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# Comparison Between Bromocriptine and Cabergoline Drugs as a Treatment of Hyperprolactinemia Among Sudanese Infertile Amenorrhic Women

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## Abstract

This is a retrospective study, conducted at Reproductive Health Care Centre, Khartoum. The study aimed to compare between bromocriptine and cabergoline medications for treatment of hyperprolactinema among infertile a menorrhic Sudanese Women. 105 women were selected for the study, 54 were treated with bromcriptine and 51 treated with cabergoline. The study continued for 22 weeks. Serum prolactin level was measured initially and after weeks 2, 4, 6, 8, 10, 12, 16, 18, 20, and 22. The efficacy of both treatments was assessed by normalization of serum prolactin level, menstrual cycle resumption, pregnancy achievement and side effects of both medications. The results showed that cabergoline is more effective compared to bromcriptine in terms of normalization of prolactin serum level, menstrual cycle resumption and pregnancy achievement. Both medications showed common side effects but to a lesser extent by cabergoline.

## Keywords

Pregnancy, Prolactin, Infertility, Amenorrhea

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## 1. Introduction

Amenorrhea is the absences of menses if the woman has never menstruated; it is called primary amenorrhea [1]. When a women who has at least one cycle of menstruation and a subsequent cessation for minimum of 3-6 months, it is termed secondary amenorrhea [2]. Hyperprolactinemia is a common endocrine disorder that can be associated with significant morbidity [3] It is characterized by the presence of high level of prolactin in the blood more than 10-28 mg/ L in women [4]. Bromocriptine is the first dopamine agonist which is introduced 35 years ago into clinical practice, Its half-life is 3 hours, action duration = 8 – 12 hours, so it must be taken twice or three times daily [5]. Bromocriptine successfully normalized serum prolactin levels within 6 months [6]. Cabergoline is an ergoline derivative with extremely long plasma half-life of 63 to 109 hours [7]. Cabergoline is a potent and long - acting inhibitor for prolactin secretion, which exhibits high specifity and affinity to dopamine D2 receptor [8]. Several comparative studies considered cabergoline to be superior to bromocriptine for the treatment of hyperprolactinemia and its effective in many patients resistance to bromocriptine [9]. A study in Irag revealed that 87.7% and 67.7% of hyperprolactinemic females with a menorrhea treated with cabergoloine and bromcriptine respectively have achieved normal prolactin level [10]. Meta- analysis controlled trials revealed that a significant difference in favour of cabergoline regarding normalization of serum prolactin, menstruation with return of

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ovulatory cycle [11]. Lower prevalence of side effects were reported in subjects treated with cabergoline and pregnancy was more achieved among 82% of women treated with cabergoline compared to 56.4% treated with bromocriptine (p- value < 0.001) [12]. The same authors concluded that the presence of glactorrhea and irregular menstrual cycle were significantly lower in the group treated with cabergoline.

# 2. Materials and Methods

This is a retrospective study aimed to compare between bromocriptine and cabergoline as medications for treatment of hyperprolactinemic amenorrheic infertile women. The study was performed during the period 2008 to 2010. 105 infertile amenorrheic women with hyperprolactinemia attended Reproductive Health Care Centre were selected for this study. A complete history and general physical examination was performed before infertility examination. The selected group was hyperprolactinemic with amenorrhea for at least 3 months with at least one year infertility. The study group was randomly divided into two groups, group A = 54 females treated by bromocriptine, group B =51 females treated by cabergoline. Serum prolactin level was measured twice before the start of the treatment. The efficacy of the two medications was evaluated according to the achievement of normal prolactin level, menstrual cycle resumption, pregnancy achievement and side effects. Serum prolactin and progesterone were measured by Enzyme Immune-Assay (EIA).

## 2.1. Inclusion Criteria

Women with primary or secondary infertility, primary or secondary a menorrhea, hyperprolactinemia with or without glactorrhea (prolactin > 800 IU/l) and normal FSH, LH and TSH, normal Complete Blood Count and negative pregnancy test.

## 2.2. Exclusion Criteria

Infertile women with hyperprolactinemia with polycystic ovary disease, thyroid disorders, renal or hepatic diseases, male factor or un- explained infertility.

An informed consent was obtained from each participant before study started. Initial prolactin serum level was 1698.87 ± 683.7 IU and 1722.00 ± 629.8 IU of group A and B respectively (p =0.816).

## 2.3. Study Design

Bromocriptine started as a daily dose of 1.25 mg / day for 3 days then the dose increased to 2.5 mg / day for the next 4 days, then increased to 2.5 mg twice a day and the dose was adjusted (if necessary) until the end of the experimental period. Women assigned to cabergoline initially received 0.25 mg on the first week and the dose increased to 0.50 mg/week and the dose was adjusted if necessary until the end of experimental period. Treatment was stopped if pregnancy was achieved or menstrual cycle was resumed.

## 2.4. Follow Up

Serum prolactin was measured initially (before treatment started), then at weeks 2, 4, 6, 8, 14, 16, 20, 22 and 24. Pregnancy test was performed a week before the start of the treatment. If menses was resumed, plasma progesterone was measured during the luteal phase (day 21) as indicator of ovulation. At each visit, women were asked about side effects of each medication .Blood samples were collected after 2, 4, 6, 8, 10, 12, 14, 16, 20, 22 and 24 weeks. Treatment was stopped if pregnancy was confirmed by measurement of B-H CG and documented by trans-vaginal sonography at 6-7 weeks gestational age.

# 3. Results

**Table 1.** Demographic Data of the Study Group.

| Characteristics of study group | Group (A) N=54 | Group (B) N=51 | P-value |
|---|---|---|---|
| Age (years) | 31 ± 6.0 | 29 ± 5.6 | 0.13 |
| Weight (Kg) | 63 ± 7.0 | 62 ± 7.6 | 0.45 |
| Duration of infertility (years) | 3.98 ± 3.5 | 3.3 ± 2.3 | 0.26 |
| Duration of a menorrhea (months) | 9.7 ± 8.9 | 7.5 ± 9.3 | 0.21 |
| Prolactin serum level (mIU/L) | 1698.7 ±683.7 | 1722 ± 629.8 | 0.82 |
| FSH (IU/L) | 7.0 ± 3.43 | 7.2 ± 3.0 | 0.75 |
| LH (IU/L) | 4.0 ± 2.3 | 4.2 ± 2.5 | 0. 80 |

Table 1 showed the demographic and clinical data of both study groups. Most of demographic data showed no significant difference between two groups. Age of test groups ranged between 29 ± 5.6 and 31 ± 6.0 years.

**Table 2.** Prolactin serum level of study groups throughout the study period.

| Weeks | Study groups | | p- value |
|---|---|---|---|
| | Group A | Group B | |
| Initial Prolactin serum level (mean ± SD) | 1698.9 ± 685.6 | 1722.0 ± 676.3 | 0.834 |
| Week 2 | 1252.8 ± 521.7 | 1268.1 ± 436.3 | 0.420 |
| Week 4 | 963.3 ± 625.4 | 1030.9 ± 369.2 | 0.326 |
| Week 6 | 833.2 ± 437.2 | 837.1 ± 349.9 | 0.222 |
| Week 8 | 722.4 ± 487.5 | 712.3 ± 326.4 | 0.457 |
| Week 10 | 627.4 ± 389.6 | 576.0 ± 237.5 | 0.049 |
| Week 12 | 787.0 ± 156.1 | 214.3 ± 214.5 | 0.000 |
| Week 14 | 562.2 ± 24.6 | 441.4 ± 150.8 | 0.000 |
| Week 16 | 550.2 ± 431.6 | 425.5 ± 150.8 | 0.005 |
| Week 18 | 451.6 ± 297.8 | 370.9 ± 184.3 | 0.021 |
| Week 20 | 318.8 ± 271.0 | 305.2 ± 187.4 | 0.137 |
| Week 22 | 334.0 ± 65.3 | 277.9 ± 184.9 | 0.001 |

Normal prolactin serum level = 400mIU/L

Bromocriptine and cabergoline successfully normalized prolactin serum level serum level which was significantly different between two medications (P – value = 0.001).

Menstrual cycle was resumed in both groups. After week 4 of treatment, 14.8% from group A resumed menstrual cycle, in the other group menstrual cycle resumption was recorded by 45.1% (table 3). Menstrual cycle was resumed by 83.6% and 98.1% of participants after weeks 22 and 20 of treatment with bromcriptine and cabergoline respectively.

**Table 3.** Menstrual Cycle Resumption Period of study Group after treatment with bromocriptine or cabergoline.

| Bromocriptine | | | Cabergoline | | |
|---|---|---|---|---|---|
| Group A | | Resumption period (weeks) | Group B | | Resumption period (weeks) |
| Total = 54 | | | Total = 51 | | |
| N = 5 | 9.3% | 2.0 | N= 23 | 45.1% | 4.0 |
| N = 8 | 14.8% | 4.0 | N= 13 | 25.5% | 12.0 |
| N = 3 | 5.6 % | 6.0 | N =8 | 15.7% | 16.0 |
| N = 4 | 7.4 % | 8.0 | N = 5 | 9.8% | 18.0 |
| N = 1 | 1.9 % | 12.0 | N = 1 | 2.0% | 20.0 |
| N = 3 | 5.6 % | 14.0 | Total=50 | 98.1% | - |
| N = 1 | 1.9 % | 16.0 | N* = 1* | 2.0% | - |
| N=19 | 35.2% | 20.0 | - | - | - |
| N = 1 | 1.9 % | 22.0 | - | - | - |
| Total=45 N* = 9* | 83.6 % 16.6% | - | - | - | - |

N*: Number of participants discontinued the treatment.

**Table 4.** Frequency of Pregnant Women after treatment with bromocriptine or cabergoline.

| Medication | Pregnant Women | | Non pregnant Women | |
|---|---|---|---|---|
| | NO | % | NO | % |
| Bromocriptine N=45 | 18 | 40 | 27 | 60 |
| Cabergoline N=50 | 34 | 68 | 16 | 32 |

Pregnancy was achieved in 40% of women after treatment with bromocriptine and in 68% of the group under cabergoline treatment

**Table 5.** Common side effects of bromocriptine and cabergoline medications.

| Side effect | Bromcriptine | | Cabergoline | |
|---|---|---|---|---|
| | (group A) N= 54 | | (group B) N =51 | |
| Nausea | N = 38 | 70.4 % | N = 36 | 70.6 % |
| Vomiting | N = 24 | 44.7 % | N = 14 | 27.4 % |
| Constipation | N = 49 | 90.7 % | N = 39 | 76.5 % |
| Headache | N = 45 | 83.3 % | N = 42 | 82.4 % |
| Dizziness | N = 22 | 70.4 % | N =12 | 23.5 % |
| Abdominal pain | N = 30 | 55.6 % | N = 16 | 31.4 % |
| Fatigue | N = 49 | 90.7 % | N = 39 | 76.5 % |
| Breast pain | N = 39 | 66.7 % | N = 25 | 49 % |
| Hot flash | N = 31 | 57.4 % | N = 24 | 47.1 % |

Both medications showed common side effects but to a lesser extent by cabergoline (table 5). Constipation and fatigue were reported by both test groups. Vomiting and dizziness were more frequent among women treated by bromocriptine.

## 4. Discussion

The results of the present study showed that both bromocriptine and cabergoloine normalized serum prolactin level of infertile amenorrhic women with hyperprolactinemia. Similar findings were reported by many authors [6, 13, 14, 15]. Bromocriptine has the longest history of use for the treatment of hyperprolactinemia, and is well to established as a safe and effective therapy and successfully normalized serum PRL level in 27 patients over a period of 6 months and reduced tumor size by more than half in 26% of patients [6].

According to the present study cabergoline significantly decreased prolactin serum level compared to bromcriptine (p= 0.001) indicating that it is more efficient than bromcriptine (table 2). Cabergoline normalized PRL level in 75-90 % of patients with micro and macroprolactinoma with an average decrease in tumor volume of 72-92% [14]. These findings were further confirmed by a previous study [16] which revealed that cabergoline significantly decreased serum PRL level compared to bromocriptine ($p < 0.05$). Moreover a study in Saudi Arabia revealed that prolactin level reduction was more prominent in cabergoline group in hyperprolactinemic patients (23 females and 13 males) compared to the group under bromocriptine after treatment of 3 months [17], the same authors observed that rate of normalization of serum prolactin was higher in cabergoline group (63%) compared to (41%) of patients under bromcriptine treatment and adverse effect were less frequent in cabergoline group (13.6%) compared to (40%) in bromcriptine group. Furthermore, a study in Turkey showed that cabergoline was more effective than bromcriptine in controlling symptoms with hormone excess, normalizing serum prolactin [18]

In the present study, menstrual cycle resumption was faster and with higher frequency of the group treated with cabergoline, similar findings showed that menstrual cycle was resumed by 96.1% in cabergoline group compared to 83.3% in the other test group [19]. In addition, serum prolactin levels and mensuration with return of ovulatory cycle showed a significant difference in favour of cabergoline [11]. Glactorrhea and irregular menstruation were significantly lower in patients treated with cabergoline than patients treated by bromcriptine ($p < 0.001$ and $p < 0.011$) respectively [12]. Furthermore, bromocriptine or cabergoline normalized prolactin levels, reduce tumor size, and restore ovulation and fertility. Cabergoline is preferred over bromcriptine due to its higher efficacy and tolerability [15]. Another study revealed that cabergoline was more effective than bromcriptine in reducing persistent hyperprolactinemia, amenorrhea/ oligomenorrhea and glactorrhea [3].

Pregnancy was achieved in 22 females and 33 females treated with bromcriptine and cabergoline respectively (table 3). In a previous study [10] a menorrhea persisted in 9 women treated with cabergoline compared to 20 treated with bromcriptine. These findings were confirmed by previous investigators [18, 20], they concluded that significant and better outcome was observed in women who received cabergoline treatment and pregnancy was achieved in a majority of women receiving cabergoline compared to those received bromcriptine.

A study in India, revealed that cabergoline treatment of infertile women with prolactinoma is more effective, it lowers prolactin with better tolerability and much more effective in the achievement of pregnancy in 82% among women treated with cambergoline compared to 56.4% treated with bromcriptine [12].

Common side effects were reported by both test groups, but often higher frequency was reported by the group treated with bromocriptine. Similar findings were previously reported by some authors [10, 12, 17, 19] who concluded that cabergoline induces significant less frequent and short- lived side effects and more effective and better tolerated than bromcriptine in the treatment of patients with hyperprolactinemia. Adverse effect were less frequent in the group treated with cabergoline (13.6%) compared to (40%) in the group treated with brmocriptine [17]. In addition, cabergoline effectively treats hyperprolactinemia, micro and macroprolactinomas with a low incidence of side effects [21]. A retrospective study in Turkey showed that symptoms relief was higher in the cabergoline group than in bromcriptine group, more side effects were recorded by individuals treated with bromcriptine (29.1% and 5.3%) respectively ($p< 0.001$) [18].

Moreover, cabergoline offers considerable advantage over bromocriptine in terms of efficacy and tolerability and adverse effect was noted in 53% of bromcriptine group and 12% in cabergoline group [16].

One of the advantages of treatment by cabergoline, is the easy regimen, since it is taken weekly with a low dose, but bromocriptine should be taken daily with a high dose. These results confirmed that cabergoline is more effective than bromocriptine as reported by previous studies [9, 11] which showed that cabergoline is the most effective drug for treatment of prolactinomas with very good patient compliance with long - term treatment regimen.

## 5. Conclusion

Bromcriptine and cabergoline normalized prolactin level, and they are useful as a treatment of infertile a menorrhic women with hyperprolactinemia. Cabergoline is superior and efficient treatment compared to bromcriptine, in terms of low dose regimen to normalize prolactin serum level, menstrual cycle resumption, pregnancy achievement with less frequent side effects.

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