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An audit of early complications after endonasal transsphenoidal resection of pituitary adenomas at Chris Hani Baragwanath Academic Hospital: a 5 year review of record

Mohale, Masedi Selby

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AN AUDIT OF EARLY COMPLICATIONS AFTER ENDONASAL-TRANSSPHENOIDAL RESECTION OF PITUITARY ADENOMAS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL: A 5 YEAR REVIEW OF RECORDS

MASTER OF MEDICINE

(NEUROSURGERY)

Dr MASEDI SELBY MOHALE

2023

AN AUDIT OF EARLY COMPLICATIONS AFTER ENDONASAL-TRANSSPHENOIDAL RESECTION OF PITUITARY ADENOMAS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL: A 5 YEAR REVIEW OF RECORDS

BY

Dr MASEDI SELBY MOHALE

A research report submitted in fulfilment of the requirement for the degree of **Master of Medicine (Neurosurgery),** in the Faculty of **Health Sciences, School of Clinical Medicine at University of Witwatersrand,** Johannesburg, South Africa.

Prepared under supervision of

Prof J.R Ouma (WITS)

DECLARATION

I declare that this dissertation, which is submitted in consideration of the award of a Master of Medicine degree in Neurosurgery at the University of the Witwatersrand, is my own personal effort. Where any of the content presented is the result of input or data from related collaborative research programme this is duly acknowledged in the text such that it is possible to determine how much of the work is my own. I confirm that this work has not previously been submitted by me for a degree at this or any other university. Furthermore, I took sensible care to ensure that the work is original and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and duly acknowledged within the text.

Initial & Surname: …… Signature: ……

Student Number: …… Date: ……..…..

DEDICATION

I would like to dedicate this research report for the Master of medicine degree in Neurosurgery to my late father, **Mr Norman Mohale** whom I never got the chance to say goodbye on February 2018 (I pray you are pleased with the progress your son is making) and secondly my family for their understanding, support and undying love for me. Their faith in me and their prayers for my success caused me to carry on and not look back, even when things were not going too well.

Acknowledgements

Throughout my graduate studies at the University of the Witwatersrand, I have received assistance from many others, without whom this research report would not have been possible. As a results, I would like to express my heartfelt gratitude to each of them.

First and foremost, there is nothing better for me to do than to thank God for the grace and strength he has given me to complete this study and for enabling me to persevere when challenges came my way. Without him, I would be nothing.

Secondly, I would like to express my heartfelt gratitude to my Supervisor, Prof. J.R Ouma, for his constant guidance, support, and encouragement throughout my Master of Medicine Studies. His enthusiasm for science and dedication to research have always inspired me. I am grateful to him because he always wants the best for his students, both academically and personally. I am also grateful for the freedom he gave me to think freely and explore research directions, which prepared me to be an independent researcher.

I am thankful to all the faculty staff members in the Department of Neurosciences, for their contribution, never-ending support, and advice regarding my field of study. I'd also like to thank people outside of the department/university for their assistance with my research project. Despite their busy schedules, I am grateful to Mr M. Nemukula and Mr S. Mkhwanazi of Sefako Makgatho Health Sciences University for their valuable suggestions and critical advice on my research report.

Finally, I want to thank my family and friends for their unwavering love and support. Most importantly, I'm blessed to have a wonderful mother who accepts my decisions,

respects them, and always has my best interests in mind. I would not have progressed this far without her. I owe my wife, Mrs. **Charity Mohale**, a debt of gratitude for her unceasing support, wonderful advice, as well as some astute comments and fascinating social discussions regarding my research.

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List of Abbreviations

Adrenocorticotropic Hormone ..... **(ACTH)**

Antidiuretic Hormone ..... **(ADH)**

Cerebrospinal Fluid ..... **(CSF)**

Chris Hani Baragwanath Academic Hospital ..... **(CHBAH)**

Computerized Tomography ..... **(CT)**

Diabetes Insipidus ..... **(DI)**

Endonasal Transsphenoidal Surgery..... **(ETS)**

Endoscopic Endonasal Transsphenoidal Surgery ..... **(EETS)**

Follicle-Stimulating Hormone ..... **(FSH)**

Growth Hormone ..... **(GH)**

Magnetic Resonance Imaging ..... **(MRI)**

Multiple Endocrine Neoplasia ..... **(MEN)**

National Health Laboratory Services ..... **(NHLS)**

Non-Functioning Pituitary Tumours ..... **(NFPTs)**

Picture Archiving And Communication System ..... **(PACS)**

Pituitary Adenoma ..... **(PA)**

Protein Kinase Type I-Alpha Regulatory Subunit ..... **(PRKAR1A)**

Statistical Package For The Social Sciences ..... **(SPSS)**

Statistical Software ..... **(STATA)**

Syndrome Of Inappropriate Anti Dureitic Hormone Secretion ..... **(SIADH)**

Thyroid Stimulating Hormone ..... **(TSH)**

ABSTRACT

Background

Endoscopic endonasal transsphenoidal surgery (EETS) for pituitary adenomas is a common procedure done at Chris Hani Baragwanath Academic Hospital (CHBAH) due to a significant number of patients requiring the procedure at the institution. Post-transsphenoidal tumour resection complications may not be common but if unrecognised, they may result in significant morbidity and even mortality and hence it is of paramount importance to evaluate factors that may predict the occurrence of these various complications so as to improve vigilance and be able to monitor and manage them appropriately to avoid disastrous outcomes following EETS. However, there is no study has ever been conducted to clinically audit early complications associated with EETS at CHBAH. Even though literature suggests that complications associated EETS are not common. It is with outmost importance that they are monitored and managed appropriately as some of them may lead to chronic disability or death.

Aim of the study

The aim of the study is to evaluate early complications following endoscopic endonasal transsphenoidal surgery of pituitary adenoma.

Methodology

The study is a retrospective research study which evaluated early complications following EETS of PA at CHBAH. Also, investigated in this study was the factors that are associated with the occurrence of the complications, including the clinical

outcomes following EETS. The study was a clinical audit that collected and analysed data from the medical records. Data was collected from medical records of patients with PAs who have undergone EETS's from January 2016 until December 2020. CHBAH does an average of four EETS's every month. A period of five years is defined as a suitable criterion for a clinical audit, and it is a reasonable period for a pool of study participants. The determination of sample size was performed in consultation with a biostatistician who recommended an estimated sample size of one hundred twenty (120). Descriptive analysis of all statistical data was analysed using Statistical Package for the Social Sciences (SPSS) version 24 (SPSS inc., Chicago, IL, USA).

Results

The sociodemographic characteristics indicated that the majority of the study participants in non-functional PA group were males while the majority of the study participants in the functional pituitary adenoma group were females. The observation that there were more males than females in the non-functional pituitary adenoma group was expected, and the findings of the current study are in agreement with other several research studies. Also, the observation that there were more females in the functional pituitary adenoma group was not unexpected. These findings were also not surprising and were also in agreement with other previous studies. In bivariate analysis, study participants whose age were 20 - 40 years, and ages above 40 years were found be associated with the likelihood of occurrence of early complications of EETS of PA, including study participants whose tumour extensions were suprasella and parasella. These findings were not unexpected considering that prevalence of early complications vary depending on several factors, such as the size and location

of the tumour, the experience and skill of the surgeon, and the patient's overall health status.

Conclusion

The result of the current study confirms the notion that early complication of EETS of PA are rare.

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CHAPTER 1

Introduction, Research problem statement, Motivation and Research question, Purpose, and Organization of the research report

1.1 Introduction

This is a research report of study that probed a clinical audit of early complications after endonasal transsphenoidal resection of pituitary adenomas at Chris Hani Baragwanath Academic Hospital (CHBAH): a 5-year review of medical records of patients who have undergone endoscopic endonasal transsphenoidal surgery (EETS) from January 2016 until December 2020 at CHBAH. EETS is a minimally invasive surgical procedure for removal of sellar and parasellar lesions. Although EETS is considered a safe and effective procedure, complications may occur and they are relatively rare. These complications include cerebrospinal fluid leak, bleeding, visual impairment, hormonal imbalance etc. The study was a retrospective collection and analysis of data from clinical cases in which the incidence of early complications after EETS was investigated. Also, investigated in this study were the factors that are associated with the occurrence of the complications, including the clinical outcomes following EETS. In addition, bivariant analysis was performed to determine whether the factors are independently associated with the occurrence of the complications following the EETS.

1.2 Research Problem Statement

The sella turcica is key anatomical area in the cranium, which important neural, skull based, and vascular structures exist in proximity with one another, and it is also a site

of important pathological conditions such as pituitary adenomas, meningiomas and craniopharyngiomas just to mention a few. Pituitary adenomas (PA) are the commonest tumour type found in this area and are the third most common brain tumours (1). The endoscopic endonasal transsphenoidal approach has superseded all other approaches such as the microscopic transsphenoidal and transcranial approaches and it is currently the most used surgical approach for resection of pituitary adenomas. However, there is no study has ever been conducted to clinically audit early complications associated with EETS at CHBAH, even though literature suggests that complications associated EETS are not common (2–4). It is with outmost importance that they are monitored and managed appropriately as some of them may lead to chronic disability or death.

The sella turcica is contiguous with the cribriform plate and planum sphenoidale anteriorly, which form part the floor of the anterior cranial fossa. Caudally, the sphenoid becomes the clivus. The cavernous sinuses flank the pituitary fossa and are connected anteriorly and posteriorly by intercavernous (circular) sinuses (1). The cavernous sinus houses the cavernous segment of the internal carotid artery, as well as oculomotor nerve, trochlear nerve, and abducens nerve and two branches of the trigeminal nerve (ophthalmic nerve and maxillary nerve) (3). The abducens nerve enters the cavernous sinus after exiting Dorello's canal and courses in a medial-to-lateral direction to the internal carotid artery. Unlike other cranial nerves within the cavernous sinus, which line the lateral wall of the sinus, the abducens nerve is found mobile next to the internal carotid artery and thus is more susceptible to injury and compressive pathologic processes (5). The cavernous carotid artery and its surrounding sympathetic plexus

within the cavernous sinus demarcates the working distance of the coronal plane during transsphenoidal resection of pituitary masses (6).

EETS involves the use of a neuro-endoscope and long pituitary instruments. A neuroendoscope is a surgical tool that has a lens, and it is connected to a monitor and light source and enables the surgeon to have a panoramic view during surgery. During surgery, once adrenaline-soaked patties are removed from the nostrils, the endoscope is advanced into nostril and superior, middle, and inferior turbinates are identified laterally (7). The nasal septum is located medially. The middle turbinate is lateralised, and sphenoid ostium is identified above the choana. An incision is made at the junction of the bony and cartilaginous septum and carried inferiorly and posteriorly. Bilateral ostia are identified and enlarged to reach the sphenoid sinus (8).

Mucosa within the sphenoid sinus is removed together with septations. At this point one should be able to identify sellar floor at the centre, planum sphenoidale superiorly, the rostral clivus inferiorly, the wings of the optic nerves supero-laterally in relation to the sella, the bulge of the internal carotid siphon immediately juxtaposed to the sella, and the optico-carotid recess in between the optic nerve and the carotid protuberance (9,10).

The sellar floor is opened with a kerrison punch instrument at the centre and the dura is identified and incised and the pituitary tumour is resected using curretes starting from inferiorly, laterally and the superiorly. Reconstruction of sellar floor is done when

there are suspicions of a cerebrospinal fluid (CSF) leak likely due to violation of the diaphragm and it involves a combination use of fat free graft, gel foam and fascia (11).

1.3 Motivation and Research questions

The research report was motivated by the need to answer the following research questions.

i. What is the incidence of early complications after endonasal transsphenoidal resection of pituitary adenomas at CHBAH?
ii. What are the factors that are associated with the occurrence of the complications after EETS of pituitary adenomas at CHBAH?
iii. What are the clinical outcomes following EETS?

1.4 Purpose of the study

1.4.1 Aim of the study

The aim of the study is to evaluate early complications following EETS of pituitary adenoma at CHBAH. The aim was achieved through the following study objectives:

1.4.2 Study Objectives

i. To identify and document the early complications that occurred in patients who underwent EETS of pituitary tumors at CHBAH over a period of five years.
ii. To assess the prevalence and severity of these complications, and to determine if there were any trends or patterns in their occurrence.

iii. To identify potential risk factors for early complications, such as patient age, sex, comorbidities, and tumor characteristics.

iv. To evaluate the management strategies used to address early complications after EETS of pituitary tumors and their effectiveness.

v. To compare the incidence and types of early complications observed at CHBAH with those reported in other studies to determine the hospital's performance and identify areas for improvement.

1.5 Organization of the research report

Preliminary Pages: Includes the title page, candidate's declaration, abstract, acknowledgement, list of tables, list of tables, list of figures, the list of non-standard abbreviations, table of contents.

Chapter one: This chapter contains an introduction to the research report, background information for study, a statement of the research problem, the study's aim, and objectives, as well as the research questions that motivated the study's design and organization of the research report.

Chapter two: This chapter provides literature review of the themes and sub-themes relevant to the study. Both primary and secondary literature resources relevant to the study are reviewed in this chapter.

Chapter three: This chapter provides information on the research methodology and strategy. This section covers, but not limited to, the following: research study participants, tools, supplies and statistical evaluation of various variables.

Chapter four: This chapter summarizes the findings of the analyses as well as any conclusions drawn from study. Results are presented without any commentary.

Chapter five: This chapter provide an overview of the general findings in the light of the research question and as interpreted in accordance with the literature, limitations, conclusions, and implications for future research study.

Supplementary pages: Appendix including ethics clearance.

CHAPTER TWO

Literature Review

The aim of the literature review was to establish the current status of knowledge regarding the early complications after endonasal transsphenoidal resection of pituitary adenomas. The literature review covered mostly primary literature sources (journal articles) relevant to the research question/problem that are published during the last decades (from 2006 to date). The review covered specifically literature resources, written in the english language that addressed themes relevant to the study including pituitary adenoma (definitions, etiology, epidemiology; clinical presentation, examination and treatment and management), EETS and minor and major complications of EETS.

2.1 Pituitary adenoma

Pituitary adenomas (PA) are anterior pituitary tumours. Most pituitary tumours are slow-growing and harmless (12). They are classified according to their size or cell of origin. PAs are classified into three types based on size: micro-adenoma, macro-adenoma, and giant tumours. A micro-adenoma is a tumour that is less than 10 mm in size, whereas a macro-adenoma is a tumour that is larger than 10 mm in size. Giant pituitary tumours are more than 40 mm in size (12,13). There are functional pituitary adenomas in which the cell type that makes them causes increased secretion of one or more anterior pituitary hormones. Non-functioning adenomas, on the other hand, do not secrete hormones but can potentially compress the anterior pituitary, resulting in hormonal deficiencies (4). PA patients must be evaluated by an inter-professional team that includes endocrinology, ophthalmology, and neurosurgery (10,14).

2.1.1 Etiology of Pituitary adenoma

PA is also known as a tumour that develops in the pituitary gland, which is situated behind the nasal passages at the base of the brain. Some research studies have shown that a small percentage of cases may be genetic, PA are rarely characterized by genetic mutation (15). The exact pathogenesis of PA is still unclear (11). Most PA are generally sporadic. Although PA are rarely characterized with various gene polymorphisms, genetic mutations in the following genes have been linked to the development of PA. Type 1 Multiple Endocrine Neoplasia this gene's loss of function causes tumours to form in the parathyroid, pancreatic, and pituitary glands (16). Type 4 Multiple Endocrine Neoplasia (MEN): A mutation in the cyclin-dependent kinase inhibitor 1B gene causes PA, hyperparathyroidism, testicular neuroendocrine tumours, and cervical neuroendocrine tumours in MEN 4 (12, 17). The Carney Complex: A germline mutation of the tumour suppressor gene protein kinase type I-alpha regulatory subunit (PRKAR1A) causes primary pigmented nodular adrenocortical disease, testicular tumours, thyroid nodules, spotty skin hyperpigmentation, and acromegaly in the Carney complex (16). (18–20). Genetic evaluation is not necessary for patients presenting with adenomas unless there is a compatible family history (20).

2.1.2 Epidemiology of Pituitary Adenoma

PA was considered rare, but recent studies indicate that the prevalence is higher than previously thought, this being due to the increase in and improvement of diagnostic tests. Asymptomatic PAs might appear as accidental discoveries during autopsy or radiography and are usually non-malignant yet common and place an overwhelming burden on patients and health care system (21,22). According to epidemiologic research, PA are increasing in incidence (between 3.9 and 7.4 cases per 100,000 per

year) and prevalence (76 to 116 cases per 100,000 population) in the general population (approximately 1 case per 1000 of the general population). They are the second most common intracranial neoplasm following meningioma (20,21).

Congruently, individuals who are age 40 to 60 are more likely to have the highest incidence of PA. PA incidence varies by tumour type, sex, and race. Prolactinomas, for example, tend to emerge earlier than non-functioning pituitary tumours (NFPTs), and their frequency tends to decline with aging. The most common PA in early childhood is Adrenocorticotropic hormone (ACTH)-secreting pituitary tumours; between the ages of 20 and 40 years, prolactinomas, followed by NFPTs, are the most frequent (23). Most clinically relevant PA occur in females; these tumours are clinically heterogeneous (13). In several population-based studies, tumour distribution was indicated to have been different. In a series of 471 patients, Agustsson et al, identified NFPTs (43.0%) as the most common PA, followed by prolactinoma (39.9%); Fernández et al, in their population study discovered prolactinomas in 57% of the 63 patients with PA described, NFPTs in 28% of those patients, and other PA less frequently; in Richard 's study, 31.6-35.7% had prolactinomas and 32.1–36.8% had NFPTs, while Daly et al, reported prolactinomas in 66% of patients, and secondly NFPTs (14.7%) (24–26).

Growth hormone (GH) secreting adenomas represent approximately 20-30% of all functioning tumours. Macro--adenomas make up almost 75 percent of GH-secreting adenomas. Acromegaly affects 40 to 60 people per million people. Every year, between 3 and 4 new cases per million are identified (27-28) . Most of pituitary tumours identified in pre-pubertal children are ACTH adenomas, which make about 15 to 25%

of all functional adenomas. Regardless of age, micro-adenomas constitute most ACTH adenomas. An ACTH-secreting adenoma causes Cushing's disease in about 39 people per million people, with a 2.4 per million yearly incidences. Most women who develop Cushing's illness do so in their third and fourth decades of life (29).

2.1.3 History and physical manifestation of pituitary adenoma

The presentation of PA depends on tumour size and functional status. Pituitary micro-adenoma is usually an incidental finding on Magnetic resonance imaging (MRI) brain. In the absence of a hormonally active tumour, patients have no symptoms. Pituitary macro-adenoma manifests as widespread symptoms and may be associated with hormonal excess or insufficiency. An unusual sudden bleeding into a PA is known as pituitary apoplexy. It manifests as a multitude of symptoms, including hormone insufficiency, abrupt headaches, and abnormalities in vision (30). Approximately 40% to 60% of patients report having visual impairment because of mass effect. PA suprasellar extension compresses the optic chiasm, resulting in vision field abnormalities. The most frequent pattern is a bi-temporal deficiency, followed by homonymous faults (31). Diplopia may result from oculomotor nerve involvement, and invasive tumours may also affect the fourth, fifth, and sixth cranial nerves. Although there are common PA symptoms, headache is an unspecific symptom. Hormonal deficiency can be seen leading to one or more anterior pituitary hormonal deficiencies can be observed in patients with pituitary macro-adenoma (32,33).

The clinical manifestation of functioning or secreting adenomas depends on the hormone secreted. Increased prolactin inhibits gonadotrophin levels, causing infertility, a decline in libido, and osteoporosis in both sexes. Prolactin-secreting

adenoma leads to men presenting with erectile dysfunction and gynecomastia, while women with amenorrhea and galactorrhoea (34).

Headaches, visual abnormalities, an increase in ring or shoe size, arthritis, carpal tunnel syndrome, and excessive perspiration are all symptoms of GH secreting adenoma (33). Patients have rough facial characteristics, frontal bossing, an enlarged nose, prognathism, an expanded tongue, and skin tags clinically. At the time of diagnosis, there may also be additional comorbidities such hypertension, cardiomyopathy, obstructive sleep apnea, and many colonic polyps (29).

ACTH-secreting adenoma (Cushing disease) presents with weight gain, muscle weakness, mood disorders, easy bruising, and multiple fractures. A round face, facial plethora, supra-clavicular fat, ecchymoses, and purple striae on the abdomen and armpits are all clinical features. Whereas patients with thyroid stimulating hormone (TSH) secreting adenoma experience palpitations, arrhythmias, and weight loss. They may have tremors and a goiter on examination (35).

2.1.4 Examination of pituitary adenoma

Most PAs are discovered by chance during routine computerized tomography (CT) imaging. An MRI with gadolinium is required to distinguish a mass from a differentials such as aneurysms or other sella and parasella mass lesions; and to evaluate for haemorrhage into the mass. It is also necessary to screen for hypopituitarism and assess for hypersecretion. Even in asymptomatic patients, the Endocrine Society clinical practice guidelines recommend a complete biochemical assessment. Prolactin, TSH, free Thyroxine, follicle-stimulating hormone (FSH), Insulin-like growth

factor-1, growth hormone, adrenocorticotropic hormone, oestradiol, testosterone, basic metabolic panel, and fasting early morning cortisol are all measured during this evaluation (29,36).

2.1.5 Treatment and management of pituitary adenoma

PAs require a close collaboration between an endocrinologist and a neurosurgeon in order to develop an "individualized patient-centric" approach. PAs are treated using a variety of modalities, which can be used individually or in combination at different times: Surgery, radiotherapy, intensity-modulated radiotherapy, stereotactic radiosurgery, and, of course, medication are all options. In symptomatic patients with macro-adenomas, transsphenoidal resection is advised (12, 13). Most patients see an improvement in their visual symptoms and hormonal dysfunction after surgery (2). Radiotherapy is an option for patients who have a persistent residual or recurrent tumour. Annual endocrinology follow-up is important in non-functional adenomas that do not require surgical management to monitor tumour growth and the development of hypopituitarism. MRI of head is obtained annually for three years and if stable, thereafter less frequently (37, 38).

EETS surgery and craniotomy are two procedures used to remove a pituitary tumour. Transcranial surgery and EETS are both relatively safe procedures. Complications are rare. However, there are risks, as with any surgery. Bleeding, infection, anaesthesia reaction, temporary headache and nasal congestion, brain injury, double vision or loss of vision, pituitary gland damage, and Cerebrospinal fluid (CSF) leak are all possible complications following pituitary tumour surgery (3,7,39).

Radiation therapy uses high-energy sources of radiation to treat pituitary tumours. Radiation therapy can be used after surgery, or it can be used alone if surgery isn't an option. The goal of radiation therapy for PAs is to either control or prevent the adenoma from producing hormones (36). Potential side effects and complications of radiation therapy for PAs include damage to the pituitary gland that limits its ability to make hormones, healthy tissue near the pituitary gland is damaged, and damage to the optic nerves causes vision changes. Other nerves near the pituitary gland are damaged. A slight increase in the likelihood of developing a brain tumour (32).

Pituitary hormone replacement therapy is another option for treating PAs. The pituitary gland regulates growth, thyroid function, adrenal function, reproductive function, and the body's water balance. A PA, or its treatment with surgery or radiation, can harm one or all of these. This is because they can cause hormonal changes. If hormone levels fall to dangerously low levels, patients may require hormone replacement therapy. This can help to restore hormone balance (40).

2.2 Complications of Endonasal Transsphenoidal Surgery of Pituitary Adenoma

Common complications following EETS can be categorized or grouped into major and minor complications. Major complications include Permanent Diabetes Insipidus (DI), Bacterial meningitis, severe epistaxis, carotid artery injury, permanent visual impairment, and post-operative CSF leak (41,42). Minor complications include Transient DI, Transient symptomatic Syndrome of inappropriate antidiuretic hormone secretion (SIADH), epistaxis, sinusitis, transient visual impairment, abdominal wound dehiscence, and aseptic meningitis and thromboembolic events (43). In patients who

underwent EETS, complication rates were similar or less than complication rates of microscopic endonasal transsphenoidal surgery reported in literature and tumour resection was superior for endosellar lesions with endoscopic surgery (37,42).

Complications following EETS for pituitary tumours may not be common but are important to anticipate. Mortality rate is generally low at 0.4%-2%. The rate of other complications ranges from 3.3%-9.3%. In general, patients going for transsphenoidal surgery are at higher risk if it is a repeat operation or recurrent disease(44). In a study done in United States of America (California and Florida), It was shown that complication rates were higher following revision surgery compared to primary surgery, but it was not statistically significant(42,43).

DI is one of the most common transient disturbances after transsphenoidal surgery. Overall incidence is 8.7%-18.3%. It has been associated with repeated operations for recurrent disease, Cushing's disease and microadenoma (41). In a prospective study carried out in India, it was shown that there was no relationship between the size, histological type and presence of cerebrospinal leak and the occurrence of DI. Transient DI occurs as a result of temporary dysfunction of antidiuretic hormone (ADH) secreting neurons (13). DI may occur after transsphenoidal surgery due to compression, destruction of the posterior pituitary gland, blood supply compromise to the gland or oedema to the infundibulum (4). It usually occurs within 24-48 hours post operatively and resolves when ADH secreting cells recover. It is suspected if there is polyuria (≥ 3L of urine per day), polydipsia in combination with low urine osmolality, hyper-osmolality and hyper-natraemia (44). Treatment involves oral ingestion of water for awake patients and requires desmopressin for patients unable to drink in response

to thirst. In very rare instances, DI can be permanent, and this is regarded as a major complication (41).

Syndrome of inappropriate ADH secretion (SIADH) occurs in the first 3-7 days post operatively. Estimated incidence of 4%-20% and may be due to excessive manipulation of the posterior pituitary gland during surgery, resulting in excessive ADH release (45). It is characterised by hyponatraemia, hypo-osmolality and decreased urine output and a urine osmolality of greater than 100 mosmol/kg. In rare instances, it may be severe, and life threatening and can cause hyponatraemia (44). Treatment strategies involve fluid restriction, administration of hypertonic saline or vasopressin two receptor antagonist treatment (45).

Infections can occur as a complication of transsphenoidal surgery. These are rare and three most common forms are meningitis, sinusitis and dehiscence of abdominal fat graft wound. Meningitis occurs in 0.4%-1.8% of transsphenoidal operations and usually resolve after a course -of antibiotics (9,15). Meningitis is common in patients who experience post-operative CSF leak. Sinusitis incidence is estimated to be 1%-15%. Abdominal wound is at risk for dehiscence and haematoma formation for patients who undergo abdominal fat grafting, but this is rare, and it usually resolves after oral antibiotic administration (46,47).

Visual loss after transsphenoidal surgery for PAs reported in most series is 0.2%-1.2% (33). It can be transient or permanent. The highest incidence is seen in patients with apoplexy. It has been reported that size of the tumour does not influence the occurrence of this complication. It can be due to direct neuronal injury,

devascularisation of the nerves or compression of the optic apparatus. It can also occur as a result orbital fracture, cerebral vasospasm or optic chiasm prolapse into empty Sella (48,49).

Epistaxis can be severe and adversely affect patient outcome. It can be immediate or delayed. Immediate post-operative epistaxis is associated with internal carotid artery injury and acute post-operative hypertension. Treatment of epistaxis depends on severity and ranges from bedside nasal packing (mild form) to endovascular embolization and/or reoperation exploration (46).

Cerebrospinal fluid (CSF) leak incidence ranges from 0.6%-10% post-transsphenoidal surgery. Predictors of post-operative leak include a large tumour, invasion of Sella diaphragm, tumour adherence, suprasellar extension and extended skull base approaches (46). If cerebrospinal leak is identified intra-operatively, sellaplasty can be done using nasal septum, gel foam and abdominal fat graft to prevent CSF leak. CSF leak can present as CSF rhinorrhoea or patients may complain of having a salty taste from CSF ingestion. CSF leak is usually managed by inserting a lumbar drain and if it does not resolve then direct operative repair is done (32,36,44,49).

Thrombo-embolic events (Pulmonary embolism/Deep vein thrombosis) have an estimated incidence of 2.5% and it is higher in patients with hyper-cortisolaemia. It is thought to be due to increased procoagulant production, coagulation cascade activation and impaired fibrinolytic capacity. These results in shortened activated partial thromboplastin time and hence increased time required for thrombolysis (42). Carotid artery injury is one of the most devastating complications and its incidence is

0.4%-3.8%. It can be innocuous to fatal. Risk factors for arterial injury are unrecognised abnormalities of the vascular anatomy preoperatively e.g., persistent trigeminal artery, Intra-sellar aneurysm, tortuous carotid loop protruding into the Sella and anastomosis of two carotid arteries within the Sella(50). Potential sequelae include formation of pseudo-aneurysms, carotid cavernous fistulas, post-operative vasospasm and even vascular occlusion resulting in clinical ischaemia and stroke(51). Intracranial vessel injury may present with decreased level of consciousness after anaesthesia, severe headache, nausea and vomiting and signs of meningism implying subarachnoid haemorrhage (50). Haemostasis may be achieved by reoperation or by endovascular means. Hypothalamic injury is a serious and sometimes irreversible complication and estimates range from 0.1%-0.4% after transsphenoidal surgery (2). It can occur as a result of direct trauma, ischaemia or haematoma (50).

EETS for pituitary tumours is a common procedure done at Chris Hani Baragwanath Academic Hospital (CHBAH) due to a significant number of patients requiring the procedure at the institution. Post-transsphenoidal tumour resection complications may not be common but if unrecognised, they may result in significant morbidity and even mortality and hence it is of paramount importance to evaluate factors that may predict the occurrence of these various complications so as to improve vigilance and be able to monitor and manage them appropriately to avoid disastrous outcomes following EETS (52).

CHAPTER THREE

Research design and Methodology

3.1 Study Design

The study is a retrospective research study which evaluated early complications following endoscopic endonasal transsphenoidal surgery (EETS) of pituitary adenoma (PA) at Chris Hani Baragwanath Academic Hospital (CHBAH). Also, investigated in this study was the factors that are associated with the occurrence of the complications, including the clinical outcomes following EETS. The study was a clinical audit that collected and analysed data from the medical records.

3.2 Methods

3.2.1 Study population, sampling, and sample size

The study was conducted at the Department of Neurosurgery, CHBAH situated in Johannesburg Soweto. Data was collected from medical records of patients with PAs who have undergone EETS's from January 2016 until December 2020. CHBAH does an average of four EETS's every month. A period of five years is defined as a suitable criterion for a clinical audit, and it is a reasonable period for a pool of study participants. The determination of sample size was performed in consultation with a biostatistician who recommended an estimated sample size of one hundred twenty (120). The sample size was selected to ensure an ample statistical power.

The inclusion and exclusion criteria for the study were as summarized in Table 3.1

Table 3.1: Inclusion and exclusion criteria for the study participants

Inclusion Criteria	Exclusion Criteria
• All adults above 18 years of age who underwent endonasal transsphenoidal resection of pituitary adenoma. • Patients diagnosed with functional and non-functional pituitary adenoma treated with endonasal transsphenoidal resection. • Patients with complete medical records who underwent endonasal transsphenoidal resection of pituitary adenoma.	• Patients who developed complications after discharge. • Patients who present with cerebrospinal fluid leak prior surgery. • Patients with missing relevant information such as histological confirmation of pituitary adenoma in the medical records.

3.2.2 Data collection methods

a. Initial Evaluation

The present study consisted of cases of PAs treated with EETS in CHBAH between January 2016 and December 2020. These patients were diagnosed with functional and non-functional PA, moreover the EETS were performed by multiple consultant neurosurgeons at CHBAH using the standard surgical techniques. Pre-operative assessment of the study participants included hormonal profile, chemical and histopathological examination data. These data were collected from the National Health Laboratory Services (NHLS). The radiographic evaluation consisted of a magnetic resonance imaging (MRI) scan, with and without contrast. The radiological

data was collected from the Picture Archiving and Communication System (PACS) in the Department of Radiology. The medical records were reviewed to examine the pre- and post-operative hormonal state, pathological reports, MRI characteristics, operational notes, and clinical follow-up notes from the patient's neurosurgeon.

b. Hormonal Range

To ascertain the overall effect on the pituitary gland function, each patient had a baseline pre-operative pituitary panel and a post-operative hormonal evaluation in a retrospective manner. The normal hormone range was established based on the findings of the nearby lab. The results of each patient's hormonal and clinical status prior to the surgery was evaluated by either the neurosurgeon or referred to the endocrinologist.

c. Imaging Characteristics

The MRI and CT brain results from both the pre-operative periods were reviewed. A = maximum tumour diameter, B = maximum tumour diameter perpendicular to A, and C = maximum tumour height as recorded on the MRI scan were employed in the formula ABC/2.

d. Complications

Complications such as permanent DI, bacterial meningitis, severe epistaxis, carotid artery injury, permanent visual impairment and post-operative CSF leak, transient DI, SIADH, epistaxis, sinusitis, transient visual impairment, abdominal wound dehiscence, aseptic meningitis, and thromboembolic events) were classified and categorized into major and minor complications. Furthermore, these major and minor complications were categorized based on their severity and clinical impact. Major complications were those to have a major clinical impact and severe; and can lead to life threatening

situations while minor complications were those with lower clinical impact, and less severe; and do not significantly impact the patients overall health.

e. Statistical Analysis

Descriptive analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 24 (SPSS inc., Chicago, IL, USA). All data will be expressed in term of percentages or frequencies, whereas continuous variables will be expressed as mean and standard deviation in tables. Bivariate analysis using chi-square and multivariate analysis using logistic regression will be used to examine the relationship between study groups with respect to the gender and age of the participants. Strength of association will be analysed using the 95% confidence interval, a p-value of <0.05 will be considered as statistically significant. The correlation between the research groups and their complications will be investigated using a chi-square test together with Fisher's exact test.

CHAPTER FOUR

Results

4.1 Demographic and clinical characteristics of the study subjects

In this study, a total of one hundred six patients underwent endoscopic endonasal transsphenoidal resection of pituitary adenomas at Chris Hani Baragwanath Academic Hospital (CHBAH) were included from 2016 – December 2020.The demographic and clinical characteristics of the study subjects are summarized into graph 4.1 and Table 4.1. In this study, a total number of 106 patients, diagnosed with PA and underwent EETS, were included from 2016 until 2020. Of these, 94 patients (87%) were diagnosed with non-functional PA, and 12 patients (13%) were diagnosed with functional PA.

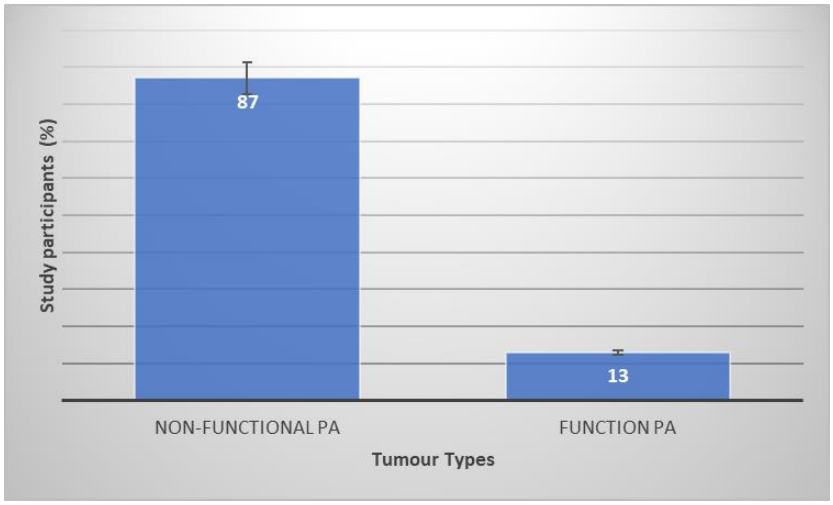


Figure 1: Total number (%) of patients diagnosed with non-functional PA and function PA; PA: pituitary adenoma.

There were more females than males in the functional PA group while there were more males than females in the non-functional PA group.

Table 4.1: Demographic and clinical characteristics of the study subjects.

Variables	Non-functioning pituitary adenoma, n (%)	Functioning pituitary adenoma, n (%)
Average age (yrs)		
≤ 20	4 (4.3)	2 (17)
20-40	22 (23.4)	4 (33)
≥ 40	68 (72.3)	6 (50)
Gender		
Male	54 (57)	2 (17)
Female	40 (43)	10 (83)
Ethnic group:		
Black, n (%)	92 (98)	12 (100)
White, n (%)	2 (2)	0 (0)
EETS		
Primary surgery	78 (83)	10 (83)
Repeat surgery	16 (17)	2 (17)
Tumour size		
Microadenoma	0 (0)	0 (0)
Macroadenoma	94 (100)	12 (100)
Tumour Extension		
Suprasella extension	58 (62)	6 (50)
Suprasella and parasella extension	36 (38)	6 (50)

EETS: Endoscopic endonasal transsphenoidal surgery, Yrs:years

The average age of the non-functional PA group compared to those of the functional PA group were higher. There were more black people than white people in the function PA group as well as in the non-functional PA group. There was no micro-adenoma found in both the non-functional pituitary and functional PA group.

4.2 Complications post Endoscopic endonasal transsphenoidal surgery of pituitary adenoma.

The current study showed that are were less major complication in both non-functional and functional PA group (Table 4.2). However, study participants who presented with non-functional PA showed that n=2 (2%) were suffering of severe epistaxis, n=2 (2%) were also suffering from carotid artery injury while only n=2 (17%) of the study participants were suffering from post-operative CSF leak. No mortality occurred post-endoscopic endonasal transsphenoidal resection.

Table 4.2: Major complications post endoscopic endonasal transsphenoidal surgery of pituitary adenoma.

Major Complications	No/Yes	Non-Functional Pituitary adenoma, n (%)	Functional pituitary adenoma, n (%)	P-value
Permanent DI	No Yes	94 (100)	12 (100)	N/A
Bacterial meningitis	No Yes	94 (100)	12 (100)	N/A
Severe epistaxis	No Yes	92 (98) 2 (2)	12 (100) 0	0.2949
Carotid artery injury	No Yes	92 (98) 2 (2)	12 (100) 0	0.2949
Post-operative CSF	No Yes	94 (100) 0	10 (83) 2 (17)	0.0194

DI: Diabetes insipidus, CSF: Cerebrospinal Fluid

The current study also showed that there is less minor complication in both non-functional and functional PA groups. Although there was less complication, the current study showed that were more minor complications for the non-functional PA group compared to the functional PA group. Table 4.3 showed that only 11 % (n=10) suffered

from transient DI, 6.4 % (n=6) suffered from epistaxis and 2 % (n=98) suffered both abdominal wound dehiscence and aseptic meningitis in the non-functional PA group.

Table 4.3: Minor complications post endoscopic transsphenoidal surgery of pituitary adenoma.

Minor Complications	No/Yes	Non-Functional Pituitary adenoma	Functional pituitary adenoma	P-value
Transient DI	No	84 (89)	12 (100)	
	Yes	10 (11)	0	0.0251
SIADH	No	94 (100)	12 (100)	
	Yes	0	0	N/A
Epistaxis	No	88 (94)	12 (100)	
	Yes	6 (6.4)	0	0.0749
Sinusitis	No	94 (100)	12 (100)	
	Yes			N/A
Transient visual impairment	No	94 (100)	12 (100)	
	Yes	0	0	N/A
Abdominal wound dehiscence	No	92 (98)	12 (100)	
	Yes	2 (2)	0	0.2949
Aseptic meningitis	No	92 (98)	12 (100)	
	Yes	2 (2)	0	0.2949
Thromboembolic events	No	94 (100)	12 (100)	
	Yes			N/A

DI: Diabetes insipidus, SIADH: syndrome of inappropriate secretion of antidiuretic hormone

4.2 Factors that are associated with the occurrence of early complication of pituitary adenoma.

Bivariate odds ratios were calculated in order to determine the associations between variables of the study participants. These includes age of the study participants, gender, ethnic group, EETS, tumour size, and tumour extension.

Table 4.4: Bivariate logistic regression analysis of factors associated with early complications of post-endoscopic transsphenoidal surgery of pituitary adenoma.

Variables	Non-functioning pituitary adenoma	Functioning pituitary adenoma	COR, 95%CI	P-value
Average age (yrs)				
≤ 20	4 (4.3)	2 (17)	1.0 (ref)	
20-40	22 (23.4)	4 (33)	2.962 (0.881-9.957)	0.0792
≥ 40	68 (72.3)	6 (50)	0.458 (0.2254 - 0.932)	0.0312
Gender				
Male	54 (57)	2 (17)	1.0 (ref)	
Female	40 (43)	10 (83)	0.155 (0.080 - 0.298)	< 0.0001
Ethnic group:				
Black, n (%)	92 (98)	12 (100)	1.0 (ref)	
White, n (%)	2 (2)	0 (0)	5.102 (0.242 - 107.625)	0.295
EETS				
Primary surgery	78 (83)	10 (83)	1.0 (ref)	
Repeat surgery	16 (17)	2 (17)	1.00 (0.478 - 2.092)	1.00
Tumour size				
Microadenoma	0 (0)	0 (0)	1.0 (ref)	
Macroadenoma	94 (100)	12 (100)	1.00 (0.020 to 50.894)	1.00
Tumour Extension				
Suprasella extension	58 (62)	6 (50)	1.0 (ref)	
Suprasella and parasella extension	36 (38)	6 (50)	0.613 (0.349-1.076)	< 0.088

EETS: Endoscopic endonasal transsphenoidal surgery, Yrs: years

The results shown in Table 4.4 indicated early complications of PA are more likely to develop in patients who are between the ages of 20 to 40 (COR = 2.962, 95% CI (0.881-9.957) and ages of 40 years and above; and females (COR =0.155, 95% CI (0.080 - 0.298) $p < 0.001$, tumour extension which is suprasella and parasella (COR = 0.613, 95% CI (0.349-1.076) $p < 0.088$.

CHAPTER FIVE

Discussion, Limitations, Conclusion and Recommendations

5.1 Discussion

Endoscopic endonasal transsphenoidal surgery (EETS) is an established surgery technique that is increasingly used for pituitary adenomas (PA). EETS is highly indicated in sellar, suprasellar, intraventricular, retro-infundibular, and invasive tumors. EETS is also known to manage the recurrent and residual lesions, pituitary apoplexy and empty sellar syndrome. Thus, we are investigating the clinical outcomes of EETS of PA including factors that are associated with the occurrence of the complications (53).

5.1.1 Sociodemographic characteristics of the study subjects

The current research study focused on patients treated with EETS conducted by multiple neurosurgeons in single setting institution. The study analysed the early complications of EETS of PA. In this study, a total of 106 patients, diagnosed with PA and underwent EETS, were included from 2006 until 2015. Of these, 94 patients were diagnosed with non-functional PA, and 12 patients were diagnosed with functional PA. The non-functional PA group consisted of n= 54 males (57%) and n= 40 females (43%), while the functional PA group consisted of n= 2 males (17%) and n= 10 females (83%). Consequently, the majority of the study participants in non-functional PA group were males while the majority of the study participants in the functional pituitary adenoma group were females. The observation that there were more males than females in the non-functional pituitary adenoma group was expected, and the findings

of the current study are in agreement with other several research studies (54–56). Also, the observation that there were more female in the functional pituitary adenoma group was not unexpected. These findings were also not surprising and were also in agreement with other previous studies (57,58). The prevalence of PA differs depending on the population studies and the diagnostic methods used. However, in general, PA are more common in women than in men (59,60). It is important to note that the prevalence of PAs can vary depending on the type of tumour and the hormonal profile of the individual. Some types of PAs, such as prolactinomas, are more common in women, while others, such as somatotrophic adenomas, are more common in men (59). In the current study, among the 12 diagnosed patients with functional PA, 4 (33%) had prolactinoma, 4 (33%) had somatotrophic adenoma and 2 (16%) had mixed secretion of both prolactin and growth hormone. There was no patient with the Cushing's disease.

Furthermore, the fact that there were more black people than white people in both non-functional and functional PA group was not surprising given that the study setting Chris Hani Baragwanath Academic Hospital (CHBAH) is an institution that is traditionally known to persistently serve black people compared to the white people. It also worth noting, that there is inadequate data on the prevalence of PA in certain racial or ethnic groups. Some studies have indicated that there may be differences in the occurrence of PA in different populations (61,62). More research is needed in general to fully understand the prevalence of PAs in different racial and ethnic groups. It is important to note that PAs should be diagnosed and treated based on individual patient characteristics rather than solely on racial or ethnic factors(63)

The distribution of the tumour on size was based on MRI finding, 90 (100%) patients with non-functional pituitary adenoma were found with macro-adenoma while 12 (100%) patients with functional pituitary adenoma were also found with macro-adenoma.

5.2. Complications post Endoscopic endonasal transsphenoidal surgery of pituitary adenoma.

EETS is a minimally invasive technique for removing PAs through the nasal cavity. It carries the same risk of complications as any other surgical procedure (60). These complications can present either as minor or major. These complications include permanent DI, bacterial meningitis, severe epistaxis, carotid artery injury, permanent visual impairment and post-operative CSF leak, transient DI, SIADH, epistaxis, sinusitis, transient visual impairment, abdominal wound dehiscence, aseptic meningitis and thromboembolic events (64,65). Post EETS, it's important to note that not all patients will experience complications, and many of these complications are rare. This is notion supports the findings of current study.

According to literature sources, the most common complication of EETS of PA is a temporary or permanent loss of pituitary gland function, which can lead to hormonal imbalances (66). The pituitary gland produces several hormones that regulate various functions in the body, including growth, reproduction, and metabolism. If parts of the gland are damaged or removed during surgery, the patient may require hormone replacement therapy to restore normal function (44). Other common complications

include a cerebrospinal fluid (CSF) leak, which occurs in up to 10% of cases, and temporary swelling or discomfort in the nasal passages (67).

Major complications in non-functional pituitary adenoma after EETS are uncommon, with most studies reporting rates of less than 5% (68). This was in agreement with the findings of the current study, reporting 2% (n=2) of the study participants were suffering of severe epistaxis, and 2% (n=2) were suffering from carotid artery injury. CSF leak is one of the most common complications in non-functional pituitary adenoma following EETS (69), however in our study there was no study participant suffering from CSF leak. In the functional PA group, 17% (n=2) p=0.0194 study participants suffered from CSF leak. The management of CSF leak in our practice involves insertion of a lumbar drain including bed rest for five days. In the case where the CSF leak doesn't stop, a surgical repair to close the leak is performed. While the management of epistaxis involves insertion of nasal packs until it resolves, if this fails it is embolized.

The occurrence of minor complications following EETS for non-functional pituitary adenoma is relatively common, with most studies reporting rates between 10-30% (68). In our current study, we found that only 11 % (n=10) suffered from transient DI, 6.4 % (n=6) suffered from epistaxis and 2 % (n=98) suffered both abdominal wound dehiscence and aseptic meningitis in the non-functional pituitary adenoma group. This was unexpected considering that several studies reported rates of 10-30% (66). Compared to other studies, our rates are relatively lower. The management of transient DI involves monitoring of urine output, osmolality and specific gravity. The treatment involves the intake of water when a patient is thirsty. While patients that can

not take water, they are given desmopressin twice a daily orally, with adjusted dose to urine output.

5.3 Factors that are associated with the occurrence of early complication of pituitary adenoma.

In bivariate analysis, study participants aged 20 to 40years, and age above 40 years and tumour extension which are suprasella and parasella were found to be associated with the likelihood of occurrence of early complication of EETS of PA among the study participants. These findings were not unexpected considering that prevalence of early complications vary depending on several factors, such as the size and location of the tumour, the experience and skill of the surgeon, and the patient's overall health status. Also in the current study, we observed that sex differences are associated with early complications of pituitary adenoma, with a p value of < 0.0001. The effect of sex differences was significant for early complications of PA at CHBAH. There were more male who were likely to develop early complications. This was mainly due to the fact that were more males than females.

In the current study, the researcher didn't check if these factors are independently associated with the occurrence of complication of EETS of pituitary. However, the observation of the current research study could offer insight into the clinical outcomes or early complications associated with EETS of PA at CHBAH

5.4 Limitations and recommendation of the study

The current study's findings could have been influenced by a number of limitations. For starters, the sample size was small, making generalization difficult. Second,

because the study was a retrospective study, the results could not be used to infer a cause-and-effect relationship due to non-availability of data in the medical records. Third, rather than being a community-based sample, patients were drawn from a single hospital. Thus, the current study's findings could not be generalized beyond this study sample. Nonetheless, regardless the limitation, the current findings of the study offer insight into the clinical outcomes or early complications associated with EETS of PA at CHBAH. Although the EETS of PA is associated with early complications, it can be hypothesised that EETS surgery like other interventions may have complications that are rare. Further studies are needed in order to support or reject this hypothesis. A prospective study that will follow up study participants is recommended and a multiple centre study that involves different study settings around the country will be important to support the existing data of early complications following EETS.

5.5 Conclusion

The result of the current research study confirms the notion that early complications of EETS of PA are rare. The result also suggests that most patients who undergo EETS of PA at CHBAH are unlikely to experience early complications. It can be hypothesized that early complications following EETS of are rare. Further studies are needed in order to support or reject this hypothesis.

ANNEXURE

DATA COLLECTION SHEET

VARIABLES	CATEGORIES			
Age				
Gender	Male		Female	
Race	Black	Indian	White	Other
Endonasal transphenoidal surgery	Primary surgery		Repeat surgery	
Tumour size based on MRI Imaging	Micro-adenoma (<1cm)		Macro-adenoma (≥1cm)	
			Supra-sellar extension	Para-sellar extension
Major Complications	Permanent DI			
	Bacterial meningitis			
	Severe epistaxis			
	CSF Leak			
	Carotid artery injury			
	Permanent visual impairment			
Minor Complications	Transient DI			
	SIASH			
	Epistaxis			
	Sinusitis			
	Transient visual impairment			
	Donor site wound dehiscence			
	Aseptic meningitis			
	Thrombo-embolic events			
Histopathology				
chemistry				
Hormone profile	Prolactin			
	LH			

	FSH		
	Cortisol		
	TSH		
	T4		
	Testosterone		
	IGF-1		
	Estrogen		
	Progesterone		
Outcome	Better	Same	Worse

References

1. Kucharczyk W, Truwit CL. Diseases of the Sella Turcica and Parasellar Region. In 2020. p. 3–9.

2. Esposito D, Olsson DS, Ragnarsson O, Buchfelder M, Skoglund T, Johannsson G. Non-functioning pituitary adenomas: indications for pituitary surgery and post-surgical management. Pituitary. 2019 Aug 22;22(4):422–34.

3. Zhan R, Li X, Li X. Endoscopic Endonasal Transsphenoidal Approach for Apoplectic Pituitary Tumor: Surgical Outcomes and Complications in 45 Patients. J Neurol Surg B Skull Base. 2015 Aug 20;77(01):054–60.

4. Komotar RJ, Starke RM, Raper DMS, Anand VK, Schwartz TH. Endoscopic endonasal compared with microscopic transsphenoidal and open transcranial resection of giant pituitary adenomas. Pituitary. 2012 Jun 22;15(2):150–9.

5. Azarmina M, Azarmina H. The six syndromes of the sixth cranial nerve. J Ophthalmic Vis Res. 2013 Apr;8(2):160–71.

6. Ajlan A, Achrol A, Albakr A, Feroze A, Westbroek E, Hwang P, et al. Cavernous Sinus Involvement by Pituitary Adenomas: Clinical Implications and Outcomes of Endoscopic Endonasal Resection. J Neurol Surg B Skull Base. 2017 Jun 23;38(03):273–82.

7. Ali Kawsar K. Endoscopy in Neurosurgery. In: Frontiers in Clinical Neurosurgery. IntechOpen; 2021.

8. Alsaied AS. Paranasal Sinus Anatomy: What the Surgeon Needs to Know. In: Paranasal Sinuses. InTech; 2017.

9. Famurewa O, Ibitoye B, Ameye S, Asaleye C, Ayoola O, Onigbinde O. Sphenoid sinus pneumatization, septation, and the internal carotid artery: A computed tomography study. Nigerian Medical Journal. 2018;59(1):7.

10. Dziedzic T, Koczyk K, Gotlib T, Kunert P, Maj E, Marchel A. Sphenoid sinus septations and their interconnections with parasphenoidal internal carotid artery protuberance: radioanatomical study with literature review. Videosurgery and Other Miniinvasive Techniques. 2020;15(1):227–33.

11. Zanoletti E, Mazzoni A, Martini A, Abbritti R v., Albertini R, Alexandre E, et al. Surgery of the lateral skull base: a 50-year endeavour. Acta Otorhinolaryngologica Italica. 2019 Jun;39(3, SUPPLEMENT 1):S1–146.

12. Xekouki P, Azevedo M, Stratakis CA. Anterior pituitary adenomas: inherited syndromes, novel genes and molecular pathways. Expert Rev Endocrinol Metab. 2010 Sep 10;5(5):697–709.

13. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas. Cancer. 2004 Aug 1;101(3):613–9.

14. Jemel M, Alaya W, Boubaker F, Berrich O, Zantour B. Pituitary Apoplexy. In: Pituitary Diseases. IntechOpen; 2019.

15. Melmed S, Kaiser UB, Lopes MB, Bertherat J, Syro L v, Raverot G, et al. Clinical Biology of the Pituitary Adenoma. Endocr Rev. 2022 Nov 25;43(6):1003–37.

16. Tatsi C, Stratakis CA. The Genetics of Pituitary Adenomas. J Clin Med. 2019 Dec 21;9(1):30.

17. Beckers A, Aaltonen LA, Daly AF, Karhu A. Familial Isolated Pituitary Adenomas (FIPA) and the Pituitary Adenoma Predisposition due to Mutations in the Aryl

Hydrocarbon Receptor Interacting Protein (AIP) Gene. Endocr Rev. 2013 Apr 1;34(2):239–77.

18. Coopmans EC, Korbonits M. Molecular genetic testing in the management of pituitary disease. Clin Endocrinol (Oxf). 2022 Oct 29;97(4):424–35.

19. Rostomyan L, Potorac I, Beckers P, Daly AF, Beckers A. AIP mutations and gigantism. Ann Endocrinol (Paris). 2017 Jun;78(2):123–30.

20. Daly AF, Vanbellinghen JF, Khoo SK, Jaffrain-Rea ML, Naves LA, Guitelman MA, et al. Aryl Hydrocarbon Receptor-Interacting Protein Gene Mutations in Familial Isolated Pituitary Adenomas: Analysis in 73 Families. J Clin Endocrinol Metab. 2007 May 1;92(5):1891–6.

21. Raishan S, Alsabri M, Hanna AM, Brett M. Resolution of pituitary microadenoma after coronavirus disease 2019: a case report. J Med Case Rep. 2021 Dec 1;15(1):544.

22. Chin SO. Epidemiology of Functioning Pituitary Adenomas. Endocrinology and Metabolism. 2020 Jun 30;35(2):237–42.

23. McDowell BD, Wallace RB, Carnahan RM, Chrischilles EA, Lynch CF, Schlechte JA. Demographic differences in incidence for pituitary adenoma. Pituitary. 2011 Mar 1;14(1):23–30.

24. Agustsson TT, Baldvinsdottir T, Jonasson JG, Olafsdottir E, Steinthorsdottir V, Sigurdsson G, et al. The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study. Eur J Endocrinol. 2015 Nov;173(5):655–64.

25. Fernandez A, Karavitaki N, Wass JAH. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf). 2010 Mar;72(3):377–82.

26. Daly AF, Jaffrain-Rea ML, Ciccarelli A, Valdes-Socin H, Rohmer V, Tamburrano G, et al. Clinical Characterization of Familial Isolated Pituitary Adenomas. J Clin Endocrinol Metab. 2006 Sep 1;91(9):3316–23.

27. Bogusławska A, Korbonits M. Genetics of Acromegaly and Gigantism. J Clin Med. 2021 Mar 29;10(7):1377.

28. Chanson P, Salenave S, Kamenicky P, Cazabat L, Young J. Acromegaly. Best Pract Res Clin Endocrinol Metab. 2009 Oct;23(5):555–74.

29. Perry A, Graffeo C, Marcellino C, Pollock B, Wetjen N, Meyer F. Pediatric Pituitary Adenoma: Case Series, Review of the Literature, and a Skull Base Treatment Paradigm. J Neurol Surg B Skull Base. 2018 Feb 24;79(01):091–114.

30. Banskota S, Adamson DC. Pituitary Adenomas: From Diagnosis to Therapeutics. Biomedicines. 2021 Apr 30;9(5):494.

31. Kumar S, Kumar A, Gill M, Maheshwari V. Optic tract edema: A rare entity in pituitary macroadenoma. Asian J Neurosurg. 2019 Mar 9;14(01):307–9.

32. Gatto F, Perez-Rivas LG, Olarescu NC, Khandeva P, Chachlaki K, Trivellin G, et al. Diagnosis and Treatment of Parasellar Lesions. Neuroendocrinology. 2020;110(9–10):728–39.

33. Saffra N, Kaplow E, Mikolaenko I, Kim A, Rubin B, Jafar J. Isolated sixth cranial nerve palsy as the presenting symptom of a rapidly expanding ACTH positive pituitary adenoma: a case report. BMC Ophthalmol. 2011 Dec 27;11(1):4.

34. Majumdar A, Mangal N. Hyperprolactinemia. J Hum Reprod Sci. 2013;6(3):168.

35. Buliman A, Tataranu LG, Paun DL, Mirica A, Dumitrache C. Cushing's disease: a multidisciplinary overview of the clinical features, diagnosis, and treatment. J Med Life. 2016;9(1):12–8.

36. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al. Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011 Apr 1;96(4):894–904.

37. Cortet-Rudelli C, Bonneville JF, Borson-Chazot F, Clavier L, Coche Dequéant B, Desailloud R, et al. Post-surgical management of non-functioning pituitary adenoma. Ann Endocrinol (Paris). 2015 Jul;76(3):228–38.

38. Rieken S, Habermehl D, Welzel T, Mohr A, Lindel K, Debus J, et al. Long term toxicity and prognostic factors of radiation therapy for secreting and non-secreting pituitary adenomas. Radiation Oncology. 2013 Dec 23;8(1):18.

39. Dekkers OM, Pereira AM, Romijn JA. Treatment and Follow-Up of Clinically Nonfunctioning Pituitary Macroadenomas. J Clin Endocrinol Metab. 2008 Oct 1;93(10):3717–26.

40. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Nov 1;101(11):3888–921.

41. Chowdhury T, Prabhakar H, Bithal P, Schaller B, Dash H. Immediate postoperative complications in transsphenoidal pituitary surgery: A prospective study. Saudi J Anaesth. 2014;8(3):335.

42. Thakur JD, Corlin A, Mallari RJ, Yawitz S, Eisenberg A, Sivakumar W, et al. Complication avoidance protocols in endoscopic pituitary adenoma surgery: a retrospective cohort study in 514 patients. Pituitary. 2021 Dec 2;24(6):930–42.

43. Schreckinger M, Szerlip N, Mittal S. Diabetes insipidus following resection of pituitary tumors. Clin Neurol Neurosurg. 2013 Feb;115(2):121–6.

44. Krings JG, Kallogjeri D, Wineland A, Nepple KG, Piccirillo JF, Getz AE. Complications following primary and revision transsphenoidal surgeries for pituitary tumors. Laryngoscope. 2015 Feb;125(2):311–7.

45. Pillai B, Unnikrishnan A, Pavithran P. Syndrome of inappropriate antidiuretic hormone secretion: Revisiting a classical endocrine disorder. Indian J Endocrinol Metab. 2011;15(7):208.

46. Bennett S, Meghji S, Syeda F, Bhat N. Neurological Complications of Acute Rhinosinusitis: Meningitis. Allergy & Rhinology. 2021 Jan 24;12:215265672199625.

47. Tohge R, Takahashi M. Cerebrospinal Fluid Rhinorrhea and Subsequent Bacterial Meningitis due to an Atypical Clival Fracture. Internal Medicine. 2017;56(14):1911–4.

48. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the Treatment of Prolactinomas. Endocr Rev. 2006 Aug 1;27(5):485–534.

49. Lithgow K, Batra R, Matthews T, Karavitaki N. MANAGEMENT OF ENDOCRINE DISEASE: Visual morbidity in patients with pituitary adenoma. Eur J Endocrinol. 2019 Nov;181(5):R185–97.

50. Imahori T, Fujita A, Hosoda K, Kohmura E. Acute Ischemic Stroke Involving Both Anterior and Posterior Circulation Treated by Endovascular Revascularization for Acute Basilar Artery Occlusion via Persistent Primitive Trigeminal Artery. J Korean Neurosurg Soc. 2016;59(4):400.

51. Lee TS, Ducic Y, Gordin E, Stroman D. Management of Carotid Artery Trauma. Craniomaxillofac Trauma Reconstr. 2014 Sep 1;7(3):175–89.

52. Carampatana-Jandug C, Esguerra JM, Panilagao G, Mejia A, Rama J, Bilocura FE. In-Hospital Postoperative Complications in Patients With Pituitary Adenoma Who Underwent Pituitary Surgery From January 2010 to December 2015: A Multicenter Study. J Endocrinol Metab. 2017;7(4):122–30.

53. Van Gerven L, Qian Z, Starovoyt A, Jorissen M, Meulemans J, van Loon J, et al. Endoscopic, Endonasal Transsphenoidal Surgery for Tumors of the Sellar and Suprasellar Region: A Monocentric Historical Cohort Study of 369 Patients. Front Oncol. 2021 May 7;11.

54. Olsson DS, Nilsson AG, Bryngelsson IL, Trimpou P, Johannsson G, Andersson E. Excess Mortality in Women and Young Adults With Nonfunctioning Pituitary Adenoma: A Swedish Nationwide Study. J Clin Endocrinol Metab. 2015 Jul;100(7):2651–8.

55. Budan RM, Georgescu CE. Multiple Pituitary Adenomas: A Systematic Review. Front Endocrinol (Lausanne). 2016 Feb 1;7.

56. McDowell BD, Wallace RB, Carnahan RM, Chrischilles EA, Lynch CF, Schlechte JA. Demographic differences in incidence for pituitary adenoma. Pituitary. 2011 Mar 1;14(1):23–30.

57. Budan RM, Georgescu CE. Multiple Pituitary Adenomas: A Systematic Review. Front Endocrinol (Lausanne). 2016 Feb 1;7.

58. Zijlker H, Schagen S, Wit JM, Biermasz N, Furth W van, Oostdijk W. Pituitary Adenoma Apoplexy in an Adolescent: A Case Report and Review of the Literature. J Clin Res Pediatr Endocrinol. 2017 Sep 1;9(3):265–73.

59. Vlassoff C. Gender differences in determinants and consequences of health and illness. J Health Popul Nutr. 2007 Mar;25(1):47–61.

60. Cerri S, Mus L, Blandini F. Parkinson's Disease in Women and Men: What's the Difference? J Parkinsons Dis. 2019 Jul 30;9(3):501–15.

61. Vásquez E, Shaw BA, Gensburg L, Okorodudu D, Corsino L. Racial and Ethnic Differences in Physical Activity and Bone Density: National Health and Nutrition Examination Survey, 2007–2008. Prev Chronic Dis. 2013 Dec 26;10:130183.

62. Dahodwala N, Siderowf A, Xie M, Noll E, Stern M, Mandell DS. Racial differences in the diagnosis of Parkinson's disease. Movement Disorders. 2009 Jun 15;24(8):1200–5.

63. McGuire TG, Miranda J. New Evidence Regarding Racial And Ethnic Disparities In Mental Health: Policy Implications. Health Aff. 2008 Mar;27(2):393–403.

64. Thakur JD, Corlin A, Mallari RJ, Yawitz S, Eisenberg A, Sivakumar W, et al. Complication avoidance protocols in endoscopic pituitary adenoma surgery: a retrospective cohort study in 514 patients. Pituitary. 2021 Dec 2;24(6):930–42.

65. Aibar-Durán JÁ, Oladotun-Anka M, Asencio-Cortés C, Valassi E, Webb S, Gras-Cabrerizo JR, et al. Complication Rates after Endoscopic Transsphenoidal Surgery for ACTH-Secreting Pituitary Adenomas: A Comparative Analysis with

GH and Nonfunctioning Adenomas. J Neurol Surg B Skull Base. 2022 Jun 2;83(S 02):e274–83.

66. Kim SY. Diagnosis and Treatment of Hypopituitarism. Endocrinology and Metabolism. 2015;30(4):443.

67. Oh JW, Kim SH, Whang K. Traumatic Cerebrospinal Fluid Leak: Diagnosis and Management. Korean J Neurotrauma. 2017;13(2):63.

68. Chen Y, Xu X, Cao J, Jie Y, Wang L, Cai F, et al. Transsphenoidal Surgery of Giant Pituitary Adenoma: Results and Experience of 239 Cases in A Single Center. Front Endocrinol (Lausanne). 2022 May 6;13.

69. Wang AR, Gill JR. The Pituitary Gland: An Infrequent but Multifaceted Contributor to Death. Acad Forensic Pathol. 2016 Jun 1;6(2):206–16.