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Perioperative Complications Associated with Routine Preoperative Glucocorticoid Use Among Patients Undergoing Pituitary Surgery with Normal Preoperative HPA Axis: A Retrospective Cohort Study

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Abstract

Objective. This study determined the incidence of perioperative complications associated with routine preoperative glucocorticoid use in patients undergoing pituitary surgery with normal preoperative hypothalamo-pituitary-adrenal axis (HPA axis).

Methodology. From 2011-2021 retrospective chart review, 243 patients undergoing pituitary surgery with normal preoperative HPA axis were analyzed into 2 groups: 1) with preoperative steroids; and 2) without preoperative steroids. Development of postoperative complications was subsequently evaluated.

Results. Incidence of primary composite postoperative complications of in-hospital mortality, postoperative infection and postoperative diabetes insipidus (DI) was significantly increased among those who had preoperative steroids compared to those without (58.33% versus 33.33%, *p*-value 0.004) with an adjusted odds ratio of 2.90 (CI 1.29 to 6.53, *p*-value 0.010). Among the components of the composite outcome, post-operative DI was statistically higher among those who were given preoperative steroids (52.45% versus 28.21%, *p*-value 0.006) with an adjusted OR of 3.31 (CI 1.43 to 7.67, *p*-value 0.005). The incidence of postoperative adrenal insufficiency was similar between the 2 groups (20.15% with steroids versus 8.70% without steroids, *p*-value 0.258).

Conclusion. Among patients undergoing pituitary surgery with normal preoperative HPA axis, routine preoperative steroids use was associated with an increased risk of composite postoperative complications.

Key words: pituitary-adrenal system, pituitary gland / surgery, postoperative complications, glucocorticoids, steroids

INTRODUCTION

A strategy of giving routine doses of glucocorticoids preoperatively in all patients undergoing pituitary surgery started around the 1950s when studies noted that fatal outcomes occur among patients with impaired hypothalamo-pituitary-adrenal (HPA) axis undergoing pituitary surgery.[1] Those who give preoperative glucocorticoids rationalize that postoperative adrenal insufficiency (AI) remains a life-threatening condition. Some also have a notion that adrenocorticotrophic hormone (ACTH) secretion can be compromised by trauma of surgery.[2] Lastly, there is an assumption that glucocorticoids are safe to use when given for short courses. However, in 2002, Inder and Hunt et al., advocated a restrictive approach in the use of preoperative corticosteroids. They promoted a glucocorticoid-sparing regimen for those who had intact or presumed intact function of HPA axis.[3] This recommendation was from small retrospective and prospective trials revealing that postoperative AI is rare among patients with intact HPA axis preoperatively and that HPA function is not compromised during or after this procedure.[2,4,5] A meta-analysis of small studies from western countries, revealed that the incidence of postoperative AI among patients undergoing pituitary surgery with normal preoperative morning cortisol levels ranges from 0.96% – 12.9% (mean incidence of 5.55%) and therefore concluded that proof is lacking to demonstrate clinically important benefits of preoperative administration of glucocorticoids.[6] Moreover, the study of De Tomassi et al., reported that transsphenoidal surgery can be performed safely in patients with preoperative morning serum cortisol less than 9 μg/dl (250 nmol/l).[7] Despite the 2002 guidelines released by Inder and Hunt et al., high doses of glucocorticoid are still being used in patients with intact HPA axis undergoing pituitary surgery in numerous institutions worldwide. Possible reasons for

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this practice include difficulties in diagnosing and defining a suboptimal function of the HPA axis, local traditions and fear of inadequate pituitary function triggered by pituitary surgery.[1] Currently, there is still a gray area in the preoperative management of pituitary surgery among patients with normal preoperative HPA axis. Predicament lies on whether to give prophylactic glucocorticoid coverage perioperatively or apply a glucocorticoid-sparing method, giving only when AI ensues.[5]

Numerous factors are associated with poor perioperative outcomes among patients undergoing pituitary surgery and the physician must address each of these factors when possible. Corollary to this, there is paucity of studies that looked extensively at the perioperative complications associated with preoperative glucocorticoid use among patients undergoing pituitary surgery with normal preoperative HPA axis. Based on studies from general surgical and neurosurgical cases that revealed worse outcomes among those who were given preoperative steroids,[8,9] it is hypothesized that preoperative glucocorticoids in patients undergoing pituitary surgery are likely to be associated with an increased risk of surgical site infections, pneumonia, myocardial infarction, cardiac arrest and death, to name a few.[9]

This study aimed to determine the incidence of perioperative complications associated with routine preoperative glucocorticoids given to patients undergoing pituitary surgery with normal preoperative HPA axis. More specifically, the study determined the effects of giving preoperative glucocorticoids on the composite of overall in-hospital mortality rate, postoperative infection and postoperative diabetes insipidus (DI). The study also analyzed the effects of routine preoperative steroid use in the incidence of postoperative AI and other secondary outcomes pertinent to endocrinologists such as: perioperative hyperglycemia, perioperative uncontrolled hypertension, incidence of cardiovascular events (MI, stroke and CV death), rate of glucocorticoid use upon discharge, incidence of perioperative hypotension, postoperative hypoglycemia and hyponatremia, CSF leak and hospital length of stay.

METHODOLOGY

Setting

The study was a retrospective cohort study done at the Philippine General Hospital (PGH), Manila, Philippines. This hospital is one of the largest tertiary government hospitals in the Philippines and is a subspecialty referral center for numerous complicated cases from the entire country including pituitary cases. The study protocol was approved by the local institutional review board of the hospital (University of the Philippines Manila- Research Ethics Board) with UPM-REB code 2021-111-01 and received a research grant from the Philippine College of Endocrinology, Diabetes and Metabolism.

Study population and sampling

Medical records of adult patients 18 years old and above at PGH who underwent pituitary surgery from 2011 to 2021 with normal preoperative 8 am serum cortisol levels (138-690 nmol/L) were included in the study. Patients were included regardless of pituitary pathology or surgical approach. On the other hand, patients with confirmed preoperative AI, pituitary apoplexy and Cushing's syndrome who required perioperative steroids were excluded from the study. Patients on chronic steroid use preoperatively for other medical conditions were also excluded. By reviewing the existing databases from the Division of Endocrinology, Diabetes and Metabolism pituitary census and from logbooks of pituitary specimens submitted to the Department of Pathology, convenient purposive sampling of patients that met the eligibility criteria were included in the study.

Sample size computation

Data collection continued until the computed sample of at least 242 patients was reached. Type I error was assigned a value of 0.05 so that the confidence level is at 95% while the Type II error was assigned a value of 0.20 so that the study can have a power of 80%. The ratio of sample size (unexposed/exposed) is at 0.5 derived from the study of De Tomassi et al.[7] The percentage of patients unexposed with the primary outcome is 14.8% which was derived from previous studies [composite of in-hospital mortality (1.6%),[9] postoperative infection (7.2%)[9] and postoperative DI (6%)].[10] Moreover, the percentage of patients exposed with the primary outcome is 32.1% [composite of in-hospital mortality (6%),[9] postoperative infection (16.5%)[9] and postoperative DI (9.6%)[10]]. Using these values, a total sample size of 242 was derived.

Data collection

Databases from the Pituitary Census of the Division of Endocrinology, Diabetes and Metabolism were reviewed to identify patients who underwent pituitary surgery from 2011 to 2021. The list was verified by reviewing the pituitary specimens sent to the Division of Pathology during the same period, ensuring the inclusion of eligible patients from 2011 to 2021. These patients were selected for the study using convenient purposive sampling. Once a list of patients who underwent pituitary surgery was identified, medical records were retrieved and data collection was accomplished by the principal investigator and research assistant who was trained in the process of data collection. Individual medical records were reviewed and screening for inclusion and exclusion criteria was performed to identify eligibility to the study. Once deemed eligible, data collection proceeded using a standardized anonymized data collection form. Since review of medical records was done and no direct patient interaction was involved, obtaining informed consent was waived.

Overview of methods

Once eligibility of inclusion to the study was ascertained, standardized data collection forms were used to collect data that was used in the subsequent analysis. The following demographic information were collected: age, sex, comorbidities and year of pituitary surgery. Preoperative data gathered were: 8 am serum cortisol levels, presence or absence of Cushing's syndrome, use of glucocorticoid, presence or absence of pituitary apoplexy and hormonal functionality (if pituitary adenoma). During the perioperative period, information on occurrence of hyperglycemia or hypoglycemia and uncontrolled hypertension or hypotension were gathered. Postoperatively, tumor size, histopathologic diagnosis, surgical approach and completeness of surgical resection were assessed. Postoperative complications which include in-hospital mortality, infection (within 30 days of operation and site of infection), DI, AI, hyponatremia, CSF leak, incidence of cardiovascular events (composite of incidence of cardiovascular death, non-fatal myocardial infarction and stroke) were noted. Day 1-day 3 postoperative 8am serum cortisol levels, preoperative and postoperative (within 7 days) serum sodium levels and urine specific gravity were compared. Lastly, use of glucocorticoids as home medication and hospital length of stay in days were gathered. Data collection was accomplished by the principal investigator and research assistant who was trained regarding the process of data collection. As authorized by the local IRB (UPM-REB), proper ethical conduct of the study was observed and compliance to data privacy act was ensured.

Outcomes

The primary outcome of the study was a composite indicator comprising in-hospital mortality, postoperative infection and postoperative DI. This composite variable is binary, wherein patients who had at least 1 component of the outcome indicator was assigned a code of 1, while those who did not experience any of these outcomes were coded as 0. This was deemed as the primary outcome of interest by the investigators because these outcomes were the most common and clinically significant morbidity of pituitary surgery in the context of giving glucocorticoids based on literature review. The independent variable is the presence of preoperative steroid use while the dependent variables are the primary outcome (composite of in-hospital mortality, postoperative infection and postoperative DI). Other clinically significant secondary outcomes (dependent variable), from an endocrinologist's point of view such as incidence of postoperative AI, perioperative hyperglycemia, perioperative uncontrolled hypertension, cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, and cerebrovascular disease), perioperative hypotension, perioperative hypoglycemia, CSF leak and rate of glucocorticoid use upon discharge and lastly the hospital length of stay were included in the study. Potential confounders include age,[3,8] sex,[3] presence of DM[8], presence of CSF leak[9,11] and histopathology[5,11] for which sensitivity analysis was performed.

Operational terms

- Normal HPA axis – a basal morning serum cortisol value of 138-690 nmol/l in the absence of overt signs and symptoms consistent with hypocortisolism.[2,6]
- Post-operative infection – any infection, regardless of site, that occurs within 30 days of operation and may be related to the operation itself or the postoperative course.[12]
- Post-operative DI – presence of documented voluminous urine output (>2.5 mL/kg body weight per hour or at least 4 L per day) with a urine specific gravity of ≤1.005 or urine osmolality <200 mOsm/kg H_2O, with or without hypernatremia or hyperosmolality or, as clinically diagnosed by the attending endocrinologist, developing anytime during hospital admission following pituitary surgery.[11]
- Post-operative AI – basal serum cortisol levels below 138 nmol/L or clinically diagnosed by the attending physician based on presence of signs and symptoms of AI for patients with postoperative serum cortisol levels of 138-270 nmol/L.[6,13]
- Perioperative hyperglycemia – any capillary glucose value >200 mg/dL within 24 hours prior to and 48 hours after the operation (Turina et al.).[14]
- Perioperative uncontrolled hypertension – BP of 160/90 mm Hg or higher or an SBP elevation of at least 20% of the preoperative value that persists for longer than 15 minutes (ACC/AHA 2017).[15]
- Perioperative hypotension – systolic BP less than 90 mm Hg for a total of 10 min or more during surgery or for any duration after surgery and for which intervention was initiated (Roshanov et al.).[16]

Statistical methods

Descriptive statistics were done to analyze and compare the baseline characteristics of the patients with preoperative steroids versus without preoperative steroids. For normally distributed data, mean and standard deviation were used and were compared using Student's t-test. For non-normally distributed data, median and interquartile range (IQR) was used and 2 groups were compared using two-sample Mann-Whitney test to identify significant differences between groups. Categorical data were summarized as frequencies and percentages and compared using either Pearson's Chi-squared test or Fisher's exact test as appropriate. Data normality was assessed using Shapiro-Wilk test.

In terms of analysis of the primary outcome of the study, significant differences between the 2 groups were assessed using Pearson's Chi-squared test and Fisher's Exact test. For the analysis of incidence of postoperative AI, it was reported as frequency and its association with preoperative steroid use was analyzed using Fisher's exact test. The other

secondary outcomes were analyzed as follows: Pearson's Chi-Square test, Fisher exact test and Mann-Whitney test as appropriate.

To identify the extent by which preoperative steroid use affects the different outcomes of interest, generalized linear models with log link function was performed adjusting for possible known confounders such as age, sex, histopathology, surgical approach, completeness of surgical resection and comorbidities.

STATA 15 was used for all analyses and a *p*-value of less than 0.05 was considered significant for all the tests.

RESULTS

From the years of 2011-2021. a total of 243 patients were deemed eligible for inclusion in the study. Of these, 204 patients received routine preoperative steroids while 39 patients did not receive preoperative steroids stating that routine preoperative steroid use was the most common practice in this cohort. Demographics and baseline clinical characteristics showed no statistically significant difference between the 2 groups except solely for admission type (Table 1). Mean patient age was 44.17 years. The overall mean largest tumor diameter was 3.59 cm and with a mean tumor volume of 16.38 ml. There was no statistical difference between tumor size (both largest diameter and tumor volume) between the 2 groups (*p*-value 0.4581 and *p*-value 0.9397, respectively). In terms of surgical approach, most cases (82.2%) underwent transsphenoidal surgery (200/243) while the transcranial approach was used in 17.70% (43/243). More patients had complete surgical resection of the tumor at 54.42% (123/243). The overall mean preoperative 8 am serum cortisol was 371.66 nmol/L. Routine preoperative steroids were given to patients with mean preoperative 8 am serum cortisol of 373.73 nmol/L while those without preoperative steroids had a mean value of 361.55 nmol/L, showing no statistically significant difference at baseline (*p*-value 0.6269).

Considering the primary objective, Table 2 shows us that the primary composite outcome of in-hospital mortality, postoperative infection and postoperative DI was significantly higher among patients given routine preoperative steroids at 58.33% (119 out of 204) compared to 33.33% (13 out of 39) of those without preoperative steroids (*p*-value of 0.004). Scrutinizing the individual components of the composite outcome, the in-hospital mortality rate among those given steroids was at 5.39% (11/204) while there was no reported in-hospital mortality among those who were not given preoperative steroids though it did not reach statistical significance (*p*-value 0.220). For post-operative infection, there were higher rates among patients given steroids 12.25% (25/204) in contrast to those who were not given steroids 5.13% (2/39), although this did not reach statistical significance (*p*-value 0.270). Lastly, for postoperative DI, this individual outcome reached statistical significance as more patients developed postoperative DI among those who were given preoperative steroids at 52.45% (107 of 204) compared to 28.21% (11 of 39) patients who did not receive preoperative steroids (*p*-value of 0.006).

Table 1. Baseline characteristics of the study population

Characteristics	Without preoperative steroids (n = 39)	With preoperative steroids (n = 204)	Total (n = 243)	*p*-value
Age, Mean (SD)	44.36 (12.50)	44.14 (12.17)	44.17 (12.20)	0.92[a]
Sex				
Male	16 (41.03)	81 (39.71)	97 (39.92)	0.88[b]
Female	23 (58.97)	123 (60.29)	146 (60.08)	
Histopathology				
Others	2 (5.13)	17 (8.33)	19 (7.82)	0.82[c]
Pituitary Adenoma	37 (94.87)	185 (90.69)	222 (91.36)	
Rathke's cleft cyst	0 (0.00)	2 (0.98)	2 (0.82)	
Tumor size, Mean (SD)				
Largest diameter (cm), n = 218	3.35 (0.92)	3.64 (2.11)	3.59 (1.97)	0.46[d]
Volume (ml), n = 204	13.99 (11.88)	16.84 (19.05)	16.38 (18.09)	0.94[d]
Surgical Approach				
Transcranial	3 (7.69)	40 (19.61)	43 (17.70)	0.07[b]
Transsphenoidal	36 (92.31)	164 (80.39)	200 (82.30)	
Complete resection of tumor, n = 226	19 (55.88)	104 (54.17)	123 (54.42)	0.85[b]
Comorbidity				
Hypertension	16 (41.03)	62 (30.39)	78 (32.10)	0.19[b]
Diabetes mellitus	9 (23.08)	49 (24.02)	58 (23.87)	0.90[b]
Any cardiovascular disease	1 (2.56)	9 (4.41)	10 (4.12)	1.00[c]
Admission type				
Service	19 (48.72)	145 (71.08)	164 (67.49)	**0.01[b]**
Pay	20 (51.28)	59 (28.92)	79 (32.51)	
Preoperative systolic BP	123.38 (13.43)	120.27 (13.95)	120.77 (13.89)	0.20[a]
Preoperative diastolic BP	79.10 (7.54)	79.10 (9.69)	79.10 (9.34)	0.93[d]
Preoperative 8 am serum cortisol	361.55 (170.64)	373.73 (174.42)	371.77 (173.53)	0.63[d]
Preoperative serum sodium, n=238	139.84 (3.32)	140.86 (3.04)	140.70 (3.10)	0.06[d]
Preoperative urine specific gravity, n=222	1.02 (0.01)	1.02 (0.01)	1.02 (0.01)	0.95[d]

Statistical test: [a] Student's t-test, [b] Pearson's chi-squared test, [c] Fisher's exact test, [d] Mann-Whitney test

Regarding the effect of giving preoperative steroids on the incidence of postoperative AI, the rates of development showed no statistically significant difference between those given versus not given preoperative steroids [20.13% vs 8.70%, *p*-value 0.258 (Table 2)]. Equally important, none of the groups had in-hospital mortality attributable to postoperative AI.

For the secondary outcomes, the incidence of perioperative hyperglycemia showed no statistical significance between the 2 groups (27.98% with steroids vs. 23.08% without steroids, *p*-value 0.531). The incidence of uncontrolled hypertension also showed no statistically significant difference between groups (52.94% with steroids vs. 41.03% without steroids, *p*-value 0.173). There was no associated increase in the incidence of cardiovascular events (cardiovascular mortality, non-fatal MI and non-fatal stroke) at 4.41% occurring in those given preoperative steroids and 2.56% in those without preoperative steroids (*p*-value 1.0). Moreover, clinical features of postoperative AI namely: perioperative hypotension, perioperative hypoglycemia and postoperative hyponatremia showed no statistically significant difference between the 2 groups (*p*-value 0.065, 1.0, 0.184, respectively). The incidence of CSF leak, which may be a risk factor in one of our primary outcomes and postoperative infection also showed no statistically significant difference between the 2 groups (*p*-value 0.913). On the other hand, more of those who were given preoperative steroids were discharged on glucocorticoids at 29.41% (60/204) compared to those who were not given preoperative steroids at 12.82% (5/39), *p*-value 0.032). For the length of hospital stay, there was a longer hospital length of stay among patients who were given preoperative steroids compared to those who were not given steroids (14.25 days versus 11 days, respectively, *p*-value 0.0154).

Generalized linear models were performed to show the strength of association of preoperative steroids use with the different outcomes of interest and adjusting for the following possible confounders: age, sex, presence of DM, presence of CSF leak and histopathology (Table 3). Evidence showed that the use of preoperative steroids was associated with 1.80 times (CI 1.14, 2.83, *p*-value 0.013) increased risk of developing the primary composite outcome. There is also an associated 1.87 times increased risk of developing DI among patients given preoperative steroids (CI 1.12, 3.13, *p*-value 0.017). The risk of developing in-hospital mortality when given preoperative steroids cannot be estimated and the adjusted RR of developing postoperative infection did not reach statistical significance, likely due to few events. (Adjusted RR 2.39, CI 0.59, 9.70, *p*-value 0.220).

Furthermore, looking at the association of primary composite outcome with other various clinical subgroups and patient characteristics, it is evident that age, sex, histopathology, surgical approach, completeness of surgical resection, comorbidities and admission type did not show significant increase in the incidence of primary composite outcome, except for presence of diabetes mellitus with an adjusted RR 1.35 (CI 1.04, 1.75, *p*-value 0.026) (Table 4).

Table 2. Comparison of incidence postoperative complications among with preoperative steroids versus without preoperative steroids

Perioperative outcomes	Without preoperative steroids (n = 39)	With preoperative steroids (n = 204)	Total (n = 243)	*p*-value
***Primary Outcome, composite*[1]**	13 (33.33)	119 (58.33)	132 (54.32)	**0.004**[b]
In-hospital mortality	0 (0.00)	11 (5.39)	11 (4.53)	0.220[c]
Postoperative infection	2 (5.13)	25 (12.25)	27 (11.11)	0.270[c]
Postoperative diabetes insipidus	11 (28.21)	107 (52.45)	118 (48.56)	**0.006**[b]
Postoperative adrenal insufficiency, n=182	2 (8.70)	32 (20.13)	34 (18.68)	0.258[c]
Perioperative hyperglycemia	9 (23.08)	57 (27.94)	66 (27.16)	0.531[b]
Perioperative uncontrolled hypertension	16 (41.03)	108 (52.94)	124 (51.03)	0.173[b]
Incidence of cardiovascular events (composite of cardiovascular disease, nonfatal MI, and stroke)	1 (2.56)	9 (4.41)	10 (4.12)	1.000[c]
Perioperative hypotension	3 (7.69)	41 (20.10)	44 (18.11)	0.065[b]
Perioperative hypoglycemia	2 (5.13)	11 (5.39)	13 (5.35)	1.000[c]
Postoperative hyponatremia	4 (10.26)	39 (19.12)	43 (17.70)	0.184[b]
CSF leak	6 (15.38)	30 (14.71)	36 (14.81)	0.913[b]
Rate of glucocorticoid use upon discharge	5 (12.82)	60 (29.41)	65 (26.75)	**0.032**[b]
Hospital length of stay (days)	11 (6.41)	14.26 (15.34)	13.74 (14.33)	**0.0154**[d]

[1]Primary Outcome, composite: in-hospital mortality, postoperative infection, and postoperative diabetes insipidus
Statistical test: [b] Pearson's chi-squared test, [c] Fisher's exact test, [d] Mann-Whitney test

Table 3. Association of routine preoperative steroid use with the primary composite outcome

Perioperative outcomes	Crude RR (95% CI)	*p*-value	Adjusted RR (95% CI)	*p*-value
Primary Outcome, composite	1.75 (1.10, 2.76)	**0.017**	**1.80 (1.14, 2.83)**	**0.013**
In-hospital Mortality*	-	-	-	-
Postoperative infection	2.38 (0.59, 9.68)	0.222	2.39 (0.59, 9.70)	0.220
Postoperative diabetes insipidus	1.86 (1.10, 3.12)	**0.019**	**1.87 (1.12, 3.13)**	**0.017**

Table 4. Primary composite outcome and its association with various clinical subgroups

Characteristics	Crude RR (95% CI)	*p*-value	Adjusted RR (95% CI)	*p*-value
Age	1.01 (0.99, 1.01)	0.267	1.01 (0.99, 1.02)	0.232
Sex				
Male	0.98 (0.77, 1.24)	0.856	1.08 (0.85, 1.38)	0.524
Female, Ref				
Histopathology				
Others, Ref				
Pituitary Adenoma	0.94 (0.62, 1.41)	0.769	1.07 (0.70, 1.62)	0.756
Rathke's cleft cyst	-	-		
Surgical Approach				
Transcranial, Ref				
Transsphenoidal	0.76 (0.60, 0.98)	**0.033**	0.78 (0.57, 1.07)	0.123
Complete resection of tumor	0.91 (0.72, 1.15)	0.414	0.82 (0.63, 1.08)	0.164
Comorbidity				
Hypertension	1.13 (0.89, 1.43)	0.305	0.91 (0.67, 1.24)	0.564
Diabetes mellitus	1.34 (1.06. 1.68)	**0.013**	1.35 (1.04, 1.75)	**0.026**
Any cardiovascular disease	1.50 (1.08, 2.10)	**0.016**	1.10 (0.71, 1.70)	0.675
Admission type				
Charity, Ref				
Pay	0.94 (0.73, 1.21)	0.604	1.02 (0.78, 1.35)	0.862

DISCUSSION

The most important finding of this study is that the use of routine preoperative steroids among patients with normal HPA axis undergoing pituitary surgery is associated with a 1.80 times increased risk of developing composite postoperative complications (in-hospital mortality, postoperative infection and DI). This refutes the hypothesis that giving preoperative steroids among those with normal HPA axis is safe and without consequent postoperative complications. The individual outcome that has driven the statistically significant result was the postoperative DI. There was a trend towards increased risk of developing post-operative infection among those given preoperative steroids, but the rare occurrence of these events in both groups likely resulted in non-statistically significant results. The increased risk of postoperative DI among those given preoperative steroids was similarly demonstrated in the study of Rajaratnam et al.,[17] and have recommended that among those with normal basal cortisol levels, intraoperative hydrocortisone is not required.[17] The increased risk of DI among those given preoperative steroids is due to the increased threshold for anti-diuretic hormone (ADH) release after administering intravenous cortisol, as was demonstrated in the study of Aubry, et al.[18] In that study, they showed that administration of intravenous cortisol showed a delayed release of ADH to a much higher osmotic threshold.[18] In relation to this, it is evident that the rates of DI is higher in this cohort compared to what is seen in literature. The investigators believed that the main reason for this is that the norm in this cohort is to routinely administer glucocorticoids (83.95%), which is not in magnitude of what is seen internationally (52.34% received steroids in the study of Hattori et al.[19]).

Equally important outcome, no in-hospital mortality occurred among those who were not given preoperative steroids. In terms of incidence of postoperative infection, there was no statistical difference between the 2 groups, but an important characteristic in this specific cohort is that, 34 out of 39 (87.17%) among those not given preoperative steroids had prophylactic antibiotics continued for more than 24 hours postoperatively and 178 out of 204 (87.25%) patients among those given preoperative steroids had their preoperative antibiotics continued for more than 24 hours translating to low rates to post-operative infection overall.

The previous justification for giving preoperative steroids even for those with normal HPA axis is that post-operative AI remains to be a life-threatening condition.[1] Our study however showed that in-hospital mortality is not increased by withholding preoperative steroids. There was no in-hospital mortality attributable to postoperative AI in both groups. The overall incidence of postoperative AI is higher in this cohort (18.68%) compared to the meta-analysis of Tohti et al., showing a mean incidence of 5.55% (0.96% to 12.90%) across 12 studies.[6] The incidence of postoperative AI in both groups showed no statistically significant difference demonstrating that the steroid-sparing method among patients with normal HPA axis is safe and does not increase the incidence of postoperative adrenal insufficiency. Four other international studies[2,19,20,21] have similar findings, therefore, the fear of postoperative AI should not be the reason to give preoperative steroids. Paradoxically, the incidence of postoperative AI was higher (not statistically significant) among those given preoperative steroids (20.13%) compared to those not given steroids (8.70%). The incidence of postoperative AI in those not given steroids was more reflective of its overall incidence globally.[6] The reason for the higher rate of postoperative AI among those given steroids is possibly the use of long-acting steroids intraoperatively (i.e., dexamethasone), which could have interfered with the postoperative 8 am serum cortisol results. Specifically, dexamethasone, which in this study was given at least once in variable doses in 45.09% (92/204), can suppress the secretion of ACTH, inducing the decreased level of serum cortisol, effects of which may last up to 36 to 72 hours postoperatively.[22] This phenomenon is

reflected in our study's results that those given preoperative steroids had a significantly lower postoperative 8 am serum cortisol at 352.20 nmol/L compared to 553.75 nmol/L seen among patients not given preoperative steroids (*p*-value 0.0124). This emphasizes a possible consequence of using preoperative steroids in patients with normal HPA axis, that is, when not clinically indicated, the steroid use can interfere with postoperative HPA axis testing. Lee et al., in 2022, had a similar observation that the practice of routinely giving preoperative steroids among those with normal HPA axis renders postoperative interpretation of the HPA axis function difficult.[21] Furthermore, there was a higher rate of patients using glucocorticoids upon discharge among those who were given preoperative steroids likely secondary to difficulty interpreting postoperative 8 am cortisol results in the context of administering preoperative steroids. On the other hand, important clinical features of postoperative AI namely: perioperative hypotension, perioperative hypoglycemia and postoperative hyponatremia were not significantly different between the treatment groups. Hence, even subtle presentations of AI are not increased whether you use preoperative steroids or not among patients with normal HPA axis.

The secondary outcomes such as the risk of perioperative hyperglycemia, perioperative hypertension and incidence of cardiovascular disease showed no statistically significant difference between groups answering the question of whether these theoretical side effects of steroid use translate to actual clinical practice. Our findings should be taken with caution, however, since this study was not adequately powered for the secondary outcomes. Lastly, one pertinent outcome is the length of hospital stay was longer in patients with preoperative steroids. This is possibly related to the increased incidence of postoperative DI in this group.

Other relevant results revealed a very variable steroids dose used in this cohort. Both dexamethasone and hydrocortisone were used singly or concomitantly in a few cases. Most commonly, 42.64% (87/204) patients received 50 mg hydrocortisone before surgery which was slowly tapered until day 3 postoperatively as per Inder and Hunt et al.,[3] the rest of the patients received higher doses of steroids with an overall mean hydrocortisone equivalent dose of 142.35 mg, with a range of 50 mg to 583.3 mg/day. Reasons for variability include different practices between endocrinologists and anesthesiologists and the development of an indication for intraoperative steroid use such as cerebral edema.

Limitations of the study include its retrospective nature. There was limited control over sampling of the population such that there were more patients with preoperative steroids compared to those without it which poses a potential bias against those with exposure. The performance of a randomized controlled trial will provide more robust evidence regarding the causal relationship between preoperative steroid use and perioperative complications, especially in-hospital mortality and postoperative infection. However, since the incidence of these individual complications is low in general, a large sample size will be necessary to power this study. As part of the recommendation, a consensus from multidisciplinary subspecialties is a must to standardize management among patients with normal HPA axis undergoing pituitary surgery.

CONCLUSION

Among patients with normal preoperative HPA axis, the routine use of preoperative steroids is associated with an increased risk of composite postoperative complications (in-hospital mortality, postoperative infection and postoperative DI). Steroid-sparing protocol is not associated with an increased risk of postoperative AI. The findings will encourage more rational use of steroids and minimize preventable complications.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
FMM: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation; Writing – review and editing, Visualization, Project administration, Funding acquisition; **EPP:** Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft preparation, Writing – review and editing, Supervision

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

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