]. By contrast, this study showed a relevant association between inhalation anesthesia and 3-month postoperative hypocortisolism. This discrepancy may be due to differences in the preoperative ACTH functional status. In the previous study, NFPA patients with preoperative hypocortisolism and normal HPA axis (20% and 80%, respectively) were included; however, in the present study, only NFPA patients with preoperative normal HPA axis were evaluated. Patients with preoperative hypocortisolism tends to have persistent postoperative hypocortisolism. Notably, 37–50% of NFPA patients with preoperative hypocortisolism undergoing endoscopic transsphenoidal surgery show 3-month postoperative hypocortisolism due to impaired HPA axis function [15, 25]. Based on the results of this study, propofol-based intravenous anesthesia may be more beneficial than sevoflurane-based inhalation anesthesia in reducing the rate of 3-month postoperative hypocortisolism in NFPA patients with preoperative normal HPA axis undergoing endoscopic transsphenoidal surgery. However, to verify the beneficial effects of propofol anesthesia on postoperative hypocortisolism, a large-scale prospective study is necessary.

In the present study, postoperative steroid administration was also predictive of 3-month postoperative hypocortisolism with an odds ratio of 2.9. Postoperative steroid was administrated to patients with postoperative morning cortisol < 8 μg/dL. A low level of early postoperative morning cortisol is known to be associated with 3-month postoperative hypocortisolism. A previous study showed that 2-day postoperative morning cortisol level was a significant predictor of postoperative hypocortisolism in pituitary adenoma patients undergoing transsphenoidal resection [29]. Postoperative hyponatremia is caused by transient endocrine function disorder such as syndrome of inadequate secretion of antidiuretic hormone (ADH) [40]. Glucocorticoid deficiency can result in excessive secretion of ADH by glucocorticoid negative feedback [32]. In this study, patients with postoperative hyponatremia were treated with oral hydrocortisone. A previous study demonstrated that postoperative hyponatremia was associated with postoperative hypocortisolism in pituitary adenoma patients [11]. Taken together, NFPA patients who require steroid supplements after transsphenoidal surgery may be at risk of postoperative hypocortisolism.

Age was a significant predictor of 3-month postoperative hypocortisolism before propensity score matching in this study. Old age is associated with changes of endocrine functions [39]. In the elderly, decreased functional activity of the HPA axis, increased adrenal sensitivity to ACTH, and reduced levels of cortisol regulatory hormones (e.g., dehydroepiandrosterone) result in dysregulation of cortisol and thus a high serum cortisol level [1, 10]. In addition, the duration of stress response induced by surgery is likely to be prolonged in older patients [37]. A sustained high serum cortisol level induces HPA axis dysfunction via a negative feedback mechanism as well as atrophy of the normal adrenal cortex [33]. This may in part explain the high incidence of postoperative hypocortisolism in old patients in the present study. Similarly, in a previous study, old age was associated with new-onset pituitary failure in patients undergoing endonasal transsphenoidal pituitary adenoma removal [7].

Long surgical time was also predictive of 3-month postoperative hypocortisolism in the present study before propensity score matching. Prolonged surgical time can cause more severe inflammatory and neuroendocrine stress response. In addition, suprasellar extension or tumor adhesion may extend the surgical time, which can in turn cause pituitary gland injury and postoperative hypocortisolism.

Musculoskeletal disease was a significant predictor of 3-month postoperative hypocortisolism before propensity score matching. Musculoskeletal diseases are common in old patients. In addition, arthralgia can be caused by hypocortisolism [16, 34]. Impairment of HPA axis causes a high pain sensitivity due to inadequate stress response [4]. Thus, musculoskeletal disease may be associated with postoperative hypocortisolism in NFPA patients.

The present study had several limitations. First, some potential biases (i.e., selection bias) associated with the retrospective design could have affected the results. Also, only the association, not causality, between sevoflurane-based inhalation anesthesia and postoperative hypocortisolism was implied because this was a retrospective and observational study. Second, the presence or absence of postoperative hypocortisolism was evaluated only at 3 months postoperatively; thus, further research is necessary to determine the association of anesthetics with long-term postoperative hypocortisolism in NFPA patients undergoing endoscopic transsphenoidal surgery. Third, the Nagelkerke R^2 values were relatively low, which indicates that other key predictors of postoperative hypocortisolism may have been omitted from the analysis. Fourth, because the number of patients in the sevoflurane anesthesia group was relatively small, the study may have been underpowered. However, changes in the proportion of two anesthetic techniques used and incidence of 3-month postoperative hypocortisolism over time were not significantly different.

Conclusions

In conclusion, sevoflurane anesthesia and postoperative steroid administration were associated with 3-month postoperative hypocortisolism in patients with preoperative normal HPA axis undergoing endoscopic transsphenoidal surgery for NFPA removal. A large-scale prospective study is necessary to confirm the negative association between sevoflurane-based anesthesia and postoperative ACTH functional outcome. Also, even though patients in the propofol group more frequently suffered from postoperative permanent DI, they showed a low incidence of 3-month postoperative hypocortisolism, suggesting that propofol may have a significant protective effect on postoperative hypocortisolism.

Author contribution Conception and design: CS, OH, KYH, PHP. Acquisition of data: CS, KYJ, KN. Analysis and interpretation of data: CS, KYJ, OH. Drafting the article: CS. Critically revising the article: OH, KYH, PHP. Study supervision: PHP.

Declarations

Ethics approval This retrospective study was conducted after approval from the Institutional Review Board of Seoul National University Hospital (IRB no. H-2110–126-1264). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Because this was a retrospective study, for this type of study, formal consent is not required.

Consent to participate This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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