Management of prolactinomas associated with very high serum prolactin levels

DANIEL L. BARROW, M.D., JUNICHI MIZUNO, M.D., AND GEORGE T. TINDALL, M.D.

Department of Surgery (Neurosurgery), Emory University School of Medicine, Atlanta, Georgia

The authors have reviewed the results of transsphenoidal microsurgical management in 69 patients with prolactin-secreting pituitary adenomas who had preoperative serum prolactin levels over 200 ng/ml. The patients were divided into three groups based on their preoperative serum prolactin levels: over 200 to 500 ng/ml (Group A); over 500 to 1000 ng/ml (Group B); and over 1000 ng/ml (Group C). The percentage of successful treatment ("control rate") was 68%, 30%, and 14%, respectively, in these three groups of patients. Based on these results, the authors offer guidelines for the management of patients with prolactin-secreting pituitary adenomas associated with exceptionally high serum prolactin levels. The surgical control rate of 68% in Group A seems to justify surgery for these patients, while primary medical care with bromocriptine is recommended for most patients with serum prolactin levels over 500 ng/ml.

KEY WORDS □ prolactin □ pituitary adenoma □ transsphenoidal surgery □ bromocriptine

The pharmacological efficacy of the dopamine agonist, bromocriptine, in treating hyperprolactinemia and reducing the size of prolactin-secreting pituitary adenomas has made the use of this drug a practical option in the treatment of prolactinomas. The availability of more than one therapeutic option makes it necessary to periodically reassess the effectiveness of all potentially practical therapeutic approaches. The rate for successful treatment ("control rate") of prolactinomas by surgery is related to the preoperative serum prolactin level, with that rate dropping sharply in patients with preoperative serum prolactin levels over 200 ng/ml. To better define the control rate and to determine if surgical therapy is the most appropriate therapeutic choice, the authors have retrospectively studied 69 patients with preoperative serum prolactin levels over 200 ng/ml who were treated by transsphenoidal microsurgery at Emory University Hospital between 1976 and 1985. It was hoped that the results will provide guidelines for recommending surgical or medical therapy for patients with markedly elevated serum prolactin levels.

Clinical Material and Methods
Patient Population and Evaluation
Over a 9-year period (1976 through 1985) a total of 891 patients underwent transsphenoidal microsurgery at Emory University Hospital. From the 220 patients with prolactinomas, 69 patients (53 women and 16 men) with preoperative serum prolactin levels over 200 ng/ml were selected for analysis on the basis of completeness of their pre- and postoperative evaluations. The women in this series ranged in age from 18 to 54 years (average 30 years) and the men from 18 to 68 years (average 45.5 years). Table 1 outlines the presenting signs and symptoms in this series of patients.

The transsphenoidal surgery involved a unilateral septal technique which has been described in previous publications. All operations were performed by the same surgeon (G.T.T.). Serum prolactin was measured by radioimmunoassay before surgery and at several times after surgery and during the follow-up period. The normal serum prolactin range at our institution is 2 to 12 ng/ml for men and 2 to 20 ng/ml for premenopausal women. Pathological specimens were examined by light microscopy, immunocytochemistry, and electron microscopy.

Postoperative serum prolactin levels were determined for all patients in this study 7 to 10 days, 3 months, and 6 months after surgery, and, whenever possible, at yearly intervals thereafter. Postoperative computerized tomography (CT) scans were performed in all patients with persistent hyperprolactinemia. Twenty-five patients with persistent postoperative hyperprolactinemia were treated with bromocriptine.
Pituitary adenoma with high prolactin levels

**TABLE 1**

Presenting signs and symptoms in 69 patients with serum prolactin over 200 ng/ml*

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>No. of Cases</th>
</tr>
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<tbody>
<tr>
<td>females</td>
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<tr>
<td>amenorrhea</td>
<td>51</td>
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<tr>
<td>galactorrhea</td>
<td>37</td>
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<td>headache</td>
<td>9</td>
</tr>
<tr>
<td>visual acuity/field defect</td>
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<td>hypopituitarism</td>
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<td>seizure</td>
<td>1</td>
</tr>
<tr>
<td>cranial nerve palsy</td>
<td>1</td>
</tr>
<tr>
<td>males</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>5</td>
</tr>
<tr>
<td>headache</td>
<td>4</td>
</tr>
<tr>
<td>decreased libido</td>
<td>4</td>
</tr>
<tr>
<td>hypopituitarism</td>
<td>3</td>
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<tr>
<td>visual acuity/field defect</td>
<td>2</td>
</tr>
<tr>
<td>seizure</td>
<td>1</td>
</tr>
<tr>
<td>galactorrhea</td>
<td>1</td>
</tr>
<tr>
<td>diabetes insipidus</td>
<td>1</td>
</tr>
</tbody>
</table>

* Totals do not add up to 69 as some patients presented with multiple signs and/or symptoms.

**Criteria for Control**

For the purposes of this study, the disease was considered to be controlled if the patients’ most recent postoperative serum prolactin determination was normal (≤ 20 ng/ml), they were not taking a dopamine agonist (bromocriptine), and their postoperative CT scan did not show residual or recurrent tumor. The disease was also considered under control if: the postoperative serum prolactin was over 20 ng/ml but less than 150 ng/ml and not progressively increasing during the follow-up period; the patient was not receiving bromocriptine; and the postoperative CT scan was negative for recurrent tumor. Any patient with either a serum prolactin level over 150 ng/ml or a positive postoperative CT, or who was taking bromocriptine was not considered to be successfully treated.

A comment should be made about these criteria for disease control. Postoperative hyperprolactinemia may be the result of either residual or recurrent tumor, or pituitary stalk damage resulting from the neoplasm, from surgical manipulation, or from a combination of both. Such an injury to the stalk impairs the delivery of prolactin-inhibitory factor to the gland, resulting in an unrestrained release of prolactin from the normal pituitary gland. In this situation, the serum prolactin level is usually less than 100 ng/ml and not more than 150 ng/ml and will not progressively increase with time.

Therefore, a patient with a postoperative serum prolactin level over 150 ng/ml is assumed to have residual or recurrent tumor regardless of the CT findings. Those patients with postoperative serum prolactin levels between 20 and 150 ng/ml (that is, not progressively increasing) could be cured of the tumor but have stalk injury, or they could harbor residual or recurrent prolactin-secreting neoplasm. It is in this group of patients that we depend heavily upon the postoperative CT scans to determine the etiology of the hyperprolactinemia.

Because of these variables and the increasing recurrence rate of disease with long-term monitoring, it is difficult to assess a true cure rate for prolactin-secreting pituitary adenoma. Therefore, we have decided to report our results in terms of control of disease rather than cure.

**Results**

All tumors in this group of patients proved to be prolactin-secreting pituitary adenomas on pathological examination. The patients were separated into three groups on the basis of their preoperative serum prolactin levels. Group A included 38 patients whose preoperative levels were over 200 to 500 ng/ml; Group B comprised 10 patients with prolactin levels over 500 to 1000 ng/ml; and Group C contained 21 patients with preoperative prolactin levels over 1000 ng/ml.

Table 2 summarizes the control rates in each group. Of the 38 Group A patients, 14 had postoperative prolactin levels less than 20 ng/ml but two of these were either receiving bromocriptine or had a CT scan that demonstrated a recurrent tumor. Of the 21 patients with postoperative serum prolactin levels between 20 and 150 ng/ml, six were taking bromocriptine or had a positive CT scan, leaving 14 patients with their disease controlled. The remaining three patients in Group A had postoperative serum prolactin levels over 150 ng/ml. Therefore, a total of 26 (68%) of the 38 Group A patients were considered to be controlled.

Of the 10 Group B patients, four had postoperative prolactin levels less than 20 ng/ml but two of these were receiving bromocriptine. Four patients had prolactin levels between 20 and 150 ng/ml, three of whom were on bromocriptine. The remaining two patients had postoperative prolactin levels over 150 ng/ml. Thus, only three (30%) of the 10 Group B patients met the criteria for disease control after surgery.

Of the 21 Group C patients, only three (14%) met the criteria for disease control. The two patients with postoperative serum prolactin levels less than 20 ng/ml were both taking bromocriptine and also had positive postoperative CT scans. Nine patients had postoperative serum prolactin levels between 20 and 50 ng/ml.

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**TABLE 2**

Control rates in prolactinomas with preoperative serum prolactin > 200 ng/ml

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Preop Serum Prolactin Level (ng/ml)</th>
<th>Total Cases</th>
<th>Control Rate</th>
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<tbody>
<tr>
<td>A</td>
<td>&gt; 201-500</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>B</td>
<td>&gt; 501-1000</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>C</td>
<td>&gt; 1000</td>
<td>21</td>
<td>3</td>
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</table>
but six were either receiving bromocriptine or had positive postoperative CT scans. The remaining 10 patients had serum prolactin levels over 150 ng/ml in the later postoperative period.

Discussion

This study reaffirms a finding noted by our group as well as others that the prognosis for control of prolactin-secreting pituitary tumors following surgical treatment is related to the preoperative serum prolactin levels. This finding was of more prognostic value than the size of the tumor. The surgical disease control rate for prolactin-secreting pituitary adenomas is in the range of 75% to 88% when the preoperative serum prolactin level is less than 200 ng/ml.1,3,10,12,17,24,35 Although this control rate was believed to drop off with higher preoperative prolactin levels, the precise control rates have been analyzed in only a few studies.6,13,28

The results of our investigation confirm that the control rate of prolactinomas following transsphenoidal surgery is significantly reduced when the preoperative serum prolactin level is over 200 ng/ml. Furthermore, the operative control rate drops progressively in those patients with serum prolactin levels over 500 ng/ml and especially for those over 1000 ng/ml. Table 3 compares the control rates of our three groups with those in the series of Bertrand, et al.,6 and Hardy.13 These series were selected from a larger number of reported cases because these investigators further divided their patients who had preoperative serum prolactin levels over 200 ng/ml. As indicated in Table 3, the disease control rate of patients with a preoperative serum prolactin level between 200 and 500 ng/ml (250 to 500 ng/ml in Hardy’s series) ranges from 48% to 68%. In the Group B patients (prolactin level of over 500 to 1000 ng/ml) the control rate drops to a range of 21% to 36%. The control rate further declines to a range of 6% to 22% when the preoperative serum prolactin level is over 1000 ng/ml.

Hyperprolactinemia is a good diagnostic indicator for diseases of the pituitary and hypothalamus.6 Furthermore, markedly elevated prolactin levels over 150 ng/ml are highly specific for prolactin-secreting pituitary adenomas. The prolactin cell adenoma or prolactinoma is the most common tumor type that autonomously secretes prolactin. Other pathological entities that contain prolactin granules and are capable of autonomous prolactin secretion include the mixed prolactin-cell and growth-hormone-cell adenomas, acidophil stem-cell adenomas, and mammosomatotroph-cell adenomas.14-16,28 Any structural lesion exerting pressure on the pituitary stalk and/or inferior hypothalamus (such as a craniopharyngioma, nonfunctional pituitary adenoma, or aneurysm) can cause modest elevations of serum prolactin levels. In patients with sellar lesions in whom the serum prolactin is only moderately elevated (≤ 100 ng/ml), it is difficult to determine the mechanism for the hyperprolactinemia. In patients with serum prolactin levels over 200 ng/ml, one can reasonably assume that the hyperprolactinemia is due to autonomous secretion of prolactin by a prolactin-secreting pituitary adenoma. Certainly, when the serum prolactin level is 500 ng/ml or greater, there is no other pathological entity that can account for this finding and the diagnosis is established. Levels in the range of 1000 ng/ml imply invasiveness of the prolactin-secreting pituitary adenoma, especially into the cavernous sinus.20,27

Regarding the issue of performing surgery to obtain a tissue diagnosis, it is our opinion that there is no necessity to perform a surgical procedure solely to obtain a biopsy specimen prior to the institution of medical or radiation therapy if the serum prolactin level is over 200 ng/ml. If there is a small chance of curing or controlling this group of patients with surgery, medical therapy with bromocriptine may be a more reasonable therapeutic option. Our experience and that of others has indicated that the regular daily administration of bromocriptine will decrease serum prolactin levels regardless of the etiology of the hyperprolactinemia.2,5,7,9,21,23,32,34 The great majority of pituitary tumors that contain prolactin granules and autonomously secrete prolactin will demonstrate a reduction in size following the institution of bromocriptine therapy.5,30 This reduction in size, which persists as long as the patient is taking bromocriptine, is frequently accompanied by improvement or resolution of clinical symptoms and signs, particularly visual field defects and diminished acuity. The pathological changes underlying these clinical improvements include a decrease in cytoplasmic volume resulting from a reduction of ribosomes, rough endoplasmic reticulum, and Golgi complexes.5,25,30 There is, however, no evidence of lysosomal accumulation, necrosis, vascular or endothelial cell damage, platelet aggregation, or thrombosis.5 Bromocriptine, therefore, is not tumoricidal. When the drug is withdrawn one can expect the tumor to reexpand, the symptoms to recur, and the hyperprolactinemia to return.

In patients with preoperative serum prolactin levels over 200 ng/ml but less than 500 ng/ml, the disease control rate following transsphenoidal surgery in our

<table>
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<th>Authors &amp; Year</th>
<th>Preop Serum Prolactin Levels (ng/ml)</th>
<th>Total Cases</th>
<th>Control Rate</th>
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<tr>
<td>Bertrand, et al., 1983</td>
<td>200–500</td>
<td>18</td>
<td>9</td>
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<tr>
<td></td>
<td>&gt; 500–1000</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt; 1000</td>
<td>9</td>
<td>2</td>
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<tr>
<td>Hardy, 1983</td>
<td>250–500</td>
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<td></td>
<td>&gt; 500–1000</td>
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<td>&gt; 1000</td>
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<tr>
<td>Barrow, et al., 1988</td>
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<td>26</td>
</tr>
<tr>
<td></td>
<td>&gt; 500–1000</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt; 1000</td>
<td>21</td>
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The favorable shrinkage of cells without allowing time was that the 6-week period was adequate time to induce a significant increase in perivascular fibrous tissue in those who had not received bromocriptine. In a subsequent series was 68%. Although this is lower than the control rate in patients with prolactin levels less than 200 ng/ml, it is our opinion that transsphenoidal microsurgery is a good option for most patients with preoperative serum prolactin levels under 500 ng/ml. However, for patients with preoperative prolactin levels over 500 ng/ml and especially for those over 1000 ng/ml, the chance of surgical control of the disorder is such that initial treatment with bromocriptine is probably the best option. These patients usually have a reduction in prolactin levels, their tumors usually shrink, and symptoms often improve or resolve. Even patients with significant visual field defects will usually experience rapid improvement in vision after the institution of bromocriptine therapy.

It should be stressed that these surgical control rates may possibly be even lower than is being reported if these patients are followed for longer periods of time. Serri, et al., reviewing Hardy's series, emphasized the necessity for long-term monitoring in assessing a true control rate in patients undergoing transsphenoidal surgery for prolactinomas. They found that 12 of 24 patients with microprolactinomas and four of five patients with macroprolactinomas exhibited recurrence of hyperprolactinemia 6.2 ± 1.5 years after surgery. A longer follow-up period in our patients with preoperative serum prolactin values over 500 ng/ml may make surgical therapy even less attractive.

Also to be considered in patients with very high levels of serum prolactin is the possibility that preoperative treatment with bromocriptine will cause reduction in tumor size such that subsequent management by surgery will provide a better chance of achieving a cure. We have had some experience with this method and, from a review of the results, we are not convinced that this therapeutic approach improves the disease control rate. Furthermore, the data suggest that the prolonged and regular use of bromocriptine in patients with microprolactinomas reduces the cure rates in patients who subsequently undergo transsphenoidal surgery. Landolt, et al., showed that the success rate in patients with macroprolactinomas treated with bromocriptine for at least 1 year was 44% compared with 78% in those who had not received bromocriptine. In a subsequent study, Landolt and Osterwalder showed that there was a significant increase in perivascular fibrous tissue in the treated group as compared to those patients who did not receive bromocriptine. They postulated that the shrinkage of tumor cells induced by bromocriptine caused enlargement of the extracellular and perivascular spaces, which then became filled by the deposition of collagen, thus producing a denser consistency of the adenoma. Based on this finding, when we used bromocriptine as a preoperative adjunct to shrink a large prolactinoma prior to surgery, the drug was given for a period of about 6 weeks before surgery. Our reasoning was that the 6-week period was adequate time to induce the favorable shrinkage of cells without allowing time for increased fibrosis.

The disease control rates for the patients in this series are provided as a reference to indicate the expected results based on preoperative serum prolactin levels. They should be used as guidelines to individualize recommendations for management of each patient. Based on our surgical results in this series, the following therapeutic guidelines are proposed for patients with pituitary tumors and very high serum prolactin levels:

1. In patients with preoperative serum prolactin levels over 200 ng/ml but less than 500 ng/ml, the surgical control rate of 68% is high enough to recommend surgery as the initial therapy in the majority of patients.

2. Surgery is not recommended as primary therapy in patients with a serum prolactin level over 500 ng/ml but under 1000 ng/ml or for those with a level over 1000 ng/ml, because the expected control rates are only 30% and 14%, respectively. We prefer to give the patient the option of treatment with bromocriptine alone or a 6-week course of bromocriptine followed by transsphenoidal microsurgery if the post-bromocriptine CT scan shows a significant reduction in tumor size. In either case, the initial bromocriptine dosage is 2.5 mg three times daily with increases in the dosage if there is no clinical or CT improvement.

3. In the unusual case where the serum prolactin level is over 500 ng/ml and the tumor enlarges and/or symptoms of mass effect (especially visual) do not resolve in patients receiving bromocriptine, surgery would be indicated to debulk the tumor. In this situation postoperative radiation therapy is usually recommended.

References


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Address reprint requests to: Daniel L. Barrow, M.D., Division of Neurosurgery, The Emory Clinic, 1365 Clifton Road N.E., Atlanta, Georgia 30322.

D. L. Barrow, J. Mizuno, and G. T. Tindall

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