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Treatment for premenstrual syndrome with Vitex agnus castus: A prospective, randomized, multi-center placebo controlled study in China

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ABSTRACT

Objectives: To investigate the efficacy and safety of VAC BNO 1095 extract in Chinese women suffering from moderate to severe premenstrual syndrome (PMS).
Methods: Prospective, double-blind, placebo controlled, parallel-group, multi-center clinical trial design was employed. After screening and preparation phase lasting three cycles, Eligible patients were randomly assigned into treatment or placebo groups and had treatment with VAC extract or placebo for up to three cycles. Efficacy was assessed using the Chinese version PMS-diary (PMSD) and PMTS.
Results: Two hundred and seventeen women were eligible to enter the treatment phase (TP) and were randomly assigned into the treatment group (108) or the placebo group (109), 208 provided the efficacy data (treatment 104, placebo 104), and 202 completed the treatment phase (treatment 101, placebo 101). The mean total PMSD score decreased from 29.23 at baseline (0 cycle) to 6.41 at the termination (3rd cycle) for the treatment group and from 28.14 at baseline (0 cycle) to 12.64 at the termination (3rd cycle) for the placebo group. The total PMSD score of 3rd cycle was significantly lower than the baseline in both groups ($p < 0.0001$). The difference in the mean scores from the baseline to the 3rd cycle in the treatment group (22.71 ± 10.33) was significantly lower than the difference in the placebo group (15.50 ± 12.94, $p < 0.0001$). Results of PMTS were similar, the total scores for PMTS were significantly lower between the two groups ($p < 0.01$) and within each group ($p < 0.01$). The score was decreased from 26.17 ± 4.79 to 9.92 ± 9.01 for the treatment group, and from 27.10 ± 4.76 to 14.59 ± 10.69 for the placebo group. A placebo effect of 50% was found in the present study. No serious adverse event (SAE) occurred in both groups.
Conclusion: Vitex agnus castus (VAC BNO 1095 corresponding to 40 mg herbal drug) is a safe, well tolerated and effective drug of the treatment for Chinese women with the moderate to severe PMS.

1. Introduction

Premenstrual syndrome (PMS) was first described by Frank as the premenstrual tension syndrome 70 years ago [1]. It is a set of physical, emotional and behavioral symptoms during the week preceding menstruation that are alleviated when the menstrual flow begins [2].

More than 80% of women experienced one of the premenstrual symptoms as defined by ICD-10 criteria [3] and the prevalence of severe and moderate PMS which need to be treated are around 8–30% in different ethnic groups. Approximately 5% of North American women consider their symptoms to be severe enough to have a substantially negative impact on their health and social well being [4–7].

During the past several decades, investigators have contributed to clarifying the pattern of symptom experience across the menstrual cycle by charting how the severity of symptoms waxes and wanes. Symptoms vary among different individuals in the women studied [8]. Typical symptoms are performance impairment, easy fatigue, tenderness and fullness of breasts, change in appetite, abdominal bloating, swelling of extremities, chest pain, itching, backache and others. Premenstrual dysphoric disorder (PMDD) described as severe PMS is characterized by depression or aggression, expressed irritability, unstable nervous system, and performance impairment during the last week of the luteal phase [9].

PMS was associated with reduction in health-related QOL and work productivity [10]. The impacts of PMS also include direct and indirect economic consequences because of significantly reduced productivity at work and increased healthcare costs [11].

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The etiology of PMS remains unknown and may be complex and multifactorial. The role of ovarian hormones is unclear, but symptoms often improve when ovulation is suppressed [12]. Studies attempting to attribute the disorder to an excess of estrogen, a deficit of progesterone, a withdrawal of estrogen, or changes in estrogen-to-progesterone ratio have been unable to find the disorder. The current consensus seems to be that normal ovarian function rather than hormone imbalance is the cyclical trigger for PMDD-related biochemical events within the central nervous system and other target tissues [13].

Therapeutic interventions for PMS range from conservative (lifestyle and stress management) to treatment with psychotropic medications and hormonal therapy or surgical procedures to eliminate ovulation or ovarian function. While of all of these treatments are successful in relieving symptoms for some of the women treated, to date no one intervention has proven to be effective for all [13].

As one of the traditional therapeutic interventions, extracts from the fruit of Vitex agnus castus (VAC) chaste tree are the longest used and best investigated phytotherapeutics for PMS. For the VAC BNO 1095 extract, dopaminergic effects have been proven in animal and clinical trials [14,15]. Bicyclic diterpenes isolated from VAC BNO 1095 extract have dopaminergic activity. Additionally, unknown substances have affinity to opioid receptors [16,17]. Several placebo controlled clinical trials have been done to test the efficacy and the side effects of VAC extract. These studies confirmed that VAC relieves symptoms of PMS successfully without notable side effects [15,18–20]. However, all of these studies were done in western people. Therefore, the aim of the present study is to investigate the efficacyand safety of VAC BNO 1095 extract in Chinese women suffering from moderate to severe PMS.

2. Methods

2.1. Setting

The study was completed from February 2005 to January 2007 in four centers in Beijing, China. The clinical trial was approved by the State Food and Drug Administration (SFDA). The study protocol and patients' informed consent form were approved by the ethics committee of Peking Union Medical College Hospital.

2.2. Study design

The prospective, double-blind, placebo controlled, parallel-group, multi-center clinical trial design was employed in this study. Based on the results of previous studies, the treatment effect could be shown with the sample size at $\alpha = 0.05$ and with a statistical power of 80%. The sample size is at least 100 subjects in each group. As the anticipated drop-out rate was about 20%, the enrollment of 120 subjects was recommended with 30 per group in each center.

2.3. Data collection instruments

Premenstrual syndrome diary (PMSD), a self-assessment symptom rating scale, was used to monitor and diagnosis both moderate to severe PMS. The PMSD is a concise questionnaire consisting of 17 items with factor scales measuring negative affect, water retention, food and pain. It has been used in studies of European women with moderated symptoms of PMS [21]. It is a single page questionnaire using a 4-point rating scale from absent (0) to severe (3). Although there are four factor scales, only the total scale was used in the present study. The main efficacy of the treatment in the present study was the PMSD total scores of the last 7 days prior to menses, which were considered as the luteal phase scores. Reliability of the Chinese version of the PMSD was tested among 50 subjects in the pilot study during two cycles before the study started. The Cronbach's Alpha of PMSD in follicular phase and luteal phase were 0.88 and 0.92, respectively. Test and retest reliability of the Chinese version of the PMSD was tested in both of the follicular phase and the luteal phase were test also. The correlation of luteal phase was 0.5 ($p < 0.01$) and it was 0.42 ($p < 0.01$) in the follicular phase.

The Premenstrual Tension Syndrome Self-Rating Scale (PMTS) [22], is a 36-item questionnaire comprised of the core PMS symptoms in ten different domains with the answer of 'yes' (1) or 'no' (0). PMTS is a self-assessment tool. Cronbach's alpha of PMST in the previous study was 0.93 [22]. Cronbach's alpha of Chinese version PMST in the present study was 0.77. The test and retest reliability was 0.64.

The instruments listed above are English versions. A translation and back translation process was employed in the pilot study. A group of experts from the mental health and gynecological field made the final decision on the Chinese version after a formal discussion and the test of reliability.

A screening questionnaire (SQ) including 11 items was developed by the group of researchers based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [9]. The answer was 'yes' or 'no'. It was used to screen potential PMS patients in the present study.

2.4. Data collecting procedure

The study consisted of three phases including the screening phase, the preparation phase and the treatment phase. Written Informed consent was obtained at the screening phase (SP) which was on any day of the first SP cycle (−2) except menstruation. The gynecologists of each center screened for the potential PMS by using the SQ. If the first 4 items had at least 1 'yes' answer and the all 11 items had at least 4 'yes' answers, the woman would be considered as a potential subject. Potential subjects were given the PMSD for two cycles. Demographic data were also obtained at the screening phase. The preparation phase lasted two cycles (−1 and 0) and had two scheduled visits (1st and 2nd). It was used to determine the eligibility. The potential subject would be diagnosed as having the moderate to severe PMS if the average of her total PMSD scores during the last 7 days prior to menstruation in both cycles revealed an increase of at least 16 points as compared to the average total score of the preceding follicular phase (cycle days 3–9). At the 2nd visit of SP, the diagnosis of PMS was confirmed. The treatment phase (TH) included 3 menstrual cycles (1, 2, and 3) and consisted of 3 scheduled visits (3rd, 4th and 5th visit). All visits were between the first to 3rd day of the menstrual cycle 1st, 2nd and 3rd. The PMSD, BBT chart and study drug or the placebo for one menstrual cycle were presented to the subjects by a trained research assistant in each center. At the same time all records for the last cycle were collected and checked. The PMTS score was also obtained. All changes in subjects' condition during the treatment phase were recorded on the condition changes form (CRF) and medical documents. Scheduled telephone contact with each subject was used to estimate the start of the 2nd and 3rd cycle. The study termination visit was scheduled for the first 10 days of the first post-study cycle.

2.5. Subject

Potential subjects were recruited by advertisements, in hospital newsletters, physician referral, and word of mouth. Prescreening conducted by a trained assistant reviewed the subjects' willingness to comply with the study design and retrospectively assess the severity of PMS by using the screening questionnaire. All participants provided written informed consent. The inclusion criteria were healthy women between 18 and 45 years of age; had regular menstruation in last 12 months: 22–35 days; the total score of

PMTS self-assessment scale ≥18 at visits 1 and 2, PMSD scores of the last 7 days of the two SP cycles showed an increase of at least 16 points as compared to the follicular phase. The exclusion criteria were: intake of hormonal contraceptives, hypothalamic hormones, pituitary hormones or their inhibitors, neuroleptics, antidepressants, selective serotonin reuptake inhibitors (SSRIs), or prolactin inhibitors during last 6 months; treatment for mental disorders; presence of endocrinological diseases such as diabetes mellitus, hypo/hyperthyroidism, pituitary tumour; chronic kidney or chronic liver disease; endometriosis; benign or malignant breast diseases; any planned surgical intervention; pregnancy, planned pregnancy or lactation; any treatment of premenstrual symptoms. Women were excluded if their mean total score of PMSD in the follicular phase > 20, and/or their mean total score of PMSD during the "symptom-free phase" (i.e. cycle days 6–19) > 15 [15]. Subjects were randomized in a double-blind manner to receive either the study drug or the placebo for 3 treatment cycles.

2.6. Study drug

The VAC BNO 1095 extract was administrated orally once daily throughout the three cycles during the treatment phase (TP) to the subjects of treatment group. The VAC extract was provided by Bionorica AG, Germany, in the form of film-coated tablets. Each tablet of VAC BNO 1095 contained 4.0 mg of dried ethanolic (70%) extract of VAC (corresponding to 40 mg of herbal drug) and is identical to Agnucaston®/Cyclodynon® (manufacturer: Bionorica AG, Neumarkt, Germany), Batch No. 0411288041. Women in the placebo group received identical looking tablets without drug.

2.7. Statistical analyses

All data were processed and analyzed using SAS 9.1 by the department of epidemiology and statistics at Peking Union Medical College. The main efficacy variable was changes in the mean PMSD total score during seven days before menses from the cycle zero (baseline) to the cycle 3 (last cycle of treatment). The secondary outcomes of the treatment group and the control group included: the change of the average total PMSD score after one and after two menstrual cycles under the treatment compared to baseline according to the calculation method of main efficacy; change of the total PMTS self-assessment sum score after three menstrual cycles of treatment compared to the baseline.

The descriptive data summarized the number of patients, and the mean, standard deviation, minimum and maximum of the treatment and placebo for the PMSD and PMTS. Paired t test was used to calculate the difference within groups. Student's t was used to analyze the difference between two the groups. Cochran–Mantel–Haenszel and Chi-square test were used to analyze the efficacy rate between the two groups. Full analysis set (FAS) and per-protocol set (PPS) were used to calculate the main efficacy of the treatment. FAS were used to analyze the subjects provided efficacy data, and PPS were used to analyze subjects finished the TP. We considered the mean of the total PMSD scores decreasing 60% from the baseline as efficacy.

3. Results

After the screen phase and the preparation phase (PP), 217 women were eligible to enter the TP and were randomly assigned into the treatment group (108) or the placebo group (109). Two hundred and eight subjects (treatment 104, placebo 104) provided efficacy data, which were included in the FAS. During the TP, fifteen subjects withdrew (treatment 7, placebo 8). The reasons were the subjects' requirements (treatment 3, placebo 2); adverse event (treatment 2, placebo 2); loss of contact (treatment 2, placebo 3) and pregnancy (placebo 1). Two hundred and two subjects (treatment 101, placebo 101) finished the TP which were analyzed in the PPS.

The demographic data such as age, height, weight, age of menarche and menstrual variables of each group were calculated. No statistical difference was found between the two groups (Table 1).

The total PMSD and PMTS scores of subjects in the zero menstrual as the baseline level of PMS are presented in Table 2. The PMSD total scores were the mean total score of luteal phase (7 days prior to menses). The baseline PMSD scores were 29.13 ± 7.88 for the treatment group and 28.14 ± 7.59 for the placebo group. No statistical difference was found between two groups ($p = 0.4017$). The baseline PMTS self-assessment scores were 26.17 ± 4.79 for the treatment group and 27.10 ± 4.76 for the placebo group. No statistical difference was found between these scores either ($p = 0.1649$).

The results of the effect of VAC BNO 1095 treatment on PMSD sum score are presented in Table 3 and Fig. 1. In FAS, the mean total PMSD score decreased from 29.23 at baseline (0 cycle) to 6.41 at the termination (3rd cycle) for the treatment group and from 28.14 at baseline (0 cycle) to 12.64 at the termination (3rd cycle) for the placebo group. The total PMSD score of 3rd cycle was significantly lower than the baseline in both groups ($p < 0.0001$). However, the difference in the mean scores from the baseline to the 3rd cycle in the treatment group (22.71 ± 10.33) was significantly lower than

Table 1
Demographic data.

	N	Age (years)	Height (cm)	Weight (kg)	Menses (days)	Menstrual cycle (days)	Age of menarche (years)
T	104	34.51 ± 7.34	161.69 ± 5.73	58.46 ± 7.92	5.80 ± 1.33	28.73 ± 2.21	13.57 ± 1.32
P	104	35.27 ± 6.16	161.50 ± 4.95	57.34 ± 7.22	5.56 ± 1.30	28.77 ± 2.22	13.53 ± 1.44
t		−0.80	0.25	1.07	1.32	−0.13	0.20
P		0.4235	0.8008	0.2875	0.1890	0.9006	0.8411

T: treatment group, P: placebo group.

Table 2
Baseline scores of PMSD, PMTS self-assessment.

Group	N	Mean	S.D.	Median	Maximum	Minimum		p
PMSD score							$Z = -0.8386$	0.4017
Treatment	104	29.13	7.88	28.00	51.00	16.00		
Placebo	104	28.14	7.59	27.00	51.00	16.00		
PMTS							$t = -1.39$	0.1649
Treatment	104	26.17	4.79	26.00	36.00	18.00		
Placebo	104	27.10	4.76	27.00	36.00	18.00		

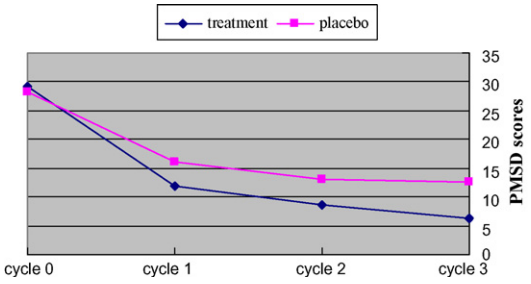

Fig. 1. Changes of total PMDS scores from baseline to the end of treatment.

the difference in the placebo group (15.50 ± 12.94, $p < 0.0001$). After one or two cycles, a significant decreases was in both group ($p < 0.01$). The PMSD total score for both groups compared to baseline (Table 3). In PPS, a similar result was found. In order to eliminate the influence of subjects in difference centers, Cochran–Mantel–Haenszel analysis was used to calculate the decreasing level from baseline to the 3rd cycle. A significant difference was found.

Efficacy rates of PMSD were calculated in the present study (Table 4). The rate of efficacy in the treatment group was significantly higher than that of the placebo group in different treatment cycles.

After the treatment for 3 menstrual cycles, the total scores for PMTS self-assessment were significantly lower between the two groups ($p < 0.01$) and within each group ($p < 0.01$). The score was decreased from 26.17 ± 4.79 to 9.92 ± 9.01 for the treatment group, and from 27.10 ± 4.76 to 14.59 ± 10.69 for the placebo group (Table 5).

Nineteen adverse events (AE) were reported (treatment group 9, 8.5%; and placebo group 10, 9.4%). Five AEs were judged at least possibly related to study medication or PMS (treatment group 3, 2.8%; and placebo group 2, 1.9%). The most frequently reported AE was headache (treatment group 2, and placebo 2), which may be related to PMS itself. A statistically significant difference was not found in the rate of AE between the two groups. No serious adverse event (SAE) occurred. No significant differences were found in blood routine test, urinary routine test and EKG before and after treatment in each group.

4. Discussion

PMS afflicts millions of premenopausal women and has been described as one of the most common disorders in women [4–7]. Some previously conducted controlled clinical trials enrolled subjects suffering from moderate to severe PMS [15,18–20,23]. The present trial tested the efficacy of VAC BNO 1095 extract on PMS by conducting the prospective, double-blinded, placebo controlled, parallel-group, multi-center clinical study in Chinese women. In China, there is no systematic assessment instrument for PMS employed in clinical and research settings. Our trial used a validated instrument and diagnostic process for PMS patients. The two instruments in Chinese version in the present study were

Table 3
Comparison of changes in total PMSD scores from baseline to each of treatment cycle in difference groups.

	FAS			PPS		
	Treatment $n = 104$	Placebo $n = 104$	Inter-group p	Treatment $n = 101$	Placebo $n = 101$	Inter-group p
Cycle 0 (baseline)	29.13 ± 7.88	28.14 ± 7.59	0.4017	29.06 ± 7.85	28.26 ± 7.65	0.5082
Cycle 1	11.83 ± 10.13	16.10 ± 10.33	$p < 0.0001$	11.62 ± 10.11	16.30 ± 10.29	$p < 0.0001$
Cycle 0–1	17.29 ± 10.96	12.05 ± 10.87	0.0016	17.44 ± 11.07	11.96 ± 10.91	0.0012
Intra-group p (cycle 1 and cycle 0)	$p < 0.0001$	$p < 0.0001$		$p < 0.0001$	$p < 0.0001$	
Cycle 2	8.57 ± 8.58	13.18 ± 9.98	$p < 0.0001$	8.25 ± 8.40	13.36 ± 9.97	$p < 0.0001$
Cycle 0–2	20.56 ± 10.24	14.96 ± 12.07	0.0003	20.81 ± 10.28	14.90 ± 12.16	0.0002
Intra-group p (cycle 2 and cycle 0)	$p < 0.0001$	$p < 0.0001$		$p < 0.0001$	$p < 0.0001$	
Cycle 3	6.41 ± 7.94	12.64 ± 10.35	$p < 0.0001$	6.04 ± 7.62	12.65 ± 10.41	$p < 0.0001$
Cycle 0–3	22.71 ± 10.33	15.50 ± 12.94	$p < 0.0001$	23.02 ± 10.31	15.61 ± 13.09	$p < 0.0001$
Intra-group p (cycle 3 and cycle 0)	$p < 0.0001$	$p < 0.0001$		$p < 0.0001$	$p < 0.0001$	

FAS: full analysis set; PPS: per-protocol set.

Table 4
The comparison of the clinical efficacy (FAS, $n = 104$).

	After 1st cycle		After 2nd cycle		After 3rd cycle	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Efficacy	55 (52.9%)	40 (38.5%)	70 (67.3%)	49 (47.1%)	83 (79.8%)	52 (50.0%)
Inefficacy	49 (47.1%)	64 (51.5%)	34 (32.7%)	58 (52.9%)	21 (20.2%)	52 (50.0%)
p (FAS)	0.0368		0.0033		<0.0001	

Efficacy: PMSD mean score decrease ≥60% from the baseline in lectual phases in different treatment cycles.

Table 5
Comparison of changes in sum scores of PMTS from baseline to cycle 3 in difference groups.

	FAS			PPS		
	Treatment $n = 104$	Placebo $n = 104$	Inter-group p	Treatment $n = 101$	Placebo $n = 101$	Inter-group p
Cycle 0 (baseline)	26.17 ± 4.79	27.10 ± 4.76	0.1649	26.17 ± 4.83	26.99 ± 4.70	0.2326
Cycle 3	9.92 ± 9.01	14.59 ± 10.69	$p < 0.05$	6.04 ± 7.62	14.55 ± 10.56	$p < 0.05$
Cycle 0–3	16.25 ± 10.28	12.51 ± 10.53	$p < 0.05$	16.63 ± 10.07	12.44 ± 10.43	$p < 0.05$
Intra-group p (cycle 3 and cycle 0)	$p < 0.01$	$p < 0.01$		$p < 0.01$	$p < 0.01$	

FAS: full analysis set; PPS: per-protocol set.

reliable and stable in further study of PMS in Chinese population.

This trial found that the total score for PMSD in the luteal phase and PMTS self-assessment were decreased in both the treatment group and the placebo groups. But the decreasing level of the treatment group was significantly higher than that of the placebo group. Nonetheless, the improvements in efficacy variables we assessed were in line with those published in clinical trials.

Some investigators have defined clinical relevance as percent improvement from baseline in luteal phase symptom scores. In such studies, a 50% improvement from baseline represented moderated symptom improvement [24,25]. In our trial, we defined the clinical efficacy as 60% improvement of total scores of PMSD and we found that the rate of clinical efficacy was significantly higher in the treatment group.

Placebo effect was found in the present trial. Fifty percent of the subjects in the placebo group met the efficacy standard. This result was similar to that of Freeman and Rickels [25], but it was higher than other randomized controlled trials of response to placebo rates, which were 23–34% [26]. The mechanism of placebo effect remains unclear. Symptom severity has previously been reported as a significant predictor, with subjects who do not respond to placebo having more severe symptoms or having longer or more chronic illnesses. However, symptom severity did not differentiate the response groups in the present study, possibly because the study required a severe symptom level in this study group. The placebo effect was obvious in this double-blinded trial. The main reason might be the PMS symptoms were self-identified and may have been easily affected by feelings.

Safety is of primary concern with any medication. Prospective, double-blinded, placebo controlled, parallel-group, clinical trials are accepted to analyze the safety and tolerability. We calculated the AE and SAE after treatment. No SAE was found during the treatment period. The rates of AE in both groups were similar in the present study. The most frequently reported AE was headache, which may be related to PMS itself.

Patient acceptance and tolerability aspects are crucial in the treatment of this condition. The effects of VAC BNO 1095 treatment on PMS were gradually decreased over time in the prior trials [15]. The acceptance and tolerability were good in this study. The rates of completed treatment in both groups were above 93% and similar although the subjects were aware of the chance of receiving either a tablet of study drug or placebo.

5. Conclusion

Vitex agnus castus (VAC BNO 1095 corresponding to 40 mg herbal drug) is a safe, well tolerated and effective drug of the treatment for patients with the moderate to sever premenstrual syndrome, the effects being confirmed by physicians and patients alike. The medication and the dose ought to be considered a therapeutic option in Chinese women who had moderate to sever PMS. The present study also provided Chinese version of PMSD and PMTS for the similar study in Chinese population in the future.

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