

Measurements of Prolactin Serum Level Following Transsphenoidal Surgery of Prolactinoma

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Abstract

Background: Prolactinomas account for around 40% to 50% of functional hypophysis adenomas. Over the last 20 years, surgical procedures for pituitary surgery have vastly advanced. For individuals who are resistant or not tolerant to dopaminergic agonists, transsphenoidal surgery is recommended as a second-line therapy.

Aim of Study: The purpose of this study is to determine the average time for PRL serum level normalization following transsphenoidal prolactinoma surgery and its relationship to the clinical outcomes.

Patients and Methods: This is an observational prospective study of 20 patients with prolactinoma who were treated using an endonasal, endoscopic, transsphenoid approach at Kasr Al-Ainy University Hospitals. All patients underwent a serum PRL level measurement before operation, immediately after-operative, on day one after the operation, the sixth day after the operation, after 3 weeks and 6 weeks later.

Results: Twenty patients, 11 men and 9 women, ranging in age from 20 to 60, participated in the study (mean age 36 years). Remission was achieved in 11 patients (55%) along time of study. The surgical complications in our series were CSF leakage in 2 patients, prolonged DI in 2 cases, and one patient with severe postoperative epistaxis.

Conclusion: In conclusion, we show here that sequential measurements of prolactin serum level after trans sphenoidal prolactinoma surgery reveal that the time required for normalization of PRL serum level ranges from day one after the operation to more than 1.5 months, with an average of six weeks. And that needed time is decreased in the case of macroprolactinoma patients and can reach 24 hours and increases in macroprolactinoma patients, which can reach 42 days. Clinical outcomes chronologically are closely related to chemical remission in the form of relief or disappearance of manifestations caused by high serum levels of prolactin.

Key Words: Value – Sequential measurements – Prolactin – Transsphenoidal prolactinoma surgery.

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Introduction

PROLACTINOMA is the most prevalent hormone-secreting pituitary adenoma, accounting for around 30% of all pituitary tumors and 50-60% of functional adenomas [1]. Menstrual irregularities and/or galactorrhea in women, and loss of libido or impotence in males, are the most common clinical signs of prolactinoma. Symptoms due to the mass effect arise from tumor compression in adjacent structures that causes a decrease in vision or visual field defect, panhypopituitarism, and palsy of the cranial nerves [2]. Pituitary apoplexy can result in fast tumor growth, hypopituitarism, and acute compression of suprasellar and parasellar structures [2]. Diagnosis of prolactinoma requires, in addition to clinical diagnosis, laboratory documentation of the presence of sustained hyperprolactinemia and radiological evaluation by magnetic resonance imaging (MRI) or computed tomography (CT) showing the tumor and its relation to surrounding structures [3]. The objective of treatment is to decrease the high level of prolactin with its consequent clinical symptoms, reduce the size of the tumor and its mass effect, and preserve residual pituitary function. Treatment options include medical treatment with dopamine agonists, surgical excision, and radiation treatment [3].

The first line of treatment is medical treatment, which is successful in minimizing serum levels of prolactin, decreasing tumor bulk, and helping gonadal function restoration [4]. Surgery is considered the second line of treatment indicated in patients with failed medical treatment, patients who do not tolerate or refuse medical treatment with a dopamine agonist, patients with marked deterioration of vision, and some patients with apoplexy who need urgent decompression [4,5].

Radiation treatment, including radiosurgery, is seldom used to treat prolactinoma and is linked with a high rate of serious adverse effects, including hypopituitarism and optic system impairment [5].

This work aims at determining the average time needed to normalize PRL serum level following surgical trans sphenoidal management of prolactinoma and the relation to clinical outcome.

Patients and Methods

This is an observational prospective study of 20 patients with prolactinoma who were surgically treated using an endonasal endoscopic transsphenoid approach in Kasr Al-Ainy University Hospitals in the period 1 January to 30 July 2019 (n=20).

Inclusion criteria: Failure of medical treatment. Patients' age ranges 18-60 years. Serum PRL level >200ng/dl. **Exclusion criteria:** Patients with malignant and recurrent prolactinoma, subtotal excision, pituitary apoplexy, or associated hormonal disease.

Careful history, thorough neurological examination, preoperative and postoperative ophthalmological and endocrinological evaluation were performed for all patients. The ophthalmological evaluation consisted of visual acuity, visual field testing, and fundus examination. Endocrinological evaluation consisted of preoperative and postoperative evaluation that included fasting morning cortisol, adrenocorticotrophic hormone, thyroid hormones (T3, T4 and TSH), FSH, LH, GH, and prolactin. In this study sequential measurements of the serum level of prolactin were made day before the operation, immediately after the operation, day one after the operation, the 6th day after the operation, after 3 weeks and 6 weeks later. Preoperative CT scans of the brain and paranasal sinuses, magnetic resonance imaging (MRI) scans with IV contrast were performed on all patients, postoperative CT scans were performed 24 hours after surgery, and magnetic resonance imaging (MRI) was performed after 1.5 months.

Macro-prolactinoma (diameter >10mm), micro-prolactinoma (diameter <10mm), and invasive macro-prolactinoma are the three types of prolactin-secreting tumors.

Results

A prospective study of 20 cases underwent surgery for prolactin secreting adenomas were collected, remission in 11 cases, 72.72% of patients with macroprolactinoma and 27.27% of patients with noninvasive macroprolactinoma. The study included 11 males and 9 females, ages ranged from

20 to 60 years, mean age 36 years, duration of follow-up was 6 weeks. The chief complaint was headache in 14 cases (70%), visual disturbances in 8 cases (40%), galactoria-amenorrhea in 6 cases (30%) erectile dysfunction in 2 cases (10%), and decreased libido in 2 cases (10%). 9 patients (45%) had been operated on for a microprolactinoma, 7 patients (35%) for a macroprolactinoma, and 4 patients (20%) for an invasive prolactinoma.

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At the onset of the diagnosis, median PRL level was 957.5ng/dl (extreme values: 200-8000ng/dl). Female patients were found older at the time of diagnosis (40 ± 9 vs 29 ± 14 years: $p < 0.001$), but with a higher median PRL level in men than in female patients (2000 in men vs 278.1ng/dl in females) 14 patients received dopamine agonist before surgery in the form of cabergoline.

Indications for surgery included resistance to dopamine agonists in 8 patients (40%), drug intolerance in 6 patients (30%), patient choice in 3 cases (15%), and acute complications in 3 patients (15%).

Biochemical remission was obtained a long period of follow-up in 55% (11 patients 6 males and 5 females, 8 patients with microprolactinoma and 3 with macroprolactinoma).

Remission occurred in one patient after the operation, in three patients on day one after the operation, four patients on day 6, nine patients after 3 weeks, and they reached 11 patients 6 weeks after the operation. There was no detected remission in individuals with invasive macro-prolactinoma, as predicted. There was no statistically significant difference in postoperative remission rates between individuals who were given a dopamine agonist before to surgery and those who were not. Sex, age, PRL levels, prolactinoma measurements and invasiveness, and residual postoperative tumor in MRI have been linked to the likelihood of recurrence in multivariate analysis. Postoperative complications were observed in 5 patients (25%), including prolonged DI in 2 patients, CSF leak in 2 patients, and one case with severe epistaxis that necessitated hemostatic intervention.

Medical treatment was restarted in 9 patients with recurrent or persistent hyperprolactinemia after three weeks, with significantly higher efficacy and less average dosing after surgery (1.5mg/week of cabergoline) than before surgery (2.6mg/week of cabergoline) compared to patients who received medical treatment (cabergoline). However, we

found no changes in the percentage of reduction in PRL levels using dopamine agonist therapy pre-operative (average drop of $31 \pm 16\%$) or post-operative (average decrease of $23 \pm 26\%$), demonstrating that the susceptibility of tumoral PRL-secreting cells to dopaminergic inhibition did not alter as a result of surgery.

Table (1): Patients' statistic data.

	Mean	Median	Mini.	Maxi.	SD	Percentile 25	Percentile 75
Age	36	33	20	61	12	28	42
Prolactin before operation	1673.20	957.50	200.00	8000.00	2066.00	250.00	2264.05
Post-operative	516.03	244.50	17.96	1968.44	617.82	33.50	846.57
Day one after	219.24	115.10	8.00	1243.53	300.07	25.25	301.37
After 6 days	206.77	32.86	3.10	1030.21	319.95	21.75	291.10
After 3 Ws	1267.60	23.25	1.00	881.91	276.70	11.50	208.05
After 6 Ws	215.43	13.25	1.00	1869.00	456.54	8.45	126.00

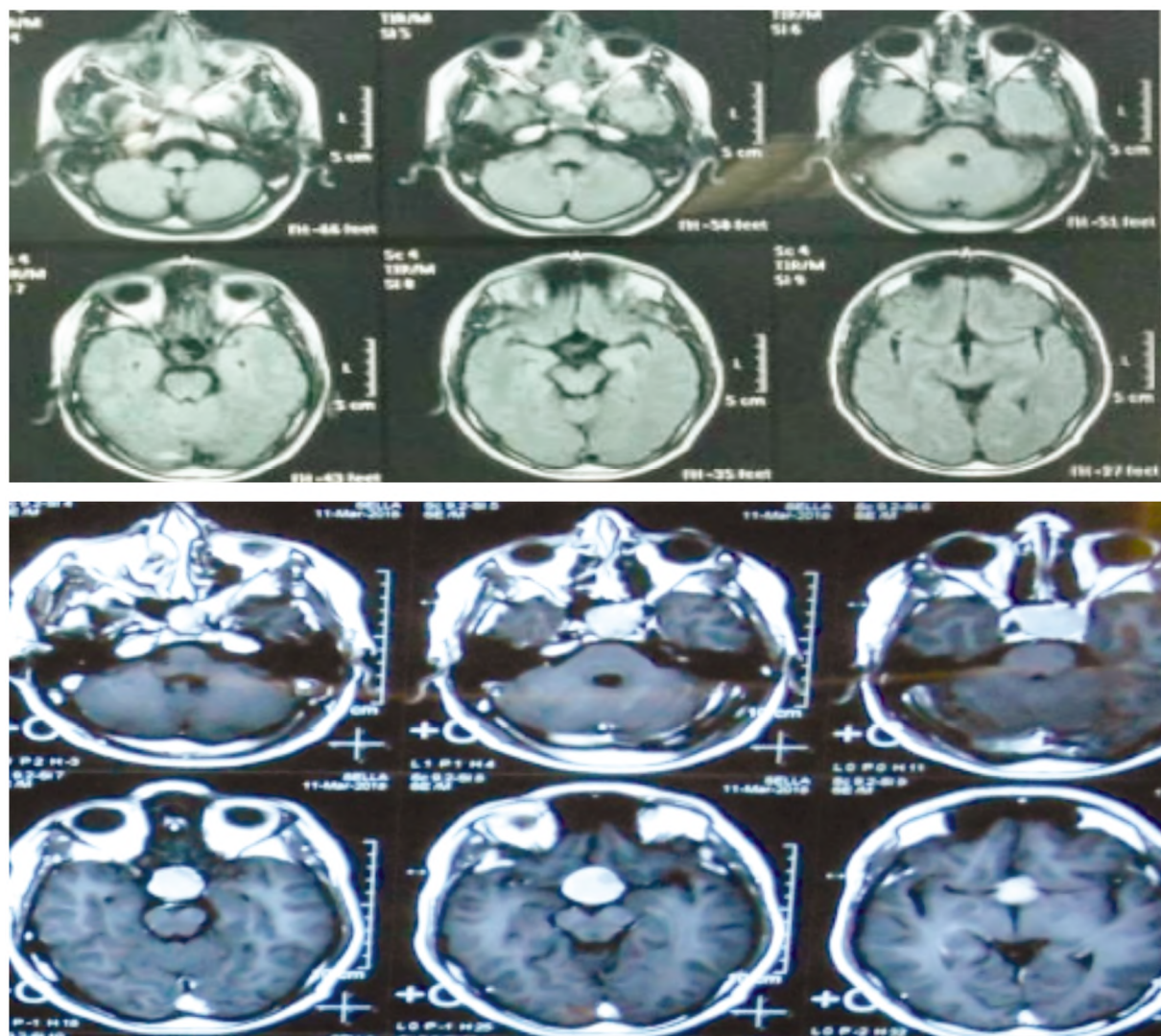


Fig. (1): 46 years old female with progressive course of diminution of vision and field affection for 5 months despite full medical treatment MRI sella with contrast showed large sellar and suprasellar mass, post-operative improvement was denoted by the post-operative CT.

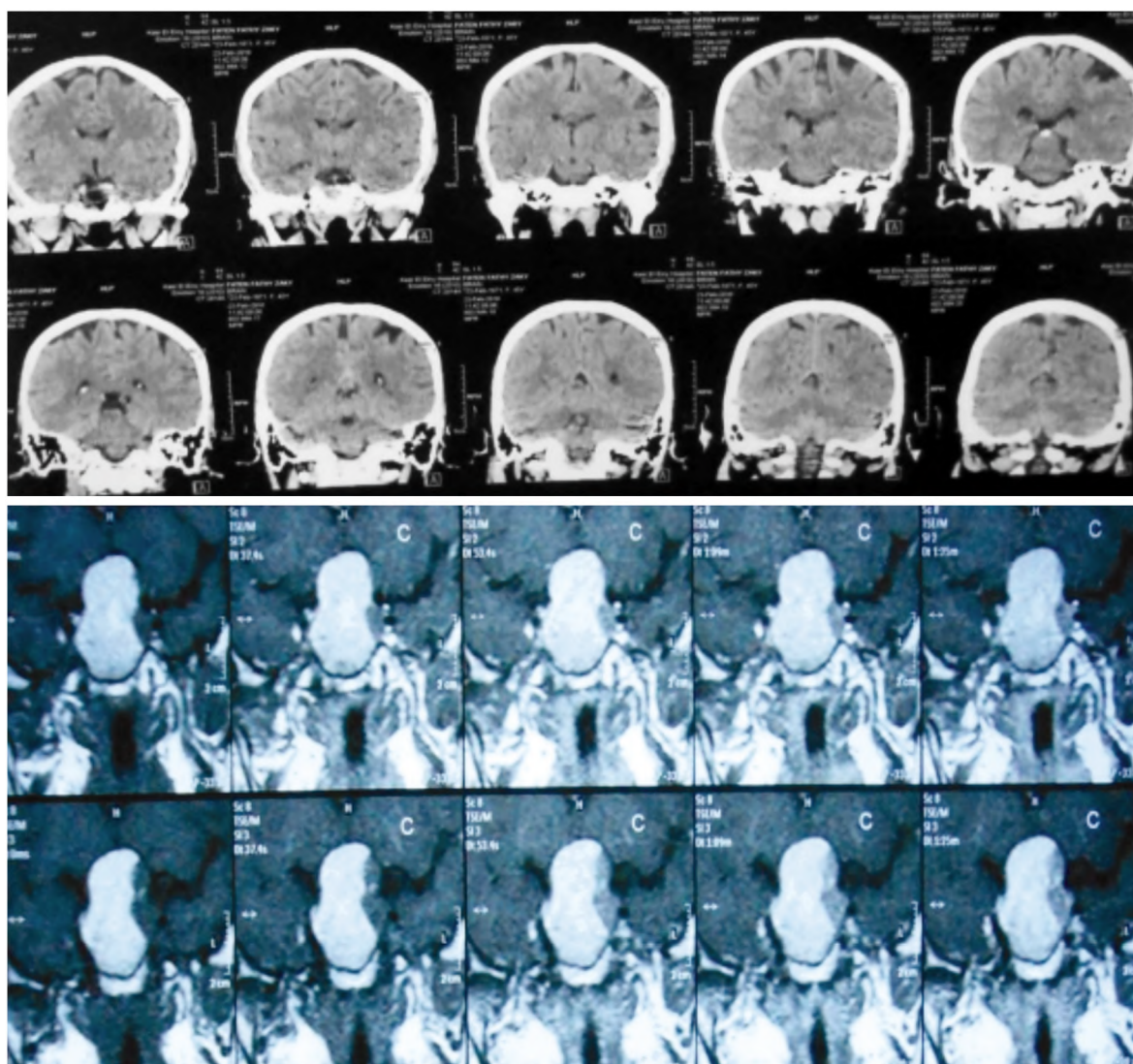


Fig. (2): 38 years old male with pituitary macroadenoma, prolactin level reached 180pg after 6 months of proper treatment, and he was advised surgical excision to alleviate persistent symptoms.

Discussion

Dopamine agonists have been introduced in clinical practice for over 25 years, less patients with PRL secreting tumors have been indicated for surgery; therefore, our present series includes surgical indications and outcomes in the age of dopamine agonists. The mean age of the operated cases ranged between 29 and 40 years, with males accounting for 55 percent of the total. An intriguing observation was that the mean age of our male patients upon diagnosis was younger than the mean age of our female patients (40.9 vs 29.14 years). This is most likely due to variations in surgical indications chosen by men (mostly dopamine agonists and acute problems) and women (mostly dopamine agonists and chronic complications) (more frequent intolerance to intolerance to dopamine agonists or personal wish), but with a

higher median PRL level in men than in female patients (2000 in men vs 278.1 ng/dl in females) results Losa and Hamilton reported similar incidents [6,7], with larger tumors in male patients.

In the Webster et al., trial, after surgical correction of hyperprolactinemia, almost 90% of women with infertility at presentation were able to conceive, which explains why pituitary function was preserved after surgery [8]. Other programmed have previously reported on the restoration of fertility [9-11]. However, few studies have linked the number of women who want to become pregnant with the number of women who are able to conceive. In one research, after surgical correction of hyperprolactinemia, 11 out of 13 women (85%) of those who wanted to conceive were able to do so [12,13]. Pregnancy rates were also high (90 percent and 88.3 percent, respectively).

Later trials included all women who wanted to conceive, regardless of their post-operative levels of PRL. Indeed, Cooper et al., [14] came to the conclusion that chronic hyperprolactinemia was the cause of infertility. In our study, there is one woman in the period of childbirth of childbirth of childbirth who reached the normal level of level of prolactin serum during the study, and she had become pregnant and did not initiate post-operative dopamine agonist treatment.

As regard predictive value of sequential measurements of prolactin serum level after surgery of prolactinoma, patients whose prolactin reached normal level of prolactin lower than 10 ng/dl within short time, may anticipate a long-lasting chemical cure, a similar result was reported in study of Primau et al., [14], which concluded that prolactin levels less than 10 ng/dl on first postoperative day predicted chemical cure for long period, as a result, the findings highlight the need of following these individuals for a long time (at least five years).

In our current study, micro-prolactinomas constituted 55% (11 of 20 patients) of operated tumors, a percentage similar to what has been reported by Losa et al., [6] (49%) and Hamilton et al., [7] (32%). Lu et al., [15] stated that their surgical indications had changed over time. Cabergoline, which is more effective and well tolerated than bromocriptine, is now available, decreasing the rate of surgeries performed for dopamine agonist intolerance or dopamine agonist resistance and evolving new indications for surgery, such as cystic tumors or patients' preferences.

Patients' preferences accounted for a considerable part of surgical indications in our research (15%, 3 cases), having only one case of cystic tumor. Resistance to dopamine agonists, on the other hand, is still the most common trigger of surgeries, accounting here for about 40%, a percentage close to that observed by Mattogno et al., [16]. In our present series, post-surgical in 72.72 percent of microprolactinomas, and 27.27% of non-invasive macroprolactinomas remission was achieved. This may be considered low when compared with those (78-93%) addressed in some recent series [17], but similar to the success rate in one study [17].

In fact, although most recent studies were from single experienced facilities, our analysis included patients who received surgery by multiple neurosurgeons during a short period of time between January and July 2019. When all macroprolactin-

omas (noninvasive and invasive) were considered combined, the chance of remission was substantially lower (55 percent). This rate could be compared with those reported in previous studies [18-20]. A decreased PRL level at diagnosis was independently related to a favorable surgical result in various analytic studies, preoperative dopamine agonist medication does not appear to have a substantial impact on the likelihood of surgical success, as shown in other research [21,22], regardless of tumor size at presentation, prior dopaminergic drug treatment had no influence on surgical results. Starting with the first report by Landolt et al., in 1982, the subject of whether the intake of dopamine agonists may jeopardize operative results has been disputed [23]. They discovered that the surgical cure rate in patients with micro-prolactinomas dropped from 81 percent in untreated cases to 33 percent in medically treated cases. The production of perivascular fibrosis by bromocriptine [23,24] was blamed for the detrimental impact of medical pretreatment, which might render surgical excision of the lesion more challenging. However, later research with microprolactinomas failed to corroborate this observation [25]. The majority of research found that macroprolactinomas treated with dopamine agonists had poorer outcomes [24,25]. This was applicable in our study on patients who were recently discovered and refused medical treatment, remission was reached in 66.6% (2 of 3 patients) of them, one patient with macroprolactinoma and another with microprolactinoma and were compared with patient who received and were resistant to medical treatment, remission was reached in 66.6% (6 of 9 patients) of them, 2 patients with macroprolactinoma and 4 patients with microprolactinoma, a result that denote there is no difference between pretreated and not pretreated patients with dopamine agonists in case of macro- or microprolactinoma.

The recurrence of hyperprolactinemia is considered one of the biggest side effects of surgery for PRL-secreting tumors. Which range from 0% to 55 percent (Table 1). According to one research, roughly 34% of patients who were in remission following surgery relapsed 7-164 months later [27]. Hyperprolactinemia recurrence appears to recur in a linear fashion with time, having half of the relapsing patients relapsed three years or longer after surgery. As a result, the longer the follow-up lasts, the higher the recurrence appears, this is consistent with what has been depicted in individuals with nonfunctioning lesions [15,27]. There were no relapses in our research throughout the short time frame (1.5 months), highlighting the need of reviewing these patients for several years after

surgical remission, highlighting the need of reviewing these patients for several years after surgical clearance.

Another crucial and novel result in our study is the considerable advancement in hormonal control with surgery in previously drug-resistant individuals on dopamine agonist treatment.

Many authors have reported that surgical reduction of GH-secreting lesions improves acromegaly regulation by somatostatin analogs [15,22], but this surgical effect has not been satisfactorily proven for PRL-secreting pituitary adenomas until now. In almost fifty percent of the resistant individuals, surgery allowed PRL concentrations to return to normal, allowing them to take a less dose of dopaminergic receptors agonists [30]. As noted by Honegger et al., resistance to dopamine receptors-stimulators or the necessity to increase the dose higher than the standard dosage of cabergoline to regulate PRL, and tumor size may be regarded legitimate criteria for surgical removal of prolactinomas [30]. All of them had been given dopamine agonists prior to surgery, and one of them had a tumor that the neurosurgeon described as fibrous and adherent. This implies that tumor cell sensitivity to dopaminergic inhibition did not alter as a result of surgery. The inherent sensitivity of the tumor to dopamine agonists is primarily connected to the expression of the D2 dopamine receptor in pituitary tumor cells, as demonstrated by Wei et al., [30], a characteristic that should not be changed by partial adenoma resection. Transsphenoidal surgery should be considered in patients with newly diagnosed intrasellar PRL secreting tumors, in addition to the already established reasons of intolerance or resistance to medical therapy, whereas extrasellar expanding tumors with high preoperative PRL levels should be avoided [29,30].

The 25% risk of postoperative complications was greater than other writers had reported (13%-17%).

The majority of complications were observed in patients who had a microprolactinoma, and also observed in one subject with a macroprolactinoma. All of them have been taking presurgical dopamine agonists, and one of them had a fibrous and adherent tumor, as reported by the neurosurgeon.

Many authors have stated that: For surgical cure rates to be maximized, while minimizing adverse effects, careful patient selection is critical [18]. The surgeon's experience is also vital, and each surgical team should evaluate its own findings

for efficacy and safety [18,20,31]. Surgery can get rid of the need for long-term medication and, on time basis, may be less expensive than medical care [18,20,31].

Conclusion and Recommendations:

Our current recommendations to patients with PRL-secreting tumors is to advicemedical therapy in the conditions of extrasellar extension of macroadenomas and to elaborate the benefits and drawbacks of medical and operative treatment in the condition of intrasellar tumors openly and objectively with the patient, giving him the chance to decide which approach is better for his/her situation.

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قيمة تتابع قياس هرمون البرولاكتين فى الدم عقب إجراء جراحة استئصال أورام الغدة النخامية المنتجة للبرولاكتين عبر الطريق الأنفى الخفاشى

تعتبر أورام الغدة النخامية المنتجة لهرمون ادرار اللبن الرولاكتين من أكثر أورام الغدة النخامية حدوثاً.

تهدف الدراسة إلى بحث تأثير استئصال أورام الغدة النخامية المنتجة للبرولاكتين عبر الطريق المنظارى الأنفى على مستويات هرمون البرولاكتين بعد الجراحة.

تمت الدراسة على ٢٠ مريضاً خضعوا جميعاً قبل الجراحة للفحص بالرنين المغناطيسى مع إعطاء الصبغة وإجراء تحليل هرمونى كامل لهرمونات الغدة الدرقية، ثم خضعوا لإجراء جراحة عبر الطريق الأنفى الخفاشى لاستئصال الورم وتم إعادة تحليل هرمون الرولاكتين لكل منهم بعد العملية مباشرة وبعدها بيوم واحد وبعدها بستة أيام ثم بعدها بثلاثة أسابيع.

خلصت الدراسة إلى أن مستوى هرمون البرولاكتين انخفض بشكل ملحوظ بعد اليوم السادس وبشكل تام بعد الأسبوع الثالث.

توصى الدراسة بعمل تحليل هرمون البرولاكتين بعد اليوم السادس من الإجراءات الجراحية لتجنب الحصول على نتائج إيجابية خاطئة.