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Comparative Clinical Trial to Evaluate the Efficacy of Fluoxetine over Placebo in the Treatment of Premenstrual Tension

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Summary

Although its etiology is unknown, it has been hypothesized that premenstrual syndrome (PMS) is inked to a deficiency of central serotoninergic activity. In the present study, we evaluated the effect of fluoxetine, a specific serotonin uptake inhibitor, on PMS symptoms and compared it's efficacy with placebo. Following strict exclusion and inclusion criteria, 18 women with severe PMS participated in a 6 month study which included 2 months of control cycle followed by 20mg/day fluoxetine or placebo in the luteal phase of the menstrual cycle for the next 4 months, administered in randomized order. Symptoms were evaluated using the calendar of premenstrual experiences. Compared with placebo, treatment with fluoxetine was associated with an improvement in PMS symptoms as judged by significant improvement in affective (P=0.0339), CNS (P=0.0039), behavioural (P=0.0039), Pain (P=0.0391) and autonomic symptoms (P=0.0391). Therefore, fluoxetine appears to be a highly effective treatment for the psychological and physical symptoms accompanying PMS.

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 psychological and/or behavioural changes of sufficient severity to result in deterioration of interpersonal relationship and/or interference with normal activities. Aim of the present study was to study the effect of Fluoxetine in treatment of PMT syndrome and to compare it's efficacy with placebo and thus also evaluating some of the known etiological aspects of PMT syndrome.

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 the females having symptoms of premenstrual syndrome. Criteria for diagnosis of premenstrual syndrome included physical and behavioural symptoms while carefully rigorously excluding other medical and psychological conditions simulating premenstrual syndrome.

A total of 18 patients meeting the above criteria were included in the study. These patients were allocated in 2 groups (of 9 patients each) in a random order. Following drugs were given: Group-I Placebo; Group-II: fluoxetine hydrochloride (Cap. 'Fludac') 20mg/day. Placebo or drug was given from the 14th day of the menstrual cycle till menstruation started. After 2 control cycles i.e. without placebo or drug either placebo (Group-

D or drug (Group II) were given for next 4 cycles. Premenstrual syndrome symptoms were measured using MODIFIED 'PRISM' CALENDAR. The calendar was completed by the patient for one 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) Dermatologic (I) Behavioural. Patients started charting on the first day of menstruation and indicated the number of days of bleeding or spotting in the calendar. 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 day period 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 both the groups (416.66% in Group-I and 560% in Group II) while minimum percentage change was in the dermatologic symptoms (20% in Group-I and no change in Group II). In neurovegetative symptoms in Group-II even pre treatment follicular phase score was more (16) than luteal phase score (13). Therefore neurovegetative symptoms in Group II were not attributed to PMT.

Table II shows that there is definite improvement in almost all the symptoms in both the groups (except cognitive pain and behavioural symptoms in Group I) as shown by less percentage change in scores from follicular to luteal phase in post treatment phase. In CNS symptoms in Group II pretreatment there was difference from follicular to luteal phase of 66.66% whereas posttreatment it was 50%, therefore total improvement after treatment was 116.66%.

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 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 his was not statistically significant (P=0.7266). Thus, our study showed marked placebo effect in overall improvement of affective,

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	05	33	560.00
B. Cognitive	05	08	60.00	05	09	87.50
C. Pain	10	23	130.00	08	15	87.50
D. Neurovegetative	12	15	25.00	16	13	-18.75
E. Autonomic	10	15	50.00	10	10	0.0
F. CNS	02	06	200.00	03	05	66.66
G. Fluid /Electrolyte	07	13	85.71	06	12	100.00
H. Dermatologic	05	06	20.00	07	07	0.0
I. Behavioural	06	09	50.00	06	09	50.00

F=Follicular phase score L=Luteal Phase Score
%change Percentage change in score
(-)=Denotes deterioration 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	04	08	100.00
B. Objective	03	06	100.00	05	07	40.00
C. Pain	08	21	162.50	09	12	33.33
D. Neurovegetative	10	12	20.00	10	09	-10.00
E. Autonomic	08	12	50.00	07	07	0.00
F. CNS	02	05	60.00	02	01	-50.00
G. Fluid/Electrolyte	06	10	66.66	08	11	37.50
H. Dermatologic	05	06	20.00	06	07	16.66
I. Behavioural	04	10	150.00	04	05	25.00

F=Follicular phase score L=Luteal Phase Score
%age change= Percentage change in score
( )=Denotes deterioration in score

Table – III
Median Pre & Post Treatment Symptom Scores in Group I (With Placebo)
(At the end of 6th Month)

Symptoms	Follicular Phase Score			Luteal Phase Score			'P' Value
	Pre Treatment	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	1.000 NS
I. Behavioural	06	04	33.33	09	10	11.11	0.7266 NS

** Highly significant * Significant NS Not significant

Table – IV
Median Pre & Post Treatment Symptom Scores in Group II (With Fluoxetine)
(At the end of 6th Month)

Symptoms	Follicular Phase Score			Luteal Phase Score			'P' Value
	Pre treatment	Post treatment	%age change	Pre treatment	Post treatment	%age change	
A. Affective	05	04	20.00	33	08	75.75	0.0039**
B. Cognitive	05	05	1.00	09	07	22.22	0.1798 NS
C. Pain	08	09	12.50	15	12	20.00	0.0391*
D. Neurovegetative	16	10	37.50	13	09	30.76	0.1250 NS
E. Autonomic	10	07	30.00	10	07	30.00	0.0391*
F. CNS	03	02	33.33	05	01	80.00	0.0039**
G. Fluid/Electrolyte	06	08	33.33	12	11	8.33	1.0000 NS
H. Dermatologic	07	06	14.28	07	07	0.00	1.0000 NS
I. Behavioural	06	04	33.33	09	05	44.44	0.0039**

** Highly significant * Significant NS Not significant

neurovegetative symptoms and little improvement in fluid electrolyte symptoms.

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 effect of fluoxetine in premenstrual tension. We find that with fluoxetine there was statistically highly significant improvement in affective (P 0.00039), CNS (P=0.039) and behavioural (P 0.0039) symptoms. Statistically significant improvement was also found in pain (P=0.0391) and autonomic (P 0.0391) symptoms. No significant change was observed in cognitive, neurovegetative, fluid and electrolyte and dermatologic symptoms. Fluoxetine is a highly selective serotonin uptake inhibitor and has antidepressant action. Some studies of serotonin in PMS patients versus controls have shown decrease in the platelet serotonin recognition sites or the level of serotonin premenstrually). (Taylor et al, 1984). Because fluoxetine is believed to enhance central serotoninergic activity, it is not surprising that psychological symptoms were improved more than physical symptoms. It is possible that amelioration of physical symptoms may have been an indirect effect resulting from marked improvement in psychological symptoms. Fluoxetine has been reported to have a beneficial effect in subjects with late luteal phase dysphortic disorders (Samuel et al, 1992).

Our study also correlates well with the study by Steiner et al, 1995 who found fluoxetine very beneficial in reducing symptoms of tension, irritability and dysphoria as measured by visual analogue scale (P less than 0.001) at a dose of 20mg/day.

Table V compares the efficacy of fluoxetine with placebo. We found that fluoxetine was better than placebo in affective, cognitive, pain, fluid/electrolyte and behavioural symptoms. For neurovegetative and dermatologic symptoms fluoxetine was inferior to placebo but on statistical analysis this was not found significant (with fluoxetine for post treatment change in neurovegetative symptoms [P=0.1250 (NS) and dermatologic symptoms P=1.0000 (NS)]. For CNS symptoms, though apparently placebo was better, showing 140% improvement but statistically it was not significant (P=0.1250NS) whereas with fluoxetine there was 116.66% improvement in CNS symptoms which was statistically highly significant (P 0.0039)

Table V
Post-Treatment Percentage Change in Score of Different Symptoms in Two Groups

Symptoms	Groups	
	I	II
A. Affective	266.66	460.00
B. Cognitive	-40.00	47.50
C. Pain	-32.50	54.17
D. Neurovegetative	5.00	-8.75
E. Autonomic	0.00	0.00
F. CNS	140.00	116.66
G. Fluid/Electrolyte	19.05	62.50
H. Dermatologic	0.00	-16.66
I. Behavioural	-100.00	25.00

(-) Showing deterioration in symptoms

Conclusion

In conclusion our study supports psychological and central serotonin deficiency hypothesis of premenstrual tension syndrome. It also demonstrates fluoxetine to be a highly effective treatment, better than placebo for both the central and somatic symptoms accompanying PMS. Larger studies are needed to compare the efficacy of this drug with other treatment modalities and to assess its long-term effectiveness and safety.

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