



Original Article

Determinants of visual and endocrinological outcome after early endoscopic endonasal surgery for pituitary apoplexy

Ahmed Galal^{1,2}, Omar El Farouk Ahmed¹

¹Department of Neurosurgery, Ain Shams University, Cairo, Egypt, ²Department of Neurosurgery, Dr Erfan and Bagedo General Hospital, Jeddah, Saudi Arabia.

E-mail: *Ahmed Galal - ahmedoc2004@yahoo.com; Omar El Farouk Ahmed - omarelfarouk@hotmail.com



*Corresponding author:

Ahmed Galal,
Department of Neurosurgery,
Ain Shams University, Cairo,
Egypt.

ahmedoc2004@yahoo.com

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ABSTRACT

Background: Patients diagnosed with pituitary apoplexy and presenting with acute visual deterioration require urgent surgical resection. This is also commonly associated with pituitary hypopituitarism that requires hormonal replacement for correction. This study was undertaken to evaluate the clinical recovery of 45 patients diagnosed with symptomatic pituitary apoplexy who underwent early (within 72 h of symptom onset) endoscopic transsphenoidal surgical resection with an emphasis on visual, ocular craniopathy, and endocrinological outcome.

Methods: This is a retrospective analysis of a consecutive series of patients diagnosed with pituitary apoplexy between 2011 and 2020 treated by early (within 72 h of symptom onset) endoscopic transsphenoidal surgical resection. All tumors were histologically proven as pituitary adenomas. Clinical and neuro-ophthalmological examinations, imaging studies, and endocrinological evaluation were retrospectively reviewed. Patients with a minimum of 6 months follow-up were included in the study. The influence of patients' demographics, extent of visual and ocular motility impairment, preoperative endocrinological dysfunction, tumor size and extent, degree of resection, and surgical complications were analyzed as potential prognostic factors for recovery.

Results: Forty-five patients were included in this retrospective study. Ages ranged from 27 to 57 years (mean: 42 years). All patients presented with headache and variable degrees of visual loss and visual field deficit. Ophthalmoplegia was present in 22 (48.9%) patients with 17 (37.8%) having bilateral ocular cranial nerve palsy. All patients had variable degrees of endocrinological deficiencies. All patients showed evidence of low cortisol, 14 (31.1%) showed hypothyroidism and 11 (24.4%) showed hypogonadism. There was evidence of hyperprolactinemia in 16 (35.6%) patients. All patients harbored a pituitary macroadenoma. Tumor resection was complete in 33 (73%) of patients, with residual tumor related to cavernous sinus or retrosellar extension. Operative complications were mainly related to short-term nasal complications occurring in 14 (31%) patients. Cerebrospinal fluid leak requiring revision surgery occurred in only one patient harboring a modified SIPAP Grade 3s tumor. Transient diabetes insipidus occurred in 9 (20%) patients, with 2 (4.4%) requiring long-term hormonal replacement. The mean follow-up was 25 months. Baseline visual improvement was achieved in 39 (86.7%) patients. Ocular cranial nerve palsy showed complete recovery in 17 (77.2%) patients. Endocrine follow-up showed that patients with panhypopituitarism (11 [24.4%]) failed to recover.

Conclusion: The current surgical series showed safety in terms of low complication rate and efficacy in terms of clinical outcome. The significant prognostic factor related to visual recovery was the degree of preoperative visual deficit. Recovery of ocular cranial neuropathy showed a higher recovery rate when it was unilateral as opposed to bilateral. Pituitary hormonal recovery was less favorable with pituitary panhypopituitarism being a poor prognostic factor.

Keywords: Endoscopic surgery, Outcome, Pituitary apoplexy, Vision

INTRODUCTION

Pituitary apoplexy is a clinical condition with a classic triad of symptoms including acute onset of headache/vomiting, visual loss/diplopia, and pituitary hormonal dysfunction associated with a hemorrhagic pituitary adenoma. Acute symptoms are defined as occurring within 24–72 h. A confirmatory magnetic resonance imaging (MRI) sella (pituitary protocol) confirms the diagnosis of pituitary apoplexy if a hemorrhagic pituitary adenoma is noted. A hemorrhagic pituitary adenoma in the absence of these symptoms is not categorized as a pituitary apoplexy.

The reported incidence among pituitary adenomas is 0.6–13%.^[2,5,9,14,29] Surgery is recommended in most cases with visual decline with the exact timing being controversial. The previous reports have studied different timings ranging from <3 days to more than 7 days with variable results on visual and endocrinological outcomes.^[1,11,30,31]

In this study, 45 patients with pituitary apoplexy who were surgically treated within 72 h of symptom onset were retrospectively analyzed to evaluate possible determinants of visual, ocular motility, and endocrinological recovery. The results were compared to those published in the recent literature.

MATERIALS AND METHODS

Study design

Over a 9-year period (2011–2020), patients surgically treated for pituitary apoplexy were included in this retrospective study. Only patients presenting and treated within 72 h of symptoms onset were included in the study. Patients presenting late (beyond 72 h or subacute presentation) were excluded from this study. Clinical and neuro-ophthalmological examination, imaging studies, endocrinological evaluation, and follow-up data were retrospectively reviewed. Only patients with a minimal of 6-month follow-up and documented follow-up were included in the study.

Clinical evaluation

Clinical evaluation included assessment of the conscious level, visual status, cranial nerve function, as well as general condition and medical comorbidities. The previous known diagnosis of pituitary adenoma (managed conservatively) was also noted. Postoperative assessment of clinical recovery and its course in the postoperative period and at each follow-up visit was also noted. Formal visual assessment by ophthalmology was assessed preoperatively and at 1 week, 3 months, 6 months, and 1 year.

Radiological evaluation

Radiological investigations included both a preoperative noncontrast computed tomography (CT) brain and MRI of the

brain. Characteristics such as the largest diameter of the tumor, cavernous sinus invasion, suprasellar and retrosellar extension, and tumor characteristics were noted. CT angiogram of the brain was occasionally ordered if there was any concern regarding the diagnosis or to assess the related vascular anatomy if the tumor had a lateral or posterior sellar extension. A postoperative day 1 CT brain was done to exclude any postoperative complications. MRI sella with contrast was done after 1 month of surgery, 6 months, and then yearly depending on the degree of resection and concerns for tumor recurrence.

Endocrinological evaluation

It included preoperative assessment of anterior pituitary hormones (serum ACTH, cortisol, TSH, free T4, prolactin, growth hormone, insulin-like growth factor 1, and testosterone/estradiol levels). Endocrine protocol for postoperative hormonal assessment included the following: if preoperative serum cortisol level was normal, the level was checked 9 am postoperative days 1 and 2. If already on hydrocortisone replacement, the evening dose of the previous day was omitted before checking. In patients with proven serum cortisol deficiency before surgery, intravenous hydrocortisone 50 mg/6 h is continued before changing to oral maintenance dose once the patient is stable and tolerating oral intake. These patients are then further assessed by endocrinology at 4–8 weeks to determine whether long-term cortisol is needed or not.

Thyroid function (TSH and free T4) was tested on day 3 after surgery. This was then tested again at 4–8 weeks to determine long-term replacement requirements.

For functioning pituitary adenomas, early postoperative hormonal assay was done as well as long-term hormonal follow-up was assessed to confirm remission. This was done every 3 months in the 1st year and then every 6 months–1 year.

Surgical management

A direct endoscopic endonasal approach was performed in all patients within 72 h of symptom onset. A binostril technique was used. The abdomen was routinely prepped for fat if needed. Low-flow cerebrospinal fluid (CSF) leaks were treated in the standard multilayered closure fashion (inlay dural substitute graft, onlay glued dural substitute graft, and supported by a fat graft). A pedicled nasoseptal flap was dissected for closure^[15] if a high-flow CSF leak was identified during surgery. In those patients, a lumbar drain was also kept in place for 48 h before removal.

Statistical analysis

The influence of the patient's age, sex, extent of visual and ocular motility impairment, endocrinological deficit, tumor size and extension, and degree of resection were analyzed as

potential prognostic factors for postoperative recovery after an early surgery performed in the first 72 h after symptom onset.

Statistical analysis was performed using SPSS software (version 22, IBM Corp). Univariate analysis of clinical and surgical parameters was performed using Fisher's exact test. Statistical significance was accepted at $P < 0.05$.

RESULTS

Patient demographics

Forty-five patients were included in this retrospective study. Twenty-seven (60%) were female and 18 (40%) were male. Ages ranged from 27 to 57 years (mean: 42 years).

Clinical presentation

Headache was a common symptom in all patients. Six patients (13.3%) had altered mental status. All patients had variable degrees of visual loss and visual field deficit. Ophthalmoplegia related to the III, IV, and VI nerve palsy was present in 22 patients (48.9%); in 17 patients (37.8%), ocular nerve palsy was bilateral. Medical comorbidities included diabetes mellitus, hypertension, and use of oral anticoagulants (for cardiac valve replacement or atrial fibrillation). All patients had variable degrees of endocrinological deficiencies. Preoperative hormonal deficiencies were related to adrenal, thyroid, and gonadal axis. All patients showed evidence of low cortisol; 14 patients (31.1%) showed

evidence of hypothyroidism, 11 patients (24.4%) showed evidence of hypogonadotropism. There was evidence of hyperprolactinemia in 16 patients (35.6%); with a known history of pituitary adenoma in 7 (15.6%) patients; the other 29 (64.4%) patients had nonfunctioning pituitary adenomas. Table 1 outlines the clinical presentation.

Tumor radiographic characteristics

Radiological investigations included preoperative CT and contrasted MRI brain for all patients. CT angiogram of the brain was ordered for patients with a questionable diagnosis or to assess related vascular anatomy in tumors extending into the cavernous sinus or having a retrosellar extension. All patients in the study had a pituitary macroadenoma. Tables 2 and 3 show the preoperative radiological parameters (according to the SIPAP classification^[12] and Knosp-Steiner classification for parasellar extension.^[17] A suggested modification for suprasellar tumor extension is Grade 3s for those tumors elevating and penetrating the diaphragma sella (extradiaphragmatic extension) with a tumor bud extending into the subarachnoid space.

A postoperative day 1 CT brain was routinely done to exclude any surgical complications as pneumocephalus or sellar hematoma. A follow-up MRI brain with contrast was done within a month of surgery to assess extent of resection and residual tumor.

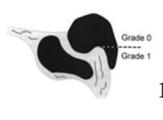
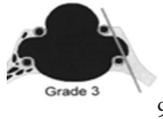
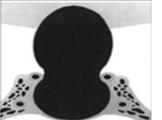
Extent of resection

Tumor removal was complete in 33 (73%) patients (as evident by a postoperative contrasted sellar MRI done within

Patient and hormonal characteristics	Number (%)
Age (years)	Range: 27–57 (mean: 42 years)
Gender	
Male	18 (40)
Female	27 (60)
Symptoms	
Headache	45 (100)
Altered mental status	6 (13.3)
Visual loss	45 (100)
Ocular cranial nerve palsy (III, IV, and VI)	
Unilateral	5 (11.1)
Bilateral	17 (37.8)
Known history of pituitary adenoma	7 (15.6)
Medical comorbidities	
Diabetes mellitus	7 (15.6)
Hypertension	8 (17.8)
Oral anticoagulants	6 (13.3)
Hormonal status	
Panhypopituitarism	11 (24.4)
Hypocortisolism	45 (100)
Hypothyroidism	14 (31.1)
Hypogonadism	11 (24.4)
Hyperprolactinemia	16 (35.6)

Radiographic parameter	Number of patients (%)
Size	
<2 cm in maximum tumor dimension	6 (13.3)
>2 cm in maximum tumor dimension	39 (86.7)
SIPAP grade (superior/inferior/parasellar/posterior):	
Suprasellar extension	
Grade 3 – compressing optic chiasm	44 (97.8)
Grade 3s – compressing chiasm with subarachnoid tumor budding	1 (2.2)
Infrasellar extension	
Grade 1 – focal bulging into sphenoid sinus	12 (26.7)
Parasellar extension (Knosp-Steiner grading)	
Grade 0	–
Grade 1	23 (51.1)
Grade 2	8 (17.8)
Grade 3	9 (20)
Grade 4	5 (11.1)
Retrosellar extension	1 (2.2)

Table 3: Illustrations of radiographic tumor extension according to SIPAP^[12] (with modification) and Knosp-Steiner^[17] grading systems.

SIPAP grade (number of patients (%))			
Suprasellar	Parasellar (Knosp-Steiner grading)	Infrasellar	Retrosellar
 Grade 0 0	 Grade 1 0	 Grade 0 33 (73.3%)	 Grade 0 Grade 1 1 (2.2%)
 Grade 1 0	 Grade 2 23 (51.1%)	 Grade 1 12 (26.7%)	
 Grade 2 0	 Grade 3 9 (20%)	 Grade 2 0	
 Grade 3 44 (97.8%)	 Grade 4 5 (11.1)		
 Grade 3s 1 (2.2%)			
 Grade 4 Monro block 0			

a month of surgery). Residual tumor (mainly cavernous sinus residual tumor and one patient with a retrosellar extension) was evident in 12 (26.6%) patients. The small residual tumor was followed radiographically at 6 months intervals. For any tumor progression noted during follow-up, patients were referred for Gamma Knife treatment (five patients had interval residual tumor progression noted over a 2–3-year period). Of the 12 patients with residual tumor, two patients harbored a prolactinoma and were continued on medical treatment with oral cabergoline in a twice weekly dose with radiographic evidence of residual tumor stabilization or regression noted with radiographic follow-up.

Operative complications

There was no surgery-related mortality. Operative complications included intraoperative CSF leak which was evident in 21 (46.7%) patients, all of which were identified surgically repaired at the time of surgical resection in a manner as described previously. One patient with a Grade 3s

tumor (suprasellar tumor budding through the diaphragma sella into the subarachnoid space) had a persistent postoperative CSF leak, pneumocephalus, and disturbed conscious level that required an urgent revision surgery with a pedicled nasoseptal flap augmented repair. No other patient required a second revision surgery for a CSF leak. No patients developed meningitis. Nasal complications in the form of early nasal bloody ooze and late nasal crustations or sinusitis were evident in 14 (31%) patients. Transient diabetes insipidus was evident in 9 (20%) patients with only two patients requiring long-term desmopressin acetate (DDAVP) replacement.

Visual, ocular cranial nerve palsies, and endocrinological outcomes

The follow-up duration ranged from 6 months to 48 months (mean: 25 months). Progressive visual improvement (both visual acuity and visual field) was noted in all patients, starting from the 1st postoperative day up to 5 months of

surgery. Baseline visual acuity was achieved in 39 (86.7%) of patients, though visual field deficit did not show a complete recovery at last follow-up in 6 patients (13.3%). Ocular cranial nerve palsies also showed a complete recovery in 17 (77.2%) patients and partial recovery in 5 (22.7%) patients at last follow-up. Ocular cranial nerve palsies showed a longer recovery course of up to 6 months.

Endocrine follow-up showed that patients with panhypopituitarism 11 (24.4%) failed to show evidence of hormonal recovery and required ongoing hormonal replacement therapy. Hormonal recovery was observed in 16 (35.5%) patients with hypocortisolism and 9 (64%) patients with hypothyroidism. None of the patients with hypogonadism showed hormonal recovery. Patients with hyperprolactinemia showed complete postoperative hormonal regression except in two patients who harbored a residual cavernous sinus tumor and required postoperative oral cabergoline medical treatment. Transient diabetes insipidus was evident in 9 (20%) patients with only two patients requiring long-term DDAVP replacement.

Univariate analysis of clinical, radiographic, and surgical parameters thought to be related to clinical outcome (ocular and endocrinological) was done as shown below. The patients were classified by demographics, extent of visual impairment, preoperative endocrinological dysfunction, tumor size and extent, and degree of resection.

Age

Age ranged from 27 to 57 years (mean: 42 years). Age was not a statistically significant factor affecting visual or endocrinological recovery ($P > 0.05$).

Gender

There were 27 females (60%) and 18 males (40%). The difference in gender as it relates to visual or endocrinological recovery did not have any statistical significance ($P > 0.05$).

Preoperative visual deficit

There were 61 (67.8%) eyes with a partial visual deficit, all patients showed a complete recovery of their visual deficit. On the other hand, 29 (32.2%) eyes had a severe visual deficit (counting fingers, hand movement, and perception of light) with 23 (79.3%) eyes showing a complete recovery. This difference was statistically significant ($P < 0.05$).

Preoperative ocular cranial nerve palsy

There were 5 (11.1%) patients with a unilateral ocular cranial nerve palsy all of which showed a complete recovery. There were 17 (37.8%) patients with bilateral ocular cranial nerve

palsy with only 12 (70.6%) patients showing a complete recovery. The difference in recovery in patients with a unilateral versus bilateral ocular cranial nerve palsy was statistically significant ($P < 0.05$).

Preoperative hormonal status

All patients showed a low level of cortisol, 11 (24.4%) of which low cortisol were part of a panhypopituitarism; 14 (31.1%) patients showed hypothyroidism, 11 (24.4%) patients showed hypogonadism, and there were 16 (35.6%) patients with hyperprolactinemia (7 [15.6%] of which had a known history of pituitary adenoma). No patients with panhypopituitarism or hypogonadism showed evidence of hormonal recovery. Sixteen of the 34 patients with hypocortisolism (not part of panhypopituitarism) showed recovery while the 9 (20%) patients with hypothyroidism showed recovery. The difference in hormonal recovery between the subgroups of patients with hormonal deficiency showed statistical significance toward lack of hormonal recovery for patients with panhypopituitarism and hypogonadism ($P < 0.05$). There was no statistical significance ($P > 0.05$) for hormonal recovery in patients with hypocortisolism (not part of panhypopituitarism) or hypothyroidism.

Tumor characteristics

Thirty-nine patients (86.7%) harbored a tumor that was more than 2 cm in its maximum dimension, while 6 (13.3%) had tumors <2 cm in its maximum dimension. All patients who harbored a tumor <2 cm in its maximum dimension showed a complete ocular and hormonal recovery. Six patients in the subgroup with larger than 2 cm in maximum dimension (Grade 3 and Grade 3s) did not show a complete visual recovery.

There were 22 patients with ocular cranial nerve palsy, eight of these patients had a Grade 2 parasellar extension, while 14 of these patients had a Grade 3 or Grade 4 parasellar extension. Seventeen patients showed a complete recovery. The five patients who did not show a complete ocular cranial nerve recovery harbored a Grade 3 or 4 parasellar extension. The differences in visual outcome as it relates to size were not statistically significant ($P > 0.05$). There was also no statistical significance ($P > 0.05$) to ocular nerve palsy recovery as it relates to parasellar extension.

Extent of resection

Thirty-three (73.3%) patients had a gross total tumor resection while 12 (26.7%) patients had a subtotal resection (residual parasellar or retrosellar extension of tumor). There was no statistical significance to visual, ocular craniopathy, or hormonal recovery as it relates to the extent of resection ($P > 0.05$).

DISCUSSION

Pituitary apoplexy by definition is symptomatic hemorrhagic pituitary adenoma, with the classic presentation of sudden and intense headache, associated with visual decline, diplopia, and in severe cases altered conscious level. This is also associated with variable degrees of pituitary hormonal dysfunction. In more than 80% of patients, pituitary apoplexy is often the first presentation of an underlying pituitary tumor.^[22,23] Apoplexy is thought to occur when an existing adenoma outgrows its blood supply; hence, it is more common with larger pituitary adenomas. Moreover, an increased intratumoral and intrasellar pressure adds to the reduction in tumor perfusion, contributing to further ischemia and further damage of normal residual tissue; together with the associated compression on the optic chiasm and cavernous sinus resulting in chiasmatic and cavernous sinus compression.

This study was undertaken to evaluate the clinical recovery of 45 patients diagnosed with symptomatic pituitary apoplexy who underwent early (within 72 h of symptom onset) endoscopic endonasal surgical resection with an emphasis on visual, ocular craniopathy, and endocrinological outcome and its determinants. The mean follow-up was 25 months. Of note, only 7 (15.6%) of patients had a known history of a prolactinoma and were being managed conservatively, while in 38 (84.4%) patients, pituitary apoplexy was their first presentation.

The risk factors for pituitary apoplexy are inconsistent between studies. Known risk factors include large size of the tumor; increased hypophyseal blood flow associated with uncontrolled hypertension, diabetes mellitus or hormonal stimulation of the pituitary gland and tumor; and anticoagulation or antiplatelet therapy.^[5,7,21] In this case series, there were 7 (15.6%) diabetic patients; 8 (17.8%) hypertensive patients; and 6 (13.3%) patients on oral anticoagulants. Thirty-nine (86.7%) patients harbored a tumor larger than 2 cm in its maximum dimension. These risk factors seem to be similar to those published in the literature with a larger tumor size (>2 cm in maximum dimension) evident as the most common risk factor. Reported incidence of pituitary apoplexy is similar in males and females,^[18] but the current series showed a higher incidence in females (27 [60%] patients).

In the current patient series, all patients presented with acute headache and variable degrees of visual decline. Five (11.1%) patients had a unilateral ocular cranial nerve palsy, while 17 (37.8%) patients had a bilateral ocular cranial nerve palsy. Only 6 (13.3%) patients had an altered mental status. These symptoms are within the classic triad of acute pituitary apoplexy, with an altered conscious level being a more severe presentation. Jho *et al.*^[16] proposed a clinical grading system

of five grades (Grade 1: asymptomatic, with radiographic apoplexy; Grade 2: endocrinopathy with radiographic apoplexy; Grade 3: headache; Grade 4: ocular palsies; and Grade 5: visual deficit or altered sensorium). This grading system can guide treatment choice with tendency for surgery for the higher grades. There are other similar grading systems published in the literature as the UK pituitary apoplexy scoring system.^[20] The patients in the current case series fall in the higher grades category, and hence, early surgical treatment was undertaken after preoperative assessment, glucocorticoid replacement, and correction of any electrolyte disturbance in a multidisciplinary management approach. All patients in the current series showed hypocortisolemia, and in 11 (24.4%) patients, hypocortisolism was as a part of panhypopituitarism.

There is a lot of controversy in the literature about the ideal management for pituitary apoplexy (whether conservative medical treatment or surgery) and optimum timing for surgical intervention. The apparent literature controversy can be explained by the heterogeneity of the study cohorts and selection bias. In general, patients with headache and minimal visual symptoms are managed conservatively and those with significant visual and neurological symptoms are managed surgically.^[4,13] A multidisciplinary team is best for the decision-making and management. The present study outlines outcomes as it relates to a patient cohort with more severe symptoms that were managed by an early endoscopic surgery with an attempt to outline possible prognostic factors for recovery. The clinical outcomes are summarized in Table 4 as compared to outcomes of some of the more recently published surgical series.

In the current series, the overall visual and ocular craniopathy outcomes were very favorable. A complete visual recovery was achieved in 39 (86.7%) patients. All eyes (61/61) with a partial visual deficit had a complete recovery. On the other hand, 23/29 patients with a severe visual deficit had a complete recovery. The difference in visual recovery as it relates to the severity of the visual deficit was statistically significant ($P < 0.05$). The favorable visual outcome after surgery is comparable to those published in the literature as outlined in Table 4. Of note, many of the studies listed in the table compared conservatively managed and surgically managed patients and found no significant difference in visual outcome. This, however, should be looked at carefully as the comparative groups selected for conservative treatment are those with a low clinical grade with minimal visual symptoms as compared with the surgical group. As such the correct conclusions from such publication comparison are that both conservative and surgical treatments are appropriate for the given clinical grade. The current cohort of patients was treated within 72 h of symptom onset, which did achieve a good overall visual outcome, with the results

Table 4: Recent studies of pituitary apoplexy patients treated surgically.

Study (Ref. no.)	Number of patients (surgical/conservative)	Patient characteristics	Outcome
Bujawansa <i>et al.</i> (2014) ^[18]	55 (32/23) Surgery was either done within 7 days or delayed elective	- Visual deficit (36%) - Diplopia (47.2%)	No difference in the rates of complete/near-complete resolution of visual deficit and cranial nerve palsy between both groups. Endocrine outcomes were also similar.
Singh <i>et al.</i> (2015) ^[24]	87 (69/18) 61 (70.1%): early surgery 8 (9.2%): delayed surgery	- Visual deficit (47.1%) - Cranial nerve palsy 39% (67.6% unilateral) - Known adenoma 25.3% (22 patients) - 9 prolactinomas; 2 ACTH secreting; 1 gonadotrophic tumor, remaining 10 had a nonfunctional tumor Low cortisol (45.5%) Low testosterone (60%) Low TSH (36.8%)	- No statistically significant differences in outcome across the treatment groups. - Three patients had no improvement in peripheral vision Limitation in eye movement improved in all cases - Long- term hormonal therapy: Glucocorticoids in 2/3 of patients Levothyroxine in ½ of patients Testosterone in ½ of men Desmopressin in 23% of all surgical patients
Zaidi <i>et al.</i> (2016) ^[30]	42 (all underwent endoscopic transsphenoidal surgery; time to surgery ranged from 1 to 60 days (average 15 days))	Visual deficit 22 (53.7%) Cranial nerve palsy: III - 8 (19.5%) VI - 2 (4.9%) Hormonal deficit: Adrenal: 16 (36.4%) Thyroid: 17 (38.6%) Gonadal 14 (31.8%) Prolactinoma 1 (2.3%) Growth hormone 5 (11.4%)	- Visual recovery: 100% (average time to recovery 8 days) - Cranial nerve palsy 83.3% recovered (average time to recovery 2.4 months (range 1–6 months)) - No change in hormonal deficiencies after surgery
Teixeira <i>et al.</i> (2018) ^[27]	23 (14/9) Surgical group: 5 microscopic and 9 endoscopic	- Visual deficit: 13 (56.5%) - Cranial nerve palsy : 17 (73.9%) - Hormonal deficit: Adrenal: 14 (60.9%) Hypothyroidism 19 (82.6%)	- No statistically significant difference in visual outcome between the treatment groups - Endocrinological outcome was better in the surgical group - Endoscopic group had a better endocrinological outcome
Almeida <i>et al.</i> (2019) ^[3]	67 (49/18) Surgical group: endoscopic transsphenoidal surgery <3 days: 33 (67.3%) >3 days: 27 (55.1%)	- Visual deficit: Surgical group 37 (75.5%) Conservative group 7 (38.8%) - Cranial nerve palsy: Surgical group 27 (51%) Conservative group 5 (27.7%) - Hypopituitarism Conservative group: 9 (50%) Surgical group: 31 (64.3%) 18 (36.7%): normal hormonal functions 18 (36.7%): panhypopituitarism 18 (36.7%): hypocortisolism 12 (24.5%) Hypothyroidism 1 (2%)	Surgical group: - Visual deficit: Full recovery: 21 (43.8%) Partial recovery: 1 (22.9%) Stable normal visual field: 12 (25%) - Cranial nerves: Complete recovery: 18 (69.2%) Partial recovery: 8 (38.4%) (Timing of surgery did not affect visual or cranial nerve outcomes) - Endocrinological outcome: Panhypopituitarism: no improvement Hypocortisolism: 9 (18.7%) Hypothyroidism: 2 (4.1%) Diabetes insipidus: 3 (6.25%) Conservative group yielded similar visual, cranial nerve, and endocrinological outcomes
Pangal <i>et al.</i> (2020) ^[19]	50 (All managed surgically through an endoscopic endonasal transsphenoidal)	- Visual deficit: 31 (62%) Cranial nerve palsy: 20 (40%)	- Visual deficit: Improved: 29 (94%) Stable 2 (4%)

(Contd...)

Table 4: (Continued).

Study (Ref. no.)	Number of patients (surgical/conservative)	Patient characteristics	Outcome
	approach)	Endocrine dysfunction: Panhypopituitarism 23 (48%) Hypocortisolism 8 (17%) Hypothyroidism 8 (17%) Hypogonadism 6 (13%) Cushing 1 (2%) Acromegaly 1 (2%) Normal 9 (19%)	- Cranial nerve palsy Improved: 13 (72%) Stable: 2 (11%) No improvement: 3 (17%) - Endocrinological outcome: Improved: 10 (21%) Stable: 16 (33%) New onset panhypopituitarism: 3 (6%) 22 (48%) of patients with panhypopituitarism
Cavalli <i>et al.</i> (2020) ^[10]	30 (18/12) 10 (33%): emergency surgery (Mean time: 3 days 8 (26.7%): elective surgery (after initial conservative management) Surgery: endoscopic transsphenoidal surgery	- Surgical group: Visual acuity deficit: Emergency: 8 (100%) Elective: 5 (62.5%) Visual field deficit: Emergency: 8 (100%) Elective: 3 (37.5%) Cranial nerve deficit: Emergency: 5 (62.5%) Elective: 2 (25%) Hormonal deficit: Emergency: 8 (100%) Elective: 7 (87.5%) Conservative group: Visual acuity 6 (50%) Visual field 3 (25%) Cranial nerve deficit: 7 (58.3%) Hormonal deficit: 11 (96.6%)	- Surgical group: Visual acuity: Emergency: 6/8 (75%) Elective: 1/5 (20%) Visual field: Emergency: 7/8 (87.5%) Elective: 0/3 (0%) Cranial nerve deficit: Emergency: 4/5 (80%) Elective: 1/2 (50%) Conservative group: Visual acuity: 4/5 (80%) Visual field: 2/3 (66.6%) Cranial nerve deficit: 4/6 (66.6%) There was no significant difference in hypopituitarism rates between the treatment groups.
Sun <i>et al.</i> (2021) ^[26]	24 (all treated surgically through an endoscopic transsphenoidal approach)	- Visual acuity deficit: 18 (75%) - Visual field deficit: 8 (33.3%) - Cranial nerve deficit: 7 (29.2%) - Hormonal deficit: Hypopituitarism: 10 (41.6%) 7 (29.1%)	- Visual deficit improved in 17 (94.4%) of patients (1 patient with complete loss of vision did not improve) - Ophthalmoplegia resolved in all patients - Hypopituitarism: Improved to varying degrees: Five patients recovered with no replacement needed. Six patients: Biochemical cure (Bromocriptine given to one patient with prolactinoma)
Current study (2022)	45 (all treated surgically through an endoscopic transsphenoidal approach)	- Visual deficit: 45 (100%) patients 61 (67.8%) eyes: Partial visual deficit 29 (32.2%) had a severe visual deficit - Ocular cranial neuropathy: 22 (48.9%) Unilateral: 5 (11.1%) Bilateral: 17 (37.8%) - Hormonal deficiency: Panhypopituitarism 11 (24.4%) Low cortisol 45 (100%) Hypothyroidism 14 (31.1%) Hypogonadism: 11 (24.4%) Hyperprolactinemia: 16 (35.6%)	- Visual recovery: Complete: 39 (86.7%) patients Incomplete: 6 (13.3%) patients All eyes (61/61) with a partial visual deficit had a complete recovery. 23/29 eyes with severe visual deficit showed complete recovery. Ocular cranial neuropathy recovery: Complete: 17 (77.2%) Incomplete: 5 (22.7%) Hormonal recovery: Panhypopituitarism: no recovery Isolated hypocortisolism: 16 (35.5%)

(Contd...)

Table 4: (Continued).

Study (Ref. no.)	Number of patients (surgical/conservative)	Patient characteristics	Outcome
		Known history of pituitary adenoma 7 (15.6%) Nonfunctioning 29 (64.4%)	Hypothyroidism: 9 (64%) Hypogonadism: no recovery Hyperprolactinemia: Complete regression in 14 (87.5%) Transient diabetes insipidus: 9 (20%); 2 (4.4%) patients requiring long- term hormonal replacement.

comparable to those published in the literature and treated beyond the 72 h period. Hence, it can be noted that patients with a significant visual deficit should undergo surgery on presentation even though delayed surgical results seem to match early surgery. It seems that a significant prognostic factor can be related to the degree of visual deficit, which, in turn, reflects the degree of optic apparatus compression and consequent potential damage. This, however, does not imply delaying surgery or not offering surgery for patients presenting late as the duration of irreversible damage as it relates to symptom duration and degree of optic apparatus compression is not clearly identified in the literature. One study suggests that surgical intervention after 1 week of symptom presentation can significantly impact postoperative visual field improvement.^[6] Another study by Souter *et al.*^[25] showed that a longer time to surgery is associated with a worse outcome.

In the current series, ocular cranial neuropathy recovery had a statistically significant ($P < 0.05$) favorable outcome if symptoms were unilateral as opposed to bilateral. This may be explained by the degree of cavernous sinus compression, with a more significant compression causing bilateral symptoms. Recovery was still favorable in both groups with a complete recovery occurring in 17 (77.2%) patients and incomplete recovery in 5 (22.7%) patients. This compares to similar published outcomes as outlined in Table 4.

Endocrine results were, however, less favorable, with preoperative panhypopituitarism and hypogonadism showing as statistically significant negative prognostic factors for recovery. Hormonal recovery did occur in 16 (35.5%) in patients hypocortisolism (not part of panhypopituitarism) and 9 (64%) patients with hypothyroidism. Accordingly, most patients received long-term hormonal replacement therapy which is a similar outcome to prior studies. This may be related to the sudden massive necrosis of the pituitary gland with panhypopituitarism indicative of the greatest necrotic effect and, hence, the lack of any hormonal recovery. Many of the studies as outlined in Table 4 did not show a statistically significant hormonal recovery difference between conservatively managed patients and those surgically managed, despite an important overlooked difference in the

size of tumor in both groups (smaller tumors less likely to significantly compromise the optic chiasm and hence more likely to be managed conservatively). This may indicate that hormonal recovery relates more to the initial damage done. There are, however, some surgical studies as by Teixeira *et al.*^[27] reporting improved hormonal recovery in the surgical group over the conservative group. This has been explained in terms of pituitary dysfunction related to compression, which is relieved by surgery, with the knowledge that the pituitary gland remains capable of secreting adequate amounts of hormones when as little as 10% of residual tissue remains.^[28] This entails careful pituitary gland preservation during surgical resection. Then again, panhypopituitarism more likely implies a significant pituitary gland necrosis rather than a compressive element. This, in turn, points to the importance of pituitary gland identification and preservation during surgery. As noted by Souter *et al.*,^[25] the gland can be identified at the margin of the tumor resection by subtle differences in the color, tendency to bleed, and consistency. In the current series, the posterior pituitary gland function preoperative was preserved, with postoperative transient diabetes insipidus occurring in 9 (20%) patients and 2 (4.4%) patients requiring long-term hormonal replacement.

In terms of the degree of resection, 33 (73.3%) patients had a gross total resection with no statistical significance to visual, ocular cranial neuropathy, or hormonal recovery as compared to a subtotal resection. Tumors with a subtotal resection were related to cavernous sinus and retrosellar extensions indicating that adequate optic apparatus decompression was performed in all cases. The differences in visual outcome as it relates to tumor size were also not statistically significant ($P > 0.05$). There was also no statistical significance ($P > 0.05$) to ocular nerve palsy recovery as it relates to parasellar extension.

Postoperative complications were minor and related to nasal complications occurring in 14 (31%) patients. Only one patient had a significant CSF leak and pneumocephalus causing alteration of his conscious level, requiring urgent revision surgery with a pedicled nasoseptal flap augmented repair. This patient harbored a tumor with a suprasellar extension penetrating the diaphragma sella with a tumor

bud extending into the subarachnoid space (a proposed modification of the SIPAP classification of Grade 3s). It is worth noting that Grade 3s tumors pose a risk for a high-flow CSF leak and hence an upfront preparation of pedicled nasoseptal flap for closure would be best for closure.

CONCLUSION

The current series of 45 patients with pituitary macroadenoma presenting with acute pituitary apoplexy treated with endoscopic transsphenoidal resection within 72 h of presentation showed safety in terms of low complication rate and efficacy in terms of clinical outcome. The significant prognostic factor related to visual recovery was the degree of preoperative visual deficit. Recovery of ocular cranial neuropathy showed a higher recovery rate when it was unilateral as opposed to bilateral. Pituitary hormonal recovery was less favorable with pituitary panhypopituitarism being a poor prognostic factor.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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