

# Comparison between Bromocriptine and Bromocriptine with Clomiphene Citrate in Term of Efficacy for the Treatment of Hyperprolactinaemic Infertility

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## ABSTRACT

**Aim:** To compare the efficacy of bromocriptine versus bromocriptine with clomiphene citrate for the treatment of hyperprolactinaemic infertility.

**Methods:** This randomized controlled study was conducted at Department of Department of Obstetrics and Gynecology, D.G. Khan Medical College D.G. Khan from August 2014 to February 2015. Total 260 patients with hyperprolactinaemic infertility < 10 years and having age range from 20 years to 38 years were enrolled in this study. Patients were randomly divided into two groups A and B. Efficacy of bromocriptine alone versus bromocriptine plus clomiphene citrate in the treatment of hyperprolactinaemic infertility was compared.

**Results:** Mean age of the patients of Group A was 27. 15±3.85 year and mean age of the patients of group B was 26.27±4.73 years. Efficacy of the treatment was noted in 80(61.54%) and 104(80%) patients of Group A & B respectively. Statistically significant (P = 0.002) difference between the efficacy of Group A and Group B was found.

**Conclusion:** Results of our study are showing that bromocriptine plus clomiphene citrate is better and more effective than bromocriptine alone in the treatment of hyperprolactinaemic infertility.

**Keywords:** Prolactin, pregnancy, female infertility, bromocriptine, clomiphene citrate.

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## INTRODUCTION

Infertility is characterized as failure to conceive after one year of regular intercourse without using any contraceptive. About one in every eight couples is infertile. Among the patients with infertility, almost 35% patients may be attributed to the male and 55% patients to the female; the remaining 10% patients are undetermined<sup>1</sup>.

Most of the literature on infertility is anecdotal<sup>2</sup>. About 5 million infertile women in the USA, it is estimated that 2(40%) million have medical or hormonal infertility; about 1(20%) million have idiopathic infertility and 2(40%) million have mechanical infertility<sup>3</sup>.

Hyperprolactinemia causes infertility in up to one-third of women with reproductive disorders<sup>4</sup>. The clinical features of hyperprolactinemia are shortened luteal phase, oligomenorrhoea, amenorrhoea and galactorrhoea. The diagnostic evaluation first requires exclusion of other reasons of hyperprolactinemia, like primary hypothyroidism, pregnancy and numerous medications. The 2<sup>nd</sup> step in the diagnostic evaluation is to perform head scan, preferably a MRI<sup>5</sup>.

The purpose of hyperprolactinemia therapy is to correct the biochemical consequences of the hormonal excess<sup>6</sup>. Several dopamine agonists are currently available for the treatment of hyperprolactinemia, including bromocriptine and cabergoline. The dopamine agonist, bromocriptine mesylate is often used as initial drug of choice in hyperprolactinemic patients. It is highly effective for normalizing or reducing prolactin levels, resorting normal gonadal function and achieving pregnancy in 56% patients<sup>7</sup>. Bromocriptine has very long history of use and is a safe and effective, well-established and inexpensive treatment option. However, bromocriptine requires multiple daily dosing and some cases are resistant or intolerant to this treatment<sup>8</sup>.

Clomiphene citrate has been used for many years in the treatment of anovulatory infertility<sup>9</sup>. Nowadays, clomiphene citrate is also used with the bromocriptine in the treatment of hyperprolactinemic infertile women with menstrual irregularities and anovulatory cycles in order to achieve earlier pregnancies. A study conducted by Mahmood S et al<sup>10</sup> showed that efficacy of bromocriptine plus clomiphene citrate turned out 75% in the form of conceiving pregnancy.

This study was done to see the efficacy of bromocriptine alone and bromocriptine plus clomiphene citrate so that some practical

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recommendations could be made to achieve maximum number of pregnancies in hyperprolactinemic infertile women with more efficacious treatment regime.

## MATERIAL AND METHODS

This randomized controlled study was conducted at Department of Department of Obstetrics and Gynaecology, D.G. Khan Medical College D.G. Khan. Duration of the study was 6 months (from August 2014 to February 2015). Permission was taken from Institutional Review Committee before the start of study and written informed consent was taken from every patient. Total 260 patients by using non-probability, consecutive sampling technique were enrolled in this study. Patients with hyperprolactinaemic infertility <10 years and having age range from 20 years to 38 years were included in this study. Patients with other reasons of infertility like male factor, unexplained infertility and tubal factors, patient with history PCOS and hyperthyroidism, patients on medication like H-2 receptor blocker, dopamine depleting and dopamine receptor blocker and patients with macroadenoma of pituitary gland were excluded from the study. Infertility was characterized as inability to conceive for at least one year of unprotected intercourse. Hyperprolactinaemia was measured in term of serum prolactin level >20ng/ml, in women of reproductive age (20-38 years) presenting with amenorrhoea or irregular menstrual cycles.

All selected were randomly divided into two equal groups A & B and each group contained 130 patients. Detailed history about menarche age, menstrual cycles and duration of infertility was taken from each patient.

A dose of 1.25mg of bromocriptine was given at bedtime with a snack and gradually increased to 2.5 mg two times a day with food over 3-4 weeks and this treatment was continued for 6 months. Occurrence of pregnancy was awaited for one year after start of treatment. All the patients of Group B were treated with bromocriptine with same dosage and methodology as was mentioned in group A. With the onset of menses, at day 2-6 of menstrual cycle, clomiphene citrate was started at initial daily dose of 50 mg two times a day for first two cycles, then 50mg three times a day for third and fourth cycles and 100mg two times a day for fifth and sixth cycles. Clomiphene citrate was stopped when ovulation was achieved which was confirmed by follicular tracking on trans-vaginal sonography by researcher at day 12 of each menstrual cycle. Total duration of treatment was six months. Occurrence of pregnancy was awaited for one year after start of therapy. After

completion of treatment, efficacy was measured in terms of occurrence of pregnancy which was confirmed by measuring  $\beta$ -HCG in case of one week missed periods (levels of  $\geq 5$ mlU/ml of  $\beta$ -HCG was taken as occurrence of pregnancy and level <5mlU/ml was taken as absent pregnancy). All the findings were entered in pre-designed proforma.

Collected data was entered in SPSS V.17 and analyzed. Mean and SD was calculated for age and duration of infertility. Frequencies were calculated for categorical variables. Efficacy of both groups was compare by using chi-square test. P value  $\leq 5\%$  was considered as statistically significant.

## RESULTS

In present study, total 260 patients with infertility were divided in to equal group A & B and each group consisted on 130 patients. Mean age of the patients of Group A was 27. 15 $\pm$ 3.85 year and mean age of the patients of group B was 26.27 $\pm$ 4.73 years.

Comparison of efficacy between the both groups was done. Efficacy of the treatment was noted in 80(61.54%) and 104(80%) patients of Group A & B respectively. Statistically significant (P=0.002) difference between the efficacy of Group A and Group B was found (Table 1).

Stratification in relation to age was done. Two groups were made Age Group 21-30 years and Age Group 31-38 years for both treatment groups A & B. Total 75 patients of Treatment Group A and 78 patients of Treatment Group B belonged to Age Group 21-30 years. Efficacy of the treatment was noted in 58(77.33%) and 70(89.74%) patients respectively. Difference between the efficacy of both groups was significant (P=0.048). Total 55 and 52 patients of Group A and B were belonged to Age Group 31-38 years. Efficacy of the treatment was noted in 22(40%) and 34(65.38%) patients of treatment group A & B. Difference of efficacy between the both treatment groups was statistically significant (P=0.012) (Table 2).

Maximum duration of infertility was 10 years. Patients were stratified into two groups, duration of infertility  $\leq 5$  years and duration of infertility >5 years. Total 70 patients of Group A and 62 patients of Group B found with duration of infertility  $\leq 5$  years and efficacy was noted in 54(76.92%) and 72(92.16%) patients of Group A and B respectively. Significant (P=0.011) difference between the efficacy of both groups was observed. In patients having duration of infertility >5 years, 70 patients belonged to Group A and 62 patients belonged to Group B and efficacy of the treatment was noted in 29(41.30%) patients and 40(63.83%) patients. Significant (P=0.009) difference

was noted between the efficacy of both treatment groups. (Table 3)

Table 1: Comparison of efficacy between the both groups

Group	Efficacy		Total
	Yes	No	
A	80(61.54%)	50(38.46%)	130
B	104(80%)	26(20%)	130

P value 0.002

Table 2: Comparison of efficacy between the both groups for different age groups

Group	Efficacy		Total	P. Value
	Yes	No		
<b>Age group 21-30 years</b>				
A	58(77.33%)	17(22.67%)	75	0.048
B	70(89.74%)	08(10.26%)	78	
<b>Age group 31-38 years</b>				
A	22 (40%)	33(60%)	55	0.012
B	34(65.38%)	18(34.62%)	52	

Table 3: Comparison of efficacy between the both groups for duration of infertility

Group	Efficacy		Total	P. Value
	Yes	No		
<b>Duration of infertility ≤ 5 years</b>				
A	54 (76.92%)	16(23.08%)	70	0.011
B	72 (92.16%)	06(7.84%)	78	
<b>Duration of infertility &gt; 5 years</b>				
A	29 (41.30%)	41(58.70%)	70	0.009
B	40 (63.83%)	22(36.17%)	62	

## DISCUSSION

Hyperprolactinemia or hyperprolactinaemia or (HP) is the presence of abnormally raised levels of prolactin in the blood stream. Hyperprolactinemia can be occur due to pharmacological, physiological or pathological reasons. The most relevant physiological causes of this disorder are breast feeding and pregnancy<sup>11</sup>.

In our study mean age of the patients in Group A and Group B was 27 (15±3.85 year 26.27±4.73 years). Mean age of the patients with hyperprolactinaemic infertility were reported by Motazedian et al<sup>7</sup> and Husaynei et al<sup>12</sup> as 28 years and 29 years which is in agreement with our study. But Abd Elghani et al<sup>13</sup> reported mean age as 31 years which is higher than our study.

Bromocriptine was introduced in 1972 and still most frequently use as prolactin lowering agent<sup>14</sup>. Bromocriptine has proved its efficacy in decreasing levels of serum prolactin and restoring the regular menstrual bleeding, relieving galactorrhea in most of the cases and restores normal gonadal function in about 70% to 90% cases<sup>15</sup>.

In euprolactinemic infertile patients with or without amenorrhea and galactorrhea, successful

pregnancies have also been achieved by the use of bromocriptine which acts to reduce the normal concentrations of prolactin sufficiently to aid fertility or by acting directly on the dopamine receptors in the gonad.<sup>16</sup> Bromocriptine therapy based on clinical criteria is quite safe with minimal side effects. There is no evidence of teratogenic effect of bromocriptine; however, patients are usually instructed to stop bromocriptine therapy with the first missed period. Baseline infertility investigations, including tomography of pituitary fossa, should be performed prior to bromocriptine therapy, and when possible, serum prolactin should be monitored<sup>17</sup>.

Clomiphene citrate has been used for many years in the treatment of anovulatory infertility, although its mode of action is still incompletely understood. By competing with the binding site for estrogen at the hypothalamic level, clomiphene may stimulate the release of gonadotrophins at the pituitary level<sup>17</sup>.

In present study bromocriptine alone was found effective in 61.54% patients and bromocriptine plus clomiphene citrate was found effective in 80% patients and difference between the efficacy of both treatment groups was statistically significant (P=0.002).

In one comparative study, Mahmood et al<sup>10</sup> compared the efficacy of bromocriptine and bromocriptine plus clomiphene citrate for the treatment of hyperprolactinaemic infertility. They found bromocriptine plus clomiphene citrate effective as compare to bromocriptine alone. Bromocriptine found effective in 65% patients and bromocriptine plus clomiphene citrate was found effective in 75%. Results of this study are comparable with the results of our study. Study of Anateet al<sup>18</sup> also showed better efficacy of bromocriptine plus clomiphene citrate in achieving pregnancy as compared to bromocriptine alone.

In our study bromocriptine found effective in 61.54% patients. Findings of Sabuncuet al<sup>7</sup> and Webster et al<sup>19</sup> are in agreement with our findings. They noted the efficacy of bromocriptine as 59% and 58% respectively. But Motazedian et al<sup>7</sup> and Mahmood et al<sup>10</sup> had found efficacy of bromocriptine as 56% in their studies which is a little lower than our study.

## CONCLUSION

Results of our study are showing that bromocriptine plus clomiphene citrate is better and more effective than bromocriptine alone in the treatment of hyperprolactinaemic infertility.

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