Pituitary Apoplexy: Results of Surgical and Conservative Management Clinical Series and Review of the Literature

Joao Paulo Almeida[1,4], Miguel Marigil Sanchez[1], Claire Karekezi[1], Nebras Warsi[1], Rodrigo Fernández-Gajardo[5], Jyoti Panwar[3], Alireza Mansouri[1], Suganth Suppiah[1], Farshad Nassiri[1], Romina Nejad[1], Walter Kucharczyk[3], Rowena Ridout[2], Andrei F. Joaquim[4], Fred Gentili[1], Gelareh Zadeh[1]

■ OBJECTIVE: **Pituitary apoplexy is associated with visual, cranial nerve, and endocrine dysfunction. In this article, the results of surgical and conservative management of pituitary apoplexy in a single center are evaluated and a review of the literature is presented.**

■ METHODS: **A retrospective analysis was made of patients with pituitary apoplexy who underwent surgery or conservative management at our center between January 2007 and June 2017. Surgery was typically selected for patients who presented with acute deterioration of visual status and/or level of consciousness. Patients with no visual field deficit and those who had medical contraindications to undergo a surgical procedure because of previous comorbidities typically had conservative treatment. Baseline characteristics and clinical and radiologic outcomes were reviewed. A review of the literature (1990–2018) was performed according to PRISMA guidelines. Studies comparing the results of conservative and surgical management were identified. Visual, cranial nerve, and endocrine outcomes and tumor recurrence were analyzed.**

■ RESULTS: **Forty-nine patients (73.1%) were managed surgically and 18 (26.9%) conservatively. After careful case selection, patients underwent surgical or conservative treatment. Patients who underwent conservative treatment had fewer visual deficits. At diagnosis, visual deficit (38.8% vs. 75.5%; *P* = 0.008) and cranial nerve palsy (27.7% vs. 51%; *P* = 0.058) were less common in the conservative group. Conservative and surgical treatments had similar visual and cranial nerve improvement rates (75% vs. 58.3%, *P* = 0.63 and 75% vs. 69.2%, *P* = 1.0, respectively). In the conservative group, tumor shrinkage was observed in 76.4% of cases. The systematic review retrieved 11 studies. No significant difference between conservative and surgical treatment for clinical outcomes (visual field recovery, odds ratio [OR], 1.45; 95% confidence interval [CI], 0.72–2.92; cranial nerve recovery, OR, 2.30; 95% CI, 0.93–5.65; and hypopituitarism, OR, 1.05; 95% CI, 0.64–1.74) or tumor recurrence (OR, 0.68; 95% CI, 0.20–2.34) was observed.**

■ CONCLUSIONS: **A tailored approach to pituitary apoplexy, one that does not include an absolute need for surgery, is appropriate. Conservative management is appropriate in selected patients presenting without visual deficits.**

INTRODUCTION

Pituitary apoplexy is generally used to define the constellation of neurologic symptoms and endocrine deficits that develop secondary to hemorrhage and/or infarction of a preexisting pituitary lesion, with a reported incidence among pituitary adenoma series of 0.6%–13%.[1-8] It is an uncommon but potentially fatal clinical syndrome characterized by sudden onset of headache, nausea and vomiting, visual deterioration, cranial nerve palsies, and, in some cases, loss of consciousness, most often as a consequence of loss of pituitary hormonal support. This

Key words
- Apoplexy
- Conservative
- Endoscopy
- Pituitary tumor
- Transsphenoidal

Abbreviations and Acronyms
CI: Confidence interval
CT: Computed tomography
MRI: Magnetic resonance imaging
OR: Odds ratio

From the Divisions of [1]Neurosurgery and [2]Endocrinology, Toronto Western Hospital and [3]Department of Radiology, University of Toronto, Toronto, Ontario, Canada; [4]Division of Neurosurgery, Department of Neurology, State University of Campinas (UNICAMP), Campinas, Brazil; and [5]Department of Neurological Sciences, University of Chile, Santiago, Chile

To whom correspondence should be addressed: Joao Paulo Almeida, M.D. [E-mail: jpaulocavalcante@yahoo.com.br]

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entity places the patient at a high risk of long-term endocrine and neurologic deficits and, potentially, death if symptoms progress without appropriate treatment.[1,7]

Although surgery is the recommended intervention in most cases,[3,9,10] the exact timing of surgery is controversial. Previous reports have studied different timing (<3, >3, and >7 days from presentation) with variable results on clinical outcomes.[11-15] Moreover, some have questioned the overall concept of the need for surgery altogether.[16-18]

Considering this level of controversy, there are no clear guidelines on selecting the ideal candidates for conservative management. This situation has implications on the design of much-needed prospective series along with patient counseling.

In the current study, we evaluate clinical outcomes in patients allocated to conservative management compared with those undergoing surgical intervention at a single center. Outcomes are discussed in the context of our institutional patient selection criteria. In addition, a systemic review has been conducted to determine the range of management strategies and outcomes within the literature. Based on knowledge gleaned from this evaluation, we propose criteria for allocation of patients with pituitary apoplexy to conservative management.

METHODS

Study Design

Institutional research ethics board approval was obtained (research ethics board, University Health Network number 17-6005, Toronto, Ontario, Canada). A retrospective chart review of all consecutive patients diagnosed with pituitary apoplexy and treated at our center from January 2007 to June 2017 was performed. Our results are reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Patient Population

Patients were identified through review of our institutional pituitary surgery and radiology databases. Only patients who presented with symptoms related to pituitary apoplexy (i.e., acute headache and nausea/vomiting, visual deficit, cranial nerve deficits, endocrine deficits, and/or deterioration of level of consciousness) and with magnetic resonance imaging (MRI) or computed tomography (CT) scans suggestive of pituitary apoplexy were included in the study. Patients were categorized into those undergoing surgical intervention and those who were allocated to conservative management. Clinical data, such as age, gender, symptoms at diagnosis, treatment modality (surgery or conservative treatment), timing to surgery (≤3 days or >3 days), complications, neurologic and endocrine outcomes, adjuvant therapies, and recurrence were reviewed. Those with <3 months of follow-up were excluded.

Clinical Evaluation

Clinical data were obtained from chart review and based on documented neurologic examination performed in our center, at first assessment and follow-up visits. Specifically, level of consciousness, visual status, and cranial nerve function were systematically recorded. Endocrine evaluation included measurements of serum cortisol, adrenocorticotropic hormone, prolactin, thyroid-stimulating hormone, free thyroxine, growth hormone, insulinlike growth factor 1, luteinizing hormone, follicle-stimulating hormone, and testosterone/estradiol levels at admission, before hospital discharge, and at follow-up assessments.

Follow-up assessments were generally performed 6–8 weeks after surgery, at 3-month to 6-month intervals for the first year, and at 6-month to 12-month intervals thereafter.

Radiologic Evaluation

Unless contraindicated, all patients had an MRI scan at diagnosis. Those with contraindications had a CT scan (1 patient). Patients in the surgical group typically underwent CT scans on postoperative day 1 for assessment of potential surgical complications. Follow-up MRI scans were usually performed 3–6 months after treatment for assessment of extent of resection, and then at a yearly interval. A neuroradiologist reviewed all images of patients included in the study. Characteristics such as largest diameter of tumor, volume, cavernous sinus invasion, extension into the suprasellar space and extent of resection, and tumor characteristics at follow-up were reviewed. Tumor volume was manually calculated based on the largest diameters of the tumor according to the formula $A \times B \times C/2$. The Knosp classification[19] was applied to evaluate the relationship of the tumor with the cavernous sinus. Tumors classified as Knosp ≥3 were considered to be invading the cavernous sinus.

Treatment Selection

The decision to proceed with surgery or conservative management was based on the clinical status of the patient at the discretion of the treating surgeon. Surgery was typically selected for patients who presented with acute deterioration of visual status and/or level of consciousness. Patients with no visual deficit and those who had medical contraindications to undergo a surgical procedure because of previous comorbidities typically had conservative treatment. If surgical treatment was selected, the procedure was performed in the 24 hours after the initial assessment at our center.

Surgical Management

All patients in the surgical group underwent tumor resection via a standard endoscopic endonasal transsphenoidal approach, as previously described.[20] Tumor was resected with microcurettes and suction, in a piecemeal fashion, or in an extracapsular fashion, when possible. Routine nasoseptal flap closure was augmented with collagen-based dural graft (Duragen [Integra, Oakville, Ontario, Canada]). Patients were admitted to the intensive care unit after surgery and monitored for development of diabetes insipidus and postoperative complications. Extent of resection was assessed according to the results of postoperative scan and classified on gross total resection, if no residual tumor was observed; subtotal resection, if >90% and <100% resection was achieved; and partial resection, if <90% resection was achieved.

Conservative Management

Medical treatment typically consisted of close assessment of vital signs and neurologic status as well as monitoring of urinary

output, fluid balance, and sodium levels in a monitored nursing unit. Hypocortisolism was managed with hydrocortisone 50 mg intravenously every 6 hours in the first 48 hours and then oral replacement; levothyroxine and desmopressin were used in cases of hypothyroidism and diabetes insipidus, respectively. Once clinically stable, patients were discharged and followed in our outpatient pituitary clinic.

Statistical Analysis

Statistical analysis was performed using SPSS (version 22.0 [IBM Corp., Armonk, New York, USA]). Descriptive analyses are reported as counts (and proportions) and means (standard deviation) or medians (interquartile range) depending on the distribution of the data. Associations between the effect of treatment modality (surgery vs. conservative treatment), timing of surgery, and symptoms at diagnosis on clinical outcomes at follow-up were calculated using a χ^2 or Fisher exact test for categorical variables. Comparisons were presented as odds ratio (OR) along with the 95% confidence interval (CI). Parametric continuous variables were compared using independent-sample t test. Nonparametric analysis continuous variables were performed using the Mann-Whitney U test. The statistical threshold for significant was set at $\alpha = 0.05$ unless otherwise indicated.

Review of the Literature

A systematic review of the literature was performed using the MEDLINE database through PubMed, from January 1990 to January 2018. The terms "pituitary" AND "apoplexy" were used for the search. The review was limited to studies published in English, and humans were specified as the study category. The date of the last search was February 11, 2018. Clinical studies that reported outcomes of both treatment options (i.e., conservative and surgical treatment) for pituitary apoplexy were eligible for analysis. Editorials, commentaries, and review articles were excluded. For meta-analysis purposes, articles that focused exclusively on the results of surgical treatment were excluded.

Included studies were reviewed for study design, methodology, patient characteristics, and treatment outcomes. Data were extracted and divided into patient cohorts according to treatment strategy (surgery or conservative management). Clinical presentation (presence of visual field deficits; cranial nerve deficits; and hypopituitarism), clinical outcomes (complete visual field and cranial nerve recovery and hypopituitarism at last follow-up), and tumor recurrence were assessed. The results of our current series were included in the pooled analyses. The flow diagram of the selection of studies is shown in Figure 1, in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[21]

The quantitative meta-analysis was conducted with Review Manager (version 5.3 [The The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, 2014]). Statistical heterogeneity was tested through the χ^2 test (i.e., Cochrane Q test) and a P value $\leq$0.20 was used to indicate the presence of heterogeneity. In the case of lack of heterogeneity, fixed-effects models were used for the meta-analyses. If heterogeneity was present ($P \leq 0.20$), then, random-effects models were used for the meta-analyses. Each analysis was expressed as binary proportions with exact 95% CI. The data collected through the systematic review represent a pool of clinical series and make our review a synthesis of level 3 evidence only.

RESULTS

Institutional Population Characteristics

A total of 67 patients were included in the study. Most patients were men ($n = 41$, 61.2%) and had no previously known history of a pituitary lesion ($n = 51$, 76.1%). The mean age was 57.4 $\pm$ 16.2 years and the mean follow-up was 34.4 $\pm$ 26 months. Forty-nine patients (73.1%) were managed surgically, whereas 18 patients (26.9%) were managed conservatively (Table 1).

The surgical group was composed of 32 men (65.3%) and 17 women (34.7%) and had a median age of 58.8 $\pm$ 14.9 years. Only 8 patients in this group (16.3%) had a previous diagnosis of a pituitary lesion. At diagnosis, acute headache was the most common symptom reported ($n = 44$, 89.8%), followed by visual deficit (75.5%) and hypopituitarism (64.3%). When patients were divided into 2 subgroups, there was a trend for those in the early group (surgery $\leq$3 days) to present with altered level of consciousness (22.7% vs. 7.4%; $P = 0.21$) and cranial nerve deficits (63.8% vs. 48.1%; $P = 0.14$) more commonly than patients in the late group (>3 days), although this was not statistically significant (Table 2).

Patients who did not undergo surgical treatment represented 26.9% ($n = 18$) of the study cohort. Compared with the surgical group, these patients were more likely to have a previously known pituitary adenoma ($n = 8$, 44.4% vs. $n = 8$, 16.3%; $P = 0.02$). Visual deficit was less common ($n = 7$, 38.8% vs. $n = 37$, 75.5%; $P = 0.008$) and there was a trend for cranial nerve palsy to be less common in this group ($n = 5$, 27.7% vs. $n = 27$, 51%; $P = 0.058$, respectively) (Table 1). Nonsecreting tumors represented 77.8% ($n = 14$) of the cases, whereas the remaining 22.2% ($n = 4$) were prolactinomas.

Tumor characteristics were different in the surgical and conservative groups, as shown in Table 1. Adenomas in the conservative group had smaller sizes and volumes (2.25 $\pm$ 0.6 cm vs. 2.79 $\pm$ 0.6 cm, $P = 0.04$ and 4.41 $\pm$ 0.3cm^3 vs. 8.38 $\pm$ 0.7cm^3, $P = 0.02$, respectively) and were less associated with optic chiasm compression (55.6% vs. 95.9%; $P = 0.001$).

Clinical Outcomes

Surgical Group. Endoscopic transsphenoidal surgery achieved gross total, subtotal, and partial resection in 41 (83.7%), 7 (14.3%), and 1 (2.0%) of patients, respectively. No intraoperative complications were reported. Pathologic adenoma subtypes were gonadotroph ($n = 28$; 57.1%), silent corticotroph ($n = 7$; 14.2%), null cell ($n = 3$; 6.12%), silent somatotroph ($n = 2$; 4.0%), silent lactotroph ($n = 1$; 2.0%), and Pit-1 adenomas ($n = 1$; 2.0%); in 7 patients (14.2%), only necrotic/hemorrhagic tissue was obtained.

After surgery, 3 patients had cerebrospinal fluid leaks; 1 patient was managed with lumbar drainage for 5 days and 2 patients required reoperation for correction of the leak. There was 1 case of death secondary to myocardial infarction and cardiogenic shock after surgery in a 64-year-old patient who had multiple comorbidities, including hypertension, chronic pulmonary obstructive disease, and chronic renal failure.

Results of postoperative visual field tests of 48 patients were available for review (Table 3). No patient experienced visual decline attributable to surgery. At last follow-up (median, 39.8 $\pm$

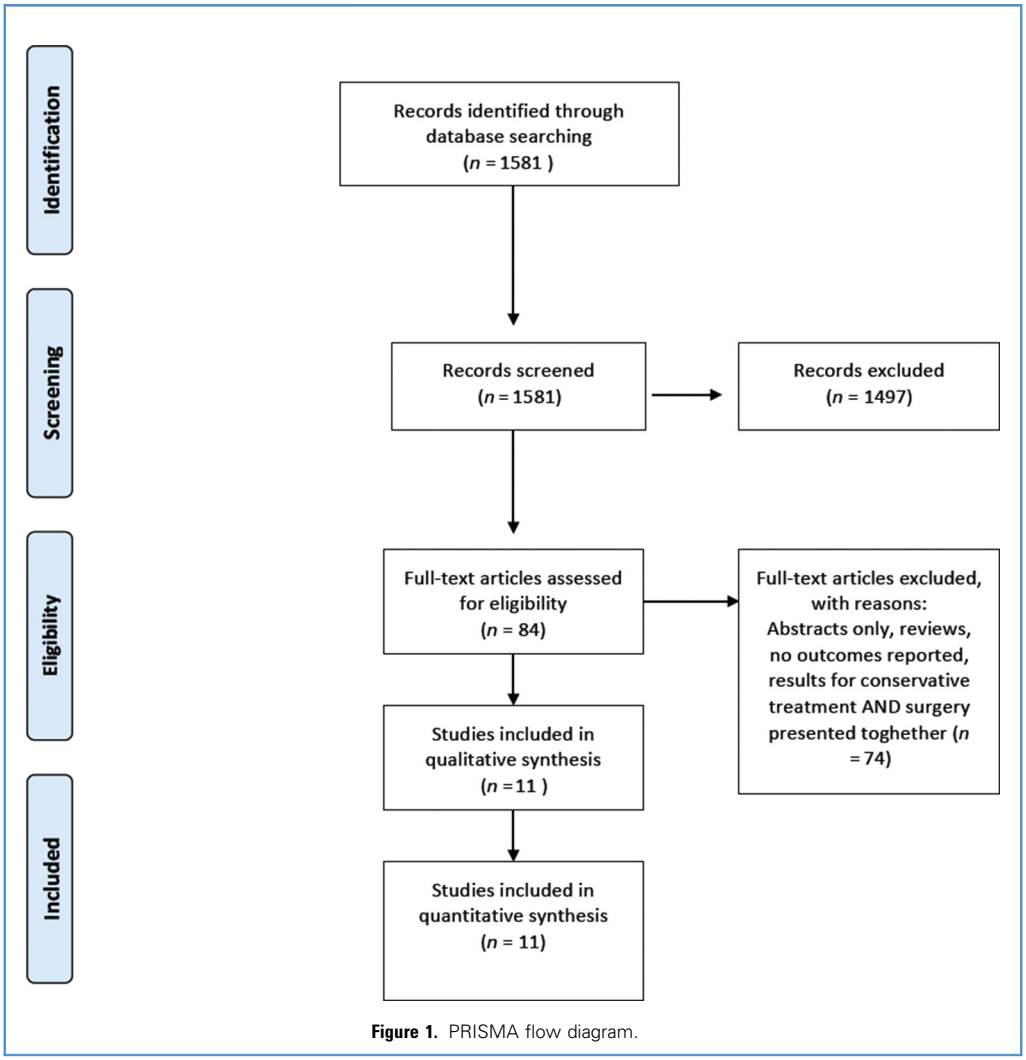

Figure 1. PRISMA flow diagram.

32 months), 58.3% of those with preoperative visual field deficits achieved full recovery. Timing of surgery did not affect visual outcomes ($P = 0.59$). Patients who achieved complete visual recovery had similar latency to surgery compared with those who had partial visual recovery (complete recovery, 6.95 ± 8.2 days vs. partial recovery, 7.09 ± 8.3 days; $P = 0.96$).

Surgery led to complete or partial recovery of cranial nerve deficits in 18 patients (69.2%) and 8 patients (38.4%), respectively (Table 3). No patient developed new cranial nerve palsy after surgery. Timing of surgery did not influence cranial nerve recovery.

The impact of surgery on the hormonal outcomes of patients was limited (Table 3). Of 18 patients who had normal hormonal function at diagnosis, 1 (5.6%) developed hypocortisolism, 1 (5.6%) hypothyroidism, and 3 (16.7%) panhypopituitarism. One (5.5%) and 3 (16.7%) patients, respectively, had preoperative panhypopituitarism ($n = 18$) had complete or partial (≥ 1 hormonal axis) restoration of the hormonal function. Postoperative transient and permanent diabetes insipidus were reported in 5 patients (10.2%) and 3 patients (6.25%), respectively.

Tumor recurrence requiring reoperation was identified in 4 patients (8.3%) (18 months and 6, 7, and 12 years after the initial surgery). Radiotherapy was in addition used in 2 of those patients (4.1%) for treatment of recurrent tumors. Stable residual tumor, which did not require further intervention, was observed in 7 patients (14.5%).

Conservative Group. Overall, conservative management yielded similar visual, cranial nerve, and endocrine outcomes as surgical intervention (Table 3). Among 17 patients allocated to conservative management with visual field assessments at last follow-up, 15 (88.2%) had normal visual status; 11 (73.3%) of these had a normal visual examination result on presentation and 4 (26.6%) presented with deficits. Of patients who presented with cranial nerve palsy, 3 (75%) had complete and 1 (25%) had partial recovery (Table 3).

Of 17 patients followed in the conservative group, 9 (52.9%) had normal pituitary function at last follow-up. Partial pituitary function recovery was observed in 3 patients, whereas complete recovery at last follow-up was observed in 1 patient. One patient

required long-term hormonal replacement with desmopressin for management of permanent diabetes insipidus.

Postoperative imaging follow-up identified 2 patients (11.7%) with tumor progression (mean, 27.05 ± 19 months). One of those patients had complete tumor regression 3 months after the ictus and no signs of recurrence for 32 months, when she then presented with new tumor growth. Shrinkage of the tumor was observed in 13 patients (76.4%) and 2 (11.7%) had a residual lesion that remained stable during follow-up.

Four patients with prolactinoma were included in this group; however, only 3 patients could be followed. One 72-year-old patient with an invasive prolactinoma died secondary to complications of a massive sellar/suprasellar hemorrhage with subarachnoid and intraventricular extension and hydrocephalus. This patient presented with decreased level of consciousness, Glasgow Coma Scale score 3, being intubated at admission. An external ventricular drain was inserted; however, the patient progressed with worsening of symptoms and died 3 days after the onset of symptoms. The other 3 patients with prolactinoma received medical therapy and achieved tumor regression and disease control. If prolactinomas are excluded, 8/14 patients (57.1%) had complete tumor regression at last follow-up. Tumor largest diameter (2.2 ± 0.3 vs. 2.0 ± 0.4 cm; $P = 0.38$) and volume (4.3 ± 2.6 vs. 2.3 ± 1.3 cm^3; $P = 0.33$) had no impact on complete tumor regression rates.

Systematic Review

Included Studies. A total of 84 published studies were identified through our initial search. After review, 11 retrospective series were selected (range, 12–87 patients in each study)[8,10,16-18,22-27] (**Figure 1**). The combination of those studies with our current series resulted in a population of 506 patients for analysis (**Tables 4–6**). The data collected through the systematic review represent a pool of clinical series and make our systematic review a synthesis of level 3 evidence only. Characteristics of the included studies and a summary of individual findings are reported in **Table 4**.

The proportion of visual field deficits at diagnosis was significantly different between the groups. Patients who underwent conservative treatment had a lower proportion of visual field deficits than did those who underwent surgical treatment (36.9% vs. 62.6%; $P = 0.004$; OR, 0.33; 95% CI, 0.15–0.69), whereas cranial nerve deficits/ocular palsy (conservative, 43.5% vs. surgery, 52.7%; $P = 0.13$) and hypopituitarism rates (conservative, 72.2% vs. 77.4%; $P = 0.07$) at baseline were similar between groups.

Effects of Intervention. Most studies did not observe a statistically significant difference in visual, cranial nerve, or endocrinologic outcomes of patients who underwent surgery or conservative treatment[8,10,16-18,23-25] (**Figure 2**).

Visual Recovery. It was possible to retrieve data from 9 studies (196 patients with visual field deficits at diagnosis). No significant statistical difference between conservative and surgical treatment was observed (OR, 1.45; 95% CI, 0.72–2.92).

Cranial Nerve Recovery. Data were retrievable from 8 studies (185 patients with cranial nerve deficits at diagnosis). No significant statistical difference between conservative and surgical treatment was observed (OR, 2.30; 95% CI, 0.93–5.65).

Hypopituitarism. Data of 381 patients from 8 studies were extracted for analysis of rates of hypopituitarism secondary to pituitary apoplexy. According to these data, at last follow-up, hypopituitarism rates were similar between surgical and conservative groups (OR, 1.05; 95% CI, 0.64–1.74).

Tumor Recurrence. Nine studies (369 patients) were included for analysis. Based on the extracted data, tumor recurrence rate was similar between those submitted to surgery and those who underwent conservative treatment (OR, 0.68; 95% CI, 0.20–2.34). Only 4 studies reported rates of tumor regression after pituitary apoplexy[10,23,24,26] and only our series and another study reported rates of complete tumor regression (57%) (**Table 6**).

DISCUSSION

Surgery has classically been considered the gold standard treatment for pituitary apoplexy.[12,25,28-31] However, in the last decades, with a better understanding of pituitary apoplexy, there has been

Table 1. Baseline Characteristics

Patients and Tumor Characteristics	Surgical Treatment	Conservative Treatment	*P*
Age (years)	58.8 (±14.9)	53.8 (±19.4)	0.27
Gender			0.25
Male	32 (65.3)	9 (50)	
Female	17 (34.7)	9 (50)	
Known pituitary adenoma	8 (16.3)	8 (44.4)	0.02*
Symptoms			
Headache	44 (89.8)	16 (88.9)	0.91
Hypopituitarism	31 (64.3)	9 (50)	0.40
Visual decline	37 (75.5)	7 (38.8)	0.008*
CN palsy	27 (55.1)	5 (27.7)	0.057
III CN	14 (28.6)	3 (16.7)	
VI CN	7 (14.3)	1 (5.6)	
Multiple CNs	6 (12.2)	1 (5.6)	
Altered level of consciousness	7 (14.3)	3 (16.7)	1.00
Tumor characteristics			
Size (cm)	2.79 (±0.6)	2.25 (±0.6)	0.04*
Volume (cm^3)	8.38 (±0.7)	4.41 (±0.3)	0.02*
Knosp classification			0.02
0	2 (4.1)	5 (27.8)	
I	17 (34.7)	3 (16.7)	
II	15 (30.6)	8 (44.4)	
III	11 (22.4)	1 (5.6)	
IV	4 (8.2)	1 (5.6)	
Cavernous sinus invasion	15 (30.6)	2 (11.1)	0.12
Optic chiasm compression	47 (95.9)	10 (55.6)	0.001*

Values are number (%) except where indicated otherwise.
CN, cranial nerve.
*Statistically significant ($P < 0.05$).

Table 2. Baseline Characteristics: Early Versus Late Surgery

Patients and Tumor Characteristics	Surgical Timing ≤3 days (N = 22)	Surgical Timing >3 days (N = 27)	P
Age (years)	59.8 (±16.3)	58 (±13.9)	0.67
Gender			0.25
Male	15 (62.8)	17 (63)	
Female	7 (38.2)	10 (37)	
Known pituitary adenoma	3 (37.5)	5 (62.5)	0.71
Symptoms			
Headache	20 (90.9)	24 (88.8)	0.59
Visual decline	17 (77.2)	20 (74)	0.53
Hypopituitarism	13 (59)	18 (66.6)	0.76
Cranial nerve palsy	14 (63.8)	13 (48.1)	0.14
Altered level of consciousness	5 (22.7)	2 (7.4)	0.21
Tumor characteristics			
Size (cm)	3.02 (±0.7)	2.60 (±0.5)	0.02*
Volume (cm^3)	10.2	6.86	0.09
Cavernous sinus invasion†	8 (36.3)	7 (25.9)	0.53

Values are number (%) except where indicated otherwise.
*Statistically significant ($P < 0.05$).
†Patients with Knosp score III and IV were considered as those with cavernous sinus invasion.

Table 3. Clinical Outcomes

Patients and Tumor Characteristics	Surgery Group, n (%)	Conservative Group, n (%)	P
Visual status at diagnosis			0.008*
No visual deficit	12 (24.4)	11 (61.1)	
Visual deficit	37 (75.5)	7 (38.8)	
Early follow-up*			0.67
Partial visual field improvement	17 (35.4)	2 (11.7)	
Complete visual field recovery	19 (39.6)	4 (23.5)	
Stable normal visual field	12 (25)	11 (64.7)	
Last follow-up†			0.63
Worsening	1 (2.1)	0	
No further improvement	3 (6.3)	0	
Partial visual field improvement	11 (22.9)	1 (6.7)	
Complete visual field recovery	21 (43.8)	3 (20)	
Stable normal visual field	12 (25)	11 (73.3)	
Cranial nerve deficit at diagnosis	27 (55.1)	5 (27.7)	0.057
Early follow-up			0.62
No improvement	1 (3.8)	0	
Partial improvement	11 (42.3)	1 (25)	
Complete recovery	14 (53.8)	3 (75)	
Last follow-up‡			1.0
Partial improvement	8 (38.4)	1 (25)	
Complete recovery	18 (69.2)	3 (75)	
Hormonal status at diagnosis			
Hypothyroidism	1 (2.0)	0	
Hypocortisolism	12 (24.5)	0	
Panhypopituitarism	18 (36.7)	9 (50)	
Hormonal function at follow-up*			
Hypothyroidism	2 (4.1)	1 (5.8)	
Hypocortisolism	9 (18.7)	2 (11.7)	
Panhypopituitarism	18 (37.5)	5 (29.4)	
Diabetes insipidus	3 (6.25)	1 (5.8)	

*No result was available for 1 patient in the surgical group and 1 patient in the conservative group. Patients with no visual decline at diagnosis did not have visual deterioration during follow-up.
†Three patients in the conservative group had no data available for assessment of long-term visual outcome.
‡Late follow-up results were available for 26 patients with preoperative deficits in the surgical group and 4 patients in the conservative group.

some debate regarding the best management of this condition, including the impact of timing of surgery and the role of conservative treatment.

Timing of surgery is a frequent point of debate. The results from the available literature are conflicting, with some studies suggesting a potential benefit of early surgery,[28,29,32,33] whereas others have not found statistically different outcomes.[3,17,18,34] In our study, no significant difference in clinical outcomes was noted when patients were stratified according to timing of surgery. Our results show the benefit of surgical treatment in patients with visual deficits, even if the onset of symptoms is not recent. We consider cases presenting with new onset of major visual deficit (bitemporal hemianopsia/amaurosis) to require urgent surgical intervention, by a specialized pituitary surgeon.

The role of conservative management in the treatment of pituitary apoplexy remains controversial. There are differences in the management of pituitary apoplexy around the world. The singular characteristics in the health system and culture of different countries may be responsible, to some extent, for differences in the management of this condition. The socialized universal health system, which is common ground in Western European countries, may facilitate the widespread application of some surgical protocols, whereas the American health system, composed of private practice and independent hospital systems, may allow more differences in the management of this condition. Also, one needs to consider the impact of medicolegal issues on medical practice. That factor may lead to a more aggressive, surgically oriented approach to such cases in regions in which lawsuits are common against surgeons.

Table 4. Review of the Literature. Studies included in the Pooled Analysis

Reference	Total Number (Surgical/Conservative)	Study Design	Study Findings
Ayuk et al., 2004[16]	33 (15/18)	Single center, retrospective	Conservative treatment reserved for patients with no or evidence of resolving visual deficit Similar clinical outcomes and tumor recurrence rates in selected cases Surgical treatment recommended for those with visual deficits
Bonicki et al., 1993[22]	39 (23/16)	Single center, retrospective	High tumor recurrence rate in the conservative group (31%) Better clinical outcomes in the surgical group Investigators concluded that surgical treatment should be used in every pituitary apoplexy case
Bujawansa et al., 2014[9]	55 (33/22)	Single center, retrospective	Patients with visual field deficits more likely to be treated with surgery Similar outcomes after case selection Pituitary apoplexy score >4 may suggest the need of surgical intervention
Giritharan et al., 2016[18]	31 (20/11)	Single center, retrospective	Surgical patients were more likely to present visual decline and ocular palsy Similar outcomes after case selection
Gruber et al., 2006[23]	30 (10/20)	Single center, retrospective	No differences in visual fields or endocrinologic outcomes Conservative treatment had better rates of ophthalmoplegia recovery (83% vs. 67%) Conservative treatment recommended for most patients, but those with progressive visual deterioration
Leyer et al., 2011[24]	44 (19/25)	Single center, retrospective	Similar outcomes after case selection Tumor regression in 80% of patients in the conservative group Except patient with severe visual deficits, conservative treatment may be selected for most patients
Lubina et al., 2005[25]	40 (34;C: 6)	Single center, retrospective	Similar outcomes after case selection Tumor shrinkage in 66% of tumors in the conservative group Surgical treatment recommended for those with visual deficits; conservative treatment in selected cases
Maccagnan et al., 1995[26]	12 (5/7)	Single center, prospective	Patients who underwent conservative treatment had recovery of cranial nerve function in 85% of cases Complete tumor regression in 57% of patients in conservative group Conservative treatment useful in selected cases who do not present with severe visual deficits
Sibal et al., 2004[9]	45 (27/18)	Single center, retrospective	Similar outcomes after case selection Patients with visual field deficits more likely to be treated with surgery Patients without neuro-ophthalmic signs can be treated conservatively
Singh et al., 2015[10]	87 (69/18)	Single center, retrospective	Similar good outcomes in patients who underwent early and delayed surgery and those treated conservatively Treatment selection is paramount; conservative treatment selected for those without severe neuro-ophthalmic deficits and good response to early medical treatment
Teixeira et al., 2018[27]	23 (14/9)	Single center, retrospective	Similar visual outcomes in patients who underwent endoscopic/microscopic surgery and conservative treatment Better endocrinologic outcomes in the surgical group Endoscopic surgery had better endocrinologic outcomes than microscopic surgery

Table 5. Surgical Group, Pooled Analysis, Characteristics, and Outcomes of Patients Who Underwent Surgery

Reference	N	Visual Field Defect, n (%)*	Cranial Nerve Palsy, n (%)*	Hypopituitarism, n (%)*	Visual Field Complete Resolution, n (%)†	Cranial Nerve Complete Resolution, n (%)†	Hypopituitarism, n (%)†	Tumor Growth /Recurrence, n (%)
Ayuk et al., 2004[16]	15	7 (46)	8 (53)	13 (83)	4 (57)	5 (63)	—	1 (6)
Bonicki et al. 1993,[22]	23	19	—	—	14/19 (73)	—	—	0
Bujawansa et al., 2014[9]	33	13	18 (54)	—	8 (61)	15 (83)	30 (91)	—
Giritharan et al., 2016[18]	20	12 (60)	10 (50)	14/16 (87)	9 (75)	—	18 (90)	4 (20)
Gruber et al., 2006[23]	10	9 (90)	3 (37)	9 (90)	2 (22)	2 (66)	8 (80)	6 (60)
Leyer et al., 2011[24]	19	14 (74)	10 (53)	15 (88)	11 (78.5)	6 (60)	13 (84)	0
Lubina et al., 2005[25]	34	12 (35)	14 (41)	—	—	10 (71)	29 (86)	0
Maccagnan et al., 1995[26]	5	—	—	—	—	—	—	1 (20)
Sibal et al., 2004[8]	27	16/25 (64)	14/26 (54)	21/24 (87)	7 (43)	9 (64)	22 (81)	1 (4)
Singh et al., 2015[10]	69	35 (50.7)	41 (59)	—	31 (88)	23/28 (82)	36 (52)	4 (5.7)
Teixeira et al., 2018[27]	14	13	—	—	10 (76)	—	5 (35)	1 (7.1)
Current series	49	37 (75)	27 (55)	31 (64.3)	21/36 (58)	18/26 (69)	30 (62)	4/48 (20)

*At diagnosis.
†At follow-up.

Table 6. Conservative Group

Reference	N	Visual Field Defect, n (%)*	Cranial Nerve Palsy, n (%)*	Hypopituitarism, n (%)*	Visual Field Complete Resolution, n (%)‡	Cranial Nerve Complete Resolution, n (%)‡	Hypopituitarism, n (%)‡	Tumor Growth/Recurrence, n (%)	Tumor Regression, n (%)
Ayuk et al., 2004[16]	18	6 (33)	7 (39)	13 (87)	6 (100)	7 (100)	—	1 (5)	—
Bonicki et al., 1993[22]	16	—	0	—	—	—	3 (18)	5 (31)	—
Bujawansa et al., 2014[9]	22	10 (45)	15 (68)	—	8 (80)	15 (100)	20 (91)	—	—
Giritharan et al., 2016[18]	11	6 (55)	2 (18)	8 (73)	5 (83)	—	8 (73)	0	—
Gruber et al., 2006[23]	20	16 (80)	12 (60)	15 (75)	8 (50)	10 (83)	19 (95)	0	18/19 (94.7)
Leyer et al., 2011[24]	25	5 (20)	11 (44)	20/23 (87)	5 (100)	10 (90)	14 (63)	4/24 (16)	17/21 (80)
Lubina et al., 2005[25]	6	3 (50)	2 (33)	—	2 (66)	1 (50)	—	0	4/6 (66)
Maccagnan et al., 1995[26]	7	—	7	—	—	6 (85)	—	1 (14.2)	4 (57.1)†,‡
Sibal et al., 2004[8]	18	4 (24)	8 (47)	13 (72)	3 (75)	6 (75)	16 (89)	4 (22)	—
Teixeira et al., 2018[27]	9	1	—	—	0 (0)	—	8 (88)	0	—
Singh et al., 2015[10]	18	3 (16.6)	6 (33.3)	15 (82)	2 (66)	4/4 (100)	9 (50)	0	7/13 (53.8)
Current series	18	7 (38)	5 (27)	9 (50)	3/4 (75)	3/4 (75)	9/17 (52)	1/17 (5.8)	13/17 (76.4) 8/14 (57)†,‡

*At diagnosis.
†At follow-up.
‡Complete tumor regression.

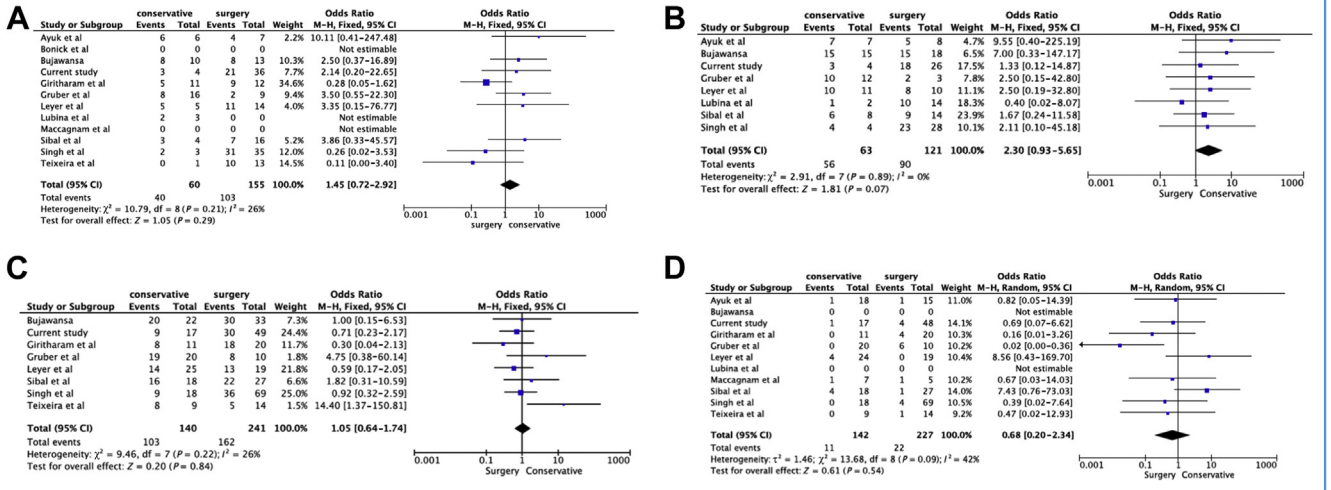

Figure 2. Surgery and conservative treatment results. Pooled analysis. (**A**) Visual field complete recovery, (**B**) cranial nerve complete recovery, (**C**) hypopituitarism, and (**D**) tumor recurrence rate. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

A major concern regarding postponing or not performing surgical treatment is the possibility of visual, cranial nerve, and endocrine deterioration. However, there is a tendency to select conservative treatment for those without visual deficits on presentation.[2,3,14] The benefit of conservative treatment in selected cases has been previously reported,[16-18,24] raising the possibility that a subset of patients with pituitary apoplexy may benefit from conservative management, eliminating the need for surgery. The conservative group in our study had fewer patients presenting with visual deficit and there was a tendency to have fewer cranial nerve palsies. Tumors in this group were smaller and fewer patients had compression of the optic chiasm (**Table 1**). These results reflect the philosophy of our department, in which patients with visual deficits (such as bitemporal hemianopsia or more severe visual field deficits) are usually treated surgically. Two exceptional cases were included in this group. One of the patients presented with an acute visual deficit followed by loss of consciousness secondary to hemorrhage of a giant pituitary adenoma and hydrocephalus. An external ventricular drain was inserted; however, the patient presented with no neurologic improvement and died after 48 hours of admission. The second patient presented with reduction of level of consciousness, bitemporal hemianopsia, and third cranial nerve palsy. The patient was selected for surgical treatment; however, the procedure was not performed because of poor clinical status at the time of intubation. The patient received hormonal replacement and was followed clinically. He had a significant recovery at follow-up, with spontaneous tumor regression. Clinical outcomes in this group were similar to the outcomes of the surgical group (**Table 3**). We believe that this finding is mainly a result of patient selection, which is, then, paramount.

Patients with cranial nerve palsy who undergo surgery or conservative treatment have similar rates of recovery, according to our clinical series and systematic review (OR, 2.30; 95% CI, 0.93–5.65). Therefore, we favor conservative treatment for those with cranial nerve palsy and preserved visual function. Patients initially selected for conservative treatment who present with progressive worsening of cranial nerve function may benefit from surgical intervention, although analysis of this subgroup was not possible in this study because of limited data.

Based on the current result, conservative treatment is associated with good outcomes in a selected group of patients with pituitary apoplexy. After case selection, of surgical patients who had higher rates of visual field deficit at diagnosis, there was no significant difference in outcomes of patients who underwent conservative or surgical treatment. These results need to be carefully assessed, considering the treatment selection bias and heterogeneity of patients selected for conservative treatment in the studies included in the analysis. In addition, other factors such as severity and duration of neuro-ophthalmic deficits, age, and comorbidities likely play a role in the neurologic recovery of those patients.

According to previous studies, the recurrence rate/growth of adenomas after pituitary apoplexy is heterogeneous and ranges from 0% to 31%.[8,16,17,23,24,35] In our study, tumor recurrence was similar between groups (OR, 0.68; 95% CI, 0.20–2.34) and results suggest that long-term clinical and radiologic follow-up is required. The surgical group (mean follow-up, 39.8 ± 32 months) had a longer average follow-up than did the conservative group (mean follow-up, 27.05 ± 19 months. Eight patients with nonsecreting adenomas (57.1%) achieved complete regression after apoplexy. Although tumor regression after apoplexy is a described event, specific data about complete tumor regression are scarce and most are case reports.[26,35-38] Our study adds data that support this association. The pathophysiology of this event may be related to ischemia of the residual adenoma, followed by tissue necrosis and tumor regression.[9,39] The different growth behavior of adenomas after apoplexy

may be related to the molecular signature, size, or extent of hemorrhage or infarction of the tumor, but this is still to be defined.

Limitations

Our study results were obtained from a retrospective analysis and have its inherent biases. Although we carefully reviewed the data of all patients included in the study, the small number of patients, especially in the conservative group, may limit the generalization of the results reported in the current study. Longer follow-up is also necessary for analysis of tumor recurrence. The review also has limitations, including but not limited to inclusion of retrospective clinical series only; scarce number of publications; treatment selection bias; and heterogeneity of studies.

The dearth of prospective multicenter studies was highlighted through our systematic review. As described, only single-center studies were found in our review. This factor limits the conclusions of our analysis and shows the importance of further studies in this field. Ideally, a randomized trial would provide stronger evidence to support the decision-making process for the management of pituitary apoplexy. However, ethical concerns may limit the development of such a study. Our institution is part of a multicenter international prospective study that likely will present stronger evidence for the treatment of this condition.

CONCLUSIONS

Adequate treatment selection is paramount in the management of pituitary apoplexy. Endoscopic endonasal surgery is an effective approach for patients with pituitary apoplexy who present with visual deterioration. Conservative treatment may be a viable alternative in patients without associated visual deficit. Pooled analysis of our results and limited available literature suggest that the rate of visual, endocrine, and cranial nerve improvements may be similar, in selected patients, treated with surgery or conservative management. Although conservative treatment is associated with tumor regression in most cases, long-term follow-up is necessary because of risk of recurrences. Therefore, a tailored approach to pituitary apoplexy is appropriate, given that surgery is not always necessary and that in a selected group, conservative management seems to be sufficient.

REFERENCES

1. Onesti ST, Wisniewski T, Post KD. Clinical versus subclinical pituitary apoplexy: presentation, surgical management, and outcome in 21 patients. *Neurosurgery*. 1990;26:980-986.
2. Yang T, Bayad F, Schaberg MR, et al. Endoscopic endonasal transsphenoidal treatment of pituitary apoplexy: outcomes in a series of 20 patients. *Cureus*. 2015;7:e357.
3. Gondim JA, de Albuquerque LAF, Almeida JP, et al. Endoscopic endonasal surgery for treatment of pituitary apoplexy: 16 years of experience in a specialized pituitary center. *World Neurosurg*. 2017;108:137-142.
4. Abbott J, Kirkby GR. Acute visual loss and pituitary apoplexy after surgery. *BMJ*. 2004;329:218-219.
5. Bi WL, Dunn IF, Laws ER Jr. Pituitary apoplexy. *Endocrine*. 2015;48:69-75.
6. Capatina C, Inder W, Karavitaki N, Wass JA. Management of endocrine disease: pituitary tumour apoplexy. *Eur J Endocrinol*. 2015;172:R179-190.
7. Rajasekaran S, Vanderpump M, Baldeweg S, et al. UK guidelines for the management of pituitary apoplexy. *Clin Endocrinol*. 2011;74:9-20.
8. Sibal L, Ball SG, Connolly V, et al. Pituitary apoplexy: a review of clinical presentation, management and outcome in 45 cases. *Pituitary*. 2004;7:157-163.
9. Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary apoplexy. *Endocr Rev*. 2015;36:622-645.
10. Singh TD, Valizadeh N, Meyer FB, Atkinson JL, Erickson D, Rabinstein AA. Management and outcomes of pituitary apoplexy. *J Neurosurg*. 2015;122:1450-1457.
11. Abdulbaki A, Kanaan I. The impact of surgical timing on visual outcome in pituitary apoplexy: literature review and case illustration. *Surg Neurol Int*. 2017;8:16.
12. Chuang CC, Chang CN, Wei KC, et al. Surgical treatment for severe visual compromised patients after pituitary apoplexy. *J Neurooncol*. 2006;80:39-47.
13. Glezer A, Bronstein MD. Pituitary apoplexy: pathophysiology, diagnosis and management. *Arch Endocrinol Metab*. 2015;59:259-264.
14. Zaidi HA, Cote DJ, Burke WT, et al. Time course of symptomatic recovery after endoscopic transsphenoidal surgery for pituitary adenoma apoplexy in the modern era. *World Neurosurg*. 2016;96:434-439.
15. Zaidi HA, Wang AJ, Cote DJ, et al. Preoperative stratification of transsphenoidal pituitary surgery patients based on surgical urgency. *Neurosurgery*. 2017;81:659-664.
16. Ayuk J, McGregor EJ, Mitchell RD, Gittoes NJ. Acute management of pituitary apoplexy—surgery or conservative management? *Clin Endocrinol*. 2004;61:747-752.
17. Bujawansa S, Thondam SK, Steele C, et al. Presentation, management and outcomes in acute pituitary apoplexy: a large single-centre experience from the United Kingdom. *Clin Endocrinol*. 2014;80:419-424.
18. Giritharan S, Gnanalingham K, Kearney T. Pituitary apoplexy—bespoke patient management allows good clinical outcome. *Clin Endocrinol*. 2016;85:415-422.
19. Micko AS, Wohrer A, Wolfsberger S, Knosp E. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *J Neurosurg*. 2015;122:803-811.
20. Dehdashti AR, Ganna A, Karabatsou K, Gentili F. Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. *Neurosurgery*. 2008;62:1006-1015 [discussion 1015-1007].
21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006-1012.
22. Bonicki W, Kasperlik-Zaluska A, Koszewski W, Zgliczynski W, Wislawski J. Pituitary apoplexy: endocrine, surgical and oncological emergency. Incidence, clinical course and treatment with reference to 799 cases of pituitary adenomas. *Acta Neurochir (Wien)*. 1993;120:118-122.
23. Gruber A, Clayton J, Kumar S, Robertson I, Howlett TA, Mansell P. Pituitary apoplexy: retrospective review of 30 patients—is surgical intervention always necessary? *Br J Neurosurg*. 2006;20:379-385.
24. Leyer C, Castinetti F, Morange I, et al. A conservative management is preferable in milder forms of pituitary tumor apoplexy. *J Endocrinol Invest*. 2011;34:502-509.
25. Lubina A, Olchovsky D, Berezin M, Ram Z, Hadani M, Shimon I. Management of pituitary apoplexy: clinical experience with 40 patients. *Acta Neurochir (Wien)*. 2005;147:151-157 [discussion 157].
26. Maccagnan P, Macedo CL, Kayath MJ, Nogueira RG, Abucham J. Conservative management of pituitary apoplexy: a prospective study. *J Clin Endocrinol Metab*. 1995;80:2190-2197.
27. Teixeira JC, Lavrador J, Simao D, Miguens J. Pituitary apoplexy: should endoscopic surgery be the gold standard? *World Neurosurg*. 2018;111:e495-e499.

28. Bills DC, Meyer FB, Laws ER Jr, et al. A retrospective analysis of pituitary apoplexy. *Neurosurgery*. 1993;33:602-608 [discussion 608-609].

29. Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA. Classical pituitary apoplexy: clinical features, management and outcome. *Clin Endocrinol*. 1999;51:181-188.

30. Peter M, De Tribolet N. Visual outcome after transsphenoidal surgery for pituitary adenomas. *Br J Neurosurg*. 1995;9:151-157.

31. McFadzean RM, Doyle D, Rampling R, Teasdale E, Teasdale G. Pituitary apoplexy and its effect on vision. *Neurosurgery*. 1991;29:669-675.

32. Seuk JW, Kim CH, Yang MS, Cheong JH, Kim JM. Visual outcome after transsphenoidal surgery in patients with pituitary apoplexy. *J Korean Neurosurg Soc*. 2011;49:339-344.

33. Woo HJ, Hwang JH, Hwang SK, Park YM. Clinical outcome of cranial neuropathy in patients with pituitary apoplexy. *J Korean Neurosurg Soc*. 2010;48:213-218.

34. Rutkowski MJ, Kunwar S, Blevins L, Aghi MK. Surgical intervention for pituitary apoplexy: an analysis of functional outcomes. *J Neurosurg*. 2018;129:417-424.

35. Briet C, Salenave S, Chanson P. Pituitary apoplexy. *Endocrinol Metab Clin North Am*. 2015;44:199-209.

36. Fraser LA, Lee D, Cooper P, Van Uum S. Remission of acromegaly after pituitary apoplexy: case report and review of literature. *Endocr Pract*. 2009;15:725-731.

37. Nishioka H, Haraoka J, Miki T. Spontaneous remission of functioning pituitary adenomas without hypopituitarism following infarctive apoplexy: two case reports. *Endocr J*. 2005;52:117-123.

38. Tamasawa N, Kurahashi K, Baba T, et al. Spontaneous remission of acromegaly after pituitary apoplexy following head trauma. *J Endocrinol Invest*. 1988;11:429-432.

39. Nawar RN, AbdelMannan D, Selman WR, Arafah BM. Pituitary tumor apoplexy: a review. *J Intensive Care Med*. 2008;23:75-90.

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