

Comparison of Efficacy of Vitex Agnus Castus Ovitex and Bromocriptine in The Management of Hyperprolactinemia

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Abstract

Objective: This study is a randomized control trial aimed at comparing bromocriptine and vitex agnus castus in terms of control of prolactin levels and the incidence of side effects.

Methodology: This randomized control trial study was conducted at the Maternal and Child Health Centre PIMS Islamabad, the duration of the study was 6 months (December 2016-May 2017). Non-probability consecutive sampling technique was used. The sample size of 88 participants were categorized into two groups. Group A was given vitex agnus castus while Group B was treated with bromocriptine. The hormonal analysis was performed before and after one month of therapy. All the patients of both groups were called in OPD after one week for an assessment of side effects and after one month for prolactin levels. Both group's data were entered and analyzed using SPSS version 20.0. Outcome variables efficacy and side effects were presented by frequency and percentages, performing chi-square test. Efficacy was measured in terms of symptomatic improvement, several side effects, and severity of side effects.

Results: According to the results of the study it was noted that there was no significant (p -value > 0.05) difference between both groups based on Prolactin and LH levels when compared between both drug groups after treatment. A higher rate of side effects was observed in the Bromocriptine group as compared with Vitex Agnus Castus Ovitex group.

Conclusion: It is concluded that Vitex agnus castus has efficacy equal to bromocriptine but has less side effects. However, the dose and side effects in some cases should be considered, but on the whole, these drugs are effective.

Keywords: Vitex agnus castus, bromocriptine, hyperprolactinemia, bromocriptine.

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Introduction

Hyperprolactinemia is a disorder in which the person has an abnormally high level of the hormone prolactin in the blood. The primary function of prolactin is to stimulate the production of breast milk after childbirth, so a high level of prolactin is normal during pregnancy. Prolactin also affects the level of sex hormones (estrogen and testosterone) in both women and men.

Prolactin produces from the pituitary gland, an organ the size of a pea at the base of the brain. A common cause of hyperprolactinemia is a mass or tumor in the pituitary gland called a prolactinoma.^{1,2} The tumor produces a high level of prolactin. Certain prescription medications can also increase the level of prolactin; among them are medicines for high blood pressure (as

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calcium channel blockers and methyl dopa), symptoms of menopause (estrogen), serious mental disorders (antipsychotics such as Risperdal and haloperidol), pain (opiates or medications derived from opium), gastroesophageal reflux disease (metoclopramide), ulcers (H2 antagonists) and depression (tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs)).^{3,4}

A blood test is used to detect excessive prolactin. If the prolactin level is high, more tests are usually done to determine the level of thyroid hormone in the blood. A normal thyroid hormone level rules out hypothyroidism as the cause of hyperprolactinemia. The doctors also ask about other disorders and medication use and rule out pregnancy. If a prolactinoma is suspected, the next step is an MRI (magnetic resonance imaging) scan of the brain and pituitary. MRI, produced by a special device that creates images of body tissues, can reveal a pituitary tumor and show its size.⁵ The treatment of Hyperprolactinemia depends on the cause, certain people with a high level of prolactin do not need treatment, but few have no signs or symptoms. Options for the treatment of tumors include prescription drugs, as bromocriptine and cabergoline decrease prolactin production, surgery to remove the tumor (if the medications are not effective), and radiation (in rare cases if medications and surgery have not worked). It should be noted that bromocriptine and cabergoline are also used to treat hyperprolactinemia of unknown cause. Hypothyroidism is treated with a synthetic thyroid hormone, which should make the level of prolactin back to normal.⁶

According to different studies, hyperprolactinemia is one of the increasingly common problems of gynecological endocrinology. It is found in 15%-30% of women with secondary amenorrhea and oligomenorrhea.⁷ Besides its presence in 30%-70% of women with galactorrhea or infertility, bromocriptine is the main agent used to manage pathological hyperprolactinemia that has been thoroughly studied. The reported efficacy of these agents is 60%-100% regarding the normalization of the menstrual cycle, 50%-80% in the restoration of ovarian function, and 80%-90% in achieving conception. These agents are considered as the gold standard of treatment.⁸ However, these agents are associated with serious side effects such as nausea vomiting, headache, tiredness, dizziness which are the most common, while others include loss of appetite stomach cramps,

weakness, drowsiness, depression, hallucinations, chest pain, and constipation.

As discussed earlier, among other consequences, having high prolactin often leads to infertility. Natural pregnancy is complicated to achieve due to menstrual disorders caused by hormonal imbalance. In this regard, it is critical to treat this disorder with great care considering the side effects of medications being used for many years. Vitex agnus castus has emerged as a new anti-prolactin drug with promising results regarding successful control of high prolactin levels, with minimal side effects.⁹ It is up to 90% efficiency in the restoration of symptoms of premenstrual syndrome. Vitex agnus-castus or chaste tree is a strong shrub that grows in the countries of the Mediterranean, Central Asia, and North America. Its dried fruits (berries) resemble the appearance, smell, and taste of common peppercorns. In Europe and North America, these dried berries have been used as a phytotherapeutic product for more than 2000 years, specifically for digestion problems, acne, irregular menstrual cycle, premenstrual discomfort, mastalgia (pain in the breasts) and fertility problems. It should be noted that Vitex agnus-castus extract is the primary ingredient of Ovitex, a medication used to treat hyperprolactinemia.¹⁰

The current research was conducted to aim at comparing bromocriptine and vitex agnus castus regarding control of prolactin levels and the incidence of side effects.

Methodology

The study was a randomized control trial, conducted at Maternal and Child Health Centre PIMS Islamabad. As the purpose of the study was to compare the efficacy of two drugs given for the treatment of hyperprolactinemia; so, the sample size of 88 participants were categorized into two groups i.e. Group A and Group B. Group A was given bromocriptine while Group B was treated with vitex agnus castus. The sample size was forty-four in each group and the duration of the study was six months; non-probability consecutive sampling technique was used to select the sample size. All patients with hyperprolactinemia and any of these conditions such as amenorrhea, oligomenorrhea, heavy cyclical bleeding, and irregular P/V bleeding, dysmenorrhea, infertility, and polycystic ovaries were included in the research; while, women with the conditions like psychotic disorders, uncontrolled hypertension and cardiac

disease, liver disease, stroke, lactating mothers, and pregnancy was excluded.

The data was collected after taking approval from the hospital ethical committee; the women fulfilling the inclusion criteria and presented in gynecology OPD were divided into two groups (i.e. 44 participants in each group). All cases in group A have treated with vitex agnus castus 20 mg OD for three months while in group B was given bromocriptine starting with 1.25 mg (1/2 tablet) at bedtime and dose increment was done at three

days interval to the maximum dose of 7.5 mg (2.5 mg TDS) unit. The hormonal analysis was performed before and after one month of therapy. All the patients of both groups were called in OPD after one week for an assessment of side effects and after one month for prolactin levels.

After the data collection procedure, the data was entered and analyzed using SPSS version 20.0. Outcome variables efficacy and side effects were presented by frequency and percentages. Efficacy was measured in terms of symptomatic improvement, several side effects, and severity of side effects. Chi-square test analyzed a comparison between the groups concerning efficacy. P value ≤ 0.05 was considered statistically significant. Post-stratification chi-square was applied to see the effect of these on outcome variables.

Results

In this cross sectional study, a total of 88 patients were included having two equal groups of 44 patients in each drug group. The mean age of Vitex Agnus Castus Ovitex group was 27.09 ± 6.22 years and the mean age of the Bromocriptine group was 28.05 ± 4.76 years. The mean value of BMI in Vitex Agnus Castus Ovitex group

Table II: Comparison of Prolactin, LH and FSH before and after treatment in both groups (n=44)

| Group | Variables | Mean \pm SD | P-Value |
|---------------------------|----------------------------|-------------------|---------|
| Vitex Agnus Castus Ovitex | Prolactin before treatment | 40.18 \pm 18.38 | 0.000 |
| | Prolactin after treatment | 23.22 \pm 5.91 | |
| | LH before treatment | 9.06 \pm 3.88 | 0.613 |
| | LH after treatment | 9.26 \pm 3.39 | |
| | FSH before treatment | 7.36 \pm 2.97 | 0.368 |
| | FSH after treatment | 7.67 \pm 2.43 | |
| Bromocriptine | Prolactin before treatment | 44.52 \pm 15.25 | 0.000 |
| | Prolactin after treatment | 23.36 \pm 3.20 | |
| | LH before treatment | 10.52 \pm 3.45 | 0.419 |
| | LH after treatment | 10.32 \pm 2.58 | |
| | FSH before treatment | 8.83 \pm 2.27 | 0.908 |
| | FSH after treatment | 8.87 \pm 2.63 | |

was 23.25 ± 2.95 and in the Bromocriptine group, the mean BMI was 24.41 ± 3.41 . In this study sample, most common presenting complaint in both drug groups was menstrual irregularity which was noted in 20 (45.5%) patients in Vitex Agnus Castus Ovitex group and in 16 (36.4%) patient in Bromocriptine group. The second common presenting complain was infertility and 16 (36.4%) patients in Vitex Agnus Castus Ovitex group and 15 (34.1%) patients in the Bromocriptine group presented with infertility complain as elaborated in table I.

The levels of Prolactin, LH and FSH were compared before treatment and after treatment in table II, which shows that only prolactin was significantly (p-value < 0.05) improved from baseline to after treatment from 40.18 ± 18.38 to 23.22 ± 5.91 in Vitex Agnus Castus Ovitex group and 44.52 ± 15.25 to 23.36 ± 3.20 in Bromocriptine group. There was no significant (p-value > 0.05) difference by LH and FSH levels from baseline to after treatment levels in both drug groups. (Table II)

According to the results of the study, it was noted that there was no significant (p-value > 0.05) difference between both groups based on Prolactin and LH levels

Table I: Demographic characteristics of the patients

| Characteristics | Drug Groups | |
|------------------------|---------------------------|------------------|
| | Vitex Agnus Castus Ovitex | Bromocriptine |
| Age of Patients | | |
| Mean \pm SD | 27.09 \pm 6.22 | 28.05 \pm 4.76 |
| BMI of the Patient | | |
| Mean \pm SD | 23.25 \pm 2.95 | 24.41 \pm 3.41 |
| Presenting Complaints | | |
| Menstrual Irregularity | 20 (45.5%) | 16 (36.4%) |
| Infertility | 16 (36.4%) | 15 (34.1%) |
| Others | 8 (18.2%) | 13 (29.5%) |

Table III: Comparison of Prolactin, LH and FSH after treatment between both groups (n-44)

| Parameters after Treatment | GROUP | Mean±SD | P-Value |
|----------------------------|---------------------------|--------------|---------|
| Prolactin | Vitex Agnus Castus Ovitex | 23.22±5.906 | 0.885 |
| | Bromocriptine | 23.36±3.199 | |
| LH | Vitex Agnus Castus Ovitex | 9.257±3.388 | 0.102 |
| | Bromocriptine | 10.318±2.578 | |
| FSH | Vitex Agnus Castus Ovitex | 7.668±2.430 | 0.029 |
| | Bromocriptine | 8.866±2.628 | |

when compared between both drug groups after treatment. Only the man's value of FSH levels was found significantly (p-value < 0.05) greater in Bromocriptine groups (8.866 ± 2.628) as compared with Vitex Agnus Castus Ovitex group with p-value of 0.029 as elaborated in table III.

The analysis showed that there was significantly (P-value < 0.05) higher rate of side effects was observed in the Bromocriptine group as compared with Vitex Agnus Castus Ovitex group. It noted that in Vitex Agnus Castus

Vitex group 41 (93.18%) patients had no side effect in contrast to the Bromocriptine group in which only 25 (56.82%) patients had no side effect. Similarly, there was no statistically significant difference was noted in symptoms improvement, when both drug groups were compared as given in table IV.

Table IV: Comparison of side effects and Symptoms improved between both groups

| | Group | | Total | P-Value |
|------------------------------|---------------------------|---------------|-------|---------|
| | Vitex Agnus Castus Ovitex | Bromocriptine | | |
| Side Effects | | | | |
| No Side Effect | 41 | 25 | 66 | 0.002 |
| Headache | 0 | 5 | 5 | |
| Gastrointestinal Side Effect | 2 | 4 | 6 | |
| Dizziness | 1 | 4 | 5 | |
| Others | 0 | 6 | 6 | |
| Symptoms improved | | | | |
| Not Improved | 22 | 25 | 47 | 0.521 |
| Improved | 22 | 19 | 41 | |
| Total | 44 | 44 | 88 | |

Discussion

Infertility is the lack of conception in the presence of unprotected sex for a year; about 40% of cases of infertility are due to gynecological disorders. Anovulation is one of the most frequent causes of infertility.¹¹ According to the World Health Organization, the causes of anovulation are divided into three categories; Category 1 includes hypogonadotropic hypogonadism and is responsible for approximately 10% of cases of infertility. Category 2, eugonadotrophic dysfunction, represents about 85% of cases of infertility, while category 3, which includes ovulation disorders attributable to ovarian failure (hypogonadotropic hypogonadism), explains the rest of the cases. Category 2, experts add, includes patients with the polycystic ovarian syndrome (PCOS), patients with hyperprolactinemia, and women with anovulation of unknown etiology.¹² In this regard, it is important to treat this disorder effectively; a study conducted by Rebar supports the efficacy of combined treatment with bromocriptine in patients with infertility associated with anovulation and galactorrhea.¹³

According to Melmed et al. several drugs have been used to treat hyperprolactinemia, until finding the best result in the dopamine antagonists.¹⁴ The effectiveness of the extracts of the chaste berry berries is attributed mainly to the direct and indirect effects on neurotransmitters and hormones. In the second half of the menstrual cycle, after ovulation, the corpus luteum (or yellow body) that produces estrogen and progesterone is formed. Latent hyperprolactinemia (which is usually caused by stress) can lead to corpus luteum dysfunction with a (strong) decrease in progesterone synthesis. The increase in the level of prolactin, with the consequent deficiency of progesterone due to insufficiency of the corpus luteum, may have an important role in the cyclic mastalgia or mastodynia and other discomforts of PMS (premenstrual syndrome), in the imbalances of the menstrual cycle such as shortening of the cycle (for a shorter luteal phase) and infertility problems. A lower activity of the dopaminergic system in the brain probably favors the psycho-emotional symptoms of SMP.¹⁵

The secretion of prolactin by the pituitary gland is under the control of dopaminergic neurons. The chaste berry extract increases the dopaminergic activity in the brain and combats the hyperprolactinemia (latent), making the luteal phase of the menstrual cycle go well and

increasing the secretion of progesterone.¹⁶ The diterpenes present in the chaste berry bind to the dopamine D2 receptors of the hypothalamus and the adenohypophysis, inhibiting the secretion of basal prolactin and that stimulated by TRH (thyrotropin-releasing hormone). This has been demonstrated in in vitro studies and animal studies. The effect on prolactin secretion may depend on the dose used: in experimental studies with healthy men, it was found that a dose of an extract of Vitex agnus-castus decreased the level of prolactin.

A study by Schellenberg et al. reveals that drug interactions are not described in the scientific literature. Considering its mechanism of action, the use of chaste berry extract is discouraged in treatments with dopamine antagonists (antipsychotics) or dopamine agonists (medication for Parkinson's). Chaste tree extract can alter the functioning of hormonal preparations (contraceptive pill, hormone replacement therapy, in vitro fertilization treatment). The use of chaste berry is contraindicated during pregnancy.¹⁷ If Vitex agnus-castus is taken to increase the chances of pregnancy, it is necessary to stop taking it at the first offense. The use of chasteberry preparations during breastfeeding is controversial.

In premenstrual dysphoric disorder, one study reported Vitex to be equivalent to fluoxetine, while in the other, fluoxetine exceeded Vitex. In latent hyperprolactinemia, one trial reported being superior to placebo in reducing prolactin-stimulated TRH secretion, normalization of a short luteal phase, which increases mean luteal progesterone and 17 β -estradiol levels, while the other Vitex found comparable to bromocriptine in reducing serum prolactin levels and improving cyclic mastalgia. Adverse events with Vitex were mild and generally infrequent.^{17,18} The methodological quality of the included studies varied but was generally moderate to high. Limitations include the small sample size in some studies, the heterogeneity of the conditions in question, and a range of reference treatments. Despite some methodological limitations, the results of the randomized and controlled trials to date suggest the benefits for Vitex extracts in the treatment of premenstrual syndrome, premenstrual dysphoric disorder, and latent hyperprolactinemia.

Comparing different medications used for the treatment of hyperprolactinemia, Van et al. indicate that

bromocriptine (Parlodel), a dopamine antagonist that suppresses prolactin secretion, is a drug used for breast pain caused by abnormalities in the secretion of prolactin. In general, it is useful for patients with hyperprolactinemia, mastodynia, and breast regurgitation. The author has also mentioned that Agnus castus (Vitex agnus castus L extract ZE 440) as an effective and well-tolerated treatment to reduce the symptoms of PMS, in a considerable sample of 178 women.¹⁸ Thus, considering both primary and secondary research findings, it is observed that bromocriptine and Vitex agnus castus has a positive influence on patients with hyperprolactinemia. However, the dose and side effects in some cases should be considered, but on the whole, these drugs are effective.

Conclusion

On the whole, the research leads to significant results but there were some limitations while conducting the research. The sample size was small, as the duration of the research was also shorter; this factor should be considered in the future.,not only the one but different hospitals from different regions should be selected to compare the efficacy of both drugs for the normally distributed data and more effective results. In a nutshell, it is concluded that vitex agnus castus has efficacy equal to bromocriptine but with less side effects.

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