Title: Comparative Study on the Effect of Matricaria CHamomile and Achillea Millefolium capsules on primary dysmenorrhea intensity of dormitory students of Kurdistan University of Medical Sciences, 2017.

Introduction:
Menstrual pain is the most common pain and one of the main causes of referral to a doctor among young women. The aim of this study was to compare the effectiveness of Achillea Millefolium (Yarrow) and Matricaria CHamomile plants to treat menstrual pain.

Methods:
This double blind randomized clinical trial study was performed on 50 female students of Kurdistan Medical Sciences residing in dormitory in 2018. Individuals were randomly divided into two groups of chamomile and yarrow using sealed envelopes. 24 people received 250 mg chamomile capsules every 8 hours and 26 people received 150 mg hydroalcoholic capsules of yarrow every 8 hours during the first three days of menstruation in two menstrual cycles. The data collection tool was a questionnaire and the severity of pain was assessed using visual analogue scale for the pain (VAS).

Results:
There was no significant difference between the two groups in terms of pain severity and duration of pain before taking the drug (p > 0.05). The average pain severity in the first menstrual cycle in the two groups decreased significantly (p< 0.05), which was more noticeable in the yarrow group, however, the average pain severity in the yarrow capsule group was lower than that of the chamomile capsule group, but this difference was not statistically significant (p > 0.05).

Conclusion:
Both capsules of yarrow and chamomile reduce the severity of pain, but the yarrow capsule, with its long-lasting sedative effect, proved more helpful to reduce the severity of menstrual pain and could be effective in solving one of the issues among women.

Keywords: Menstrual pain, Yarrow, Chamomile
**Introduction:**

The term 'initial painful period of menstruation' is used to describe contractions of the uterus during menstruation in the absence of any pelvic and pathologic damage, which occurs at the onset of the first menstrual period or shortly afterwards in ovulation cycles (1). Menstrual pain is the most common pain among women (2), and affects 80% to 97% of those in fertile life (3). The prevalence of initial painful menstruation varies according to the World Health Organization (WHO), and is reported to be between 16% and 91% (4), and the prevalence rate has been reported 43.25 % in Sanandaj (5). The results of the studies have shown that menstrual pain causes a change in physical activity, irritability (6), loss of interest in work, adverse mental effects (7), increasing absence from the university, and disturbing social relations(8). According to the results of the study, painful menstruation has led to a loss of 140 million working hours in the United States (9) and they estimated that the economic loss from one day of absence in Japan could be about $ 4.2 billion (10). The most common treatments used in this area are non-steroidal anti-inflammatory chemicals and oral contraceptives (11); but long-term use of steroidal drugs and birth control pills is associated with side effects such as damage to the liver, kidneys, skin, intestines, Gastrointestinal bleeding and myocardial infarction (12, 13), depression, loss of libido, and discontinuation of menstrual bleeding (14). Currently, due to the apparent effects of chemical drug abuse, the willingness of people to use herbs has increased dramatically (15). Several studies have been conducted on the effects of various medicinal plants such as mint capsules (16), calendula (17), phenylene and vitagnus (18) on painful menstruation. Chamomile and Yarrow are among plants whose effectiveness in treatment of primary dysmenorrhea has been examined in a number of limited studies(19, 20) . According to the researches there has been no study conducted in order to compare efficacy and complications in treatment of primary dysmenorrhea. Therefore, this study was conducted to compare the effect of chamomile capsule and yarrow capsule on the severity of primary dysmenorrhea among dormitory students of Kurdistan University of Medical Sciences.

**Materials and methods:**

This study was a parallel double blind randomized clinical trial. The study population consisted of students residing in Kurdistan University of Medical Sciences dormitories. The sample size using the formula $N = \frac{\left(\frac{Z_{1-\alpha} + Z_{1-\beta}}{\sigma_1 + \sigma_2}\right)^2}{\left(\mu_1 - \mu_2\right)^2}$ was 60 people who were randomly divided into two groups: case (30) and control (30). The criteria for entering the study included: being single, starting a menstruation at the age of 11 to 17, having regular menstruation at intervals of 21 to 35 days, and having a score of 4 to 10 for pain in the menstruation according to the visual analogue scale for the pain and the desire to participate in the study, and exit criteria included: unwillingness to continue to participate in the study, not menstruating or abnormal bleeding during the study, epilepsy, coagulation disorder, allergic asthma, digestive diseases, liver, kidney, and uterine problems detected such as: abnormal bleeding, ovarian cysts, myoma, pelvic tumors, endometriosis, pelvic inflammatory diseases, taking medications such as benzodiazepines, barbiturates, narcotics, triangular
antidepressants, anticoagulants, theophylline, hormonal contraceptives and oral contraceptive pills over the past three months, alcohol intake, failure to follow capsule administration instructions and the use of chemical sedatives one hour after taking the herbal medication.

Data were collected using a questionnaire and a visual analogue scale for the pain. The questionnaire included questions about demographic characteristics (age, field of study, educational level, occupation and BMI) and questions about menstrual characteristics (duration, amount of bleeding and severity of menstrual pain). The validity of the questionnaire was determined using content validity method. The reliability of the visual instrument for pain assessment was R=88% in Iran (21).

After introducing the project and obtaining a license from the Research Council of Kurdistan University of Medical Sciences and obtaining the code of ethics in Kurdistan University of Medical Sciences and registering the study at IRCT.ir, as well as obtaining the license and presenting an introduction letter from the vice president of research at Kurdistan University of Medical Sciences.

In order to conduct the study, the researcher selected the volunteers to participate in the study in terms of entry and exit criteria and obtained written consent. After selecting the samples, the researcher asked the participants to complete the demographic questionnaire, and their weight and height were measured using scales and stadiometer and their body mass index was determined and recorded by the researcher; then individuals learned how to use the visual analogue scale for pain. The visual analogue scale for pain was delivered to the participants one month prior to the onset of the medication intake, and they were asked to record the average of their pain severity in the first three days of the menstrual cycle for a month before treatment. After the end of the month, the pre-drug questionnaire was delivered to the participants and eligible individuals were assigned to two groups by randomly using sealed envelopes containing the A and B codes. The envelopes named "A" contained chamomile capsules (250 mg made by the Kermanshah Pharmacy Faculty) and envelopes named "B" containing capsules of yarrow (150 mg of hydroalcoholic extract made by the Kermanshah Pharmacy Faculty). Capsules were completely identical in terms of shape, color, size and aroma, and, except for the pharmacist, neither the researcher nor the participants were aware of the nature of the drug. Each of the participants received two questionnaires on menstruation questions to complete in two menstrual cycles (using the drug) and how the medications were administered to the participants as follows: Both groups should take one capsule every eight hours during the first three days of menstruation and record their pain score at the end of the first three days of the menstrual cycle and repeat this process in the second cycle of their menstruation. Participants who have been forced to take sedatives for any reason were excluded. The process of completing the questionnaires and taking the medications was regularly reviewed by the researcher in two groups. In case of irregular drug use, lack of willingness to continue cooperation or incorrect completion of the questionnaires, the participants were excluded from the study process. Finally, 26 patients were placed in the group to receive yarrow capsules and 24 were placed in the chamomile capsule group. The sampling process began from mid-April 2018 and ended on the first of July. This study was
approved by Kurdistan University of Medical Sciences and was registered with the ethics code IR.MUK.REC.1396.326 on IRCT IRCTID: IRCT20171225038058N1 on 20/2/2018. For data analysis, Fisher, T-independent and Mann-Whitney tests were used in SPSS version 22. The significance level was considered to be less than 5%.

Findings:

The findings of this study indicate that the average age of the participants was 18-22 years old, and there was no significant difference in the average age of the two groups. Moreover, most of the participants (94%) were students and they were undergraduate (86%), and the two groups did not differ significantly in terms of job status and educational level (Table 1).

The results of the study showed that there was no significant difference in pain severity (Table 2) and duration of pain (Table 3) before the drug administration between the two groups (p > 0.05). The average of pain severity in the first menstrual cycle of the two groups significantly decreased (p< 0.05), which was more noticeable in the yarrow group. However, the average pain severity in the group receiving yarrow capsule was lower than that of the chamomile capsule; this difference was not statistically significant (p > 0.05) (Table 2).

Table 1: Frequency distribution of demographic variables in the units under study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chamomile capsule users</th>
<th>Yarrow capsule users</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>category</td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>Occupation status</td>
<td>Student</td>
<td>22</td>
<td>91.67</td>
</tr>
<tr>
<td></td>
<td>± student part-time job</td>
<td>2</td>
<td>8.33</td>
</tr>
<tr>
<td></td>
<td>overall</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>Educational level</td>
<td>Associate's degree</td>
<td>1</td>
<td>4.17</td>
</tr>
<tr>
<td></td>
<td>Bachelor's degree</td>
<td>20</td>
<td>83.33</td>
</tr>
<tr>
<td></td>
<td>Master's degree</td>
<td>3</td>
<td>12.50</td>
</tr>
<tr>
<td></td>
<td>overall</td>
<td>24</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 2: comparing the severity of painful menstruation before and after taking the drug among the participating groups in the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Chamomile capsule users</th>
<th>Yarrow capsule users</th>
<th>P value Mann-Whitney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before taking the drugs</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>0.765</td>
</tr>
<tr>
<td></td>
<td>6.46±1.91</td>
<td>6.65±1.92</td>
<td></td>
</tr>
<tr>
<td>End of third day of first menstrual cycle</td>
<td>5.29±1.78</td>
<td>4.46±1.53</td>
<td>0.049</td>
</tr>
<tr>
<td>End of third day of second menstrual cycle</td>
<td>4.33±2.12</td>
<td>3.81±1.06</td>
<td>0.062</td>
</tr>
<tr>
<td>(rm) P value</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: comparing the duration of primary dysmenorrhea before and after taking the drugs among the participating groups in the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Chamomile capsule users</th>
<th>Yarrow capsule users</th>
<th>P value (Mann-Whitney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before taking the drug</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>2.45±0.93</td>
<td>2.73±0.91</td>
<td></td>
</tr>
<tr>
<td>First menstrual cycle</td>
<td>2.54±1.02</td>
<td>2.26±0.77</td>
<td>0.26</td>
</tr>
<tr>
<td>Second menstrual cycle</td>
<td>2.54±1.06</td>
<td>1.88±0.81</td>
<td>0.019</td>
</tr>
<tr>
<td>(rm) P value</td>
<td>0.765</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Discussion:
The aim of this study was to compare the effect of chamomile capsule and yarrow capsule on the severity of primary dysmenorrhea. The results of this study showed that chamomile and yarrow capsules were effective in decreasing the severity of primary dysmenorrhea, but the severity of pain reduction was significantly higher in yarrow users group, and this decrease was significantly different in both groups of chamomile and yarrow capsules before and after drug administration using repeated measurements (p< 0.001 ). One of the most important findings of the present study, was the significant relationship between the severity of initial
painful menstrual period after chamomile and yarrow capsules at the end of the first three days of the first menstrual cycle (p<0.049). The chamomile capsule reduced the severity of pain, which was in line with the results of the study by Karimian et al. (2015) in terms of drug type and method that aimed at the effect of chamomile capsule and mefenamic acid on the rate of menstrual bleeding in Kashan (20). In the study mentioned above, participants consumed 250 mg chamomile capsule every 8 hours in the first 3 days of menstruation, which is consistent with the present study. In the study by Karimian et al., in addition to menstrual bleeding, the severity of pain was studied. It was also in line with the results of the study by Modarres et al. (2011) aimed at the effect of chamomile and mefenamic acid capsules in Tehran (22), indicating that after the end of the first 3 days of menstruation, the severity of pain in the chamomile group decreased significantly. However, the present study showed contradictory results with the study by Sharifi et al. (2013), which focused on the analgesic effects of mefenamic Acid and Chamomile on severity of pain in the menstrual period (23). whereby drugs were used every 8 hours on the first three days of menstruation, but after the end of the first 3 days, there was no significant difference between the two groups of chamomile capsules and mefenamic acid. However, chamomile capsule was recommended due to lower complications of herbal medicine. In the study above, both drugs have relieved the same level of pain severity. The reason for the difference between the results of the present study and that of Sharifi et al. might be due to location differences and the types of drugs, considering that a chemical medicine was compared to an herbal, but in the present study, two medicinal herbs were compared and evaluated and, given the fact that Kurdistan province residents believed in herbal medicine, the result of the research could be effective. Moreover, in the present study, the severity of pain decreased after the administration of yarrow capsule, and this was consistent with the results of the study by Jenabi and Fereiduni (2015), which aimed at evaluation of the effect of yarrow on the severity of initial menstrual pain in the Tuiserkan (24). In the study by Jenabi and Fereiduni, brewed yarrow and 4 grams of tea bag was provided to the participants; they received one batch of tea bags brewed for 10 minutes in 300 ml of water every 8 hours during the first 3 days of menstruation. In the present study, 150 mg capsule of yarrow was used every 8 hours in the first 3 days of menstruation. In both methods, the same results were observed and the severity of pain decreased. Both chamomile and yarrow can affect the smooth muscles of the uterus and intestine due to the presence of active ingredients in their constituent parts and therefor can reduce the pain of menstrual periods. Chamomile capsule has anti-inflammatory and anti-contractile properties due to presence of flavonoids which are anti-inflammatory and analgesic compounds in plants that have a direct effect on the synthesis and reduction of prostaglandins, and consequently can relieve the pain (2). Essential oils of this plant, especially bisabolol and chamazulene, are responsible for its anti-inflammatory effect (25). Yarrow capsule inhibits cyclooxygenase enzyme due to presence of flavonoids and alkaloids, therefore, can be effective as an antiprostaglandin in treating the initial painful menstruation; moreover, yarrow causes inhibition of smooth muscle contractions in the intestine by closing calcium channels, as well as anti-contractile effects on the smooth muscles of the uterus which can have a very powerful effect in relieving pain during the menstruation (26).
One other important finding of the present study was that no significant relationship was observed between the severity of initial pain of menstruation and using chamomile and yarrow capsule at the end of the first 3 days of the second menstrual cycle (p = 0.062). The results showed that the severity of menstrual pain did not decrease significantly at the end of the first 3 days of the second cycle, which was in line with the following two studies in terms of pain severity before and 3 days after the administration of the drug, the method of work and the species of the plant; the study by Karimian et al (20), conducted in the second month of the menstrual cycle and the study by Ebrahimi Varzaneh et al. aimed at the effect of hydroalcoholic yarrow capsule on the severity and duration of dysmenorrhea in Tehran (19).

Despite the use of mefenamic acid in the study, yarrow capsule has a significant effect on reducing pain severity, but in the second month there was no significant difference in pain reduction. The reason for the lack of significant correlation was the absence of pain at the time of starting the medication by the participants during the second menstrual cycle, but this was contradictory with the study by Sattarzadeh et al. (2008) (27), using another type of yarrow to examine the severity of menstrual pain. In this study Achillea willhemsii species was used, while in the present study the Achillea Millefolium species was used. This variation in the plant species caused the results of the study to be contradictory.

Conclusion:

Yarrow capsule, given the effectiveness on controlling menstrual pain and lack of side effects, can be used as an effective herbal remedy for young women with premenstrual pain and may replace existing chemical drugs.

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