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ORIGINAL INVESTIGATION

# Prolactin response to an acute bromocriptine suppression test (ABST) following surgical debulking of macroprolactinomas

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**Abstract**

Introduction: In centers with tight budgets treating macroprolactinomas with transsphenoidal surgery remains an appealing option because it may increase the efficacy of dopamine agonists (DA) postoperatively. The aim of our study was to determine whether surgical debulking of prolactinomas enhances the response to DA using the results of an acute bromocriptine suppression test (ABST) performed pre and post operatively.

Methods: This retrospective case-control study included 12 patients with macroprolactinomas that underwent surgical debulking procedures (9 males; median age: 40 years). ABSTs were performed pre and postoperatively using the following protocol: 1) basal prolactin levels were measured through an indwelling cannula; 2) 2.5 mg of bromocriptine was administered; 3) prolactin levels were measured at hourly intervals for 5 hours after bromocriptine administration. Analyses were performed on log-transformed data.

Results: Postoperatively, patients had lower prolactin during the ABST (mean difference-0.701, 95% CI -1.170 -.231, P=0.005), but without any difference in dynamics of prolactin decrease. Baseline prolactin levels correlated positively with prolactin levels at the end of the bromocriptine test. This was evident prior (ρ=0.715, P=0.009) and after surgery (ρ=0.909, P<0.001, P=0.009). Likewise, there was no correlation between baseline prolactin levels and absolute change in prolactin levels at the end of the bromocriptine test.

Conclusion: Prolactin levels decreased significantly during the ABST both pre and postoperatively, but without any difference in dynamics of prolactin decrease. Although our results did not show that surgical debulking enhances the response to DA, further studies are required to determine whether absolute volume reduction affects this relationship.

**Key words:** acute bromocriptine suppression test, macroprolactinoma, surgical debulking

## 1. Introduction

Prolactinomas are the most common pituitary adenomas. They are divided, based on size, into microprolactinomas (<1 cm) and macroprolactinomas (>1 cm). The first-line treatment of symptomatic micro and macroprolactinomas are dopamine agonists (DA). DA effectively lower prolactin levels, decrease tumor size, and restore gonadal function [1-3]. The two most commonly used DA are bromocriptine and cabergoline. Cabergoline is more effective in normalizing prolactin (PRL) levels and in reducing tumor size but is more expensive. Common side effects of DA include nausea, postural hypotension, gastrointestinal discomfort, and dizziness, and are more often reported in bromocriptine users. Macroprolactinomas generally require higher doses of DA [4] and are more resistant to therapy [5]. Because DA are highly effective, the role of transsphenoidal surgery in the treatment of prolactinomas is debated [6]. Surgery is usually reserved for patients that do not respond or are intolerant to medical therapy, when compressive symptoms or cystic changes are present, and when pituitary apoplexy occurs [1]. However, because of the side-effect profile and costs of DA, some authors advocate that all macroprolactinomas be treated with transsphenoidal surgery with adjuvant medical therapy given as needed [7]. This is especially true in low-income countries were transsphenoidal surgery remains a reasonable alternative to life-long DA therapy, especially if this enables lower doses of DA to be used postoperatively. Moreover, several studies have linked prolonged DA use with impulsive behavioral disturbances including gambling, hypersexuality, and bulimia [8, 9].

Studies have shown that surgical debulking of growth hormone-secreting pituitary tumors enhances the response to somatostatin analogs [10, 11] and the same may hold true for prolactinomas and DA therapy. The aim of this study was to determine whether surgical debulking of prolactinomas enhances the response to DA using the results of an acute bromocriptine suppression tests (ABST) performed pre and post operatively.

## 2. Methods

This retrospective case-control study included patients with benign macroprolactinomas that underwent surgical debulking procedures in a single experienced center. Using an electronic medical database, 12 patients (9 males, 3 females) ages 25-74 years (mean age 44 years) with pre and post-operative ABSTs were identified. Macroprolactinomas were defined as pituitary tumors >10 mm seen on pituitary MRI imaging with prolactin levels five times above the reference interval. All patients underwent ABSTs preoperatively. The following protocol was used for the ABST: 1) following an overnight fast patients were placed in a stress-free environment and basal prolactin levels were measured through an indwelling cannula after 30 min; 2) patients were then asked to take a single dose of bromocriptine (2,5 mg); 3) prolactin levels were measured at hourly intervals for 5 hours after bromocriptine administration.

A skilled neurosurgeon performed an endoscopic transsphenoidal surgical debulking procedure in all patients. Postoperative ABSTs were repeated in patients with tumor residuals confirmed by postoperative MRI imaging. A 1.5-Tesla MRI was used according to the standard protocol for pituitary imaging. Tumor size was measured using the longest tumor diameter.

### 2.1 Statistical analysis

Patient characteristics were assessed using descriptive statistics presented as a median with interquartile range values. Independent continuous variables were compared using Mann-Whitney test and categorical variables were compared using Fisher's exact test. In order to normalize the distribution of data, serum prolactin levels were expressed as ratio of serum prolactin levels and the upper value of the reference interval. Afterwards, the serum prolactin ratio was transformed by logarithm to base 10. Prolactin levels during the acute bromocriptine test before and after surgery were compared with linear mixed effects model with AR-heterogeneous covariance structure. All correlations were done by using Spearman correlation coefficients. Software SPSS 20.0 for Windows was used to perform all the analyses. P value <0.05 was considered significant.

## 3. Results

Patients had a median age of 40 years (29-60). Preoperative median tumor size was 24.0 mm (12.5-34.5) and prolactin levels were 54.3 (28.8-241.2) times higher than the upper reference interval value. Postoperatively, prolactin levels decreased 8.8 times, and median prolactin levels were 6.2 (3.1-19.3) above the upper reference interval value (Table 1). Prolactin levels decreased significantly during the ABST both preoperatively and postoperatively (mean difference -.578, 95% CI -.653 -.503, P<0.001). Postoperatively, patients had lower prolactin during ABST (mean difference -.701, 95% CI -1.170 -.231, P=0.005), but without any difference in dynamics of prolactin decrease (Figure 1). Baseline prolactin levels correlated positively with prolactin levels at the end of bromocriptine test. This was evident prior (ρ=0.715, P=0.009) and after the surgery (ρ=0.909, P<0.001, P=0.009). Likewise, there was no correlation between baseline prolactin levels and absolute change in prolactin levels at the end of bromocriptine test.

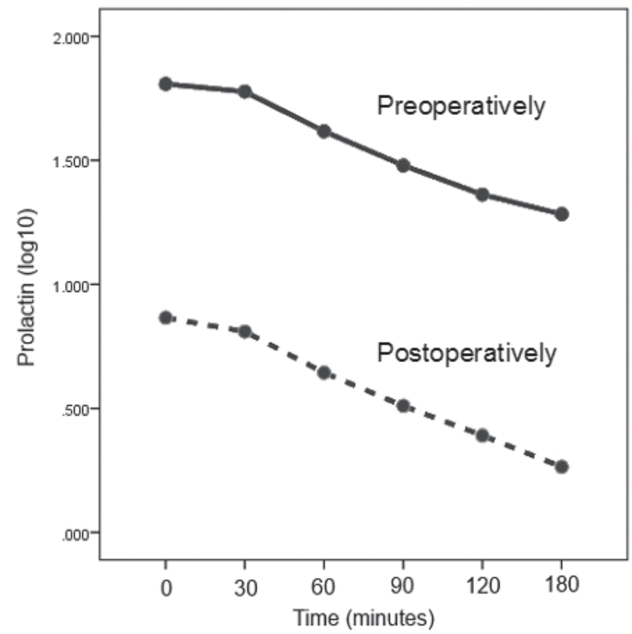


**Figure 1.** Prolactin response during the acute bromocriptine suppression test (ABST) pre and postoperatively.

**Table 1. Prolactin levels (expressed as ratio of serum prolactin levels and the upper value of the reference interval) in an acute bromocriptine suppression test before and after tumor load reduction**

| | Preoperativley | | | Postoperativley | | | |
|---|---|---|---|---|---|---|---|
| | Median | Percentile 25 | Percentile 75 | Median | Percentile 25 | Percentile 75 | P value |
| PRL 0' | 54.26 | 28.80 | 241.22 | 6.17 | 3.14 | 19.32 | <0.001 |
| PRL 30' | 47.500 | 26.267 | 224.841 | 5.163 | 2.985 | 16.749 | <0.001 |
| % Δ | .0 | -26.4 | 1.3 | -10.1 | -21.9 | -5.1 | >0.3 |
| PRL 60' | 30.75 | 16.50 | 162.63 | 3.57 | 1.60 | 9.56 | <0.001 |
| % Δ | -53.3 | -90.8 | -9.6 | -54.1 | -69.5 | -21.3 | >0.3 |
| PRL 90' | 26.63 | 10.20 | 120.05 | 2.23 | 1.28 | 5.84 | <0.001 |
| % Δ | -120.9 | -224.2 | -12.2 | -132.1 | -172.0 | -72.8 | >0.3 |
| PRL 120' | 17.05 | 7.28 | 80.30 | 1.70 | .97 | 4.05 | <0.001 |
| % Δ | -186.1 | -378.1 | -49.4 | -206.5 | -338.3 | -114.7 | >0.3 |
| PRL 180' | 11.135 | 6.138 | 63.892 | 1.362 | .768 | 2.886 | <0.001 |
| % Δ | -294.7 | -574.9 | -65.9 | -292.8 | -474.1 | -178.5 | >0.3 |

## 4. Discussion

Our study showed that following surgical debulking of macroprolactinomas dynamics of prolactin suppression remained the same following bromocriptine administration. In this study, the results of an ABST were used as an indicator of tumor response to DA therapy. Using this premise, there was no change in prolactin suppression dynamics following surgery. However, this can be due to insufficient minimal surgical reduction. A retrospective study of 86 patients with growth-hormone secreting tumors that were poorly responsive to medical therapy (somatostatin analogues) had significantly improved responses after surgical debulking of at least 75% of the tumor volume [10]. Similarly, tumor load reduction may affect response to DA therapy. Because postoperative tumor size was not recorded and the amount of tumor removed is unknown, further studies are required to test this potential correlation.

In centers with experienced neurosurgeons, surgical debulking may enable lower doses of DA to be used for hormonal control. This was shown in a recent study that compared remission rates of microprolactinomas treated with medical therapy alone and macroprolactinomas treated surgically with adjuvant DA. The authors found similar remission rates and prolactin levels in the two cohorts using similar doses of DA [7]. Furthermore, a retrospective study that included 63 patients (27 patients with microprolactinomas, 20 with macroprolactinomas and 16 with invasive macroprolactinomas) reported higher efficacy of DA treatment following surgical debulking in previously DA-resistant patients [12]. Seven out of 15 (47%) previously DA-resistant patients had PRL normalization with a significantly lower mean dose of cabergoline after surgery (2.4 mg/week preoperatively; 1.4 mg/week postoperatively, P=0.01). However, similar to our study, there was no difference in the relative reduction of PRL with DA treatment before (mean decrease of 30 +/- 17%) or after surgery (mean decrease of 22 +/- 24%). Therefore, the improved postoperative hormonal control likely results from tumor load reduction rather than enhanced tumor sensitivity to dopaminergic inhibition. As reported by Caccavelli et al. the intrinsic sensitivity of prolactinomas to DA is related to the D2 dopamine receptor expression on tumor cells, which should not be affected by surgical debulking [13]. Despite these findings, surgery or even debulking procedures remain an appealing option, especially in young motivated patients that require higher-than-standard doses of DA in order to minimize the side effects and costs of long-term treatment with DA.

Recently, studies have reexamined the outcome of patients treated by transsphenoidal surgery, reporting remission rates for microprolactinomas between 50-90% and macroprolactinomas between 30-80% [6, 14-20]. One study reported different characteristics of patients treated surgically from those in the general prolactinoma population, with a relative selection of male patients with larger tumors and a higher rate of DA resistance in those treated surgically. Because of these different patient, and therefore tumor characteristics, valid comparisons between surgical and medical remission rates cannot be made [12]. This can explain the various surgical remission rates reported between centers, which are not solely attributed to better surgical performance. Centers that more readily or routinely treat prolactinomas with transsphenoidal surgery (as is the case in our center) might have higher remission rates than those that reserve surgery for more aggressive or DA-resistant tumors.

One major limitation of our study was that postoperative tumor size was not recorded. As already mentioned, absolute change in tumor size may affect DA efficacy. Furthermore, it is unknown whether the ABST mimics real-life tumor response to DA; therefore, these results must be interpreted with caution and additional studies are required to determine if these results are comparable to prolactin levels following DA treatment. Furthermore, results may vary according to which DA is used, as it is known that cabergoline is more effective that bromocriptine.

Although our study did not show any changes in prolactin dynamics following surgery, transsphenoidal surgery of prolactinomas remains an appealing option as lower doses of DA may enable hormonal control.

## Author contributions

LSK gave the idea for the article, wrote the paper, participated in drafting the article and gave her final approval. MS, DS and VČ participated in data acquisition, drafting of the article and gave their final approval. JJ and LB performed the literature review, statistical analyses and gave their final approval. MK and MV critically revised the manuscript, gave suggestions regarding data analysis and presentation and gave their final approval.

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