Research Article

The Effects of Lemon balm (*Melissa officinalis* L.) Alone and in Combination With *Nepeta menthoides* on the Menstrual Bleeding in Students With Premenstrual Syndrome: A Randomized Controlled Trial

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Abstract

Background: An increased amount of menstrual bleeding in women causes anemia and decreased quality of life.

Objectives: The present study aimed to determine the effects of lemon balm alone and in combination with *Nepeta menthoides* on menstrual bleeding in students with premenstrual syndrome.

Patients and Methods: This triple-blind randomized controlled trial included 93 female students with aged 18 years and older. The intervention groups received 500 mg capsules of lemon balm alone or lemon balm in combination with *N. menthoides*. The control group received 500 mg capsules of placebo twice daily in the luteal phase for two consecutive menstrual cycles. A Pictorial Blood Loss Assessment Chart (Higham) was completed at baseline and 1 and 2 months after the intervention. Data were analyzed using the chi-square, one-way analysis of variance (ANOVA), analysis of covariance (ANCOVA), and repeated measures tests.

Results: The differences in baseline characteristics and Higham scores of the three groups were not statistically significant (P > 0.05). General linear model analysis with adjustment for the preintervention menstrual bleeding level showed that there was no statistically significant difference in terms of menstrual bleeding mean in the first (P = 0.602) and second menstrual periods after intervention (P = 0.148) among the three intervention groups.

Conclusions: Based on the results of this study, treatment with lemon balm and lemon balm *N. menthoides* herbs did not decrease menstrual bleeding in students with premenstrual syndrome. However, further clinical studies should be performed to assess the efficacy of lemon balm and *N. menthoides* in reproductive women to determine whether this medication is appropriate for treatment in the clinical setting.

Keywords: Menstrual Bleeding, Lemon balm, Premenstrual Syndrome, *Melissa officinalis*, *Nepeta menthoides*

1. Background

Premenstrual syndrome (PMS) is defined as a common problem in women of reproductive age. It recurs regularly as physical, psychological, and behavioral symptoms in the luteal phase of the menstrual cycle, with relief seen after the onset of the menstrual period (1).

There is limited scientific evidence about the mechanisms of PMS. But, one of the hypotheses is response to increased prostaglandin (2). An increased the amount of menstrual bleeding in women with dysmenorrhea and PMS can be associated with increased levels of prostaglandins (3). The endometria of women with menorrhagia compared to women with normal menstrual cycles produce higher levels of prostaglandins E2 and F2α (4). Moreover, an increased amount of menstrual bleeding in women causes anemia and decreased quality of life (3).

Lemon balm, known scientifically as *Melissa officinalis* and is from the Labiateae family. The major components of lemon balm leaf are hydroxycinnamic acid derivatives, particularly rosmaric acid. Lemon balm herb is recommended in traditional medicine to treat menstrual disorders (5). Studies have shown that lemon balm has anxiolytic, antidepressant (6), and antispasmodic effects (5); it also improves of sleep quality (7), cognitive and behavior functions (8), and dysmenorrhea (9). The spasmolytic

effect of lemon balm may be effective in reducing menstrual bleeding (9). The *Nepeta menthoides* herb is also from the Labiateae family and is known as "Stoechas" in the Azerbaijan region (10). *N. menthoides* is used as an anti-inflammatory (11) and antispasmodic (10) agent. Searches conducted by the researcher showed that no studies have surveyed the efficacy of these plants on the amount of menstrual bleeding.

According to the world health organization (WHO) report, because of herbal medicine's effectiveness, low risk and accessibility, there is an increasing trend toward consumption of complementary medicine for therapeutic reasons in most countries. In third world countries, most people utilize herbal medicine to treat disease due to the lower cost of herbal plants (12).

2. Objectives

Consider the use of lemon balm and *N. menthoides* in traditional medicine to treat menstrual disorders and the lack of research on this topic, this study aims to assess the effects of lemon balm alone and in combination with *N. menthoides* on menstrual bleeding in Iranian students with PMS.

3. Patients and Methods

3.1. Study Design, Participants, and Setting

This study was a triple-blind randomized controlled trial. The research ethics committee of the University of Tabriz Medical Sciences approved the study protocol (code: 9313). In addition, is the research was registered at the Iranian registration clinical trial center (code: IRCT2014031710324N17).

Students were recruited consecutively from the governmental and nongovernmental dormitories of Tabriz University of Medical Sciences, Iran. The researcher visited the dormitories (all dormitories were selected by census method), explained the research project's procedures, and invited all interested and eligible students to participate in the study. Inclusion criteria were as follows: regular menstrual cycles (21 to 35 days cycles); normal body mass index (18.5 - 25 kg/m^2) and occurrence of PMS symptoms during the luteal phase of the menstrual cycle and in two consecutive cycles; lack of epilepsy, gastrointestinal, cardiovascular, renal, and endocrine history; no use of antidepressants, herbal remedies, hormones, or vitamins within the past 3 months; no report of alcohol, tobacco, or hookah consumption; not having encountered any kind of stressful event within the past 6 months; and ability to provide telephone numbers for follow-up.

The volunteers were asked to complete the provisional PMS diagnosis form. If at least 5 symptoms from the set of the total symptoms (11 symptoms) was reported, the Beck depression questionnaire was given to the participants (for in all individuals, the Beck depression questionnaire was completed from the end of the menstrual cycle to the early luteal phase, and for participants who experienced 21-days cycles, on days 5 - 7 of the menstrual cycle). Individuals with total scores below 14 were considered non-depressed. A written informed consent letter was obtained from participants. Then, the pictorial blood loss assessment chart (Higham) questionnaire was administered along with the necessary explanations; the participants were asked to complete the chart in two consecutive menstrual cycles by the self-administered method and return it to the researcher.

G*POWER (version 3.1.2) was used to determine the sample size. Based on the information obtained from previous studies on the effect of calcium with and without magnesium on the amount and duration of menstrual bleeding in students with primary dysmenorrhea by Mohammad-Alizadeh et al. (3) (m$_1$ = 53.6, sd$_1$ = sd$_2$=11.4); with an average expectancy of a 15% decrease in the mean menstrual bleeding score (m$_2$ = 45.6), β = 0.2 and, α = 0.05, it was determined that 26 students should be included per group. Finally, 31 students were randomized to each group, which allowed for a 20% attrition rate.

3.2. Randomization

The subjects were divided into three groups (two experimental groups and one control group) consisting of 31 subjects each using a computer software program that generates a random sequence with block sizes of three and six and an allocation ratio of 1:1:1. The allocation sequence was carried out with one individual who was not involved in the study to conceal the allocation.

The drugs were placed inside closed opaque packets that were numbered sequentially. The shapes of capsules were similar in the groups. For each participant, two small packets containing drugs (each packet contained 28 capsules and was arranged for 1 month's oral intake) were delivered. It was explained to each participant that she should take two small capsules from 7 days after the end of their menstrual cycle until the onset of her next cycle and complete the Higham chart during the first treatment cycle. The next follow-up was scheduled after the end of second menstrual bleeding when the drug packets were exhausted, when a completed Higham chart was to be returned by participants. The researcher verified the daily consumption of drugs via telephone contact (every 2 weeks) and the drug consumption checklist.

3.3. Intervention

The capsule combination of lemon balm *N. menthoides* (500 mg) contained dried leaf powder of lemon balm (250 mg) and flower top offshoots of *N. menthoides* from the Azerbaijan region (250 mg). The lemon balm alone and placebo capsules contained 500 mg dried leaf powder of lemon balm and 500 mg of starch powder, respectively. The capsules were not detectable appearance and were prepared by Yashil Sahand drug corporation in the East Azerbaijan region, Iran.

3.4. Data Collection Tools

Data collection tools included the sociodemographic characteristic form, Higham chart, and drug consumption checklist.

3.5. Pictorial Blood Assessment Chart (PBAC)

The table includes a visual assessment of blood chart that represents a simple non-laboratory method for the assessment of bleeding. This table is a two-dimensional image where vertical and horizontal rows indicate the days of menstruation and the pads saturated with blood at mild, moderate, or severe levels, respectively. One point will be added for each lightly stained tampon, 5 points for each moderately soiled tampon, and 20 points for a tampon is completely saturated with blood. In addition, small clots (size of a 1p coin) and large clots (size of a 50p coin) are scored as 1 point and 5 points, respectively. Scores of 100 or greater indicate bleeding of more than 80 ml, and scores of less than 100 represent lower bleeding. PBAC has a specificity and sensitivity of > 80% (13, 14). The validity and reliability of the Higham in Iran was determined by Mazari et al. Cronbach's alpha coefficient was found to be 0.73 and 0.77 before and after treatment. In addition, measuring test–retest reliability, the ICC was found to be 0.83 (15).

3.6. Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) Version 19 was used for analyses. The normality of quantitative data was reviewed through skewness and kurtosis tests; the variables were normal for sociodemographic characteristics. The Higham total scores at pre-intervention and post-intervention were not normal, but their Log10 values were normal. In addition to the mean, the median (25th - 75th percentile) was also calculated. To assess the consistency of the groups in accordance with socio demographic characteristics, the chi-square, chi-square for trend, Fisher's exact and one-way ANOVA tests were used. One-way ANOVA was used for comparison of the baseline scores and the general linear model was used for comparison of the follow-up scores adjusted for the baseline values. In addition, repeated measures analysis was used to test within and between effects simultaneously. A P value < 0.05 was considered to be significant. Analysis was undertaken by intention to treat.

4. Results

Between May 17 and November 20, 2014, 470 students were surveyed and 129 students reported moderate to severe PMS symptoms. Of these, 123 students met the study's eligibility criteria, and 93 agreed to participate. The 93 participants were randomized to the three groups. Two students randomized to the lemon balm *N. menthoides* group (2/1%) were excluded from the study due to a lack of desire to continue. Thus, of 93 students, 91 continued to participate until the end of the study (Figure 1).

In this study, the mean (standard deviation [SD]) age of the lemon balm–*N. menthoides*, lemon balm only, and control groups were 23.8 (3.2), 22.6 (3.6), and 23.3 (3.6) years, respectively. More than half of students were undergraduates. Most of the participants had a family history of PMS. The mean age of menarche was 12 - 13 years. The average PMS duration between the intervention groups was 5 years. Mean weight and height between the intervention groups were 56 kg and 163 cm, respectively. There were no statistically significant differences among the three intervention groups based on sociodemographic characteristics (P > 0.05; Table 1).

Based on one-way ANOVA, there was no significant difference among the three groups in terms of mean score of menstrual bleeding before the intervention (P = 0.454). General linear model analysis showed that the difference in mean score of menstrual bleeding was not statistically significant in the first (P = 0.602) and second treatment months (P = 0.148) among the study groups.

The mean (SD) Higham score was 84 (66). In the lemon balm only group before the intervention, it was 72.2 (33.9), which declined to 61.4 (37; P = 0.754) and 52 (32.7; P = 0.201) in the first and second months of treatment, respectively. The mean (SD) Higham score in the lemon balm–*N. menthoides* group before the intervention was 96.6 (60.4), which declined to 71.7 (50; P = 0.783) and 64.1 (46.4; P = 0.317), in the first and second months of treatment, respectively. The mean (SD) Higham score in the placebo group before the intervention was 85.9 (92.3), which declined to 60 (43) and 63.1 (34.6) in the first and second months of treatment, respectively. Based on repeated measures test, there was no statistically significant difference between the groups (P = 0.948), and the results of the within-group tests in the lemon balm, lemon balm–*N. Menthoides*, and
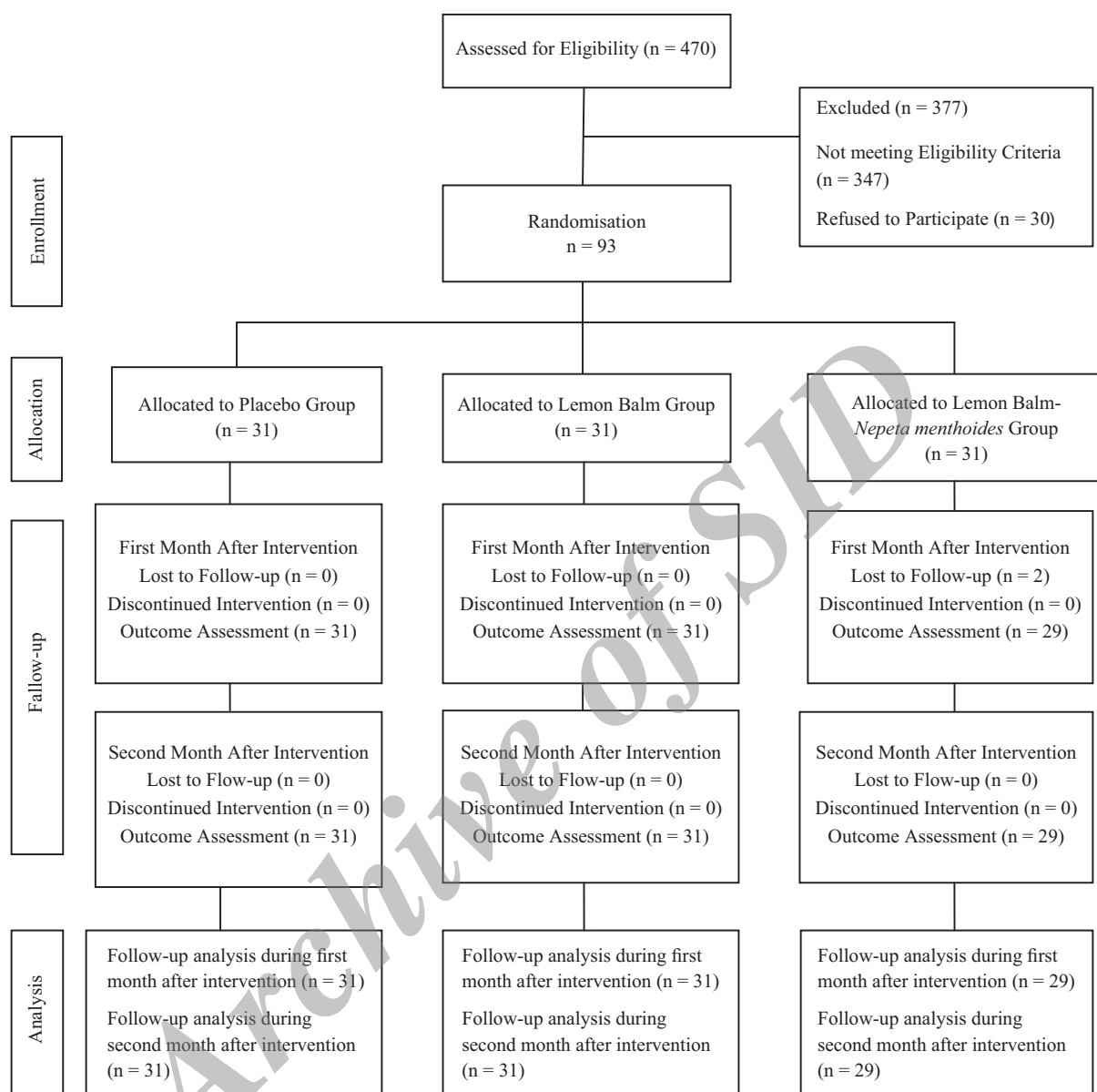
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Figure 1. Flow Chart of the Participants Through Each Stage of the Trial

placebo groups were 0.002, 0.004, and 0.033, respectively (Table 2, Figure 2).

4.1. Results of the General Linear Model With Repeated Measures for the Interaction Between Time and Group

In terms of the drug's adverse effects, in the placebo group, one (3.2%) and two students (6.5%) reported stomach pain and flatulence, respectively. In addition, in the lemon balm only group, one student (3.2%) reported sleep disturbances.

5. Discussion

Based on the results of this study, treatment with lemon balm and lemon balm–*N. menthoides* herbs did not decrease menstrual bleeding in students with PMS. In the present study, the amount of menstrual bleeding before the intervention was 84. This is higher than the average amount of bleeding in a normal menstrual cycle (30 - 40 mL), but according to the Higham table, it does not represent menorrhagia.

Table 1. Characteristics of Participants by Treatment Group[a]

Characteristics	Lemon balm (n = 31)	Lemon balm–*N. menthoides* (n = 31)	Placebo (n = 31)	P Value
Age, y	23.3 (3.6)	23.8 (3.2)	22.6 (3.6)	0.443[b]
Marital status				0.426[c]
Single	25 (80.6)	21 (67.7)	21 (67.7)	
Married	6 (19.4)	10 (32.3)	10 (32.3)	
Education				0.686[d]
Undergraduate	19 (61.3)	17 (54.8)	21 (67.7)	
Master	10 (32.3)	10 (32.3)	9 (29)	
Ph. D	2 (6.5)	4 (12.9)	1 (3.2)	
Weight, kg	56 (6)	56 (5)	57 (7)	0.648[b]
High, cm	163 (5)	163 (5)	162 (6)	0.851[b]
Doing exercise				0.612[e]
Yes	4 (12.9)	5 (16.1)	2 (6.5)	
No	27 (87.1)	26 (83.9)	29 (93.5)	
Menarche age, y	12.9 (1.3)	12.7 (1)	12.9 (1)	0.786[b]
Length of bleeding, d	6.5 (1.4)	6.2 (1.2)	6.8 (1.1)	0.139[b]

[a]Values are expressed as mean ± SD or No. (%).
[b]One-way ANOVA.
[c]Fisher's exact test.
[d]Linear-by-linear chi-square
[e]Chi-square test

Table 2. Comparison of Total Score of Menstrual Bleeding at Different Time Points by Treatment Groups[a]

Groups	Before Intervention		P Value	First Month After Intervention		P Value	Second Month After Intervention		P Value
	Med (P25 - P75)[b]	Mean (SD)		Med (P25 - P75)	Mean (SD)		Med (P25 - P75)	Mean (SD)	
Lemon balm (n = 31)	67.0 (47 - 96)	72.2 (33.9)	0.454	61.0 (26 - 83)	61.4 (37)	0.602	46.0 (31 - 72)	52.0 (32.7)	0.148
Lemon balm-*N. menthoides* (n = 31)	72.2 (49 - 140)	96.6 (60.6)		57.0 (32 - 98)	71.7 (50)	48.0 (32 - 86)	64.1 (46.4)		
Placebo (n = 31)	63.0 (45 - 89)	85.9 (92.3)		52.0 (41 - 62)	60 (43)	54.0 (42 - 69)	63.1 (34.6)		
Comparison of two by two the groups	MD (95% CI)[c]		P Value	MD (95% CI)		P Value	MD (95% CI)		P Value
Lemon balm with Placebo	-13.6 (-53.9 - 26.7)		0.916	1.4 (-24.9 - 27.9)		0.754	-11 (-34.2 - 12.2)		0.201
Lemon balm- *N. menthoides* with Placebo	10.7 (-26.6 - 51.1)		0.681	11.7 (-14.6 - 38.2)		0.783	1 (-22.2 - 24.2)		0.317
Lemon balm- *N. menthoides* with Lemon balm	-24.3 (-64.7 - 15.9)		0.435	-10.2 (-36.7 - 16.1)		1.000	-12 (-35.3 - 11.1)		0.993
Between groups Comparison[d]				0.948					
Group effect				0.002					
Time effect				0.164					
Time × Group effect				0.066					

[a]One-way ANOVA was used for comparison of the baseline scores and general linear model for comparison of the follow-up scores adjusted for the baseline values.
[b]Median (25th - 75th percentile).
[c]Mean difference (95% confidence interval).
[d]Repeated measures analysis.

According to searches conducted by the researcher, no previous study on the effects of lemon balm and *N. menthoides* on the amount of menstrual bleeding as a primary outcome have been conducted. Kalvandi et al. showed that a combination of *M. officinalis* and Salvia officinalis significantly reduced pain severity and pain duration in women with primary dysmenorrhea, but this had no significant effect on menstrual bleeding in women with dysmenorrhea (9). Raisi Dehkordi et al. studied the efficacy of lavender inhalation on the symptoms of primary dysmenorrhea and the amount of menstrual bleeding among students. These researchers reported that the symptoms of dysmen-
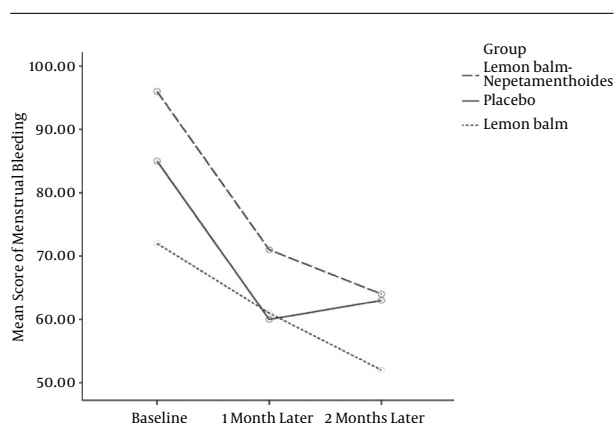
Figure 2. Trend in the Mean Score of Menstrual Bleeding at the Two Follow-Up Time Points

orrhea were significantly lowered in the lavender group compared to the placebo group, and the amount of menstrual bleeding in the lavender group was reduced in comparison to the placebo group; however, the difference was not statistically significant (16). These results are consistent with those of the present study.

Marzouk et al. studied the efficacy of aromatherapy (cinnamon, clove, rose, and lavender in a base of almond oil) abdominal massage in alleviating menstrual pain in nursing students. The results of this study showed that aromatherapy can be effective in alleviating menstrual pain and duration, as well as excessive menstrual bleeding. In our study, the lavender type *N. menthoides* was administered in combination with lemon balm in the form of capsules (17). Perhaps the possible causes listed are reasons for the differences in our results compared to those of Marzouk et al.'s study.

Other studies have been conducted on different plants. Bokaie et al.'s study showed that essential oil from the fennel plant, which is used in traditional medicine as a treatment for amenorrhea, relieves dysmenorrhea but does not increase the amount and intensity of menstrual bleeding (18). In addition, Sourteji et al. reported that in comparison to mefenamic acid, Urtica dioica can be effective in reducing the amount of bleeding in women of reproductive age with heavy menstrual bleeding (19). Zamani et al. compared the efficacy of mefenamic acid and vitex in terms of the reduction of menstrual blood loss among 90 patients with a complaint of menorrhagia. Their results showed that both drugs were effective in the reduction of menstrual bleeding (20).

The limitation of the present study was that, with respect to the primary outcome, drugs were administered during the luteal phase to influence the symptoms of PMS.

Lack of taking medication during menstruation can be considered as a potential confounder. In addition, some factors, such as psychological distress (21, 22) and lifestyle (23), were uncontrollable, representing weak points of this study. This study was the first clinical trial on the effects of lemon balm and *N. menthoides* on menstrual bleeding in students with PMS, which was the strength of this study. It is recommended that the effects of *N. menthoides* and lemon balm plants on the amount of menstrual bleeding should be assessed in the population of women of reproductive age using larger samples.

This study showed that treatment with lemon balm and lemon balm-*N. menthoides* herbs did not decrease menstrual bleeding in students with PMS. However, further clinical studies should be performed to assess the efficacy of lemon balm and *N. menthoides* in reproductive women to decide whether this medication is appropriate for use in the clinical setting.

Acknowledgments

Footnotes

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