CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4161657

Available online at: http://www.iajps.com *Research Article*

# A COMPARATIVE STUDY ON THE EFFECTS OF BROMOCRIPTINE AND CABERGOLINE IN FEMALES WITH HYPERPROLACTINEMIC AMENORRHEA

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**Article Received:** August 2020 **Accepted:** September 2020 **Published:** October 2020

**Abstract:**

***Background:*** *Dopamine agonists are the preferred treatment for most patients with hyperprolactinemia disorders. These agents are extremely effective in lowering serum prolactin levels, eliminating galactorrhea, restoring regular menstruation, and reducing tumor size. Dopamine agonists vary in efficacy and tolerability, including bromocriptine, quinagolide, and cabergoline. However, there are relatively few reports worldwide comparing the beneficial and undesirable effects of bromocriptine and cabergoline in the treatment of patients with hyperprolactinemia. Therefore, in this study an attempt was made to compare the efficacy and safety of cabergoline with bromocriptine in amenorrhoeic women with hyperprolactinemia.*

***Place and Duration:*** *In the Gynecology and Obstetric Unit II of Nishtar Hospital, Multan in collaboration with the Pharmacology department of Nishtar Medial University for six-months duration from January 2020 to June 2020.*

***Patients and Methods:*** *One hundred and thirty hyperprolactinemic amenorrhea women were randomized to either cabergoline (0.5 mg weekly) or bromocriptine (2.5 mg twice daily), randomly administered for 8 weeks. The clinical and biochemical status was assessed at the beginning and end of the study.*

***Results:*** *Amenorrhea was maintained in 9 women treated with cabergoline and 20 women treated with bromocriptine. Galactorrhea disappeared in the cabergoline group and persisted in 12 of the bromocriptine group. Normo-prolactinemia was achieved in 87.7% of women treated with cabergoline and 67.7% of women treated with bromocriptine. The reduction in prolactin levels is statistically greater in the cabergoline group compared to the bromocriptine group.*

***Conclusion:*** *Cabergoline and bromocriptine are effective in treating hyperprolactinemic amenorrhea. Cabergoline has advantages over bromocriptine in terms of both efficacy and tolerability, and is therefore the preferred treatment for hyperprolactinemic amenorrhea.*

***Key words:*** *Hyperprolactinemia, amenorrhea, galactorrhea, bromocriptine, cabergoline.*

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*Please cite this article in press Eijaz Ahmed et al* ***A Comparative Study On The Effects Of Bromocriptine And Cabergoline In Females With Hyperprolactinemic Amenorrhea.,*** *Indo Am. J. P. Sci, 2020; 07(10).*

## INTRODUCTION:

Elevated prolactin levels can be due to physiological causes, such as pregnancy and stress, and pharmacological causes, including the use of neuroleptics, estrogens, opiates, antihypertensive drugs, or calcium channel blockers. After eliminating physiological and iatrogenic stimuli as the causes of elevated prolactin levels, the presence of micro- or macro-prolactinaemia is the most likely cause of persistent pathological hyperprolactinemia. Symptoms of hyperprolactinemia include symptoms of gonadal dysfunction, and women often have oligomenorrhoea, amenorrhea, and galactorrhea. Dopamine agonists are the preferred treatment for most patients with hyperprolactinemia disorders; these agents are extremely effective in lowering serum prolactin levels, eliminating galactorrhea, restoring regular menstruation, and reducing tumor size. Mimicking the effects of dopamine, dopamine agonists including bromocriptine, quinagolide, and cabergoline differ in effectiveness and tolerability. Bromocriptine is a semisynthetic ergoline agonist, a dopamine D2 agonist with D1 agonist and antagonist properties. Due to its short half-life (3.3 hours), bromocriptine may require multiple doses throughout the day. About 12 percent of patients do not tolerate this drug at therapeutic doses. The most common side effects are nausea and vomiting, headache, dizziness, and a drop in blood pressure. Administration of bromocriptine by the vaginal route may reduce the incidence of side effects and provide an alternative to oral bromocriptine. According to reports, 5-18% of patients were refractory to treatment with bromocriptine, with only a partial reduction in plasma prolactin levels and no tumor shrinkage. Cabergoline is an ergoline derivative with high affinity and selectivity for D2 receptors. It has an extremely long plasma half-life of approximately 65 hours, allowing administration once or twice a week. In contrast to bromocriptine, cabergoline has a low affinity for D1 receptors. Cabergoline is more expensive than bromocriptine and some physicians may reserve the drug for use in patients with bromocriptine resistance or intolerance16. Cabergoline can be administered in doses of 0.5 to 1.5 mg once or twice a week. As drug dosing is less frequent and the drug is better tolerated, patient compliance may be better with cabergoline than with bromocriptine. Although no harmful effects on the fetus have been reported in more than 300 pregnant women taking cabergoline, it is currently recommended that cabergoline be discontinued one month before conception is attempted. However, there are relatively few reports worldwide comparing the beneficial and undesirable effects of bromocriptine and cabergoline in the treatment of patients with hyperprolactinemia, and such studies are also missing. Therefore, in this study an attempt was made to compare the efficacy and safety of cabergoline with bromocriptine in amenorrhoeic women with hyperprolactinemia.

## PATIENTS AND METHODS:

This study was held in the Gynecology and Obstetrics Unit II of Nishtar Hospital, Multan in collaboration with the Pharmacology department of Nishtar Medial University for six-months duration from January 2020 to June 2020. The study was a randomized 8-week study comparing cabergoline (0.5 mg tablets) with bromocriptine (2.5 mg tablets) for the treatment of amenorrhea with hyperprolactinemia. One hundred and thirty women, aged 20 to 39 years, who had amenorrhea for at least three months and had serum prolactin levels at least twice the upper limit of normal levels at least four weeks after stopping any prior therapy, participated in the study. The study excluded women with pituitary macroadenoma, any condition that could prevent normal menstruation, hyperprolactinemia associated with polycystic ovary syndrome, thyroid or adrenal disease, kidney or liver disease, and a history of ergot allergy. Women who used drugs that affect the secretion of prolactin from the pituitary gland, such as neuroleptics, were also excluded. Each woman was randomly assigned one of the study drugs. Women assigned to the cabergoline group received 1 (0.5 mg) dostinex tablets a week, and those assigned to the bromocriptine group received 2 (2.5 mg) parlodel tablets daily. Serum prolactin levels were measured at the start of the study and 8 weeks after initiation of therapy (end of study) with a commercial kit (immunoradiometric test) (IRMA) kit. The upper limit of normal serum prolactin levels was set at 16 µg / L. Women were monitored during the trial period and asked about side effects after drug administration and at each visit. Patients were not specifically asked about the possible side effects mentioned, but were simply asked if they had any problems or difficulties with the drug. Each complaint was discussed with the patient and if it appeared to be related to the drug it was reported as a side effect of the drug. The effectiveness of treatment was assessed on the basis of the onset of menstruation, the absence of galactorrhea and the normalization of serum prolactin levels. All values are mean ± SD. Paired Student's t-test was used to compare serum prolactin levels at baseline and post-treatment. The unpaired Student's t-test was used to compare the two treatments. The Z-test was used to compare the frequency of amenorrhea, galactorrhea, and side effects in both groups. The significance level was considered the level of significance at $P \leq 0.05$.

**RESULTS:**

The menstrual cycle was normalized in 56 women (86%) in the cabergoline group and 45 women (69.23%) in the bromocriptine group. Galactorrhea disappeared in all galactorrhea women (100%) in the cabergoline group, while in the bromocriptine group galactorrhea disappeared in 44 women (78.6%) with galactorrhea (Table 1). Women in the cabergoline and bromocriptine groups were comparable in terms of age (mean 28.96 ± 5.24 years for the cabergoline group and 28.2 ± 4.63 years for the bromocriptine group) and baseline serum prolactin (P> 0.5). Serum prolactin levels normalized in 57 of 65 (87.7%) women taking cabergoline and 44 of 65 (67.7%) women taking bromocriptine.

Table 1. Number of women with amenorrhea and galactorrhea before and after treatment with Cabergoline or Bromocriptine.

| Drug | Amenorrhea (No Women) | | | Galactorrhea | | |
|---|---|---|---|---|---|---|
| | Before | After | Improved | Before | After | Improved |
| Cabergoline | 65 | 09 | 56(86%) | 52 | - | 52(100%_ |
| Bromocriptine | 65 | 20 | 45(69.23%) | 56 | 12 | 44 (78.6%_ |

Table 2. Serum Prolactin Level Before and after treatment with Cabergoline.

| Parameter | Range (µg/L) | Mean± SD (µg/L) | P value |
|---|---|---|---|
| Before Treatment | 32.3-140.4 | 59.13±29.43 | P<0.001 |
| After Treatment | 0.7-43.2 | 7.18±9.84 | |

Table 3. Prolactin Level Before and After Treatment With Bromocriptine.

| Parameter | Range(µg/L) | Mean ± SD(µg/L) | P value |
|---|---|---|---|
| Before Treatment | 32.5-170.4 | 58.48±29.75 | P<0.001 |
| After Treatment | 0.9-63.2 | 18.01±15.34 | |

The mean serum prolactin level decreased after 8 weeks of treatment from the baseline 59.13 µg / L to 7.18 µg / L in the cabergoline group and from 58.48 µg / L to 18.01 µg / L in the bromocriptine group. The differences between the baseline measurement and the measurement after 8 weeks were statistically significant for both groups (p <0.001) (Tab. 2 and 3). The decrease in prolactin levels after 8 weeks of treatment was on average 51.95 µg / L in the cabergoline group and on average 40.47 µg / L in the bromocriptine group. The difference between the two treatments is significant (P <0.001) (Table 4).

Table 4. Reduction of Prolactin Level in Cabergoline and Bromocriptine Groups.

| | Cabergoline | Bromocriptine | P value |
|---|---|---|---|
| Mean ± SD | 51.95±28.19 | 40.47±22.98 | P<0.001 |
| Percentage | 87.86 | 69.2 | |

Serum prolactin levels in 8 women from the cabergoline group, whose serum prolactin level was not normalized, was felt from 70.15 ± 40.2 µg / l to 30.01 ± 7.5 µg / l, while in the case of bromocriptine the level of There were 21 women in whom serum prolactin levels were not normalized, from 82.05 ± 36.57 µg / L to 38.25 ± 9.37 µg / L after treatment. Regarding side effects of drugs, with cabergoline therapy, 28% (18) of the women experienced side effects compared with 55% (36) of the women taking bromocriptine. Headache and nausea are more common in women treated with cabergoline, while gastrointestinal side effects, including nausea, vomiting and abdominal pain are more common with bromocriptine (Table 5).

Table 5. Adverse Effects of Cabergoline and Bromocriptine.

| Adverse Effects | Cabergoline 8(28%) | Bromocriptine 6(55%) | P value |
|---|---|---|---|
| Nausea | 8(12%) | 30(46%) | <0.001 |
| Vomiting | 4(6%) | 15(23%) | <0.007 |
| Abdominal pain | 7(10%) | 18(27%) | <0.016 |
| Headache | 8(12%) | 12(18%) | 0.340 |
| Postural hypotension | 6(9%) | 6(9%) | 1.000 |
| Dizziness | 4(6%) | 8(12%) | 0.234 |
| Drowsiness | 3(5%) | 9(14%) | 0.083 |

## DISCUSSION:

Data from this study showed that cabergoline and bromocriptine are effective in treating amenorrhea with hyperprolactinemia and that cabergoline is more effective and safer than bromocriptine. The effectiveness of bromocriptine has been studied in previous studies that showed the benefits of bromocriptine in reducing serum prolactin levels and restoring regular menstrual bleeding and alleviating galactorrhea in the majority of patients, which is consistent with the results of the study. The percentage of decrease in serum prolactin concentration obtained in this study in the bromocriptine group (69.2%) is close to the value of 70% reported by Verhelst et al. And Van der Heijden et al. Our results are better than those obtained by Webster et al, Where the success rate was only 58%, and by Sabuncu et al. And Pascal Vigneron et al., Where the success rate was 59% and 48.2%, respectively. Regarding cabergoline, the current results are consistent with several other studies reported in the last 10 years showing the effectiveness of cabergoline treatment in hyperprolactinemia. Our percentage of success in achieving normal levels in the cabergoline group is within 82-93% of the success of other studies. The results showing that cabergoline is more effective than bromocriptine in both normalizing serum prolactin levels and restoring regular menstruation as well as reducing galactorrhea are consistent with results obtained by other researchers who also found cabergoline superior to bromocriptine in treating women with hyperprolactinemia and lack of menstruation. The number of patients who experienced adverse events in this study was low in the cabergoline group (28%) compared to the bromocriptine group (55%). There were significantly fewer gastrointestinal symptoms in the cabergoline group compared to the bromocriptine group. Our results are similar to those obtained in previous studies, which also showed fewer side effects with cabergoline and a higher incidence with bromocriptine. The ergot derivative quinagolide is likely to have fewer side effects compared to bromocriptine. This difference may be due to the fact that quinagolide has a high specificity for dopamine D2 receptors, while bromocriptine also acts on dopamine D1 receptors. Cabergoline has a low affinity for dopamine D1 receptors and has a high affinity for D2 receptors. Thus, the better tolerance of cabergoline compared to bromocriptine may be similar to quinagolide due to its high affinity only for D2-type receptors.

## CONCLUSION:

In summary, cabergoline and bromocriptine are effective in treating amenorrhea with hyperprolactinemia. Cabergoline has advantages over bromocriptine in terms of both efficacy and tolerability, and is therefore the preferred treatment for hyperprolactinemic amenorrhea.

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