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ROLE OF BROMOCRIPTINE AND PYRIDOXINE IN PREMENSTRUAL TENSION SYNDROME

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Abstract : Premenstrual syndrome (PMS) is a universal problem of women of reproductive age group. No satisfactory treatment is available to treat this syndrome till date. Sixty female patients with PMS in age group of 20–45 years were interviewed. A detailed history and 20 premenstrual symptoms were included for making the diagnosis of PMS. Premenstrual symptom score of each patient was recorded before treatment. Patients were followed up monthly for 3 months after starting treatment, to ascertain the change in score. The patients were divided into 3 groups of 20 patients each – control group, bromocriptine group and pyridoxine group. In control group, patients were kept on ferrous sulphate tablet 100 mg for 3 months, as placebo. There was no significant change in the premenstrual symptoms score at the end of the study period in control group. Bromocriptrine 2.5 mg twice a day and pyridoxine 100 mg/day showed a significant reduction in the mean premenstrual symptom score after 3 months of treatment. It is concluded that both the drugs are effective for treatment of premenstrual syndrome but, pyridoxine showed significantly higher response rate and lesser incidence of side effects than bromocriptine.

Key words : bromocriptine pyridoxine premenstrual syndrome

INTRODUCTION

The Pre Menstrual Syndrome (PMS) has been recognized for centuries. The original description of the syndrome was given by Frank in 1931 (1). It has significant adverse impact on work, efficiency, life and social relationships of a woman (2).

PMS is a psychological and somatic disorder of unknown etiology, which may affect almost all women of reproductive age group. It is defined by Reid (3) as the cyclical recurrence, in the luteal phase of the menstrual cycle, of a combination of distressing physical, psychological and/or behavioral changes of sufficient severity to result in deterioration of interpersonal relationship and/or interference with normal daily activities. The symptoms may be physical, emotional and/or behavioral (4).

The prevalence of PMS is reported to be between 5% and 95% (5,6). Its etiology is

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not yet fully understood, till today and neither the cause nor the most effective treatment has been resolved. Almost all possible hormones, iron, vitamins, neurotransmitters, neuromodulators and antidepressants (7, 8, 9) have been investigated for their involvement in PMS. Cole et al (10) reported role of prolactin while Elsner et al (11)suggested efficacy of bromocriptine clinically. Williams et al (12), Kleijner et al (13) and Johnson et al (14) showed significant improvement with pyridoxine.

The search for most effective therapy without unpleasant side effects is still continuing. Hence, in this study comparison of efficacy of bromocriptine and pyridoxine, along with their adverse effects is endeavored.

MATERIALS AND METHODS

The study was conducted in Department of Pharmacology in association with Department of Obstetrics & Gynaecology, S. N. Medical College, Agra. Patients attending Gynaecology OPD were interviewed during the study period. The protocol was prepared and permission was taken from the Institutional Ethics Committee. An informed consent was taken from the patients or their attendants.

Patients of age group between 20–45 years, with regular menstrual cycle (22–35 days) having premenstrual symptoms for at least 2 or 3 menstrual cycles, were selected for the present study. These symptoms were physical, psychological and behavioral. Physical symptoms included were headache, breast tenderness and swelling, swelling of extremities, bloated abdomen, weight gain, fatigue and dizziness/fainting. The psychological symptoms included were depression, irritability, anxiety, mood swings, angry outburst, over-sensitivity while the behavioral symptoms were increased appetite, food cravings, social withdrawal, forgetfulness, easy crying, confusion, sleepless-ness. For each symptom a score was given between 1 to 3 depending upon the severity of symptoms-mild, moderate or severe. Scoring and grading of the symptoms was followed according to the method of Steiner (15).

The patients having menorrhagia, chronic psychiatric illness, breast disease/ swelling, anaemia, chronic fatigue syndrome and patients taking oral contraceptives were not included in the study.

A detailed history was taken, during luteal phase of menstrual cycle, regarding age, marital status, menstrual pattern and obstetric history.

Grading of symptoms :– Premenstrual symptom score (pmss) was graded as follows :–

Grade 0 – No symptoms

Grade 1 – Mild symptoms not interfering with activities

Grade 2 – Symptoms interfere with activity but it is not disturbing.

Grade 3 – Severe, disabling symptoms

Thus possible minimum and maximum score is between 0 to 60. The patients were diagnosed as case of PMS, if premenstrual

symptom score was more than 5 or not less than twice the postmenstrual symptom score. Patients diagnosed to be suffering from PMS were selected, examined, investigated and were given a pretreatment symptom score.

The patients were categorized as mild PMS (Score 6–20), moderate PMS (score 21–40 or at least 5 symptoms of grade 2) and severe PMS (score 41–60 or at least 5 symptoms of grade 3).

Grouping, drugs and dosage

Patients were randomly divided in 3 groups of 20 patients each :

Group I (Control group) : Placebo, ferrous sulphate tablets, 100 mg, orally daily for 3 months.

Group II (Bromocriptine group) : Bromocriptine initially started in the dose of 1.25 mg at bed time for 2–3 days and then increased up to 5 mg/day in 2 divided doses, up to the beginning of the next cycle.

Group III (Pyridoxine group) : Pyridoxine. 100 mg/day, administered orally throughout the study period.

All groups were treated for 3 consecutive cycles, after giving a pretreatment score.

Improvement assessment

Patients were followed up monthly for 3 months by re-evaluating premenstrual symptoms. Reduction of symptom score (after treatment) to less than half of previous score was taken as criteria for assessment of improvement.

It was analyzed using Student's 't' test and the test of proportions by calculating the 'Z' test.

OBSERVATIONS AND RESULTS

A total of 60 patients were enrolled and randomly divided into 3 groups of 20 patients each. Majority of the patients in present study were in the age group of 20–35 years in all the three groups. The mean age was 28 ± 5.17 years, 29.05 ± 5.66 years and 28.01 ± 5.08 years in control, bromocriptine group and pyridoxine group respectively.

35–50% females were married in all three groups. Among married, 70.0 to 88.9% patients were para 1 or para 2. All patients, in the study, were having regular menstrual cycles and 75 to 100% had average flow during their menstrual period in all three groups.

In control group, physical symptoms, such as headache and fainting were complained by 90% patients; breast tenderness by 75% patients whereas 60% had bloated abdomen. Complaints of psychological and behavioral symptoms were 85% and 90% respectively.

In bromocriptine group 90% patients had breast tenderness, 95% had headache, 70% had bloated abdomen. 90% and 70% had psychological and behavioral symptoms respectively.

In pyridoxine group 80% patients had breast tenderness, 90% had headache. 95% had psychological and 90% had behavioral symptoms.

Table I shows premenstrual symptom score in control, bromocriptine and pyridoxine groups. The data were analyzed by Student's 't' test.

In control group, the score was 31.35 ± 7.67 before treatment. After one, two and three months of treatment with placebo, mean premenstrual symptom score was insignificantly reduced to 30.4 ± 7.99, 30.8 ± 7.41 and 29.2 ± 10.31 respectively.

In bromocriptine group, mean premenstrual symptom score was 33.7 ± 8.23. With the therapy, the score significantly reduced to 27.75 ± 6.83, 19.5 ± 3.87 and 15.55 ± 3.52 after 1, 2, 3 months, respectively. In Pyridoxine group, mean premenstrual symptom score was 30.15 ± 10.71 before treatment. There was significant reduction in mean premenstrual symptom score after one, two and three month treatment, which was 24.95 ± 7.81, 14.7 ± 5.77 and 10.1 ± 4.79 respectively.

Table I also shows the statistical significance of pmss. Both the drugs are effective in reducing the score. Bromocriptine shows significant reduction in the score from the very first month of the treatment, while with pyridoxine significant reduction is seen after two months of treatment.

On comparing bromocriptine and pyridoxine, it was found that pyridoxine is highly significant in reducing the pmss (Table I) after 3 months of treatment.

Table II shows the clinical improvement in the number of patients. In Control group, none of the patient showed improvement even after two months of treatment with placebo. After third month, only 2(10%) patients showed improvement.

In bromocriptine group, clinical improvement in the three types of symptoms was seen in 3 (15%) patients after 2 months and in 13 (65%) patients after 3 months of

TABLE I: Mean premenstrual symptom scores before & after treatment.

Symptom score	*Control group (C) (n=20)*	*Bromocriptine group (B) (n=20)*	*Pyridoxine group (P) (n=20)*
Before Treatment	31.35±7.67	33.7±8.23	30.15±10.71
After 1 month Initial vs 1 month	30.40±7.99 t=0.384 p=0.703	27.75±6.83 t=2.49 p=0.017	24.95±7.81 t=1.76 p=0.087
After 2 month Initial vs 2 month	30.80±7.41 t=0.231 p=0.819	19.50±3.87 t=6.98 p=0.0001	14.70±5.77 t=5.68 p=0.0001
After 3 month Initial vs 3 month	29.20±10.31 t=0.748 p=0.459	15.55±3.52 t=9.07 p=0.0001	10.10±4.79 t=7.64 p=0.0001
Mean pmss after 3 month (Group B vs P)	–	15.55±3.52	1010±4.29 t=4.102 p=0.0001

TABLE II: Patients showing improvement at 1, 2, 3 months.

Response	*Control group (C) (n=20)*		*Bromocriptine group (B) (n=20)*		*Pyridoxine group (P) (n=20)*	
	No. of patients	*%*	*No. of patients*	*%*	*No. of patients*	*%*
1 Month	0	0	0	0	0	0
2 Month	0	0	3	15	10	50
3 Month	2	10	13	65 Z=02.2 p=0.03*	17	85 Z=3.27 p=0.001*

'Z' test after 3 months C vs B & C vs P; P value *Significant, **Highly Significant.

treatment. These results are statistically significant.

In pyridoxine group, none of the patient showed improvement after 1 month of treatment while 10 (50%) and 17 (85%) patients showed improvement after 2 and 3 months of treatment respectively. The results are found to be statistically significant in both the treatment groups.

Table III shows side effects observed during the study period. In Control group, 4 out of 20 patients (20%) had - nausea-1, diarrhoea-1, constipation-2 with placebo.

TABLE III: Patients showing unwanted effects during treatment.

S. No.	*Side effects*	*Control group (C) (n=20)*		*Bromocriptine group (B) (n=20)*		*Pyridoxine group (P) (n=20)*	
		No. of patients	*%*	*No. of patients*	*%*	*No. of patients*	*%*
1.	Nausea	01	05	05	25	02	10
2.	Vomitting	00	00	01	05	00	00
3.	Diarrhea	01	05	00	00	01	05
4.	Constipation	02	10	01	05	00	00
5.	Dizziness	00	00	06	30	01	05
Total		**04**	**20**	**13**	**65**	**04**	**20**

In bromocriptine group, 13 out of 20 (65%) patients had side effects like nausea-5, vomiting-1, constipation-1, dizziness-6, but this did not require bromocriptine to be withdrawn and patients continued it during the whole study period.

In Pyridoxine group, side effects were seen only in 4 out of 20 patients (20%) like nausea-2, diarrhoea-1, dizziness-1.

DISCUSSION

Premenstrual Syndrome means cyclical recurrence of physical, mental, and behavioral symptoms in the late luteal phase of menstruation of sufficient severity to require treatment. It has yet unknown etiology, an uncertain and variable course and an unidentified family history. Till now neither the cause nor the most effective treatment has been resolved. (14)

Proper management requires accurate diagnosis with the help of detailed history and symptom charting (15). Many agents have been tried for its treatment like bromocriptine (11), pyridoxine (12, 13), primrose oil (16), fluoxetine (17, 18) and paroxetine (8). The safety data for bromocriptine and pyridoxine in PMS are scanty. Therefore this study was conducted to assess and compare the efficacy and untoward effects of bromocriptine and pyridoxine in treatment of PMS.

In placebo group, only 2 patients showed clinical improvement in symptoms of PMS. The pre-treatment pmss being 31.35 ± 7.67, which did not change significantly, even at the end of 3rd month.

In bromocriptine group, clinical improvement was seen in 15% and 65% of patients after 2nd and 3rd month of treatment respectively. The premenstrual symptom score before treatment was 33.7 ± 8.23 which gradually reduced significantly with bromocriptine treatment. Our findings are in concurrence with those of Kullander (19) and Ylostalo (20). The efficacy of bromocriptine explains the change

of prolactin levels during premenstrual syndrome. The side effects were seen in 65% of patients, but discontinuation of the drug was not required during the study period.

In pyridoxine group, clinical improvement was observed in 50% and 85% patients and pmss also reduced significantly at the end of 2nd and 3rd month. Our findings are in concurrence with those of Doll et al (21), London et al (22) and Wyattetal (23).

Pyridoxine acts as a cofactor in enzymatic steps of tryptophan metabolism, in the synthesis of GABA and is an immediate precursor of dopamine and thus it increases the concentration of dopamine and serotonin. Its deficiency may lead to reduced concentrations of noradrenaline and serotonin (24). Altered serotonin function in women and Vit B6 deficiency (25) have been reported in PMS. Our study shows that pyridoxine is, remarkably safe drug as mild side effects were seen in only 20% patients.

Response rate was statistically significant with bromocriptine ($P<0.001$) and pyridoxine ($P<0.001$), as compared to placebo ($P>0.05$). In comparison to bromocriptine, pyridoxine showed significant reduction in premenstrual symptom score and clinical improvement after two months of therapy. Higher response rate (85%) and lower incidence of side effects (20%) with pyridoxine, as compared to 65% each with bromocriptine has been observed. Pyridoxine, therefore, should be preferred over bromocriptine, provided it is used for a longer duration. Hence, it can be concluded that women should be encouraged to take pyridoxine, as it has beneficial effects in premenstrual symptomatology. However, randomized double blind studies, with larger number of populations are required to substantiate these observations.

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