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Comparison of the Vitexagnuscastusovitex and Bromocriptine in the Management of Hyperprolactinemia

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ABSTRACT

Objective: To study of the effectiveness of vitex agnus-castus and bromocriptine in women with hyperprolactinemic amenorrhea who present themselves. **Methodology:** It was a randomized controlled trial that was conducted in the Department of Obstetrics and Gynecology of the Lady Willingdon Hospital Lahore. Included were 60 women aged 18 - 35 years who had amenorrhea and had a serum prolactin level > 25 ng/ml. Patients were stratified and equally divided into two groups with a lottery. Group A was fed on Vitex agnus-castus and Group B on bromocriptine. At the baseline and after a month of treatment the levels of serum prolactin, the levels of luteinizing hormone and follicle-stimulating hormone were measured. The SPSS version 25 was used to analyze the data. Any p-value that is less than 0.05 was regarded to be statistically significant. **Results:** The mean age was 26.43 ± 4.91 years in Group A and 27.16 ± 4.62 years in Group B. Baseline serum prolactin level was 40.18 ± 18.38 ng/ml in the Vitex group and 44.52 ± 15.25 ng/ml in the bromocriptine group. One month of treatment resulted in a large drop in serum prolactin in Group A (23.22 ± 5.91 ng/ml) and Group B (23.36 ± 3.20 ng/ml) and a significant within-group decrease in each group ($p < 0.001$). But, the difference between the groups after the treatment was statistically irrelevant ($p = 0.910$). It became possible to normalize prolactin in 70.0 percent patients in the Vitex group and in 76.7 percent patients in bromocriptine group ($p = 0.559$). Both the LH and FSH levels in the treated two groups were also similar. **Conclusion:** Both Vitex agnus-castus as well as bromocriptine were effective in decreasing prolactin level in serum after 1 month of treatment. Though slight difference in prolactin normalization rate was observed between bromocriptine and Vitex agnus-castus, this was not significant. Vitex agnus-castus can be viewed as an option in a few patients with mild and moderate hyperprolactinemia.

INTRODUCTION

Hyperprolactinemia is a typical endocrine disorder, in women of reproductive age and is marked by high levels of prolactin in the serum, which exceeds the normal physiological levels (1). The secretion of prolactin is predominantly controlled by the process of inhibitory dopaminergic circuits of hypothalamic origin. High prolactin level inhibits the secretion of gonadotropin leading to menstrual abnormality, amenorrhea, galactorrhea, infertility and reduced bone mineral density (2). The condition can be a result of physiological factors like pregnancy and lactation or pathological factors like pituitary adenoma, hypothyroidism and endocrine disorders caused by drugs (3). Recent findings have also associated chronic hyperprolactinemia with metabolic impairment, stress diseases and cardiovascular morbidities (4).

Dopamine agonists like bromocriptine continue to play a leading role in the treatment since they help to lower the levels of serum prolactin and regain ovulatory rates (5). Although bromocriptine has its effectiveness, it is often accompanied by such side effects as nausea, vomiting, dizziness, headache, and postural hypotension that impairs patient adherence and ultimately long-term retention of the treatment (6). There has therefore been a focus on herbal treatments which could be equally effective with minimal side effects.

Chaste tree berry (Vitex agnus-castus (VAC), also called vitex agnus-castus, is a commonly used medicinal herb with many applications in the treatment of gynecological disorders and hormonal imbalance (7). Experimental literature indicates that VAC contains diterpenes that do react with dopamine D2 receptors in the anterior pituitary gland, and thus prevent the release of prolactin (8). Clinical research and systematic reviews have recently demonstrated the use of VAC in enhancing the menstrual disorders, cyclic mastalgia, premenstrual syndrome and mild hyperprolactinemia with good safety

and tolerability (9). Besides, comparative analyses have revealed that there have been drastic decreases in levels of prolactin using VAC and bromocriptine (10).

Nonetheless, there is a paucity of local information in the comparative effectiveness of VAC and bromocriptine in women with hyperprolactinemia. It is against this background that this study was carried out to provide comparison of the effectiveness of Vitex agnus-castus and bromocriptine in in the management of hyperprolactinemia.

METHODOLOGY

This randomized controlled trial was carried out in the Department of obstetrics and gynecology, lady Willingdon Hospital, Lahore at a time span of 30th August 2024 to 28th February 2025 after the research synopsis became approved on the part of the institutional ethics review committee. This research would have compared the effectiveness of Vitex agnus-castus and bromocriptine in the treatment of hyperprolactinemia in women who appear to have amenorrhea. The total sample of 60 patients was determined based on a confidences level of 95, 80 power of study and mean post-treatment luteinizing hormone (LH) found in other literature. Non-probability consecutive sampling was used to select the patients.

The study included women aged between 18 and 35 years who came to the outpatient department with amenorrhea of a duration longer than three months and a serum prolactin level of an amount higher than 25 ng/mL. The study did not include pregnant women, lactating women, women with psychotic disorders, uncontrolled hypertension, cardiac disease, liver disease, stroke, or with pituitary macroadenoma or history of taking drugs that depletes the dopamine or blocks dopamine receptors.

Informed consent was taken in writing and demographic, clinical history were noted on a pre-set proforma. Information about age, the course of the symptoms, smoking, family history, considering hyperprolactinemia, height, weight, and body mass index (BMI) was measured. Prior to the treatment, lab measurements were used to determine the baseline serum prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels. Lottery was used to randomly divide the enrolled participants into two equal groups. Group A had Vitex agnus-castus 20 mg orally on a daily basis and Group B had a dosage of bromocriptine 1.25 mg up to 7.5 mg with clinical need and tolerability. One week later, all participants were contacted to determine adherence and any adverse effect of the drugs used. One month after the treatment serum prolactin, LH and FSH levels were re-examined by the same laboratory techniques.

Data collected was inputted and statistical measures were performed through the use of Statistical Package of Social Sciences (SPSS) version 25. Quantitative data were provided in terms of average ± standard deviation including age, BMI, duration of symptoms, and levels of the hormones whereas qualitative data were provided as frequencies and percentages in terms of smoking status and family history. Shapiro-Wilk test was used to determine whether the data is distributed normally. Hormone levels of both groups were compared in terms of the independent sample t-test after the treatment. Potential effect modifiers such as age, BMI, smoking status, duration of symptoms and family history of hyperprolactinemia were stratified. During the analysis, 0.05 was used as a p-value that was considered significant.

RESULTS

The mean age of patients in Group A was 26.43 ± 4.91 years, while in Group B it was 27.16 ± 4.62 years. Both groups did not have a statistically significant difference in terms of p-value 0.556. The mean duration of symptoms was 7.83 ± 3.12 months in Group A and 8.10 ± 3.28 months in Group B, with a p-value of 0.746. No difference in the mean BMI of the two groups was also observed. (Table I). Distribution of qualitative baseline characteristics is shown in Table II.

Baseline serum prolactin level was 40.18 ± 18.38 ng/ml in Group A and 44.52 ± 15.25 ng/ml in Group B. In Group A and B, serum prolactin level decreased statistically significant with the reduction level of 23.22 ± 5.91 ng/ml and 23.36 ± 3.20 ng/ml, respectively. In the comparison of the level of prolactin after treatment in Group A and Group B, however, it was not significant and the p=0.910. (Table III).

Mean baseline LH level was 8.81 ± 3.01 IU/L in Group A and 9.02 ± 2.84 IU/L in Group B. After treatment, mean LH level was 9.26 ± 3.38 IU/L in Group A and 10.32 ± 2.58 IU/L in Group B. The average difference in the LH level between the groups after the treatment was statistically insignificant and the p-value of 0.177. (Table IV).

Mean baseline FSH level was 7.31 ± 2.21 IU/L in Group A and 7.94 ± 2.36 IU/L in Group B. After treatment, mean FSH level was 7.67 ± 2.43 IU/L in Group A and 8.87 ± 2.63 IU/L in Group B. The trend of the two groups was found to be statistically not significant and the p-value was 0.073. (Table V). There was a high percentage of prolactin normalization in both treatment groups. Nevertheless, there was no significant difference between Group A and Group B. (Table VI).

Table I

Baseline demographic characteristics of study participants

Variable	Group A: Vitex agnus-castus n = 30	Group B: Bromocriptine n = 30	p-value
Age, years	26.43 ± 4.91	27.16 ± 4.62	0.556
Duration of symptoms, months	7.83 ± 3.12	8.10 ± 3.28	0.746
Height, cm	158.46 ± 5.72	159.03 ± 6.11	0.710
Weight, kg	66.87 ± 8.94	68.24 ± 9.11	0.558
BMI, kg/m^2	26.61 ± 3.42	26.98 ± 3.57	0.684

Table II

Distribution of qualitative baseline characteristics

Variable	Group A: Vitex agnus-castus n = 30	Group B: Bromocriptine n = 30	p-value
Smoking status			
Smoker	4 / 30 (13.3%)	5 / 30 (16.7%)	0.640
Non-smoker	26 / 30 (86.7%)	25 / 30 (83.3%)	
BMI category			
Obese	17 / 30 (56.7%)	18 / 30 (60.0%)	0.795

Non-obese	13 / 30 (43.3%)	12 / 30 (40.0%)	
Family history of hyperprolactinemia			0.754
Present	6 / 30 (20.0%)	7 / 30 (23.3%)	
Absent	24 / 30 (80.0%)	23 / 30 (76.7%)	

Table III

Comparison of serum prolactin levels before and after treatment

Serum prolactin level	Group A: Vitex agnus-castus n = 30	Group B: Bromocriptine n = 30	p-value between groups
Baseline prolactin, ng/ml	40.18 ± 18.38	44.52 ± 15.25	0.323
Post-treatment prolactin, ng/ml	23.22 ± 5.91	23.36 ± 3.20	0.910
Mean reduction in prolactin, ng/ml	16.96 ± 13.84	21.16 ± 12.75	0.227
Percentage reduction	42.2%	47.5%	0.284
Within-group p-value	<0.001	<0.001	—

Table IV

Comparison of serum LH levels before and after treatment

Serum LH level	Group A: Vitex agnus-castus n = 30	Group B: Bromocriptine n = 30	p-value between groups
Baseline LH, IU/L	8.81 ± 3.01	9.02 ± 2.84	0.782
Post-treatment LH, IU/L	9.26 ± 3.38	10.32 ± 2.58	0.177
Mean change in LH, IU/L	0.45 ± 1.82	1.30 ± 1.94	0.086
Within-group p-value	0.184	0.002	—

Table V

Comparison of serum FSH levels before and after treatment

Serum FSH level	Group A: Vitex agnus-castus n = 30	Group B: Bromocriptine n = 30	p-value between groups
Baseline FSH, IU/L	7.31 ± 2.21	7.94 ± 2.36	0.290
Post-treatment FSH, IU/L	7.67 ± 2.43	8.87 ± 2.63	0.073
Mean change in FSH, IU/L	0.36 ± 1.42	0.93 ± 1.58	0.148
Within-group p-value	0.176	0.005	—

Table VI

Treatment outcome according to normalization of serum prolactin level

Treatment outcome	Group A: Vitex agnus-castus n = 30	Group B: Bromocriptine n = 30	p-value
Prolactin normalized, ≤25 ng/ml	21 / 30 (70.0%)	23 / 30 (76.7%)	0.559
Prolactin not normalized, >25 ng/ml	9 / 30 (30.0%)	7 / 30 (23.3%)	

DISCUSSION

Demographic characteristics of the participants at the baseline were nearly the same in both groups, which reinforces internal validity of the comparison. The average age of the Vitex group and the bromocriptine was given as 26.43, SD=4.91 and 27.16, SD=4.62 and the p-value was insignificant at 0.556. In the same manner, length of symptoms, height, weight and BMI had no statistically significant differences. The reason why age and BMI are important is that they may affect menstrual functioning, endocrine phenotype and treatment response. In the more recent position statements, it was pointed out that serum prolactin interpretation needs to be undertaken cautiously following the exclusion of physiological, pharmacological and pathological causes, especially in women within the reproductive age range [11,12]. The similarity of the baseline profile in the current study thus indicates that the differences observed after the treatment were more likely not due to imbalance in the baseline but due to the effect of the treatment.

The prolactin decline that is seen in the current study is clinically significant. Hyperprolactinemia is typically defined to be meaningful when the level of serum prolactin is higher than normal which in women is said to be more than 25 ng/ml. The biochemical improvement demonstrated by a low and close mean post-treatment level of prolactin in both groups was reached in this study. The normalization rate of prolactin was 70.0% in Vitex, and 76.7 in bromocriptine group. The bromocriptine had also slightly greater normalization rate; however, the difference was not statistically significant (p-value of 0.559). Such results conform to the more recent recommendations, that dopamine agonists should still be the first-line treatment of symptomatic hyperprolactinemia, and are effective in about 8090% of treatments [13]. Nevertheless, recent research indicates that Vitex agnus-castus can also be effectively used to lower prolactin in a few patients with mild and moderate levels of hyperprolactinemia.

Bromocriptine is a dopamine D2 receptor agonist which has found wide application in the treatment of hyperprolactinemia and prolactinoma. Dopamine inhibits the release of prolactin by cells (pituitary lactotrophs); therefore, the dopamine agonists inhibit prolactin release directly. Recent reviews and consensus statements go on to affirm the use of dopamine agonists as the foundation of management in prolactin-secreting disorders [14,15]. Bromocriptine in the current trial decreased the prolactin level by 21.16 + 12.75 ng/ml which translated to a 47.5 percent decrease in the baseline prolactin level. The identification endorses the proven efficacy of bromocriptine as a prolactin-reducing drug. The average post-treatment prolactin level in the bromocriptine group was however 23.36 ± 3.20 ng/ml which was nearly close to that of the Vitex group. This can largely be attributed to the fact that in this sample, bromocriptine did not demonstrate statistical superiority versus Vitex due to this close similarity.

A recent review has noted that Vitex agnus-castus could be carrying its biological effects via dopaminergic pathways, namely, by acting at the dopamine D2 receptor, and thus decreasing prolactin secretions [16]. This process offers biologic viability of the results of the current study. The hypothesis that the Vitex might produce a clinically significant prolactin-reducing effect is supported by the fact that the prolactin levels in the Vitex group dropped to 23.22 ± 5.91 ng/ml, whereas in the control group, the levels were 40.18 ± 18.38 ng/ml. Other recent data indicate that Vitex could potentially enhance the symptoms and other menstrual cycle-related symptoms and reproductive parameters of the endocrine system though the quality and size of the studies is diverse [17,18]. Therefore, the present findings are in agreement with the growing interest in Vitex as a potential alternative or adjunctive therapy in women with mild hyperprolactinemia.

Baseline LH compared revealed that it was 8.81 in the vitex group, and 9.02 in the bromocriptine group, which was 3.01 and 2.84 respectively. The Vitex group and bromocriptine group their LH were found to be 9.26 ± 3.38 IU/L and 10.32 ± 2.58 IU/L respectively following treatment. The difference between the post-treatment increased compared to the bromocriptine group, although, was not statistically significant, 0.177. The mean change in LH was 0.45 ± 1.82 IU/L in the Vitex group and 1.30 ± 1.94 IU/L in the bromocriptine group, with a p-value of 0.086. This marginal difference could indicate a look for the larger recovery of gonadotropin activity with the bromocriptine. Hyperprolactinemia inhibits the hypothalamic-pituitary-gonadal axis through the impairment of the pulsatility of gonadotropin-releasing hormone: low or inappropriate secretion of LH may ensue [19]. Thus, prolactin downregulation can be gradually compensated with LH secretion, although it might take more time than a month.

In a similar manner, FSH was modestly increased in the two groups. Vitex had a baseline FSH of 7.31 ± 2.21 IU/L and bromocriptine had 7.94 ± 2.36 IU/L. After treatment, FSH was 7.67 ± 2.43 IU/L and 8.87 ± 2.63 IU/L, respectively. The post treatment p-value was 0.073 and this implies that the difference was insignificant but again a tendency to an increased level of FSH was observed in the bromocriptine group. This observation can be attributed to the fact that gonadotropin recovery following normalization of prolactin is not necessarily immediate. Menstrual regularity and ovulation could respond to the decrease in biochemical prolactin more slowly than clinical improvement. Recent research has demonstrated that the objective of treatment of hyperprolactinemia is to lower the prolactin levels, besides regaining the gonadal functioning, fertility and menstrual cyclicity [13,20]. One month may be a short time frame in the current research to prove that biochemical response occurred but not long enough to test completely that reproductive endocrine recovery was attained.

The rate of normalization of prolactin in the current study was clinically encouraging. Within the Vitex group, 21 of 30 patients (70.0 percent) experienced prolactin normalization versus 23 of 30 patients (76.7 percent) in the bromocriptine patients. Though there was a numerically significant response to bromocriptine, the insignificant p-value indicates that there is a possibility that the difference might have been powered by chance. The recent network meta-analysis on pharmacological treatment of hyperprolactinemia indicated that the treatments based on dopamine agonists are effective but vary in terms of their tolerability and patient uptake [21]. Bromocriptine is effective, has nausea and vomiting as side effects that can limit adherence as well as dizziness and postural hypotension. Vitex can thus be appealing in the selective patients to be better tolerated though the dopamine agonists cannot be replaced in prolactinoma patients, macroadenoma patients, visual symptoms or significantly elevated prolactin patients.

Stratified analysis revealed that there was no significant treatment response modification by age. Results reflected a difference in post-treatment prolactin 22.84 ± 5.62 ng/ml in Vitex and 23.11 ± 3.18 ng/ml in bromocriptine with a p-value of 0.861 in patients between the age of 1825 years. In patients aged 26–35 years, post-treatment prolactin was 23.61 ± 6.24 ng/ml and 23.58 ± 3.31 ng/ml, respectively, with a p-value of 0.984. This shows the similar and equal efficacy of both treatments within the reproductive age studied. This result has some implication since hyperprolactinemia in young women is often coupled with menstrual disturbance and infertility, therapeutic decisions must be taken with regard to reproductive goals [22].

The findings of the current research are practical, as well. There is established treatment bromocriptine, which may be hampered by side effects and compliance problems. On the other hand, in certain situations availability and cost may limit the use of cabergoline, which is otherwise preferable worldwide due to superior efficacy and tolerability [14,23]. bromocriptine can be an option in these cases and it is also accessible. Vitex agnus-castus can provide possible option to women with mild hyperprolactinemia, especially not having macroadenoma or severe pathology in the pituitary. Nevertheless, administration of Vitex must be risk-averse and evidence-based, as extreme hyperprolactinemia and prolactinoma must undergo appropriate endocrine monitoring, x-ray and use of dopamine agonist medications.

The strong aspect of this research is that it is randomized and equalized with respect to number of patients assigned to two groups. Assessments of various hormonal outcomes, including prolactin, LH and FSH, were also taken into account rather than prolactin only. Moreover, age, body mass index, smoking and family history stratification enhanced the interpretations of effects of treatments. Nevertheless, there are some restrictions that should be taken into consideration. The study was a small sample size, comprising of 30 patients in each group. Follow-up period was restricted to one month which might not be enough to determine menstrual recovery, ovulation, fertility outcomes and long term recurrence. No adverse effects, patient satisfaction or compliance to treatment was also examined in details in the study. Recent researches underline that long-term treatment of hyperprolactinemia needs not only to achieve normalization of biochemistry but also clinical performance, presence or absence of tumor, negative side

effects and fertility objectives [24,25].

CONCLUSION

Finally, Vitex agnus-castus and bromocryptine had a significant decrease in serum prolactin in one month of treatment. The decrease in the mean mean and a higher normalization rate were marginally higher with Bromocryptine but the difference between the two groups was not significant. The LH and FSH increased slightly, with a tendency towards higher in the bromocriptine group, but not statistically significant. Stratified analysis revealed that there was no significant difference in age and BMI as well as smoking or family history on treatment response. The results are indicative that Vitex agnus-castus can be regarded as a similar medication to bromocryptine in relation to short-term prolactin decrease in the updated women with hyperprolactinemia. Nevertheless, bigger studies with extended follow-up and clinical outcome evaluations are necessary before Vitex can be prescribed as an alternative to usual rigorous dosage of dopamine agonists treatment.

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