ORIGINAL ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Evaluating Endocrine Changes and Surgical Complications following Endoscopic Transsphenoidal Excision of Pituitary Macroadenomas

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Abstract

Background: Intracranial lesions arising in the region of the pituitary gland are relatively common. Pituitary adenomas (PAs) with extensive suprasellar extension are a challenge for therapeutics. For evaluation of PAs, the clinical and biochemical assessment stands as the cornerstone. The easy access of advanced neuroimaging has increased the sensitivity of detection of smaller lesions in the pituitary region. Many treatment modalities have developed so far undergoing numerous refinements over the past 100 years. Transsphenoidal surgery is considered relatively safe and widely being practiced. **Materials and Methods:** This was a hospital-based cross-sectional study conducted in national neurosurgical referral center, Bir hospital, Kathmandu, Nepal, on 38 patients who underwent endoscopic endonasal transsphenoidal pituitary gland excision for pituitary macroadenomas. **Results:** The mean serum prolactin (PRL) level was observed as 706.57 ± 1196.09 ng/mL preoperatively and 42.91 ± 109.1 ng/mL postoperatively. The mean value of growth hormone (GH) was observed as 13.34 ± 12.59 ng/mL preoperatively which was reduced to 6.48 ± 6.90 ng/mL postoperatively. Postoperatively, neurogenic diabetes insipidus was observed in 12 patients. 5 patients had cerebrospinal fluid (CSF) leak postoperatively. Meningitis was seen in 2 cases. **Conclusion:** Endoscopic endonasal transsphenoidal pituitary gland excision is an effective surgical modality for the management of pituitary macroadenomas which led to significant improvements in endocrine function postoperatively. The marked decrease in serum PRL and GH levels postoperatively shows the efficacy of this surgery in treating hormone-secreting adenomas. Complications such as neurogenic diabetes insipidus, CSF leaks, and meningitis should be an important consideration in the post-operative care even though they are less frequent.

Keywords: Complication, Endocrine function, Pituitary adenoma, Prolactin, Transsphenoidal surgery

Asian Pac. J. Health Sci., (2024); DOI: 10.21276/apjhs.2024.11.3.03

Introduction

The pituitary gland or the hypophysis cerebri, also known as "the master gland," is a vital structure of the human body.[1] The gland is located within the sella turcica of the sphenoid bone and consists of two distinct functionally active regions, i.e., the anterior lobe (adenohypophysis) and posterior lobe (neurohypophysis) and an intermediate lobe in between them. The adult gland measures 8 mm anteroposteriorly and 12 mm transversely with weight 500 mg.[2]

The adenohypophyses consist well-defined acini with hormone secreting cellist in it. The hormones produced and secreted from the anterior pituitary are adrenocorticotropic hormone, prolactin (PRL), luteinizing hormone and follicle-stimulating hormone, growth hormone (GH) or somatotropin, and thyroid-stimulating hormone.[3] The posterior pituitary is divided into pars nervosa and the infundibular stalk that contains axons from hypothalamic neurons, particularly the axon terminals of the magnocellular neurons of the paraventricular and supraoptic nuclei. The secretory granules consist of precursor hormones known as herring bodies. The precursor hormones get cleaved during transport to the posterior pituitary. The hormones secreted by posterior pituitary are oxytocin and arginine vasopressin or antidiuretic hormone.[4]

Intracranial lesions arising in the region of the pituitary gland are relatively common. Pituitary adenomas (PAs) are benign neoplasms consisting of adenohypophyseal cells. PAs with extensive suprasellar extension are a challenge for therapeutics.[5] Hormonally active PAs include prolactinomas, GH producing adenomas, adrenocorticotropic hormone producing adenomas, and thyroid-stimulating hormone producing adenomas. For evaluation of PAs, the clinical and biochemical assessment stands as the cornerstone. The easy access of advanced neuroimaging has increased the sensitivity of detection of small lesions in the pituitary region. Recent developments in transsphenoidal surgery including microsurgery and endoscopic resection of small intrasellar lesions have increased the cure.[6]

The treatment depends on the biochemical and anatomical characteristics of the tumor and is focused toward preservation/restoration of pituitary function, decompression of neural structures, and prevention of tumor recurrence. Many treatment modalities have evoluted so far undergoing numerous refinements over the past 100 years. The introduction of new medications for biochemical control of tumors,[7,8] improved optimization of hormonal replacement therapies,[9] novel surgical techniques for more efficient tumor removal,[10,11] and targeted radiotherapy[12] have provided a new hope in treatment of PAs.

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How to cite this article: Gautam S, Siddiqui S, Yadav S, Dhungana P. Evaluating Endocrine Changes and Surgical Complications following Endoscopic Transsphenoidal Excision of Pituitary Macroadenomas. Asian Pac. J. Health Sci., 2024;11(3):9-13.

Source of support: Nil.

Conflicts of interest: None.

Received: 26/07/2024 **Revised:** 10/10/2024 **Accepted:** 10/10/2024

Pituitary surgery has been revolutionized by the introduction of the endoscope.[13] Surgery is often required for giant (>4 cm) pituitary macroadenomas to decompress the optic nerves. The extended endoscopic endonasal transsphenoidal approach provides the option of aggressive resection through a minimal access in comparison to traditional open or transsphenoidal microscopic methods.[14]

Transsphenoidal surgery is considered relatively safe with <0.5% operative mortality.[15] The potential complications arise from nasal dissection, opening of the sellar floor, pituitary gland and/or stalk manipulation, and intracranial neurovascular injury. Besides hormonal impairment, the most common complication is nasal cerebrospinal fluid (CSF) leakage, and a serious complication of CSF leakage is post-operative meningitis, which has been observed in between 0 and 2% of cases.

Understanding the post-operative endocrine outcome and complication following endoscopic transsphenoidal resection is significant because of the potentially severe long-term health effects. A pituitary macroadenoma can create endocrine imbalance, and after the surgery too, there is risk for hormonal deficiencies and complications. Systematic assessment of these possibilities can provide important insights to clinicians to improve the monitoring and management of the tumor. Ultimately this knowledge will contribute to improve patient care and quality of life undergoing surgery.

Materials and Methods

Study Design

This was a hospital-based cross-sectional study conducted in national neurosurgical referral center, Bir hospital, Kathmandu, Nepal. The study period was from April 2021 to August 2022.

Procedure of Study

All the patients were assessed clinically. A detailed history and clinical examination were done. Radiological investigations, including a magnetic resonance imaging (MRI) brain with pituitary protocol, were performed, and the tumor volume was noted. A pre-operative navigation computed tomography scan of the same patient was also done to facilitate intra-operative neuronavigation during endoscopic pituitary tumor excision. All patients underwent neuronavigation-guided three-dimensional endoscopic endonasal transsphenoidal excision of pituitary tumor. Operating time was calculated by digital watch from surgery start time to surgery end time in minutes. Amount of blood loss was calculated on the basis of blood in suction machine and soaked gauze pieces also acknowledging the amount of saline used. The operative time, findings of procedure, and intraoperative complications were noted. Endocrine profile was obtained at 1 week postoperatively. Postoperative complications if any were noted. Hospital stay of patient was considered from day of operation to discharge.

Sample Size Calculation

Sample size was calculated using formula $n = z^2 p (1-p)/e^2$

Where;

n is sample size,

z is the z statistic for level of confidence,

p is the proportion of an attribute, and

e is the level of precision.

According Khan *et al*., the overall rate of surgical improvement in endoscopic endonasal transsphenoidal pituitary surgery is 72%.[16]

With 95% confidence interval (z = 1.96), expecting 15% margin of error

(e = 0.15), and $P = 0.72$ (taken from study mentioned above)

$n = (1.96)\ 2 \times 0.72 \times (1–0.72)/(0.15)\ 2 = 34.34$ expecting dropout 10%

Of 34, i.e., ~ 3.4,

Required sample size = 38.

Inclusion Criteria

- All patients admitted in NNRC NAMS with diagnosis of pituitary tumor and indicated for surgery.

Exclusion Criteria

- Patients with distinct histological diagnosis or those who have been submitted to a previous transcranial resection were excluded.
- Patient with absolute contraindication (i.e., patient with active nasal infection and ectatic carotid artery) for transsphenoidal surgery.

Sampling Method

Non-probability sampling.

Data Collection Method

Primary and secondary data were obtained through interview and patients hospital records with the help of preformed pro forma. Semistructured preformed pro forma was used for all data collection. The data were entered in the Statistical Package for the Social Sciences (SPSS version 22).

Data Analysis

The results were expressed as the mean ± standard deviation (SD)/ median (range) for the quantitative data. The categorical data were compared using the Fisher's exact test. $P < 0.05$ was taken as statistically significant. The SPSS version 22 software was used to analyze the data.

Ethical Considerations

The patients involved in the research project were admitted and informed participants. Each patient was adequately informed of the aims, methods, source of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study, and the discomfort it may entail to her and the remedies thereof. Every precaution was taken to respect the privacy of the patient, the confidentiality of the patient's information and to minimize the impact of the study on his/her physical and mental integrity and personality. Due care and caution were taken at all stages of the research to ensure that the patient is put to the minimum risk, suffer from no irreversible adverse effects and, generally, benefit from and by the

research or experiment. Written informed consent was obtained from all the patients included in the study. The ethical approval letter was obtained from independent ethics committee of NAMS, Kathmandu, Nepal.

Results

In this study, total 38 patients were included, out of which 52.60% (20) were female and 47.4% (18) were male as in Figure 1. The age ranged from 18 to 62 years with mean age of the patient 40.16 ± 11.01 years [Table 1]. As in figure 2, among the presenting tumor, 47.40% were non secretory tumor, 28.70% were prolactinoma and 23.70% were acromegaly.

As shown in Table 2, hormone serum level was evaluated pre and postoperatively. The mean serum PRL level was observed as 706.57 ± 1196.09 ng/mL preoperatively which was significantly reduced postoperatively to 42.91 ± 109.1 ng/mL. Similarly, the mean value of GH was observed as 13.34 ± 12.59 ng/mL preoperatively which was reduced to 6.48 ± 6.90 ng/mL postoperatively. Both PRL level and GH level were found to be clinically and statistically significant with $P = 0.001$. The mean IGF-1 value preoperatively was 9.97 ± 20.13 and 9.40 ± 18.99 postoperatively on 7th day with $P = 0.08$ which shows no statistical significance. The mean serum cortisol level was 106.87 ± 43.99 preoperatively which raised up to 158.15 ± 172.40 but is statistically significant ($P = 0.02$).

Complications are the inevitable part of any surgical procedure. The complications reported during our procedure were managed accordingly. Postoperatively, neurogenic diabetes insipidus was observed in 12 patients. 5 patients had CSF leak postoperatively. Meningitis was seen in 2 cases. 2 cases of seizure and 3 anosmia were also reported [Table 3].

Discussion

PAs are common intracranial benign neoplasms consisting of adenohypophyseal cells. PAs with extensive suprasellar extension are a challenge for therapeutics.[5] The clinical manifestations may vary so laboratory investigations, radiological investigations along with the patient's symptomatology help to define the pathology and reach to the diagnosis. The current meta-analysis estimated the prevalence rate of PAs to be 16.7%. However, incidental finding of PAs on MRI and autopsy ranges from 14.4% to 22.5%, respectively.[17]

Transsphenoidal approach is widely accepted in pituitary surgery. Prolactinoma and NFPA were most common constituting 86–88% of cases. The incidence of prolactinomas is highest in young females (25–34 years).[18-20] We also had similar observation of more cases of prolactinoma among female population and it may be due to the reproductive age.

In the present study, the presenting age group ranged from 20 to 65 years with mean age ± SD 40.16 ± 11.01 years. This finding is quite similar to other studies where the age ranged from 40 to 50 years. However, literature also mentions presence of the lesion with all age from children to elderly.[21,22] Another study reported the common age for PAs ranged from 21 to 30 years.[23]

We observed female preponderance in our study where female accounted for about 52.6%. This female predilection in our study is also supported by other relatable study in the literature which showed that 51.3% of patients were female.[24] Further, the reproductive age of the female population may have been synergistically aiding in the development of prolactinoma. In contrary to our observation, male predilection has also been reported in the literature with the incidence of 60% while the female population accounted only for 40%.[23]

Hormone serum level was evaluated pre and postoperatively.

Table 1: Mean age±standard deviation

Variable	*Mean±standard deviation*
Age (years)	40.16±11.01

Table 2: Mean±SD value of hormones and the *P*-value using paired *t*-test

Hormones	*Mean±SD (pre-op)*	*Mean±SD (post-op)*	*P-value (using paired t-test)*
Prolactin	706.57±1196.09	42.91±109.1	0.001
Growth hormone	13.34±12.59	6.48±6.90	0.001
IGF-1	9.97±20.13	9.40±18.99	0.08
Cortisol	106.87±43.99	158.15±172.40	0.02

SD: Standard deviation

Table 3: Post-operative complications

S. No	*Complications*	*No. Of patients*
1.	Diabetes insipidus	12
2.	CSF leak	5
3.	Meningitis	2
4.	Seizure	2
5.	Anosmia	3

CSF: Cerebrospinal fluid

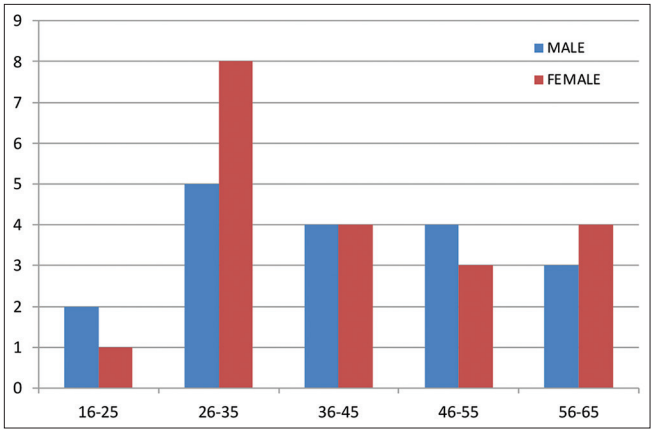

Figure 1: Distribution of study population according to age and gender

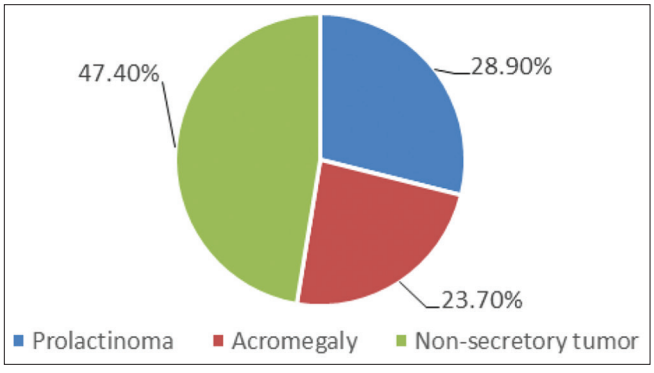

Figure 2: Diagnosis of presenting tumor

Table 4: Complications in Different Literatures

Complications	*Li et al.*[31]	*Juraschka et al.*[27]	*Koutourousiou et al.*[26]	*Dixit et al.*[29]	*Castro et al.*[30]	*Our study*
Diabetes insipidus (%)	-	-	9.6	13.3	-	31.6
Meningitis (%)	1.5	-	-	3.3	3.1	5.3
CSF leak (%)	1.7	10	16.7	13.3 (CSF rhinorrhea)	8.5	13.1
Pituitary insufficiency (%)	3.5	-	16.7	-	-	-
Anosmia/nasal complications (%)	8.6	-	-	-	-	7.9
Death (%)	0.15	-	-	3.3	0.8	-

The mean serum PRL level was observed as 706.57 ± 1196.09 ng/mL preoperatively which was significantly reduced postoperatively to 42.91 ± 109.1. Hyperprolactinemia may occur either due to the underlying prolactinoma or due to the stalk effect of the longstanding mass of the lesion. Similarly, the mean value of GH was observed as 13.34 ± 12.59 ng/mL preoperatively which was reduced to 6.48 ± 6.90 ng/mL postoperatively. Both PRL level and GH level were found to be clinically and statistically significant with $P = 0.001$. The mean IGF-1 value preoperatively was 9.97 ± 20.13 and 9.40 ± 18.99 postoperatively with $P = 0.08$ which shows no statistical significance. The mean serum cortisol level was 106.87 ± 43.99 nmoL/L preoperatively and 158.15 ± 172.40 nmoL/L postoperatively which was statistically significant ($P = 0.02$) [Table 2].

Complications are the inevitable part of any surgical procedure. Giant PAs are usually associated with a higher surgical complication rate compared to normal PAs. The most common complications reported in the literature include di, CSF leaks, post-operative intracranial hemorrhage, intracranial infections, cranial nerve palsies, hypopituitarism, and epistaxis.[26,27] In our study, we observed diabetes insipidus in 12 (31.7%) patients while only 18% ($n = 9$) was observed in a study reported by Yan *et al*.[28] In the present study, 5 (13.1%) patients had CSF leak postoperatively. 2 (5.3%) cases of meningitis were reported. 2 (5.3%) cases of seizure and 3 (7.9%) anosmia were also reported. In another study, 37% of the study population experienced complications of which, the most common complications were sinusitis (14%) and CSF leak (10%).[27] A study reported by Koutourousiou *et al*. observed apoplexy of residual adenoma (3.7%), permanent diabetes insipidus (9.6%), new pituitary insufficiency (16.7%), and CSF leak (16.7%).[26]

Similarly, Li *et al*. observed post-operative complications including 34 (1.7%) CSF leak, 72 (3.5%) pituitary insufficiency, 30 (1.5%) meningitis, 20 (0.98%) cranial nerve deficits, 5 (0.25%) hematoma, 5 (0.25%) patients with internal carotid artery injury, and nasal complications (8.6%). Overall, there were 3 deaths (0.15%) occurred in this series. However, we did not encounter any. Dixit *et al*. reported 4 patients developed temporary diabetes insipidus, 4 patients developed post-operative CSF rhinorrhea and were managed conservatively. Two patients had recurrence of tumor, one patient had meningitis and one patient expired in perioperative periods.[29] Castro *et al*. found that the main complications were CSF fistulas in 8.5%, meningitis in 3.1%, and one death due to major intracerebral hemorrhage in the post-operative period.[30]

The complication rate depends on several factors such as the extension of the tumor resection, the type of tumor, and the preservation of the surrounding structures from injury. In our study, perioperative CSF leak was managed by lumbar drain and application of DuraSeal in the sellar defect. Post-operative CSF leak was managed only with lumbar drain which closed spontaneously.

Conclusion

PAs are challenging to treat, maintaining the functional ability and preserving neurovascular structures. Although endoscopic endonasal transphenoidal approach is a commonly preferred surgical procedure for pituitary macroadenoma at our center, few intra and post-operative complication remains inevitable despite of advance surgical tools and techniques. Despite of late presentation, hormonal improvement was clinically and statistically significant.

Endoscopic endonasal transsphenoidal pituitary gland excision is found to be an effective surgical modality for the management of pituitary macroadenomas which led to significant improvements in endocrine function postoperatively. The marked decrease in serum PRL and GH levels postoperatively shows the efficacy of this surgery in treating hormone-secreting adenomas. Nevertheless, complications such as neurogenic diabetes insipidus, CSF leaks, and meningitis should be an important consideration in the post-operative care of these patients even though they are less frequent. Careful monitoring and timely intervention for such conditions are necessary in improving patient well-being. Regular advancements in surgical techniques and post-operative management protocols are crucial to further decrease complication rates and enhance recovery.

Acknowledgments

We are grateful to the participants of the study.

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