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ORIGINAL ARTICLE

Clinical Response and Patient's Tolerance to Vaginal Versus Oral Bromocriptine in Women Who Suffer Hyperprolactinaemia .

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ABSTRACT

Background: Hyperprolactinaemia is a real challenge for gynecologist and endocrinologists ,bromocriptine was used for treating hyperprolactinaemia ,bromocriptine associated with many side effect this study aimed to compare clinical response , side effects and tolerability of vaginal bromocriptine tablets and suppositories versus oral bromocriptine tablets for treatment of hyperprolactinemia

Patients and methods: Non randomized controlled clinical trial at the out-patient Clinic of Obstetrics and Gynecology,Zagazig University and Zifta general hospital (ministry of health). This study included 87 patients who suffered hyperprolactinaemia .Patients divided into 3 groups:Group A included 29 patients who used bromocriptine 2.5mg tablets vaginally once daily for one month .Group B included 29 patients who administrated bromocriptine 2.5mg vaginal suppositories once daily for one month. Group C included 29 patients who received bromocriptine 2.5mg tablets orally twice daily for one month.Serum prolactin was measured before and after therapy in all cases**. The work has been carried out in accordance with (The Code of Ethics of world Medical Association) for studies involving human.**

Results:Bromocriptine was effective in decreasing level of prolactin whether used orally or vaginally. Vaginal bromocriptine suppositories application was associated with minimal side effect both local and general .Nausea was the most frequent side effect with oral tablets ,while excessive vaginal discharge and dyspareunia was the most occurring local side effect. Most side effect in three groups occur within the first 10 day after starting therapy.

Conclusions: Bromocriptine is **a very** effective drug in treating hyperprolactinaemia, restoration of normal ovulation ,improvement of mastalgia and galactorrhea ,there was a significant difference between the three studied group regarding degree of side effect and type of side effect occurred .Based on our results vaginal bromocriptine suppositories (bromotaemia) is associated with minimal local and systemic side effect when compared with bromocriptine tablets (lactodel) when used orally or vaginally.

Key words: Hyperprolactinaemia ,Bromocriptine, oral, vagina.

INTRODUCTION

Hyperprolactinemia is **a very** common disorder, especially among female during reproductive bearing period, affecting about one-third of infertile women in the world.Prevalence of hyperprolactinaemia in female with infertility is 33.3% in Egypt.[1].Hyperprolactinaemia is one of the most known challenge for gynecologist, andrologist,endocrinologist and also

neurosurgeons.[2].Diagnosis of hyperprolactinemia is established when serum level of prolactin hormone is found on 2 separate occasions to be above the high limit of the known established range for the population (usually 20_25ng/ml) or when the prolactin level is increased once in addition to symptoms suggestive of hyperprolactinemia.[1]Prolactin hormone defined as a peptide hormone secreted from lactotrophic cells of anterior lobe of pituitary gland.[3] .Hyperprolactinaemia can be classified into physiological as with pregnancy and lactation, pathological as in cases with pituitary tumors, drug induced hyperprolactinaemia like anti-depressant and also secondary hyperprolactinaemia which occurred with renal failure ,chest trauma and liver cirrhosis.[3].Hyperprolactinemia can leads to infertility as prolactin hormone leads to inhibition of gonadotrophin releasing hormone (GNRH) which leads to reduction of follicle stimulating hormone (FSH)and luteinizing hormone (LH),so leads to gonadotrophic insufficiency and anovulation. [1]Bromocriptine is a non-selective dopamine agonist,It binds to D1 receptors present in the gut and D2 receptors present in the pituitary.[4]When bromocriptine binds to dopamine receptor it inhibits central synthesis of Prolactin .[5] Bromocriptine has many side effect ,the most common of these are nausea, headache and dizziness.[6]To overcome the side effect with bromocriptine and to treat patients who don't tolerate or resistant to bromocriptine change the route of drug administration to vaginal or other preparation can be used as quinagolide or cabergoline. [7].

Aim of the study : the aim of this study was to increase patients tolerance toward bromocriptine.

PATIENTS AND METHODS

After obtaining approval from Research Ethics Committee of Zagazig university This non randomized controlled clinical trial was carried out in out-patient Clinic of Obstetrics and Gynecology,Faculty of Medicine ,Zagazig University from January 2018 to January 2019 . This study included 87 patients who suffered hyperprolactinaemia , **With prolactin level more than 20ng/ml.**

''Written informed consent'' was obtained from each participant before the beginning of this study . Clients of age group (19 -37) years were included in this study suffered from Galactorrhea one of the associated symptoms with hyperprolactinaemia (Infertility, ,mastalgia, amenorrhea, hypo menorrhea, menorrhagia, dysmenorrhea, ,recurrent pregnancy loss and non –use of any prolactin normalizing drug before entering the study for at least one month. Included patients had high pretreatment level of serum prolactin .Exclusion criteria include breast feeder, Pregnant, patients Suffer from symptoms suggesting pituitary problem (visual and occulo-motor disorders), women Suffer hypersensitivity or contraindicated to take bromocriptine as uncontrolled blood pressure.

Patients divided into 3 groups: Group A included 29 patients who used bromocriptine 2.5mg tablets vaginally once daily for one month ,Group B included 29 patients who administrated bromocriptine 2.5mg vaginal suppositories once daily for one month, Group C included 29 patients who received bromocriptine 2.5mg tablets orally twice daily for one month.

Complete medical history was documented , breast examination was done to all patients participate in the study, Participants was examined sitting and leaning forward .We examined breast from the base toward the nipple , also gentle examination of area around the nipple. Laboratory investigation include measuring. serum prolactin level before and after treatment in all case by (Cobas 8000) **. Cobas 8000 is a device used in laboratory of Zagazig university for measurement of serum prolactin , by which immunoassay for the in vitro quantative determination of prolactin in human serum and plasma**. Patients were instructed to avoid touching nipples to avoid extra elevation of serum

prolactin. Participants were informed to report any side effect with treatment (nausea, vomiting, dizziness, fainting, headache ,fatigue, vaginal itching) And also to report degree of side effect if this side effect was tolerable or not. After completing the course of treatment were asked about stoppage of breast secretion, improvement of mastalgia ,regularity of menstrual cycle, improvement of dysmenorrhea.

Statistical analysis Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage , quantitative continues group represent by mean ± SD , the following tests were used to test differences for significance;. difference and association of qualitative variable by Chi square test (X^2) . Differences between paired data by paired t, multiple by ANOVA, . P value was set at <0.05 for significant results & <0.001 for high significant result.Data were collected and submitted to statistical analysis.

RESULTS

The characteristics of patients in term of age and BMI was analysed and show no statistically significant difference among groups regarding age and BMI shown in table(1).

There was no statistically significant difference between the three groups regard main presenting symptoms (p> 0.05), as in table (2) .

Pre treatment level of serum prolactin was high in all patients and show significant decrease after receiving therapy in all three groups (P value <0.001).

There was no significant difference among groups regarding Prolactin level before or after therapy as shown in table (3).

On studying the side effects appeared with the different methods of treatment ,we found that excessive Vaginal discharge &/or dyspareunia is the most common side effect appeared in group (A) 13patients(44.8%). In group (B) the most common side effect is excessive Vaginal discharge &/or dyspareunia which appeared in 7 patients (24.1%). In group (C) the most frequent side effects are nausea and dizziness with the same percentage (44.8%) . Side effects associated significantly more in group C then A and least at B.as shown in table (4)

We found that most side effect in three groups occur within the first 10 day after starting therapy. There was no significant difference among groups regard time of appearance of side effects as shown in table (5).Some patients suffered side effects continued till the end of the course of therapy with no significant difference among the three studied groups.

According to the severity of side effect ,we divided side effect into two goups

mild : means patients can tolerate side effect and continued the **course** of treatment

sever degree : patients cannot tolerate side effect which leads to drug discontinuation Sever degree of side effect significantly associated with group C as shown in table N.(6).

There was no significant difference among studied groups, According to effectiveness of bromocriptine with the three different routes of its administration as shown in table (7) When rebound breast secretion was studied and analysed There was no significant difference or association among studied groups as shown in table (7).Rebound breast secretion after one month after we exclude pregnancy ,any factor that leads to increase prolactin level as breast stimulation , stress , taking any drug which has anti-dopaminergic effect and also we exclude all causes which leads to hyperprolactinaemia.

Table (1) Age and BMI distribution among three studied groups

	Group A Vaginal lactodel	Group B bromotaemia	Group C Oral lactodel	P
Age	27.48±4.51	26.51±4.25	27.62±4.47	0.586
BMI	29.37±4.42	28.51±3.99	28.8±4.1	0.727

Table (2) Main Complaint distribution among studied groups

Main complaint	A N (29)	B N(29)	C N(29)	P value
1ry an-ovulatory infertility	7 (24.1%)	5 (17.2%)	4 (13.7%)	0.41
2ry an-ovulatory infertility	9 (31.0%)	8 (27.6%)	7 (24.1%)	
Amenorrhea	0 (0.0%)	0 (0.0%)	2 (6.9%)	
Dysmenorrhea	1 (3.4%)	0 (0.0%)	0 (0.0%)	
Irregular menses	2 (6.9%)	1 (3.4%)	2 (6.9%)	
Galactorrhea	9(31.0%)	13(44.8%)	12(41.45)	
Mastalgia	1 (3.4%)	2 (6.9%)	2 (6.9%)	

Table (3) Serum Prolactin level (ng/ml)between the three studied groups before and after using drug

	Group A	Group B	Group C	P Value
Before treatment	32.08±9.69	29.96±8.92	29.64±10.04	0.578
After treatment	16.15±6.82	14.25±5.2	15.66±6.8	0.723
P value	0.001	0.001	0.001	

Table (4) Side effect distribution among three studied groups

Side effect	Group A	Group B	Group C	P Value
Nausea	11 (37.9%)	6(20.7%)	13 (44.8%)	0.13
Vomiting	6 (20.7%)	3 (10.3%)	6 (20.7%)	0.48
Dizziness	8 (27.6%)	3 (10.3%)	13 (44.8%)	0.013*
Fainting	0 (0.0%)	0 (0.0%)	3 (10.3%)	0.045*
Headache	9 (31.0%)	3(10.3%)	10 (34.5%)	0.073
Fatigue	8 (27.6%)	0 (0.0%)	9 (31.0%)	0.001*
Excessive Vaginal discharge	13 (44.8%)	7 (24.1%)	0 (0.0%)	0.001*

&/or dyspareunia				

Table (5) Timing of adverse effect among studied group.

	Group A	Group B	Group C	P Value
During first 10 day of treatment	16 (55.2%)	13 (44.8%)	22 (75.9%)	0.051
Lasting more than 10 day of treatment	3 (10.3%)	5 (17.2%)	9 (31.0%)	0.12

P Value >0.05 is non _significant.

Table (6) Degree(intensity) of side effects among studied groups

Degree of side effect	Group A	Group B	Group C	P Value
No side effect appeared	12(41.4%)	16 (55.2%)	4 (13.8%)	0.012*
Mild	13 (44.8%)	12 (41.4%)	18 (62.1%)	
Sever	4 (13.8%)	1 (3.4%)	7 (24.1%)	

Table (7)Effectiveness of drug among studied groups (out come)

Effectiveness of drug	Group A	Group B	Group C	P Value
Stoppage of galactorrhea	20 (69.0%)	20 (69.0%)	13 (44.8%)	0.094
Improvement of mastalgia	12 (41.4%)	15 (51.7%)	11 (37.9%)	0.54
Regaining normal ovulation	12 (41.4%)	14 (48.3%)	14 (48.3%)	0.83
Restoring regular menstrual bleeding	7 (24.1%)	13 (44.8%)	14 (48.3%)	0.12
Improvement of dysmenorrhea	4 (13.8%)	2 (6.9%)	3 (10.3%)	0.68
Rebound breast secretion	10(34.5%)	9(31.0%)	6(20.7%)	0.48

DISSCUSION

In this clinical trail we aim to increase patients tolerance toward bromocriptine ,we studied on 87 patients in child pearing period with hyperprolactinaemia.

patients participate in the current study were divided into three groups.

first group received bromocriptine mesylate tablets vaginally.

Second group received bromocriptine mesylate suppository vaginally.

Third group received bromocriptine mesylate tablets orally.

(**Darwish et al**)[7] compare between bromocriptine orally , vaginally and rectally in treating hyperprolactinaemia, and in another study they compared the superiority of vaginal suppositories over bromocriptine tablets when

taken vaginally in treating hyperprolactinaemia.

(Kletzky and vermesh)[13] studied the effectiveness of vaginal bromocriptine tablets in treating women with hyperprolactinaemia.

(**Katz et al**)[15] compared the circulating level of bromocriptine after vaginal compared to oral administration.

Firstly,the three studied groups show no statistically significant difference as regard patients characteristics (age , BMI) as shown in In table (1)

These finding running in agreement with (Darwish et al)[11] ,in this report researchers conducted a study to compare effectiveness and side effect tolerability of bromocriptine when taken orally , vaginally and rectally ,in their randomized study performed on 69, the patients of three groups didn't show any statistically significant difference as regard patients age and BMI.

(Kletzky and vermesh)[13] and **(Katz et a**l)[15] compared the effectiveness of bromocriptine tablets when taken orally or vaginally patients participate in this study show no statistically significant difference as regard age and BMI.

When main presenting symptoms distribution among the three studied groups were studied, there was no significant difference between the three studied groups as shown in table(2). In this table we found that galactorrhea was the most frequent complain among patients receiving both vaginal bromocriptine suppositories and oral bromocriptine tablets (44.8%) and (41.4%) respectively,this percentage was greater than percentage of galactorrhea among patient receiving vaginal bromocriptine suppository and oral bromocriptine (25%) and (22.2%) respectively in (**Darwish et al**)[7].

In our study serum prolactin show significant decrease after receiving therapy in the three studied groups , P value with oral bromocriptine , vaginal bromocriptine tablets and vaginal bromocriptine suppository was <0.001 as show in table (3).

This result was in agreement with that of (**Motazedian et a**l)[10]and (**Alhusaynei et al**)[14], these studies show a significant decrease in serum prolactin level after bromocriptine administration either orally or vaginally with P value <0.001 in both study .

Results in table (3) was in contrast to (**Kletzky and vermesh**)[13] and (**Darwish et al**)[7] the first study the effectiveness of vaginal bromocriptine tablets in treating women with hyperprolactinaemia they found that daily vaginal dose of 2.5mg of bromocriptine leads more reduction in serum prolactin when compared with oral tablets.

(**Darwish et al**)[7] observed that vaginal bromocriptine suppositories more effectiveness than vaginal bromocriptine tablets in lowering level of serum prolactin this result disagree with our result which proved that no significant difference among studied group P value >0.05.This can be explained by in our study vaginal tablet was soaked with water before insertion this can increase drug absorption.

Regarding Side effects studied among the three studied groups , side effects associated significantly more in group C (oral bromocriptine)then A (vaginal bromocriptine tablets)and least at B (vaginal bromocriptine suppository) as shown in table (4).

According to side effect that occurred with each line of treatment , in this study we found that nausea and dizziness were the most common occurring side effect among patients receiving oral bromocriptine 13 cases (44.8%) as shown in table (4).This result in agreement with (Kahnamuie and Asadzadel **) [2],(Nirhale et al)[16] , (Motazedian et al)[10] ,(Darwish et al)[7], (Cho et al)[17**] in the all previous mentioned studies they observed that nausea was the most common occurring side effects among patients receiving oral bromocriptine tablets but with different percentage (39.9%) , (50%) , (43.6%) ,(70.4%) , (23%) respectively .

In table (4), the most frequent side effect among cases receiving vaginal bromocriptine tablets was excessive vaginal discharge /dysparaunea 13 case (44.8%). This result in

disagree with (**Katz et al**)[15] they compare oral and vaginal bromocriptine tablets and observed no difference in side effects between both groups as only one case in each group suffer nausea and dizziness.

Also results regarding side effects with vaginal tablets disagree with (Kletzky and vermesh)[13] they found that 1 (10%) receiving vaginal bromocriptine tablets suffered conistipation.

When side effects with vaginal bromocriptine suppositories were studied excessive vaginal discharge /dysparaunea was the most occurring side effect 7 cases (27.1%).

This result was in agreement with (**Darwish et al**)[7] they studied the effectiveness of bromocriptine by its application with different route oral tablets 2.5mg , vaginal suppository 5mg and rectal suppository 5mg for one month , they observed that excessive vaginal discharge was the most frequent one occurring among patients receive vaginal bromocriptine suppositories 8 cases (40%) .

When timing of adverse effect was studied among the three studied groups , We found that most side effect in three groups occur within the first 10 day after starting therapy. There was no significant difference among groups regard time of appearance of side effects as shown in table (5).

This result was in agreement with (**Kletzky and vermesh**)[13] they reported that side effect with oral bromocriptine administration was recorded in the first 2 week of treatment.

In table (6) degree of side effect was studied , According to the severity of side effect ,we divided side effect into two goups :

1- mild : means patients can tolerate side effect and continued the coarse of treatment.

2-sever degree : patients cannot tolerate side effect which leads to drug discontinuation .

Sever degree of side effect significantly associated with group C(oral bromocriptine) 7cases (24.1%). This results was in agreement with (Nirhale et al)[16] they studied the effectiveness of oral bromocriptine tablets on management of mastalgia , they reported that 3 cases (13.04%) suffered sever non tolerable side effects.

(**Darwish et al**)[7] reported 6 patient (22.2%) received oral bromocriptine ended with drug discontinuation due to un-tolerable side effect.

In a study by(**Kahnamuie and Asadzadel)** [2]they studied patients tolerance toward oral bromocriptine tablets and vaginal bromocriptine suppository on 180 patients dividied into two group each one composed of 90 cases , they reported percentage of sever side effect with drug discontinuation (31.2%) and (22.2%) in oral and vaginal group respectively .

Regarding number of cases suffer side effects that occurred among the studied groups oral bromocriptine administration associated with the largest number cases who suffer of side effect 25 (86.2%) as shown in table (6). This percentage was higher than percentage of side effect with oral bromocriptine in astudy by (**Alhusaynei et al**)[14] as they reported 55% suffered from many side effect .

In our study when effectiveness of bromocriptine with the three different routes of its administration was studied , There was no significant difference among studied groups as shown in table (7).

Stoppage of galactorrhea in patient receiving oral bromocriptine occurred in 13 cases (44.8%) , this percentage found to be less than that occurred in a study (**Arduc et al**) [18]who studied the effectiveness of oral bromocriptine in treatment of hyperprolactinaemia and reported (79%) stoppage of galactorrhea , we suggest that difference due to prolonged duration of therapy (17.8+_6.0 months) compared with one month treatment of our study.

(**Moatazedian et al**)[10] studied oral bromocriptine administration and fertility outcome on 94 patients received 2.5mg oral bromocriptine for one month ,they observed galactorrhea was improved in (51.1%) this percentage higher than that reported in our study.

(**Arduc et al**)[18] reported also (80%) of patients suffered irregularity of menstrual cycle were improved and restored normal regular menstrual bleeding , this percentage found to be higher than our results as we reported (48.3%) restoring of regular menstrual bleeding. This result can be due to increased duration of treatment in (**Arduc et al**)[18] (17.8+_6.0 months) versus one month of our study.

Restoration of normal regular menstrual bleeding with oral bromocriptine occurred in (48.3%) this result found to be higher than that reported by (**Moatazedian et a**l)[10] they reported (33%) .

According to effectiveness of oral bromocriptine in treatment of mastalgia , we found that 11 patients(37.4%) show improvement of mastalgia as shown in table (7).This percentage is less than that found in (**Nirhale et al**)[16] who found (56.9%) improvement of mastalgia this difference can be due to prolonged duration of therapy.

(**Alhusaynei et a**l)[14] studied effect of oral bromocriptine in women with hyperprolactinaemic amenorrhea , oral bromocriptine tablets 2.5mg twice daily for 8 weeks , they reported (78.6%) with stoppage of galactorrhea and (69.23%) with normalization of menstrual bleeding , Both results higher than our results this difference can be explained due to prolonged period of treatment.

When effectiveness of vaginal bromocriptine tablets was studied we found that stoppage of galactorrhea occurred in 20(69.0%), improvement of mastalgia and regaining normal ovulation occurred in 12 (41.4%) , restoring regular menstrual bleeding occurred in 7 (24.1%) , as shown in table (7).

In our study as shown in table (7) vaginal bromocriptine tablets and suppositories equally associated with (69.0%) stoppage of galactorrhea.

In table (7), which demonstrate rebound breast secretion after one month coarse of therapy in the three studied groups we found that there was no significant difference or association among studied groups .Rebound breast secretion after one month after we exclude pregnancy ,any factor that leads to increase prolactin level as breast stimulation , stress , taking any drug which has anti-dopaminergic effect and also we exclude all causes which leads to hyperprolactinaemia.

CONCLUSION

It could be concluded from this study that bromocriptine is a very effective drug in treating hyperprolactinaemia, restoration of normal ovulation ,improvement of mastalgia and galactorrhea ,there was a significant difference between the three studied group regarding degree of side effect and type of side effect occurred .Based on our results vaginal bromocriptine suppositories is associated with minimal local and systemic side effect when compared with bromocriptine tablets when used orally or vaginally.

No conflict of Interest .

No financial disclosures .

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