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CLINICAL STUDY OF *MUTLAZIMA QABL HAIZ* (PREMENSTRUAL SYNDROME) AND ITS MANAGEMENT WITH UNANI FORMULATION - A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background and Objectives: *Mutlazima Qabl Haiz* (Premenstrual Syndrome) is a group of menstruation related cyclical disorder manifested by emotional and physical symptoms in the second half of the menstrual cycle, which subsides after the beginning of menstruation. During the reproductive years, 80-90% of menstruating women experience symptoms like breast pain, bloating, acne, constipation, mood swings, irritability and depression that fore warns them of impending menstruation. The objective of the study was to evaluate the efficacy of *Tukhme Sambhalu (Vitexagnuscastus)* and *Arq Pudina (Menthapiperita)* in the management of *Mutlazima Qabl Haiz.*

Methods: A single blind, randomized placebo controlled study was carried out in Gynaec OPD of the Institute's Hospital, Bangalore. Patients were randomly allocated to test (n=30) and control (n=30) groups. Patients in the age group of 13-40 years with regular menstrual cycle were included in the study irrespective of marital status and parity. In test group, *Tukhme Sambhalu*1 gm and *Arq Pudina* 36 ml were administered orally twice daily, 10 days prior to menstruation in every cycle for 3 consecutive months. In control group placebo was given for the same duration. Severity of Premenstrual Syndrome was assessed by Premenstrual Tension Syndrome Scale and reduction in the Premenstrual Tension Syndrome Scale score was noted in each cycle. The data were analyzed using Analysis of variance - one way with Turkey Kramer Multiple pair comparison test and Premenstrual Tension Syndrome Scale scores of the two groups were compared by Chi Square test.

Results: In test group, 70% patients were cured while 16.66% and 10% were relieved and partially relieved respectively, while 3.33% patients showed no response. In control group, the cured, relieved, and partially relieved patients were 23.33%, 23.33% and 20% respectively where as 33.33% patients showed no response. Significant reduction in the Premenstrual Tension Syndrome Scale scores was observed in test group than compared to control group ($p<0.01$).

Interpretation and Conclusion: The test drugs, *Tukhme Sambhalu*and *Arq Pudina* were effective in reducing the somatic and psychological symptoms of *Mutlazima Qabl Haiz*as compared to placebo.

Keywords: Premenstrual Syndrome; Premenstrual Tension Syndrome Scale; *Vitexagnuscastus; Menthapiperita.*

INTRODUCTION

Premenstrual Syndrome is the cyclic appearance of one or more of a large constellation of symptoms just prior to menstruation occurring to such a degree that life style or work is affected followed by a period of time entirely free of symptoms.[1] It is a functional disorder that affects the personal and emotional life of a woman irrespective of age, marital status and parity. The symptoms are variable that occur 7-10 days prior to menstruation, disrupts the life of a woman temporarily and subsides with the onset of menses to recur again in the next cycle. Approximately 40% of menstruating women experience luteal phase symptoms that are bothersome; for 25% these are annoying but do not impair functioning; for 10-15%, the symptoms are severe and report significant impairment of one or more areas of daily life.[2,3] *Mutlazima Qabl Haiz* is the term framed from the Arabic dictionary[4,5]in which syndrome is translated as '*mutlazima'*, pre stands for '*qabl'* and menstrual is the word given for *'haiz'*. No such term was coined by ancient Unani Physicians but they had given a description on premenstrual features. The ancient physicians mentioned that, *imtelayikaifiat* exist in the premenstrual phase which leads to number of features. It is well studied that surge of *akhlatmuharrika* (hormones) are responsible for accumulation of body fluid in tissue spaces during premenstrual phase and this theory correlates with the concept given by IbnSina[6] and others.

Premenstrual Syndrome may have an onset at any time during the reproductive years and once symptoms are established, they tend to remain fairly constant until menopause.[7] It is a psychological and somatic disorder of unknown aetiology.[8] The exact cause of PMS is not known, but it is thought to be related to changes in hormone levels related to the menstrual cycle[9.]

In 1931 Frank was credited with the first published description of the "Premenstrual Tension". In 1953, Greene and Dalton called this conditionas "Premenstrual Syndrome" to allow the inclusion of both somatic and psychological complaints in the symptom complex[10]. While there is no cure for PMS, the symptoms can be successfully managed with lifestyle changes, dietary modifications and supplements, hormone treatment and medications[11]. It has been reported that herbal medicine is useful in relieving the symptoms of PMS [12, 13.] In addition clinical trials demonstrated that women taking chaste berry tree had significant improvements in irritability, depression, headaches, and breast tenderness. Theoretically, it may interact with hormones or drugs that affect the pituitary gland[14]. The main objective of the study was to evaluate the efficacy and safety of *Tukhme Sambhalu* and *ArqPudina* scientifically in the management of *Mutlazima Qabl Haiz*.

MATERIALS AND METHODS

Study design: A placebo controlled randomized single blind study was undertaken in the Dept of Ilmul Qabalatwa Amraze Niswan, National Institute of Unani Medicine, Hospital, Bangalore. Study was completed within the duration of one and half year. Study was started after obtaining the ethical clearance from the Institutional Ethical Committee

Participants: Patients were randomly allocated to test (n=30) and control (n=30) groups. Randomization was done by lottery method. Written informed consent was obtained from each participant before entering into the study.

Selection criteria: Patients in the age group of 13-40 years with regular menstrual cycle were included in the study irrespective of marital status and parity. Exclusion criteria were pregnant and lactating women, irregular menstrual cycles, organic pelvic pathology, major psychiatric disorders, hormonalcontraceptives, medication for PMS in last 2 months and systemic diseasesetc.

Procedure of the study: In each included patients, biochemical test such as LFT (SGOT, SGPT, Alkaline phosphatase) and RFT (Blood Urea, Sr. Creatinine) were carried out along with

specific investigations like Serum Progesterone and Serum Prolactin to evaluate the safety and efficacy of the research drug apart from routine investigations.

Diagnostic criteria: Premenstrual Syndrome can be diagnosed if the patient reports at least one of the following psychological and somatic symptoms during the first five days before menses in each of the three prior menstrual cycles:

Psychological symptoms like Depression, Angry outbursts, Irritability, Anxiety, Confusion, Social withdrawal etc

Somatic symptoms like Breasttenderness, Abdominal bloating, Headache, Swelling of extremities etc

These symptoms are relieved within 4 days of the onset of menses without recurrence until at least day 13 of cycle. The symptoms are present in the absence of any pharmacologic therapy, hormone ingestion, drug or alcohol use. The symptoms occur reproducibly during two cycles of prospective recording. The patient suffers from identifiable dysfunction in social or economic performance.

INTERVENTION

Test Group: Research drug comprised of *Tukhme Sambhalu* (*VitexAgnusCastus*) [15] and *Arq Pudina (Menthapiperita*)[15]which possesses antispasmodic, analgesic and diuretic properties.

Preparation, Administration & Dosage

The seeds of *Tukhme Sambhalu*were cleaned, finely powdered, sieved and filled in 500 mg capsules & administered orally in a dose of two capsules per day.

Arq Pudina was purchased from the market (prepared as per the formula of *Bayazekabir*[13]) and administered orally in a dose of 36mltwice daily.

Control Group: Wheat flour was filled in same colourcapsules as that of research drug and given with plain water containing few drops of *ArqBadiyan* for change of flavour as placebo.

Duration of treatment:In both the groups, drugs were given 10days prior to menstruation for 3 consecutive cycles.

Assessment cum follow up: Patients were followed for three consecutive cycles during treatment and one cycle after treatment. During this period, improvement in PMTS score was assessed. Patients were also enquired for any adverse effect of drug during the trial. Repeat LFT, RFT, Serum Progesterone and Serum Prolactin was carried out after completion of treatment to evaluate the effect of drug.

Parameters for Evaluation of Efficacy of Research Drug

Subjective Parameters: Breast tenderness, muscle cramps, nausea, anorexia, abdominal bloating, headache, depression, irritability, loss of concentration, sleep disturbances, altered libido, peripheral oedema etc.

Objective Parameters: Premenstrual Tension Syndrome Scale (PMTS)[16, 17, 18]

Serum Progesterone and Serum Prolactin

PMTS scoring: The scale ranges from 0 to 36. "0" is given for no features and "36" are given for full features of the Syndrome. For statistical purpose, the scale was divided into 5 categories as follows:

Severity of PMS

- Normal (0-7)
- Trivial (8-14)
- Mild (15-21)
- Moderate (22-28)
- Severe (>28)

Serum Progesterone and Serum Prolactin: The pre and post treatment basal levels of Sr. Progesterone and Sr. Prolactin were measured on 2nd day of menstrual cycle preferably in fasting condition.

Sr. Progesterone: 0.20 -1.50ng/ml[19]

Sr. Prolactin: 2 - 29 ng/mL[20]

Analysis of result: Results were analyzed on the basis of 4 categories:

Cured: When symptoms abolished completely and severity of PMTS score reduced to normal.

Relieved: When PMTS score reduced from severe to mild.

Partially relieved: When PMTS score reduced from severe to moderate or moderate to mild.

No response: when PMTS score remains in the same category during the trial.

Statistical Analysis: Effect of research drug on Serum Progesterone and Serum Prolactin was assessed by ANOVA one way with Dunn's Multiple Comparison test. Effect of research drug on PMTS scoring was assessed by ANOVA one way with Turkey Kramer Multiple Comparison Test. Over all response of the research drug was assessed by χ^2 (chi square) test.

RESULTS AND DISCUSSION

A placebo controlled randomized single blind study was carried out in the Dept. of IlmulQabalatWaAmrazeNiswan, NIUM, Hospital, Bangalore. The study was managed by *Tukhme Sambhalu* and *Arq Pudina* and its effect was assessed by using Premenstrual Tension Syndrome Scale (PMTS).

In this studypatients between the age group of 13-40 years were included and the highest incidence of PMS was observed in the age group <20 years; this may be dueto the survey conducted among the students of schools and colleges. This observation is supported by the study conducted by Johnson SR (1987) who stated that PMS can begin at any time during the reproductive years and studies that include teenagers show approximately the same percentage of severe symptoms as among the older subjects.[21]This study shows that PMS was common in patients with middle socio economic status, and it is a fact that patients attending the NIUM OPD are from low and middle income group. Positive family history of PMS was found in 38.33% patients and studies suggest that women whose mothers report PMS are more likely to develop PMS[22]. No relation was observed with fertility and parity among Premenstrual Syndrome. Highest incidence of PMS was found in patients with *Damvimizaj* (41.66%), when compared to *Saudavi* (30%) and *Safravi* (16.66%) and least in patients with *Balghamimizaj* (11.66%). This correlates well with the theory proposed by Unani physicians who states that *imtelayikaifiat* (plethora) exist in premenstrual phasewhich points towards the dominance of *khilt Dam*.[6](Table 01)

As there is no specific test or method to objectively measure the symptoms of the Premenstrual Syndrome, patient's self report remains probably the sole criteria for its determination. As stated earlier, the commonest somatic symptoms are fatigue, breast tenderness, abdominal bloating, weight gain and head ache, less common being gastro intestinal symptoms like nausea, vomiting, diarrhoea or constipation. Among psychological symptoms irritability, anxiety, depression, loss of concentration, crying spells, feeling of isolation are common. In this study, the psychological symptoms were predominant over the somatic symptoms. This finding is in accordance with the study conducted by Ellen et al (1985)[23]. Dysmenorrhoea was reported in 46.66% patient and it has been mentioned in the literature report that Patients who have PMS often have dysmenorrhoea as a major component of the symptom complex[22].(Table 02)

The research drugs consist of *Tukhme Sambhalu* which is a potent emmenagogue and antispasmodicdrug[15]. A study conducted at Germany (2001) on *Tukhme Sambhalu* shows that the fruit was effective and well tolerated remedy for the symptoms of PMS and it also states that the effect of *Tukhme Sambhalu*were similar to those of corpus luteum[24]. Further it was stated that *Tukhme Sambhalu* affects progesterone and prolactin level and it has got dopaminergic effect[25], but no significant changes were observed in Serum Progesterone and Serum Prolactin level in this study.(Table 03) *Pudina* posses emmenagogue and diuretic properties, expels out *sauda* and has *mufarreh* effect which reduces irritability and anxiety[15]. Thus the combination of

Tukhme Sambhalu and *Arq Pudina* had shown a good response in the relief of symptoms of PMS as both these drugs act as potent anti spasmodic, emmenagogue and diuretics, hence reduces the *imtelayikaifiat* responsible for PMS.

The results derived from PMTS rating scale were considered as strongly significant with $p< 0.001$ (Table 04)

Theoverall response of the research drugswas as follows: In test group 70% patients were cured while 16.66% and 10% patients were relieved and partially relieved respectively, while 3.33% patients showed no response. In control group, the cured, relieved, and partially relieved patients were 23.33%, 23.33% and 20%, respectively where as 33.33% patients showed no response. Significant reduction in the Premenstrual Tension Syndrome Scale scores was observed in test group than compared to control group with $p<0.01$. (Table 05)

Therefore it can be inferred that the test drugs, *Tukhme Sambhalu* and *Arq Pudina* were safe and effective in reducing the somatic and psychological symptoms of *Mutlazima Qabl Haiz*as compared to placebo; therefore it can be used as an alternate treatment for PMS.

This study is the first of its kind in the treatment of PMS, so it is not possible to draw any comparison with other trials. The limitation of the study was small sample size, short period of follow up and fixed dose of research drugs. Future trial can be carried out on large sample size for longer duration.

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Table 01: **Comparison of Demographic Data in two groups**

Age (in years)	**No. of patients**		**Percentage**
	Test group (n=30)	**Control group (n=30)**	
<16	01	02	05.00
16-20	11	09	33.33
21-25	05	09	23.33
26-30	05	04	15.00
31-35	01	01	03.33
>35	07	05	20.00
Occupation			
Student	12	11	38.33
House wife	13	16	48.33
Employed	03	03	10.00
Unemployed	02	00	03.33
Mizaj			
Damvi	12	13	41.66
Safravi	04	06	16.66
Balghami	03	04	11.66
Saudavi	11	07	30.00

Family history			
Nil	17	23	66.66
Mother	08	07	25.00
Sister	06	02	13.33
Twin	00	00	00.00

Table 02: Distribution of patients according to Symptoms

Symptoms	**No of patients**		**Percentage**
	Test group	**Control group**	
Irritation	20	19	65.00
Depression	19	17	60.00
Loss of concentration	21	21	70.00
Craving for foods	04	06	16.66
Anorexia	17	07	40.00
Nausea	06	07	21.66
Breast tenderness	16	14	50.00
Abdominal bloating	16	15	51.66
Feeling of wt gain	17	18	58.33
Head ache	05	05	16.66
Muscle cramps	04	10	26.66
Insomnia	08	16	40.00
Hypersomnia	04	06	16.66
Dysmenorrhoea	13	15	46.66
Others	11	08	31.66

Table 03: Effect of Research drug on Sr. Progesterone & Sr. Prolactin

SerumProgesterone (ng/ml)	**Test group**		**Control group**	
	BT	**AT**	**BT**	**AT**
Mean	8.50	14.68	11.21	12.37
SEM	1.23	4.19	1.81	2.09
Serum Prolactin (ng/ml)	**Test group**		**Control group**	
	BT	**AT**	**BT**	**AT**
Mean	11.27	14.44	10.19	11.44
SEM	1.89	1.90	1.04	1.60

Table 04: Effect of Research drug on PMTS score

PMTS score	**Test group**		**Control group**	
	BT	AT	BT	AT
Mean	22.00	07.16	18.70	11.63
SEM	1.27	1.34	1.214	1.22

$p < 0.001$

Table 05: Over all response

Response	**Test group (n=30)**	**Control group (n=30)**
Cured	21 (70)	07 (23.33)
Relieved	05 (16.66)	07 (23.33)
Partially relieved	03 (10)	06 (20.00)
No response	01 (3.33)	10 (33.33)