Comparative Clinical Trial to Evaluate the Efficacy of Bromocriptine over Placebo in the Management of Premenstrual Tension

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Summary

Although it's etiology is unknown, some studies indicate that prolactin levels increase during the luteal phase of the menstrual cycle and mastodynia is a common symptom of premenstrual tension. Therefore, in the present study we evaluated the effect of bromocriptine on PMT symptoms and compared it's efficacy with placebo. Following strict inclusion and exclusion criteria, 15 women with severe PMS participated, in a 6 month study which included 2 months of control cycle followed by bormocriptine 2.5 mg/ day or placebo in the luteal phase of the menstrual cycle for the next 4 months. Symptoms were evaluated using the calender of premenstrual experiences. Compared with placebo, treatment with bromocriptine was associated with improvement in pain ($p = 0.0312$) specially mastodynia and fluid electrolyte ($p=0.0312$) symptoms.

Introduction

The premenstrual syndrome has been recognized for centuries but only recently accepted as a symptom constellation, worthy of investigative efforts and therapeutic attempt. Premenstrual syndrome is the cyclic recurrence in the luteal phase of the menstrual cycle of a combination of distressing physical, psycholoical and/or behavioural changes of sufficient severity to result in deterioration of interpersonal relationship and / or interference with normal activities. Bromocriptine is a dopamine agonist which inhibits prolactin secretion. Some studies indicate that prolactin levels increase during the luteal phase of the menstrual cycle and mastodynia is a common symptom of PMS. Aim of the present study was to study the effect of bromocriptine for the treatment of PMT syndrome and to compare it's efficacy with placebo.

Material & Methods

The present study was conducted from August 1996 to November, 1997 at out patient department of Upper India Sugar Exchange Maternity Hospital of G.S.V.M. Medical College, Kanpur and other hospitals and Nursing Homes of Kanpur and adjoining areas. Cases comprised of females having symptoms of premenstrual syndrome. Criteria for diagnosis of premenstrual syndrome included physical and behaviour symptoms rigorously excluding other medical and psychiatric conditions simulating premenstrual syndrome. A total of 15 patients meeting above criteria were included in the study. These patients were allocated in 2 groups in a random order.

Group – I (9 patients): Placebo, Group – II (6 patients): Bromocriptine (Tab. 'Sicriptine') 2.5 mg / day.

Premenstrual syndrome symptoms were measured using MODIFIED 'PRISM' Calender. The calender was completed by the patient for the complete menstrual cycle. Alongwith general information the following clinical and behavioural parameters were studied and any change in the symptoms towards betterment or otherwise was noted: (a) affective (b) cognitive (c) pain (d) neurovegetative (e) autonomic (f) CNS (g) fluid / electrolyte (h) dermtologic (i) behavioural. Patients started charting on the first day of menstruation and indicated the number of days of bleeding or spotting in the calender. Patients performed daily self assessment regarding the presence and severity of each symptom as per instructions. Score '0' absence of symptoms. 1=mild present but does not interfere with activities, 2=severe disabling. Summation of the daily ratings across each category of symptoms produced a premenstrual experience score. Daily scores were summed across two 7 days periods yielding follicular phase (days 3 to 9) and luteal phase (last 7 days of the menstrual cycle) scores. For statistical analysis, the data were analysed by applying 'sign test of median' using 'MINITAB' package on computer.

Observations & Discussion

Table I shows that pretreatment, maximum percentage change in score was for affective symptoms in Group –I (416.66%) and pain symptoms in Group II (314.28%), while minimum percentage change in score was for dermtologic symptoms in both the groups (20% in Group I and 12.50% in Group II). Post treatment.

Table II shows that post-treatment there is definite improvement in almost all the symptoms in both the groups (except congnitive, pain and behavioural symptoms in Group –I) as shown by less percentage change in scores from follicular to luteal phase in post treatment phase.

Table III analyses the effect of placebo therapy. We find that there was highly significant (p=0.0039) improvement in affective symptoms after therapy (median score decrease from 31 to 15). In cognitive symptoms though there was highly significant improvement (p=0.0078) this improvement was more in follicular phase rather than luteal phase. In pain, significant improvement (p=0.0312) was found but again this improvement was more in follicular phase (20%) rather than in luteal phase (8.6%). Therefore improvement in cognitive and pain symptoms cannot be attributed to placebo therapy. In neurovegetative symptoms, significant improvement (p=0.0391) was found. In autonomic, CNS and fluid electrolyte symptoms, though improvement was there, it was statistically not significant. There was no change in dermatologic symptoms and in behavioural symptoms, there was deterioration rather than improvement (median score increased from 9 to 10) but this was not statistically significant (p=0.7266). Thus psychological symptoms were found to be improved by placebo but no significant improvement was found in somatic physical symptoms. This suggests incorporation of psychophysiological factors in the causation of premenstrual tension syndrome. This fact is also supported by Benedek (1988) who suggested that intense conflict over the female role was responsible for PMS symptoms.

Table IV shows the effect of bromocriptine in

Table –I
Median Pre-treatment symptom scores in two groups with percentage change from follicular to luteal phase.

Symptoms	Groups					
	I			II		
	F	L	%age Change	F	L	%age Change
A. Affective	06	31	416.66	08	33	312.50
B. Cognitive	05	08	60.00	08	14.5	81.25
C. Pain	10	23	105.00	07	29	314.28
D. Neurovegetative	12	15	25.00	13	18.50	42.30
E. Autonomic	10	15	50.00	07	09	28.57
F. CNS	02	06	200.00	1.5	05	233.33
G. Fluid Electrolyte	07	13	85.71	5.5	15.5	181.81
H. Dermatologic	05	06	20.00	08	09	12.50
I. Behavioural	06	09	50.00	09	18	100.00

F = Follicular phase score, L = Luteal Phase Score
%age Change = Percentage change in Score.

Table – II
Median Post-Treatment symptom scores in two groups with percentage change from follicular to luteal phase.

Symptoms	Groups					
	I			II		
	F	L	%age Change	F	L	%age Change
A. Affective	06	15	150.00	08	32	300.00
B. Cognitive	03	06	100.00	9.50	15	57.89
C. Pain	08	21	162.50	07	11	57.14
D. Neurovegetative	10	12	20.00	13.5	17	25.92
E. Autonomic	08	12	50.00	08	1[illegible]	[illegible]
F. CNS	02	05	60.00	1.5	04	166.66
G. Fluid Electrolyte	06	10	66.66	5.5	11	100.00
H. Dermatologic	05	06	20.00	09	10.0	11.11
I. Behavioural	04	10	150.00	8.5	17	100.00

F – Follicular Phase Score
L = Luteal Phase Score
%change = Percentage Change in Score.

Table III
Median Pre and Post-Treatment symptom scores in Group –I (with Placebo)
(At the end of 6th Month)

Symptoms	Follicuar Phase Score			Luteal Phase Score			'p' Value
	Pre treament	Post treatment	%age Change	Pre Treatment	Post Treatment	%age Change	
A. Affective	06	06	0	31	15	51.51	0.0039**
B. Cognitive	05	03	40.00	08	06	25.00	0.0078**
C. Pain	10	08	20.00	23	21	8.60	0.0312*
D. Neurovegetative	12	10	16.66	15	12	20.00	0.0391*
E. Autonomic	10	08	20.00	15	12	20.00	0.1797 NS
F. CNS	02	02	0	06	05	16.66	0.1250 NS
G. Fluid Electrolyte	07	06	14.28	13	10	23.07	0.1797 NS
H. Dermatologic	05	05	0	06	06	0	1.0000 NS
I. Behavioural	06	04	33.33	09	10	11.11	0.7266 NS

** Highly significant * Significant NS = Not significant

Table – IV
Median Pre and Post-Treatment Symptom Scores in Group –II (With Bromocriptine)

Symptoms	Follicular Phase Score			Luteal Phase Score			'p' value
	Pre Treatment	Post Treatment	%age Change	Pre Treatment	Post Treatment	%age Change	
A. Affective	08	08	0.00	33	32	9.12	0.6875 NS
B. Cognitive	08	09.5	18.75	14.5	15	3.44	1.0000 NS
C. Pain	07	07	0.00	29	11	62.06	0.0312*
D. Neurovegetative	13	13.5	3.84	18.5	17	8.1	1.0000 NS
E. Autonomic	07	08	14.28	09	10	11.11	0.0312*
F. CNS	01	01	0.00	05	04	20.00	0.6250 NS
G. Fluid/Electrolyte	5.5	5.5	0.00	15.5	11	29.03	0.0312*
H. Dermatologic	08	09	12.50	09	10	11.11	0.0312*
I. Behavioural	09	08.5	5.55	18	17	5.55	0.6875 NS

** Highly significant * SignificantNS = Not Significant

premenstrual tension. We find that bromocriptine significantly improved pain (p=0.0312) specially mastodynia and fluid/electrolyte (p=0.0312) symptoms. There was no statistically significant change in affective (p=0.6875), cognitive (p=1.000), neurovegetative (p=1.0000), CNS (p=0.6250) and behavioural (p=0.6875) symptoms. In autonomic (p=0.0312) and dermatologic (p=0.0312) symptoms, statistically significant change indicating deterioration was found. This could be explained by the fact that bromocriptine produces nausea, vomiting (autonomic symptoms) by stimulating dopaminergic receptors in brain and it may also cause hypotension (autonomic symptom). That is why, deterioration in autonomic symptoms must have been there. For deterioration in dermatologic symptoms, no suitable explanation was found and this may be due to the reason that dermatological symptoms in this group of patients were of such severity that some other proper treatment was needed for it's management.

Thus, in our study, with bromocriptine, significant improvement was observed in symptoms associated with over reactiveness to normal prolactin levels; that is pain (mastodynia) (Kullanden & Svanberg, (1979) and fluid / electrolyte symptoms i.e. bloatedness, abdominal distension, oedema etc. Our study correlates well with the study of Andersch (1983), who found improvement in breast pain with bromocriptine. Our study also correlates with the study by Meden-Vrtover and Vujii (1992), who found that bromocriptine in a daily dose of 5 mg/d in luteal phase caused significant improvement in symptoms like breast tenderness, abdominal distension, oedema and weight gain whereas it was less effectiveness in psychic syndromes.

Table V shows post-treatment percentage change in score of different symptoms in two groups. When we compared the efficacy of bromocriptine with placebo (Table V) we found that bromocriptine was better than palcebo in pain, fluid and electrolyte, cognitive, neurovegetative and behavioural symptoms. In affective symptoms, placebo was better than bromocriptine. Though apparently, placebo (showing 140% improvement) was also superior to bromocriptine (showing 66.67% improvement) for CNS symptoms this was not found significant on statistical analysis. (p value for change in CNS symptoms by placebo being 0.1250).

Table V
Post-Treatment Percentage Change in score of Different symptoms in two groups

Symptoms	Groups	
	I	II
A. Affective	266.66	12.50
B. Cognitive	-40.00	23.36
C. Pain	-32.50	257.14
D Neurovegetative	5.00	16.38
E. Autonomic	0.00	3.57
F. CNS	140.00	66.67
G. Fluid/Electrolyte	19.50	81.81
H. Dermatologic	0.00	1.39
I. Behavioural	-100.00	0.00

(-) showing deterioration in symptoms.

Conclusion

Bromocriptine is better than placebo in pain specially mastodynia and fluid and electrolyte symptoms of PMT and thus over reactiveness to prolactin levels may be an associated factor in etiology of PMT. Larger studies are needed to establish this fact and to compare the efficacy of this drug with other treatment modalities and to assess it's long term effectiveness and safety.

References

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