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Full Length Research Paper

Evaluating Shirazi (*Thymus vulgaris*) on menstrual pain using verbal multidimensional scoring system (VMS)

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Although there are many studies evaluating different medications on the pain of menstrual cycle, however, they show conflicting results. The explanation of such variation could be due to small sample sizes or different scoring of pain throughout the evaluation of menstrual cycle phases such as dysmenorrhea phase; and, in most studies such evaluation have not even been verified by performing a reliable case-control study using some new herbal therapy. The current study was designed to overcome such limitation using Shirazi (*Thymus vulgaris*) as a new pain therapy compared to standard medication Ibuprofen. Participants included 120 students who currently are studying at Ilam University of Medical Sciences, allocated in a randomized clinical trial study design. The inclusion criteria were singleness at the time of study, age between 18 to 25 years, accommodation at University campus and having primary dysmenorrhea prior to enrolment into the study. The participants were randomly divided into two groups; one received Shirazi (*T. vulgaris*) and the other Ibuprofen. Shirazi (*T. vulgaris*) was administered orally (5 ml for four times a day), while the control group received Ibuprofen orally three times a day. A verbal multidimensional scoring system (VMS) was used to record pain grade. Both medications cured the pain with similar score and similar duration at the first and the second month of trial. The current herbal medication cured the menstruation pain probably due to its antispasmodic effects, and so it can be evaluated for the pain therapy using different pain scoring methods.

Key words: Menstrual pain, pain score, Shirazi (*Thymus vulgaris*), verbal multidimensional scoring (VMS) system.

INTRODUCTION

Menstrual pain is a common condition occurring with severe contractions in uterus (Fedorowic et al., 2012). The prevalence of the pain is about 50 to 85% amongst the women of reproductive age and about 90% in women during the ovulation cycle (Loto et al., 2008; Agarwal and Venkat, 2009). Current evidences suggest that menstruation pain happen due to the myometrial contractions resulting from the secretion of prostaglandins during the secretory phase of endometrum. Prostaglandin F2α has been reported as the causative agent of the menstruation pain (Hu et al., 2011). Prostaglandin E2 stimulates uterine contractions, cervical narrowing and increases vasopressin release, which leads to ischemia and pain (Dawood, 2006). Therefore any medication should usually be based on the reduction of the endometrial prostaglandin production or decreasing the endometrial contractions (Marjoribanks et al., 2003). All NASIDs reduce the production of prostaglandins by inhibiting the cyclooxygenase enzyme, which in turn results in pain relief (Daniels et al., 2005; Lefebvre et al., 2005).

Due to the possible side effects of synthetic drugs, there are many attempts for alternatives traditional or herbal treatments. Many evidences have reported that nutrition and metabolism may play an important role in the cause and treatment of menstrual disorders. Nowadays, herbal medications are widely used in different trial designs to evaluate for the treatment of the pain from different origins and among them, the menstrual pain had been mentioned (Zhu et al., 2007; Nahid

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Table 1. The verbal multidimensional scoring system (VMS).

Grade	Working ability	Systemic symptoms	Analgesia
Grade 0: Menstruation is not painful and daily activity is unaffected	Unaffected	None	Not required
Grade 1: Menstruation is painful but seldom inhibits the woman's normal activity. Analgesics are seldom required. Mild pain	Rarely affected	None	Rarely required
Grade 2: Daily activity affected. Analgesics required and give relief so that absence from work or school is unusual. Moderate pain	Moderately affected	Few	Required
Grade 3: Activity clearly inhibited. Poor effect of analgesics. Vegetative symptoms, e.g. headache, tiredness, nausea, vomiting and diarrhea. Severe pain	Clearly inhibited	Apparent	Poor effect

et al., 2009; Iravani 2009; Mirabe et al., 2010). *Zataria multiflora* Boiss. has been used since ages in Iranian traditional medicine and its main constituents are carvacrol, thymol, linalol and *p*-cymene. It is useful in reliving the gastrointestinal disorders and menstrual pain (Gharib Naseri et al., 2006). *Thymus vulgaris is* another plant of this family and previous studies have showed the relaxant effect of this plant in tracheal smooth muscle (Boskabady et al., 2006). The mechanism of action of Shirazi (*T. vulgaris*) is the broncholytic and secretomotoric effects on beta receptors, which is an essential element (Boskabady et al., 2006) that reduces the pain grade of menstrual disorders (Iravani, 2009) and effects on smooth muscles of the trachea and ileum (Begrow et al,. 2010). Also, the effect of *T. vulgaris* on induced spasms in guinea-pig trachea has been investigated (Meister et al., 1999).

The present clinical trial study aims to compare the impact of Shirazi (*T. vulgaris*) as an herbal medication and Ibuprofen, using verbal multidimensional scoring system (VMS) in treatment of menstrual pain.

MATERIALS AND METHODS

Subjects

A randomized, single-blind clinical trial was conducted amongst 120 single students aged 18 to 25 years who suffered from menstrual pain, at the Ilam University of Medical Sciences from September 23, 2009 to June 22, 2010. Participants who were single, suffered from menstrual pain, accommodated at the campus of Ilam University of Medical Sciences and had no pathological disorders were included in this study. The eligible participants fulfilled the self-completed questionnaire and the scale form and were visited physically by a licensed gynecologist before randomization.

Experimental design

The extent of pain was evaluated using the Cox Menstrual Symptom Scale (CMSS), (having no pain ≤ 0, for ≥ 0.5 h ≤ 1, for 0.5 – 1 h ≤ 2, for several hours ≤ 3 and several days ≤ 4). Each participant was randomly assigned to Shirazi (*T. vulgaris*) or the anti-PG drug Ibuprofen, ending with 60 participants in each group equally. According to the Iranian pharmacopoeia, product of broncho-TD, each 100 ml containing 25 mg *Z. multiflora* oil, thymol and carvacrol was alternatively used in the herbal treatment for standardization. Therefore, the first trial group received 5 ml of Shirazi (T. *vulgaris*), which is commercially named BronchoT.D, orally four times daily until the pain grade reached one or less. The control group received Ibuprofen; three tablets orally three times a day. The participants were permitted to take another drug that they usually took for their pain relief, in addition to the allocated treatment in case of continued pain. However, at the end of the trial, these participants were excluded in data analysis. Changes in the grade and the duration of the pain of participants were compared at the first and second months in both groups.

A two sectioned questionnaire was used to collect the data. The first section included the demographic data, menstrual history, smoking, diet, exercise and past medical and reproductive history that was completed before the intervention of the trial. The second section was designed to cover the grade and duration of pain and the accompanying symptoms was completed during the two months follow up of the study. The primary outcome was the intensity of menstrual pain, which was determined using the verbal multidimensional scoring System (VMS) (Andersch and Milsom, 1982). The VMS grading system ranges from grade 0 to 3 for evaluating the Working ability, the systemic symptoms and whether analgesia is required or not (Table 1).

Statistical analysis

Sample size was computed using α = 5% and absolute error equal to 0.22 for correlation between medication and pain with Acceptable Absolute Precision Formula (AAPF). A p-value of 0.05 was considered statistically significant. Randomization was determined on a 1:1 basis using random number tables. Statistical comparisons were determined using the Mann-Whitney U test, unpaired t-test, and within-group comparisons were analyzed by paired t test or Wilcox on matched pairs rank sum test for paired data as appropriate.

Ethical evaluation

This study was undertaken with the approval of the Ethics Committee of the Ilam University of Medical Sciences. Participation in the study was voluntary and the participants were free to withdraw from the study whenever they wished. An informed consent was obtained from all participants before enrolment into the study.

Table 2. Comparison of characteristics between groups.

Characteristic	Group	n	Mean ± SD*	P- value
Age	Shiraz (*T. vulgaris*)	54	21.0± 1.8	
	Ibuprofen	39	20.8 ± 1.7	
Age incidence of dysmenorrhea	Shirazi (*T. vulgaris*)	54	14.5 ± 1.8	
	Ibuprofen	39	14.3 ± 1.9	
Duration of cycle	Shirazi (*T. vulgaris*)	54	26.0 ± 1.7	N.S**
	Ibuprofen	39	25.4 ± 1.9	
Duration of menstrual flow	Shirazi (*T. vulgaris*)	54	4.8 ± 1.5	
	Ibuprofen	39	4.7 ± 1.4	
Pain duration	Shirazi (*T. vulgaris*)	54	3.2 ± 1.0	
	Ibuprofen	39	3.4 ± .8	

*Standard deviations; **no significant.

Table 3. Comparison of pain relief between different the groups before Intervention.

Treatment	Shirazi (*T. vulgaris*)		Ibuprofen		P-value
	n	%	n	%	
Chemical medicine	34	36.6	25	26.9	0.914
Herbal medicine	10	10.8	13	14	
Others (massage, heat treatment, relaxation)	10	10.8	6	6.5	
Total	54	58.1	39	41.9	

RESULTS

The mean age was 21.0 ± 1.8 and 20.8 ± 1.7 years (mean ± SD) in Shirazi (*T. vulgaris*) and Ibuprofen groups, respectively. No significant difference was observed for the matched characteristics studied between the two groups (Table 2). In term of educational field of study, the higher frequency was seen for the individuals with BSc. level in paramedical science (33 out of 93 individuals or 35.48%) compared to the other groups and in term of educational degree totally. Moreover, 62 out of 93 had BSc degree in all medical sciences (66.66 %), including medical students who only were 14 out of 93 (15%). Chemical medication was the most common method used by the participants in both groups as the pain relief procedure before interventions applied by the current clinical trial. The results of the procedures employed by the participants before the intervention are summarized in Table 3. The subjects were followed up at least for two sequential periodic cycles.

Table 4 shows the comparison of pain grades between Shirazi (*T. vulgaris*) and Ibuprofen groups. The pain grades were similar in both groups before intervention. About 3 h after the intervention at the first day of menstruation the mean pain grade amongst Shirazi (*T. vulgaris*) group was decreased from 2.6 ± 0.0 5 to 1.37 ± 0.32, while in Ibuprofen group from 2.48 ± 0.6 to 1.52 ± 0.14, respectively, using the given dose (explained at method section) (p=0.325).

The pain grade was 1 and higher before intervention in both groups, while it reached zero in about 18% of the individuals of Shirazi (*T. vulgaris*) group and 15% of those in Ibuprofen group 6 h after the intervention so that they did not ask any more interventions. The comparison of the pain duration between the two groups at the first month of the intervention is shown in Table 5. There was no statistically significant decrease in pain duration for the women who received Ibuprofen compared to those who used Shirazi (*T. vulgaris*). There was no significant difference in pain grade between the groups at the second month of intervention (p=0.54). Pain duration at the second month of trial was similar between the both groups (p=0.62). Furthermore, the duration of menstrual flow was similar between the two groups before intervention, while Ibuprofen reduced the duration of menstruation compared to the Shirazi (*T. vulgaris*) at the first (p=0.02) and the second month of the intervention (p=<0.001).

Table 5. Comparison of pain duration in different groups at various time points following intervention.

Pain duration	*T. vulgaris* N (%)	Ibuprofen N (%)	Total (%)
Less than 0.5 h	12 (18.5)	9 (17.9)	21 (18.3)
0.5 - 1 h	24 (44.4)	19 (48.7)	43 (46.2)
Several hours	18 (33.3)	11 (28.2)	29 (31.2)
Total	54 (100.0)	39 (100.0)	93 (100.)

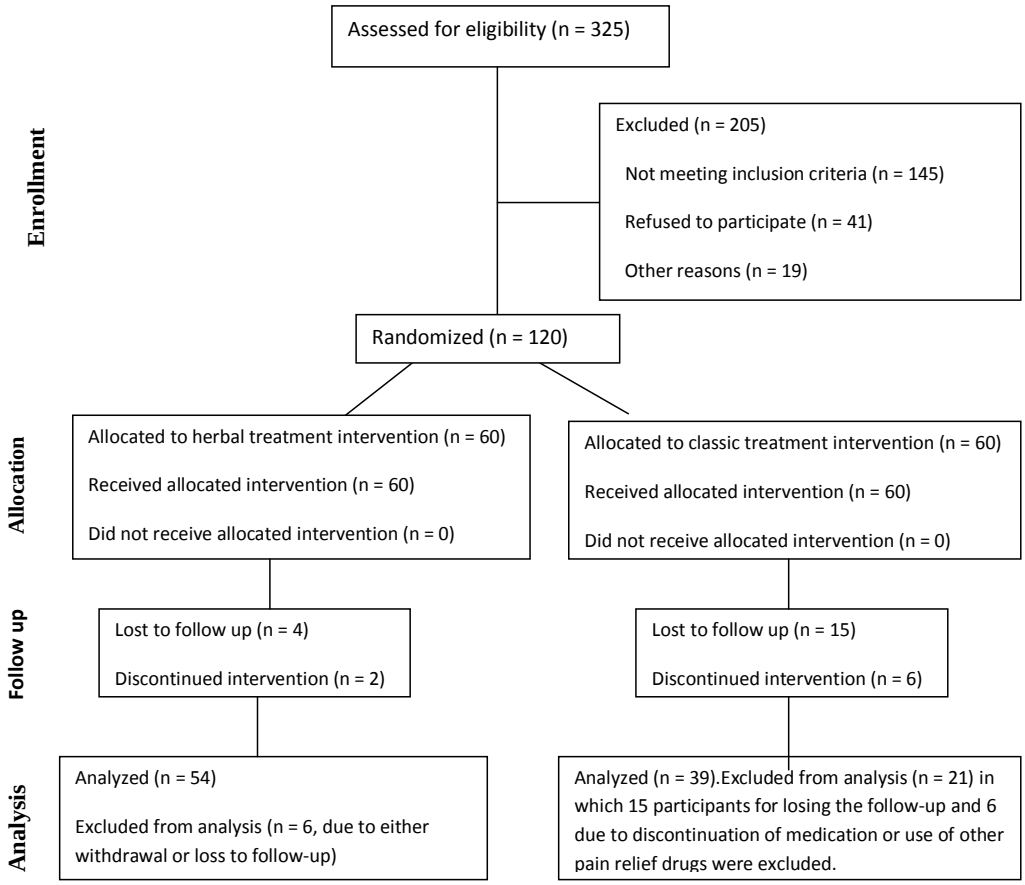

Figure 1. The consort diagram shows the flow of participants through the comparison of Shirazi (*T. vulgaris*) and Ibuprofen effects on primary dysmenorrhea; a randomized controlled trial.

DISCUSSION

Although the main cause of menstrual pain is unknown, researches have already identified the over-production of uterine prostaglandins such as prostaglandins F2α and E2 as a contributing factor to primary dysmenorrhea (Alexandrovich et al., 2003) (Figure 1).

These trials confirmed that NSAIDs inhibit the

cyclooxygenase enzymes leading to inhibition of the production of prostaglandins (Lefebvre et al., 2005). In the present study, both Shirazi (*T. vulgaris*) and Ibuprofen group had equivalently reduced the grade and the duration of menstrual pain. The effects of Shirazi (*T. vulgaris*) as an herbal pain killer can be attributed to the reduction of PG synthesis by its action as an antispasmodic and anti-PG.

Studies show that β-adrenoreceptors activation in uterus causes relaxation (Engstrom et al., 1998) and a stimulatory effect of *Z. multiflora* Boiss extract has been shown on *β*2-adrenoceptors, which is perhaps due to its constituent, carvacrol (Boskabady et al., 2006).

In a trial study, the effect hydroalcoholic leaf extract of *Z. multiflora* Boiss. (ZHLE) on rat isolated virgin uterus has been evaluated. The results showed the contraction of uterus due to potassium chloride (KCl), oxytocin and $BaCl_2$ in the presence and absence of ZHLE at different concentrations. In the oxytocin studies, animals received an injection of estradiol valerate (5 mg/kg, S.C.) 24 h prior to the experiment. ZHLE (0.125, 0.25, 0.5, 1 and 2 mg/ml) relaxed the uterus pre-contracted by KCl (60 mM) in a dose-dependent manner ($P<0.0001$) and at 2 mg/ml attenuated the $BaCl_2$ (4 mM)-induced uterus contraction ($P<0.001$) (Gharib Naseri et al., 2006). Although, several studies have reported that naloxone antagonized the anti-nociceptive effect of *Z. multiflora* (Hosseinzadeh et al., 2000), another study showed that the ZHLE spasmolytic effect was unaffected by naloxone, which may suggest that the opioid receptors are not involved in this activity (Gharib Naseri et al., 2006).

A recent research has evaluated the effects of Z. *multiflora* essential oil on menstrual pain in which participants were randomly divided into three groups: The first group received placebo, the second, the essence of *Z. multiflora* 1% and the third, the essence of *Z. multiflora* 2%. All the participants were evaluated for 3 periodic cycles. Results showed that the mean dysmenorrhea grade decreased from 7.8 ± 1.6 to 7.4 ± 1.8 in placebo group, from 7.3 ± 1.5 to 3.1 ± 1.5 in *Z. multiflora* essential oil 1% group and from 7.5 ± 1.7 to 2.6 ± 1.4 in *Z. multiflora* essential oil 2% group, respectively. A significant difference was reported between the two treated groups compared to the placebo (Iravani, 2009). In our study, Ibuprofen reduced the duration of the menstruation compared with Shirazi (*T. vulgaris*) at the first and second month of the intervention. Although the anti-inflammatory effects have also been shown for *Z. multiflora* (Nakhai et al., 2007*)*, the feature of Ibuprofen as a well established anti-inflammatory agent is more prominent (Scott, 2012).

Conclusion

These results suggest that Shirazi (*T. vulgaris*) as a novel herbal pain killer represents an effective treatment for the menstrual pain with no important side effects, although further clinical trials are recommended to look at the possible side effects in an extended spectrum of subjects.

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