Treatment of hyperprolactinemia: A single-institute experience

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Abstract

Background: Dopamine agonists such as bromocriptine and cabergoline have been found to be an effective treatment for hyperprolactinemia, not only inducing adenoma shrinkage but also lowering serum prolactin levels. Among known dopamine agonists, cabergoline is the drug of choice due to its enhanced tolerability compared with bromocriptine. This study aimed to evaluate cabergoline's effectiveness, along with transsphenoidal surgery, in the treatment of hyperprolactinemia.

Methods: We retrieved all patients with a diagnosis of prolactinoma who were treated in our hospital during 2000–2018. A total of 208 patients were enrolled in the analysis after applying exclusion criteria. Patients were divided into four groups according to the treatments received. The demographic data, dosage and duration of cabergoline, and serum prolactin levels at different time points were collected for analysis.

Results: Normalization was achieved in 59 patients (83.10%) within a short median duration of 2.80 months among those treated with cabergoline only. Although cabergoline alone was effective and well-tolerated, our data showed that long-term remission rates were more favorable when surgery was involved. The long-term remission rate of all patients enrolled was 53.8% (112 patients among 208 patients). The long-term remission rates for the different treatment groups were 17.8% (8 of 45 patients) in Group 1 (Operation→Drug), 83.3% (5 of 6 patients) in Group 2 (Drug→Operation), 79.0% (68 of 86 patients) in Group 3 (Operation only), and 43.7% (31 of 71 patients) in Group 4 (Drug only).

Conclusion: Cabergoline has been demonstrated to be effective and should be considered as a first-line treatment for hyperprolactinemia. In our study, transsphenoidal surgery was also demonstrated to achieve good results compared with medical treatment. Surgical intervention may resurface as an alternative first-line treatment. When used in combination with cabergoline, surgery offers a higher disease remission rate than either drug or operation alone.

Keywords: Cabergoline; Dopamine agonists; Extra-capsule resection; Hyperprolactinemia; Prolactinoma; Transsphenoidal surgery

1. INTRODUCTION

Hyperprolactinemia can result from various causes such as pregnancy, medication, compression of the pituitary stalk (disconnection hyperprolactinemia), or prolactinoma.[1,2] Prolactinomas are the most common type of functioning pituitary tumors.[3] Dopamine agonists, including bromocriptine and cabergoline, have been found to be effective in treating prolactinoma. Cabergoline has been the drug of choice owing to its higher efficacy and tolerability when compared to bromocriptine.[4] Normalization of hyperprolactinemia and restoration of gonadal function was reported in 80% to 90% of patients with prolactinomas who were treated with dopamine agonists.[5,6]

Although cabergoline has been proven to be effective and safe in the treatment of hyperprolactinemia, a high recurrence rate after withdraws of the drug has been reported.[7,8] Calao et al first described a successful attempt to withdraw cabergoline treatment in tumoral and nontumoral hyperprolactinemia.[9] The 2011 Endocrine Society Guidelines suggest that dopamine agonist therapy may be tapered and discontinued in patients with normal serum prolactin, after a treatment duration of over 2 years and no evidence of tumor residue found in MRI.[2]

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Cabergoline, owing to its effectiveness and tolerability, has been considered the first-line treatment for patients with hyperprolactinemia. As a result, transsphenoidal surgery has been overlooked and even regarded as unnecessary. However, with recent advancements in endoscopic pituitary surgery, surgical treatment has resurfaced as a viable alternative first-line treatment for prolactinoma patients.[10,11] This study aims at providing more data to support transsphenoidal surgery as a viable alternative option in treating hyperprolactinemia in terms of effectiveness and remission rate of the disease.

2. METHODS

2.1. Patient population

We retrieved all patients with a diagnosis of prolactinoma who were treated in our hospital during the years 2000-2018. Seven hundred sixty-two (762) patients were extracted from the medical center's database and demographic data were collected. Both the dosage and duration of cabergoline were documented. Serum prolactin levels during different time points were also taken into account as an endpoint. MRI reports, where available, were included to evaluate the effects on adenomas.

2.2. Exclusion criteria

Patients with a follow-up period of less than 6 months (defined as being the shortest interval between the initial and last serum prolactin data) were excluded. A total of 208 patients were enrolled in the analysis.

2.3. Statistical analysis

Data are shown as mean (SD) for continuous variables and as numbers (percentages) for categorical variables. All statistical analyses were performed using the R language.

3. RESULTS

A total of 208 patients were enrolled in the study according to the inclusion and exclusion criteria described above. Demographic data are shown in Table 1. Baseline serum prolactin was 326.28 μg/L with SD 2108.93 μg/L. Our data suggested that there was no significant relationship between age and gender regarding normalization rates.

Table 1

Demographic data for enrolled patients

Total cases	208
Latest date of therapy ≥1 y (%)	
No	37 (17.8%)
Yes	171 (82.2%)
Latest normalization status (%)	
Normalization	128 (61.5%)
Abnormal	80 (23.3%)
Age (y) [mean (SD)]	39.70 (13.25)
Sex (%)	
Female	163 (78.4%)
Male	45 (21.6%)
Surgery (%)	
No	71 (34.1%)
Yes	137 (65.9%)
PRL level of preoperation (μg/L) (mean)	313.82
PRL level of pre-medication (μg/L) (mean)	326.28
Duration of therapy (months) [mean (SD)]	139.75

PRL = prolactin.

Most of our patients (80, 65.6%) started with an initial dose of 1.0 mg/wk, followed by 0.5 mg/wk in 18 patients (14.8%) and 2.0 mg/wk in 14 patients (11.5%) (Table 2). Patients who began with a 1.0 mg/wk dosage tended to have higher initial serum prolactin levels when compared with those started with 0.5 mg/wk. This may imply that doctors tended to prescribe a higher dose of cabergoline to patients with a higher initial prolactin level. However, a higher initial dose was not associated with a shorter time required for achieving normalization (12.44 vs 10.68 months, $p = 0.45$).

We further stratified the patients into four groups (Table 3): 1. transsphenoidal surgery followed by cabergoline (Opeaertion→Drug), 2. cabergoline followed by surgery (Drug→Opeartion), 3. cabergoline only (Drug), and 4. surgery only (Operation).

In group 3 (drug only), patients were treated exclusively with cabergoline, normalization was achieved in 59 patients (83.10%) within a short median duration of 2.8 months.

We also investigated the percentage of long-term remission which was defined as normalization of serum prolactin at least 1 year after surgery or discontinuation of cabergoline (treatment-free). Amongst the 208 patients, normalization of serum prolactin levels was achieved in 128 patients (61.5%) at the end of follow-up, with 112 patients being treatment-free for at least 1 year. That yielded a long-term remission rate of 53.8%. The remission rates in the different treatment groups were 17.8% (8 of 45 patients) in the group 1 (Opeartion→Drug), 83.3% (5 of 6 patients) in group 3 (Drug→Operation), 79.0% (68 of 86 patients) in group 4 (Operation) and 43.7% (31 of 71 patients) in group 3 (Drug).

4. DISCUSSION

Our data confirmed the efficacy of cabergoline for the treatment of hyperprolactinemia. The dosage, response rate, and other major outcomes were compatible with previous studies.[6] By taking surgery into consideration and comparison, we have provided insights into the treatment of hyperprolactinemia which are close to real-world scenarios.

The normalization rate of serum prolactin in our study was compatible with that of previous studies. The response rate varied from 61% to 96%[5,6,12–23] and was reported to be 81% in a recent meta-analysis,[10] Most of the cabergoline prescribed in our hospital lies within the range (0.5-3.0 mg/wk) reported in other institutes around the globe. Although 3.5 mg/wk of cabergoline was considered the maximum effective dose in some studies,[21,24] doses up to 11 mg/wk were claimed to be administered in one report, which yielded a higher normalization rate.[25]

Many published guidelines and review articles have suggested dopamine agonists as a first-line treatment for prolactinoma.[2,3] Although efficacy and safety of cabergoline have been proved, potential concerns regarding patient adherence and adverse effects emerge should it became a lifelong treatment. Headache, dizziness, and insomnia, among other side effects, might be tolerable at first but may compromise medication adherence in prolonged treatment. Impulse control disorders, including compulsive shopping and pathologic gambling, and hypersexuality have also been reported.[26] In addition, cost-effectiveness analysis had highlighted the financial burden for long-term cabergoline treatment compared to transsphenoidal surgery.[27] In our own experience, patients planning for pregnancy and breastfeeding were reluctant to receive long-term medication.

However, there is no consensus concerning the duration of cabergoline therapy as well as the criteria to safely withdraw cabergoline. A series of studies were conducted addressing the problem of cabergoline withdrawal and the risk of recurrence.[7–9,28–38] Remission rates ranging from 15% to 50% in selected groups of patients were reported.

Table 2

Number and distribution of patients, according to primary and final cabergoline dosage (mg/wk)

Dosage (mg/wk)	0.125	0.25	0.5	1	1.5	1.75–3	3.5	≥7
Primary dosage	0	0	18	80	1	14	1	8
	0.0%	0.0%	14.8%	65.6%	0.8%	11.5%	0.8%	6.6%
Final dosage	1	2	20	70	2	24	1	2
	0.8%	1.6%	16.4%	57.4%	1.6%	19.7%	0.8%	1.6%

Table 3

Comparison of groups receiving different treatments

Variables/groups	OP→Drug	Drug→OP	OP only	Drug only
Number of cases	45	6	86	71
Latest date of therapy ≥1 y (%)				
No	36 (80.0)	1 (16.7)	0 (0.0)	0 (0.0)
Yes	9 (20.0)	5 (83.3)	86 (100.0)	71 (100.0)
Latest normalization status				
Normalization	23 (51.1)	6 (100.0)	68(79.1)	31(43.7)
Abnormal	22 (48.9)	0 (0.0)	18(20.9)	40(56.3)
Age (y) [mean (SD)]	35.70 (12.21)	31.47 (6.22)	43.29 (15.35)	38.59 (10.18)
Sex (%)				
Female	27 (60.0)	6 (100.0)	63 (73.3)	67 (94.4)
Male	18 (40.0)	0 (0.0)	23 (26.7)	4 (5.6)
Surgery (%)				
No	0 (0.0)	0 (0.0)	0 (0.0)	71 (100.0)
Yes	45 (100.0)	6 (100.0)	86 (100.0)	0 (0.0)
Serum prolactin level of preoperation (μg/L) [mean (SD)]	808.34 (1407.08)	–	55.06 (120.11)	–
Serum prolactin level of pre-medication (μg/L) [mean (SD)]	–	71.92 (74.17)	–	347.78 (2196.00)

OP = operation.

Transsphenoidal surgery is a popular method for prolactinoma. Although cabergoline has become the promising first-line treatment of prolactinoma, surgical intervention is still considered mandatory in several situations, such as macroadenoma with optic nerve compression or pituitary apoplexy. Furthermore, take advantage of significant advancements of endoscopic transsphenoidal surgery, grossly total removal of the tumor is possible in most prolactinomas. Recent advancement in endoscopic extra-capsule resection has promising results in treating noninvasive functional microadenomas as well as macroadenomas.[39–42] Surgical treatment has resurfaced as a viable alternative first-line treatment for prolactinoma patients, according to the latest meta-analysis. In that particular meta-analysis, the authors concluded that in the majority of patients, disease remission can be achieved through surgery and that disease remission is less often achieved with dopamine agonists.[10] Our data also support endoscopic surgery as a viable first-line treatment for selected patients because patients treated with surgery had a higher (79.0% in the OP group vs 43.7% in the Drug group) long-term remission rate. The long-term remission rate was also higher in patients who had received both cabergoline and surgery when compared to the Drug only group.

However for those with invasive macroadenoma, dopamine agonist remained the first-line option due to surgery alone yielding unsatisfactory results.[11] In fact, giant or invasive adenoma were usually coped with a multidisciplinary approach that involves endoscopic/microscopic surgery, medication, and gamma knife radiosurgery.[43–45]

There are several limitations to our study. First, as a retrospective study, it lacks a standard follow-up schedule. Therefore, we may have overestimated the period for normalization due to prolonged intervals between blood tests. Second, patients included in the analysis were treated by different neurosurgeons or endocrinologists with different strategies regarding dosage/interval of cabergoline treatment and indication/timing for surgical intervention. Third, our analysis lacks discussion about morphology and invasiveness of prolactinoma which is strongly related to drug response, remission rate as well as infeasibility for total surgical removal. Fourth, side effects from the drugs and performance assessment were not included in the study. Fifth, complications following transsphenoidal surgery such as cerebrospinal fluid leakage and diabetes insipidus were not recorded. Last but not least, pregnant women with unique hormone profiles and treatment considerations were pooled together in our analysis.

In conclusion, cabergoline is effective in the treatment of hyperprolactinemia. Our data are compatible with previous studies. Transsphenoidal surgery can also achieve a good result of long-term remission of serum prolactin and even better. Surgical intervention may resurface as an alternative first-line treatment in selected patients offering a higher disease-remission rate. Larger, prospective clinical studies aim at establishing comprehensive treatment algorithms providing tailored and individualized treatment plans that are needed in the future.

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