

The Effect of Mefenamic Acid and *Melissa officinalis* on Primary Dysmenorrhea: A Randomized Clinical Trial Study

Faranak Safdari Dehcheshmeh¹, Neda Parvin^{2*}

¹Department of Midwifery, School of Nursing and Midwifery, Shahrekord University of Medical Sciences, Shahrekord, Iran

²Department of Nursing, School of Nursing, Shahrekord University of Medical Sciences, Shahrekord, Iran.

Available Online: 10th August, 2016

ABSTRACT

Background and aim: *Melissa officinalis* was traditionally used for pain relief and treatment of some diseases. The aim of the study was to compare the effect of mefenamic acid and *Melissa officinalis* (Melissa) on pain management in primary dysmenorrhea.

Methods: In this clinical trial, forty- three eligible women with moderate to severe primary dysmenorrhea were randomly allocated into the *Melissa officinalis* and mefenamic acid groups. The mefenamic group received 250 mg capsules every 8 hours from the onset of menstruation pain until pain relief for three consecutive cycles, and the Melissa group used one tea bag in the same manner. The intensity and duration of menstrual pain were assessed by the visual analog scale and a self-reported questionnaire. Data were analyzed using student t-test, Chi-square and ANOVA.

Results: The intensity and duration of pain in both groups showed a significant descending trend (In both groups $P < 0.001$); however, this trend was greater in Melissa group in terms of pain intensity ($P = 0.008$), with no significant difference on pain duration ($P = 0.101$).

Conclusions: Melissa was more effective than mefenamic acid in relief of pain on primary dysmenorrhea. Regarding to safety of Melissa, it could be considered as an alternative treatment for primary dysmenorrhea.

Keywords: Dysmenorrhea, Mefenamic acid, *Melissa officinalis*

INTRODUCTION

Dysmenorrhea is a gynecological problem with primary and secondary forms having overall prevalence between 16% and 91% in women of reproductive age^{1,2}. Primary dysmenorrhea is painful menstruation in absence of pelvic pathology³, but abnormal uterine bleeding, dyspareunia, non-periodic pain, changes in length and duration of pain, and abnormal pelvic examination suggest the presence of secondary dysmenorrhea which require excessive investigation⁴. Dysmenorrhea has negative effects on women's quality of life, mood and sleep quality during a menstruation cycle with prevalence between 45 and 95% among menstruating women³. Despite the high prevalence of dysmenorrhea, treatment of this problem is often ineffective³. Conventional treatment for primary dysmenorrhea has a failure rate between 20% and 25% and may be contraindicated or not tolerated by some women⁵. Non-steroidal anti-inflammatory drugs (NSAIDs) are used as the first-line therapy for menstrual pain³. Mefenamic acid is a drug of choice for dysmenorrhea⁶. Because of complications due to mefenamic acid⁷, herbal medicines may be a suitable alternative⁵. Nowadays, complementary and alternative medicine is a growing area of interest in treatment of dysmenorrhea⁸. Meanwhile, *Melissa officinalis* L. (Lemon balm) belongs to Lamiaceae family have been used

directly in food or as a decoction or an infusion for medicinal purposes⁹. This herb is native to the eastern Mediterranean region and western Asia. *Melissa officinalis* (Lemon balm) is a perennial bushy plant and is upright, reaching a height of about one meter. The soft and hairy leaves are heart-shaped. Dried or fresh leaves and top aerial section of the plant are the parts which are used as medicine. The leaves emit a special fragrant lemon odor when bruised. The chemical compound of its essential oil in different climates is different¹⁰. Regarding to the adverse effects and insufficient efficacy of NSAIDs and other routine pharmacological drugs in alleviation of dysmenorrhea and trend of people to herbal drugs, replacing these drugs with herbal ones which have less side effects can be effective⁷. On the other hand, the efficacy of *Melissa officinalis* on dysmenorrhea was confirmed in a previous study in comparison with *Salvia officinalis*¹¹. Mefenamic acid is a routine medication for dysmenorrhea; therefore, the present study was carried out with the aim of comparing the effectiveness of this herb with mefenamic acid on primary dysmenorrheal pain.

MATERIALS AND METHODS

This randomized single-blind clinical trial was conducted in gynecology clinic of Hajar Hospital affiliated with Shahrekord University of Medical Sciences in April 2012.

Table 1: Demographic and Menstruation Characteristics of Women in Two Study Groups

Variable	Mefenamic acid group	Melissa Group	P-value
Age(year)	25.38±7.71	24.55±4.78	0.67
Duration of Menstrual Cycles (day)	6.10±1.17	6.64±0.72	0.07
Menarche Age (year)	11.52±7.46	11.73±4.54	0.26
Interval of Menstrual Cycles (day)	26.55±3.99	27.73±2.65	0.91

Amongst 138 eligible women with primary dysmenorrhea referred to this clinic, 60 women were selected (figure 1). The participants were randomly allocated into two groups of Melissa (n=30) and mefenamic acid (n=30).

Inclusion criteria were willingness to participate in the study, age over than 17 years, suffering from moderate to severe primary dysmenorrhea regarding to the initial evaluation by Visual Analogues Scale (score more than 3), being single, having regular menstrual cycles, and using no contraceptives. Exclusion criteria were secondary dysmenorrhea, history of pelvic inflammatory diseases, vaginal infection, use of oral contraceptive pills (OCP) or intrauterine device (IUD), any known gastrointestinal, urogenital, hematological or other systemic disorders, being under treatment of psychological disorders, consumption of any analgesic drugs, and previous history of hyper-sensitivity to NSAIDs or *Melissa officinalis*.

Ethical considerations

The study protocol was approved by the ethical Committee of Shahrekord University of Medical Sciences with ethical code no: 88-10-1 and registered in IRCT by IRCT201605292085N17. Integrated explanations about the study were given to the participants then, informed consent was taken.

Study Questionnaire

The pain severity was evaluated by Visual Analogue Scale (VAS), which is a standard pain assessment tool. In clinical practice, the percentage of pain relief which is measured by VAS is considered as a measure of the efficacy of treatment¹². In this scale, zero indicates "no feeling of pain" and 10 "severe pain"¹³ with a 10-point ruler. According to the 10-point VAS, mild dysmenorrhea was defined as score of 0-3, moderate as score of 4-7 and severe as score of 8-10 (14). Women with mild dysmenorrhea (score of 0-3) were excluded from this study¹⁸. Reliability and validity of VAS have been demonstrated in several studies¹². In addition, the demographic and menstrual condition of participants consist of demographic status such as age, educational level, menstrual history consist of menarche age, interval and duration of menstrual cycles were assessed.

Intervention

Women in the mefenamic acid group received mefenamic acid capsules 250 mg (Razak Co, Tehran, Iran) from the onset of the menstrual period until the third day, every 8 hours until pain relief for 3 cycles¹⁵. The patients in

Melissa group were administered one tea bag of Melissa (Golchai Co, Alborz, Iran) in the same manner, every 8 hours until pain relief. In present study, all of the diagnosis, medication, and follow up stages were under consideration of a gynecologist. The researchers followed the participants by telephone during the study in view of regular taking the medication. The measurement of pain intensity and duration were carried out in four stages: at the beginning of the study (initial evaluation), and three consecutive cycles late. Before administration of drug, 2, 4, and 6 hours later the pain duration and intensity were measured during the first three days of each menstrual cycle. The mean of these scores was calculated and compared in different cycles within and between two study groups. A written instruction was provided in manner of drugs consumption method and their probable side effects, as well as reporting pain intensity and duration in questionnaire. In Melissa group, the patients were instructed to put a tea bag in a cup of hot water then wait for 5 minutes, remove the bag after squeezing and drink. Statistical analysis was carried out using SPSS software (version 20, IBM Software, Chicago, Illinois). ANOVA and post hoc test using the Bonferroni correction, student t-test, and Chi square test were used to compare groups between different stages of measurement and demographic characteristics. The P value less than 0.05 was considered statistically significant.

RESULT

At the end of the study, in mefenamic acid group 21 and in Melissa group 22 women completed the study (in each group 9 women were excluded due to the irregular use of drug and loss of follow up). Regarding to Kolmogorov-Smirnov test, the distribution of data in terms of pain intensity and duration was normal ($P > 0.05$). Moreover, there was no significant difference between participants in two study groups in terms of demographic and menstrual characteristics such as age, interval and duration of menstrual cycles and menarche age (Table 1). Moreover, the majority of participants in both groups had academic education (16 in Melissa groups.13 in mefenamic acid group, $P=0.526$). In order to compare the changes of pain intensity and duration in two groups in specific times, ANOVA and student t-test were used. Student t- test showed that both groups were matched in terms of pain intensity and its duration at the beginning of the study ($P=0.181$ and $P=0.221$ respectively). Table 2 shows the condition of pain intensity and duration in different measurement stages among the patients in both study groups. Besides, it showed that the Mauchly test of Sphericity for pain intensity was insignificant ($P=0.181$). regarding to the Sphericity assumption, it was indicated a significant descending trend in both study groups $F(3, 123) = 29.44, p < 0.001$. On the other hand, test between subject effect showed a significant difference between the study groups in terms of pain intensity in four cycles ($F=7.67, P=0.008$). It can be concluded that the mefenamic acid capsule and Melissa tea bag has been able to decrease the pain intensity over a period of three cycles as compared to baseline but Melissa group experienced less pain than

Table 2: The Pain Intensity and Duration amongst Women in Both Study Groups in Four Stages of Measurement

	Stage of Measurement	Group	Mean	SD
Pain Intensity	Beginning of the Study (The First Cycle)	Melissa	5.61	1.125
		Mefenamic	6.13	1.380
	The Second Cycle	Melissa	4.697	1.462
		Mefenamic	5.714	1.820
	The Third Cycle	Melissa	3.818	1.324
		Mefenamic	4.523	1.536
	The Fourth Cycle	Melissa	3.166	.632
		Mefenamic	4.095	1.700
Pain Duration	Beginning of the Study (The First Cycle)	Melissa	85.39	51.536
		Mefenamic	110.24	77.629
	The Second Cycle	Melissa	51.3641	24.594
		Mefenamic	81.0476	80.143
	The Third Cycle	Melissa	28.8641	11.072
		Mefenamic	52.8571	56.646
	The Fourth Cycle	Melissa	24.7732	12.464
		Mefenamic	30.2381	50.011

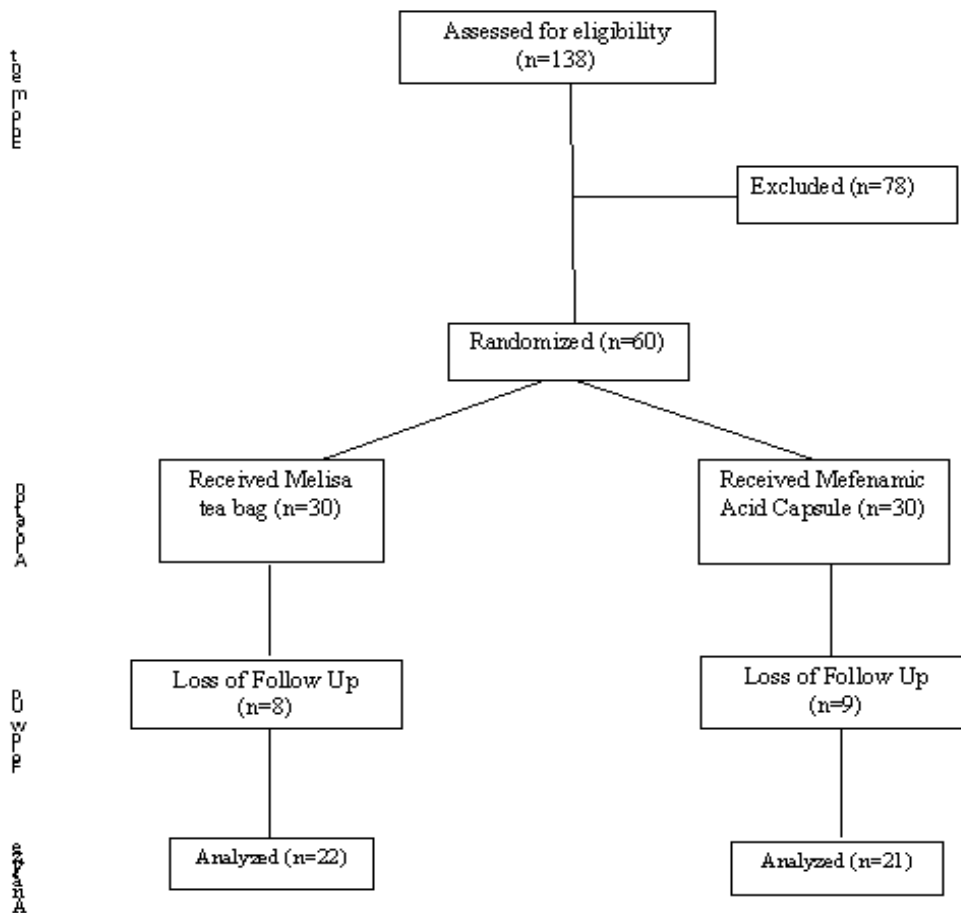


Figure 1: flow chart of Study participants

mefenamic acid group. In addition, post hoc test using the Bonferroni correction revealed a decline in the value of pain intensity at all assessment stages. Findings showed that the pain intensity between the first and third ($P < 0.001$), first and fourth ($P < 0.001$), second and third ($P = 0.003$) and second and fourth stages ($P < 0.001$) had a significant difference, even though, this difference between other stages of assessment were insignificant

($P > 0.05$) (figure 2). The results of ANOVA showed that the Mauchly test of Sphericity for pain duration is significant ($P < 0.001$), which indicates that these data violate the Sphericity assumption of the univariate approach to ANOVA. Therefore, degree of freedom were corrected using Greenhouse-Geisser correction estimates of sphericity ($\eta = 0.694$). A repeated measure ANOVA, with Greenhouse-Geisser correction, was conducted to

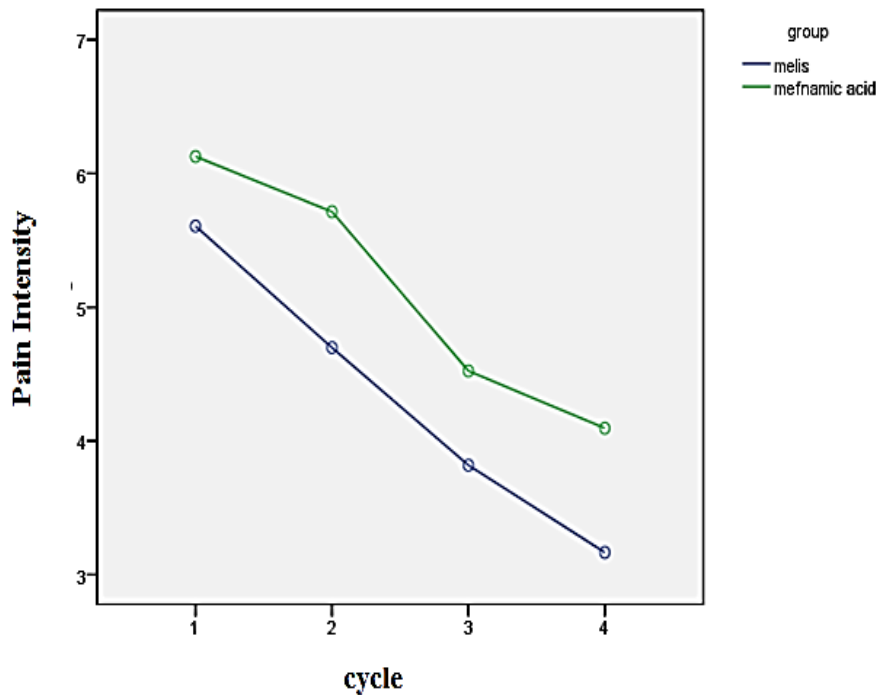


Figure 2: Trends of Pain Intensity among Study Groups

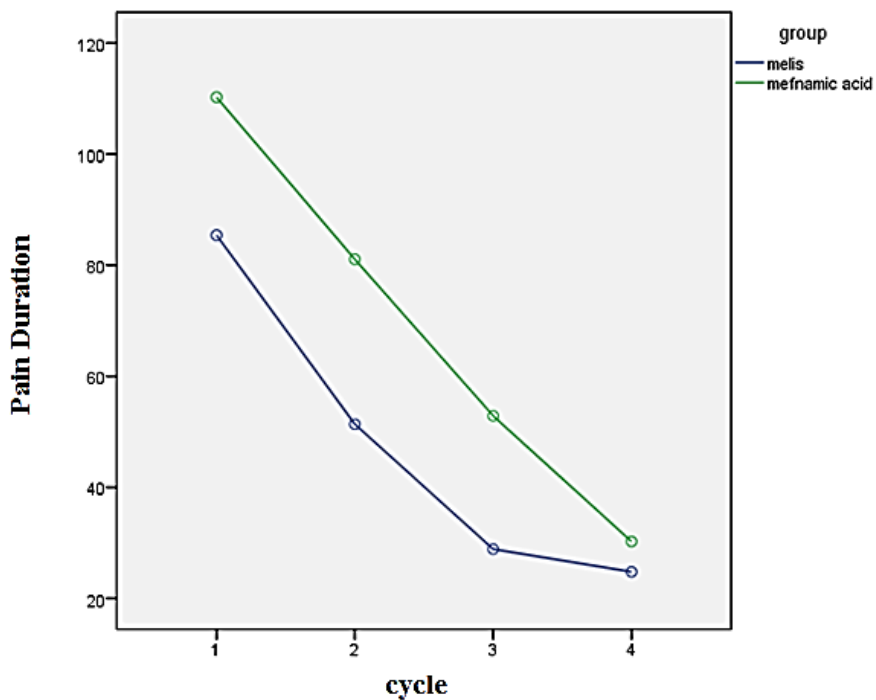


Figure 3: Trends of Pain duration among study Groups

assess whether there were differences between the average duration of pain in four menstrual cycles. Results indicated a significant difference, $F(2.082, 85.36) = 31.226, p < 0.001$. On the other hand, test between subject effect showed an insignificant difference between the study groups in terms of pain duration in four cycles ($p = 0.101$). It can be concluded that the mefenamic acid capsule and Melissa tea bag has similar effects on decrease the pain duration over a period of three cycles as compared to baseline. Post hoc test using the Bonferroni correction

revealed a significant decrease in the value of pain duration at all assessment stages (table 3, figure 3).

DISCUSSION

This study compared the effect of mefenamic acid and *Melissa officinalis* on primary dysmenorrhea. Regarding to results of the study, both mefenamic acid capsule and Melissa tea bag were able to decrease the pain intensity over a period but patients in Melissa group experienced less pain than mefenamic acid group. On the other hand,

duration of pain in menstrual cycles had a similar descending trend in both group. Many studies have investigated treatment of dysmenorrheal pain. However, the analgesic effect of mefenamic acid remains relevant for some gynecological disorders, although considerable competition from other NSAIDs¹⁶ and different studies showed the efficacy of this drug in dysmenorrhea^{17,17,18}. NSAIDs decrease the menstrual pain by decreasing intrauterine pressure and lowering prostaglandin F2 levels in menstrual fluid¹⁹⁻²¹. The effectiveness of herbal medicines in primary dysmenorrhea has been demonstrated in different studies. Park et al, in a review study concluded that effectiveness of herbal medicines on primary dysmenorrhea is associated to inhibition of uterine contractions and their peripheral analgesic and anti-inflammatory activities via the inhibition of prostaglandin synthesis. Decrease in prostaglandin level, suppression of cyclooxygenase-2 expression, superoxide dismutase activation and malondialdehyde (MDA) reduction, stimulation of somatostatin receptor, intracellular Ca²⁺ reduction, and recovery of phospholipid metabolism are some of the probable mechanism involved in primary dysmenorrhea²². Phenolic component of plant especially Rosmarinic Acid (RA) is responsible for most of the activities of Melissa^{23,24}. Melissa has been used traditionally as aromatic, digestive, antispasmodic, sedative effects²³, tonic, carminative, diaphoretic, surgical dressing, strengthening the memory, and headache relief, but in new pharmacology is effective in the management of mild to moderate Alzheimer's, migraine, and rheumatism¹⁰. Also *Melissa officinalis* contained Nerol (30.44%), Citral (27.03%), Isopulegol (22.02%), Caryophyllene (2.29%), Caryophyllene oxide (1.24%), and Citronella (1.06%) and the essential oil of Melissa possesses potential anti-inflammatory activities, supporting the traditional use of this plant in treating different diseases associated with inflammation and pain²⁵. Antinociceptive effect of Melissa was demonstrated in previous studies. Guginski G suggested that the extract of Melissa produced dose-related antinociception in several models of chemical pain through mechanisms that involved cholinergic systems through muscarinic and nicotinic acetylcholine receptors and the L-arginine-nitric oxide pathway. In addition, the rosmarinic acid in this plant appears to contribute for the antinociceptive property of the extract²⁶. In study of Boonyarikpunchai et al. rosmarinic acid showed a significant activity against PGE₂-induced paw edema by central and peripheral anti-nociceptive activities and has anti-inflammatory effects against acute and chronic inflammation²⁷. Lipid peroxidation and oxidative stress have a significant role in the pathogenesis of primary dysmenorrheal. Dikensoy et al., found that the serum levels of MDA and nitric oxide (NO) increase in subjects with primary dysmenorrhea²⁸. Flavonoids in Melissa directly interact in the synthesis of prostaglandins²⁹. Sadri et al, in their study demonstrated the inhibitory effects of Melissa on contraction of rat ileum³⁰. As it was mentioned dysmenorrhea is associated with oxidative stress and Melissa has high antioxidant activity. Therefore,

antioxidant activity of this plant might be responsible for a part of its effect. Antioxidants are involved in variety of diseases such as neurologic disorders^{31,32} ischemia/reperfusion^{33,34}, diabetes^{35,36}, atherosclerosis^{37,38}, cardiovascular diseases^{39,40} and wound complication^{41,42}. These conditions involve many changes, including alterations in redox state^{43,44}. Therefore, Melissa possessing high antioxidant activity may also be effective in these conditions.

CONCLUSION

According to findings of the present study, Melissa is as effective as mefenamic acid in pain relief on primary dysmenorrhea. Melissa is a safe medical plant which could be recognized as an alternative treatment for primary dysmenorrhea. However, the exact underlying mechanism of Melissa on dysmenorrheal pain is not clear and this herb have different ingredient which could be associated to its anti-nociceptive effects.

Limitation

The small sample size and short term follow up period are the limitation of this study.

Conflict of Interest

The authors declare that they have no conflicts of interest.

ACKNOWLEDGMENT

The authors would like to thank staff of Medicinal Plants Research Centre of Shahrekord Medical University of Sciences Especially Professor Mahmoud Rafieian and Mrs. Shahinfard. This study was financially supported and ethically approved by the Vice-Chancellor for Research, Shahrekord Medical University of Sciences, Shahrekord, Iran.

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