ORIGINAL ARTICLE

Comparison of Efficacy of Bromocriptine Alone Versus Bromocrptine Plus Clomiphene Citrate in the Treatment of Hyperprolactinaemic Infertility

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ABSTRACT

Background: Several dopamine agonists are currently available for the treatment of hyperprolactinemia, including bromocriptine. Now-a-days, clomiphene citrate is also used with the bromocriptine in the treatment of hyperprolactinemic infertile women.

Aim: To see the efficacy of bromocriptine alone and bromocriptine plus clomiphene citrate, so that some practical suggestions could be made to achieve higher number of pregnancies among the hyperprolactinemic infertile women.

Methods: A total of 196 patients, 20 to 38 years of age with hyperprolactinaemic infertility < 10 years were included in the study. Patients presenting with someother reasons of infertility like male factor, tubal factors and unexplained infertility, macroadenoma of pituitary gland and h/o drugs like dopamine depleting, dopamine receptor blocking, H-2 blocker and verapamil intakewere excluded. Then selected cases were placed randomly into 2 groups i.e., Group A (bromocriptine) & Group B (bromocriptine plus clomiphene citrate), by using lottery method. Outcome variables like efficacy i.e. occurrence of pregnancy, were noted.

Results: Mean age of the patients in group A was 28.31±4.11 and mean age in group B was 27.67±4.49 years. The mean duration of infertility in group A was 5.17±2.12years and in group B was 4.99±2.27 years. Efficacy of Group A (bromocriptine group) was 59(60.20%) while in Group B (bromocriptine plus clomiphene citrate group) was 77(78.57%) with p value of 0.0053.

Conclusion: This study concludes that bromocriptine plus clomiphene citrate is better and more effective than bromocriptine alone in the treatment of hyperprolactinaemic infertility.

Keywords: Female infertility, prolactin, development of pregnancy, bromocriptine, clomiphene citrate.

INTRODUCTION

Hyperprolactinemia causes infertility in up to one-third of women with reproductive disorders[1]. It is a situation of raised serum prolactin. Prolactin is a 198-amino acid protein (23-KD) which produced in the lactotroph cells of the anterior pituitary gland. In individuals with pathological hyperprolactinaemia, glucose and fat homeostasis have been reported to be negatively influenced[2]. This condition develped in <1% of the general population and in 10-40% of cases reported with secondary amenorrhea[3]. hyperprolactinaemia can be found in nearly 75% patients reported with amenorrhea and galactorrhea[4].

Most common physical findings encountered in cases with hyperprolactinaemia are galactorrhea and defects of visual filed in the case of prolactinomas. Increased level of prolactin interferes with normal pulsatile secretion of gonadotrophin releasing hormone (GnRH) resulting in anovulation and infertility in one third of women presenting with reproductive disorders[5,6].

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The dopamine agonist, bromocriptinemesylate 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[7].

For the treatment of anovulatory infertility, clomiphene citrate has been used for many years by the doctors. At the level of hypothalamus, by the competing with sites of binding for estrogen, discharge of gonadotrophin may be stimulated by clomiphene citrate at the level of pituitary gland[8]. 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 earliear pregnancies.

This study was conducted to see the efficacy of bromocriptine alone and bromocriptine plus clomiphene citrate so that some practical suggestions could be made to achieve maximum number of pregnancies in hyperprolactinemic infertile women with more efficacious treatment regime.

MATERIALS AND METHODS

After approval from local ethical committee of this randomized controlled trial, 196 cases of hyperprolactinaemic infertility < 10 years of age 20-38 years, presented to the OPD Department of Obstetrics & Gynaecology, Bahawal Victoria Hospital, Bahawalpur, were selected. Patients with other causes of infertility i.e., tubal factors, male factor and unexplained infertility, polycystic ovarian disease, macroadenoma of pituitary gland, hyperthyroidism and h/o drugs like dopamine depleting, dopamine receptor blocking, H-2 blocker and verapamil intake were excluded.Informed, written consent was taken from every patients. Senior gynaecologist (with five year post fellowship experience) was available for more detailed information both for patients and researcher if required. All the selected were divided into two groups (Group A and B). History was taken from every patient like menstrual cycles, age at menarche and duration of infertility.

Bromocriptine alone was advised to patients of Group A for 6 months.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. While in Group B, all cases were treated with bromocrriptine 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 50 mg 3 times a day for third and fourth cycles and 100 mg 2 times a day for 5^{th} and 6^{th} 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 treatment.

Final outcome was measured in terms that patient had reported back to researcher in OPD on monthly basis and pregnancy was confirmed by measuring serum β-HCG (≥5 mIU/ml of β-HCG was taken as occurrence of pregnancy and level <5 mIU/ml was taken as absent pregnancy) every month for total duration of one year after start of therapy. Minimum follow up was six months and maximum eighteen months with mean 11.43 ± 2.67 months. Mean follow up was 12.27±2.89 months for group A and 10.77±2.11 months for group B. All this data was recorded on a predesigned proforma.

All the collected data was entered in SPSS version 16 and analyzed. Mean and SD was calculated for numerical data and frequencies and percentages were calculated for categorical data. Efficacy of treatment in both groups was compared by applying chi-square test. P value ≤5% was considered as significant.

RESULTS

Age range in this study was from 20 to 38 years with mean age of 28.08±4.23years.The mean age of patients in group A was 28.31±4.11 years and mean age in group B was 27.67±4.49 years (p<0.0354).

Efficacy of Group A (bromocriptine group) was 59(60.20%) while in Group B (bromocriptine plus clomiphene citrate group) was 77(78.57%) as shown in Figure IV& Table I (p-value=0.0053).

Duration of infertility was < 10 years with mean duration of 5.11±2.23 years. The mean duration of infertility in group A was 5.17±2.12 years and in group B was 4.99±2.27 years (p=0.2598). Majority of the patients 103(52.55%) had <5 years of duration of infertility as shown in Table II.

Comparison between efficacy of both groups according to age groups is shown in Table III which shows significant difference in efficacy in both groups between 31-38 years age group.

Table IV have shown Comparison between efficacy of both groups according to infertility duration and shows significant difference between both groups Comparison between efficacy of both groups according to co-morbid conditions i.e., HTN,DM has been shown in Table VI.

Table I: Comparison of efficacy between the two groups

Efficacy	Group A	Group B
Yes	59 (60.20)	77 (78.57)
No	39 (39.80)	21 (21.43)
Total	98 (100)	98 (100)

P. value = 0.0053

Table-II: Duration of infertility

Duration of infertility	Group A	Group B
< 5 years	52(53.06)	51(52.04)
>5 years	46(46.94)	47(47.96)
Mean±SD	5.17±2.12	4.99±2.27

Table III: Comparison between Efficacy of both groups according to age.

Age of patients	Efficacy in Group A		Efficacy in Group B		P-value
	Yes	No	Yes	No	
21-30 years	43 (76.79%)	13 (23.21%)	52 (88.14%)	07 (11.86%)	0.1085
31-38 years	16 (39.10%)	26 (61.90%)	25 (64.10%)	14 (35.90%)	0.0193

Table IV: Comparison between Efficacy of both groups according to duration of Infertility.

Duration of Infertility	Efficacy in Group A		Efficacy in Group B		P-value
	Yes	No	Yes	No	
< 5 years	40 (76.92%)	12 (23.08%)	47 (92.16%)	04 (7.84%)	0.0328
>5 years	19 (41.30%)	27 (58.70%)	30 (63.83%)	17 (36.17%)	0.0296

Table V: Comparison between Efficacy of both groups according to co-morbid conditions i.e. HTN, DM.

Co-morbid conditions		Efficacy in Group A		Efficacy in Group B		P-value
		Yes	No	Yes	No	
Hypertension	Yes	08	18	23	04	**<0.0001**
	No	51	21	54	17	**0.4796**
Diabetes Mellitus	Yes	06	07	16	06	**0.1159**
	No	53	32	61	15	**0.0126**

DISCUSSION

In patients of hyperprolactinemic disorders, dopamine agonists are the most preferred treatment. These dopamine agonists are very effective in lowering the levels of serum prolactin, restoring regular menses and eliminating galactorrhea. Mimicking the action of dopamine, dopamine agonists, including quinagolide, bromocriptine and cabergoline differ in their tolerability and efficacy[9].

Clinical use of clomiphene citrate started since 1960. Its process of action is still not well known, but it competes for the estrogen receptor at pituitary, ovarian and hypothalamus levels. Due to the action at the level of estrogen receptor level within the hypothalamus, Clomiphene citrate reduces the negative feedback effect exerted by the endogenous estrogens. As a result, clomiphene citrate normalizes the release of GnRH; therefore, the secretion of LH and FSH is capable of normalized follicular recruitment, selection, and development to re-establish the normal process of ovulation[10].

This randomized controlled study has compared the bromocriptine alone versus bromocriptine plus clomiphene citrate in treatment of hyperprolactinemic infertility in women. The mean age of women in our study was 28.08±4.23years and most of the women 58.67% were between 21 to 30 years in bothtreatment groups. Results of our study were comparable to studies by Motazedian S et al[7] and Al-Husaynei AJ et al[9] who had also reported mean age of 28 years and 29 years respectively. On the other hand, Abd Elghani SEA et al[11] has reported a larger mean age i.e., 31 years as compared to present study. Mean duration of infertility was 5.11±2.23years in this study which is a little higher than previous studies[7,9,10,11] The reason for this late presentation may be due to hakeem culture and lack of awareness in our society.

Results of this study reveals that bromocriptine alone and bromocriptine plus clomiphene citrate are effective in treatment of hyperprolactinaemic infertility and that bromocriptine plus clomiphene citrate is safe and more effective than bromocriptine alone. Efficacy of bromocriptine alone was 60.20% while bromocriptine plus clomiphene citrate group was 78.57% with p-value of 0.0053 as shown in our study.

Bromocriptine has been the most widely used prolactin lowering agent since its introduction in 1972.[12]In many studies, efficacy of bromocriptine was evaluated which proved the benefit of bromocriptine for lowering the level of serum prolactin and to restores the regular menstrual bleeding, relieving galactorrhea in most of the cases and normalize the function of gonad[13]. The efficacy of bromocriptine found in this study was 60.20% which is very much comparable with the studies of Sabuncu T et al[14] and Webster J et al[15] who had noted this as 59% and 58% respectively. But Motazedian S et al[7] and Mahmood IH et al[16] had found bromocriptine efficacy as 56% in their studies which is a little lower than our study.

In euprolactinemic infertile patients with or without amenorrhea and galactorrhea, successful pregnancies have also been achieved by the use of bromocryptine which acts to reduce the normal concentrations of prolactin sufficiently to aid fertility or by acting directly on the dopamine receptors in the gonad.[17]Bromocryptine therapy based on clinical criteria is quite safe with minimal side effects. There is no evidence of teratogenic effect of bromocryptine; however, patients are usually instructed to stop bromocryptine therapy with the first missed period. Baseline infertility investigations, including

tomography of pituitary fossa, should be performed prior to bromocryptine therapy, and when possible, serum prolactin should be monitored[10].

For the treatment of anovulatory infertility, the clinical use of clomiphene citrate has been started many years ago. By competing with the binding site for estrogen at the level of hypothalamus, clomiphene can stimulate the release of gonadotrophins at the pituitary level.[10]MahmoodS et al[18] in their study have compared the two regime i.e., bromocriptine alone versus bromocriptine plus clomiphene citrate in treating hyperprolactinemic infertility and found the bromocriptine combined with clomiphene citrate superior as compared to bromocriptine alone. He has found the efficacy of bromocriptine as 65% and bromocriptine plus clomiphene citrate as 75% in occurrence of pregnancy in hyperprolactinemic infertile women. These results are very much comparable to our results.

In another study done by AnateMet al[19] also showed better efficacy of bromocriptine plus clomiphene citrate in achieving pregnancy compared to bromocriptine alone. On the whole it is concluded that bromocriptine is effective in the treatment of hyperprilactinemic infertility. But bromocriptine plus clomiphene citrate has the advantage over bromocriptine alone in terms of both efficacy (achieving pregnancy) and tolerability.

CONCLUSION

This study concluded that bromocriptine plus clomiphene citrate is more effective (achieving pregnancy) and much better than bromocriptine alone in the treatment of hyperprolactinaemic infertility. So, we recommend that these particular patients should be treated with bromocriptine plus clomiphene citrate instead of bromocriptine alone in order to achieve maximum number of pregnancies in hyperprolactinemic infertile women.

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