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A double-blind controlled crossover study to investigate the efficacy of salix extract on primary dysmenorrhea

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ABSTRACT

Objectives: Primary dysmenorrhea in the absence of pelvic pathology is a common gynecologic disorder affecting the quality of life of women of reproductive age. This study evaluates the effect of salix extract on primary dysmenorrhea.
Design: This study was a randomized crossover clinical trial.
Setting: The study population included 96 female students with level two or three of primary dysmenorrhea: 48 students in the treatment group (sequence I) followed by control (sequence II) and 48 students in control group (sequence I) followed by treatment (sequence II).
Interventions: The intervention was salix capsule (400 mg daily) and the active control was mefenamic acid capsule (750 mg daily) as.
Main outcomes: Pain intensity, measured by the visual analog scale (VAS), amount of bleeding, and severity of dysmenorrhea symptoms were outcomes. Generalized estimating equations were used for data analysis.
Results: The demographic and menstrual characteristics of the students were homogenous between the groups. The results showed that the students in mefenamic acid group had a significantly higher level of VAS than the students in the salix group over time (1.61 ± 0.06, $P < 0.001$). The estimated odds of the bleeding level in the salix and mefenamic acid group were not significantly different ($P = 0.31$). In average, 77.39% ± 16.18 of the students in salix group showed no symptoms followed by 22.18% ± 14.08 of the students who experienced mild symptoms. Averagely, 44.58% ± 20.16 of the students in the mefenamic acid group had mild symptoms followed by moderate symptoms (28.12% ± 15.29).
Conclusions: Salix extract significantly decreased dysmenorrhea in comparison to mefenamic acid, as the standard treatment of dysmenorrhea.

1. Introduction

Dysmenorrhea is one of the most prevalent gynecological problems, affecting 80–97% of women of reproductive age.[1] In Iran, the reported prevalence of dysmenorrhea among adolescent is between 74%–86.1%.[2] Primary dysmenorrhea or painful menstruation in the absence of pelvic pathology, can cause the limitation in daily activities, impairment of efficiency, and school and work absences, resulting in significant economic, social, and health costs.[3,4] Furthermore, dysmenorrhea negatively affects female quality of life, on the occupational, individual, family, and public health levels.[3,5]

Dysmenorrhea, which begins 1–3 years after menarche, starts with menstruation and increases during menstrual bleeding.[6] The pain is usually in the suprapubic area, radiating extending to the inner side of the thighs and to the back of the legs or lower back. Pain may be accompanied by systemic symptoms such as nausea, diarrhea, headache, reduced appetite, distraction, vomiting, depression, fatigue, and general aches.[7] It is believed that dysmenorrhea is caused by the release of prostaglandins (PGs), particularly $PGF_{2\alpha}$ and PGF_2. Cyclooxygenases (COX), which lead to uterine contractions and consequently uterine ischemia. Females with dysmenorrhea have higher levels of $PGF_{2\alpha}$ and PGF_2 during the first two days of menses, compared with that of those without dysmenorrhea.[8] In addition, other factors have an essential role in the pathogenesis of dysmenorrhea which does not depend only on

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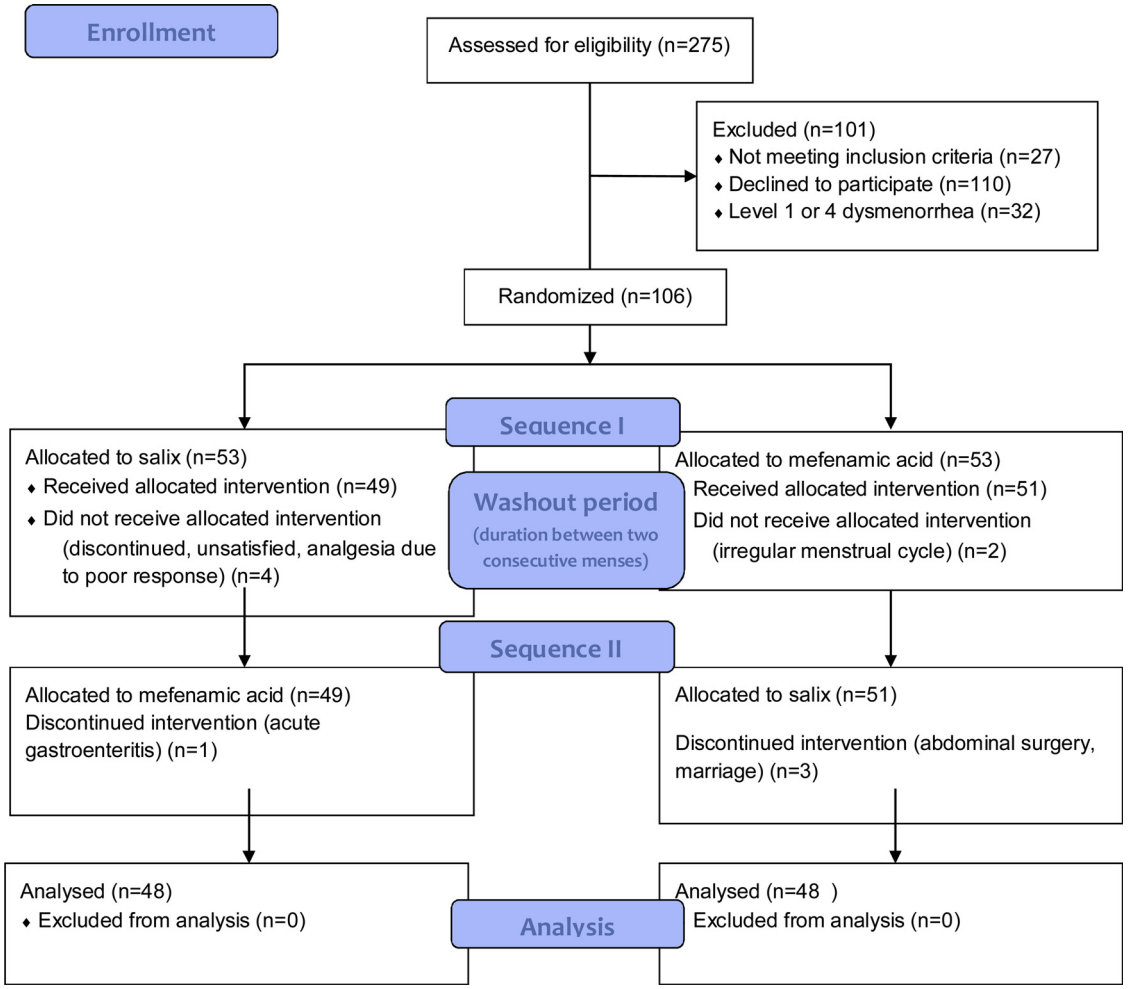

Fig. 1. CONSORT flow diagram.

endocrine factors.[9]

Various treatments including chemical agents, PG inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) have been proposed for alleviating dysmenorrhea; however, none of them is either satisfactorily available or without any side effect.[10] NSAIDs–including aspirin, naproxen, ibuprofen, and mefenamic acid– reduce the PGs production by COX enzymes and inhibit PGs receptors in the uterus.[10] Mefenamic acid, which consists of analgesics, is the first-line therapy for primary dysmenorrhea during the first seven days.[11] Despite the significant ability of NSAIDs in relieving pain, gastrointestinal and central nervous system symptoms, nephrotoxic and hepatotoxic effects, hematological abnormalities, bronco spasm, and edema have been reported as the adverse effects of NSAIDs.[10]

Recently, there has been a growing worldwide interest in using herbal medicine for treatment of various diseases, owing to its satisfactory results and lower rate of adverse events. Herbal medicine such as lavender, ginger, aloe vera, and salix have been found as the effective treatment for dysmenorrhea.[12–14] With a 3500 year history, salix extra was first used as a pain reliever and antipyretic in aspirin.[15] Salix contains salicylic acid, and its derivative salicin extract is used to treat fever, inflammatory, mild rheumatic complaints, and headache.[14,16–18] interestingly, not only does salix extract not influence COX, but also it does not damage the gastric mucosa.[15] Some of the salix species have been used as an anti-inflammatory and analgesic to alleviate back and arthritis pain.[19–21] Despite the aforementioned studies, literature is still sparse to investigate the effect of salix on primary dysmenorrhea treatment. The present study was performed to evaluate the effect of salix on primary dysmenorrhea in comparison to the mefenamic acid, as the standard treatment, in university students.

2. Materials and methods

This study was a double-blind crossover randomized clinical trial performed on 275 students in the dormitory of Shahrekord University of Medical Sciences, Shahrekord, Iran, 2015-2017. The students were aged 18 to 28 years old with regular menstrual cycles (21–35 days) and without history of allergy to salix. The students who were not sexually active and suffered from level two or three primary dysmenorrhea, regarding Andersch and Milsom's verbal multi-dimensional scoring system, were included the study.[22] To be eligible for the study, students must report as having no genital organ diseases, (i.e. myoma, fibrocyst adenoma, endometriosis, chronic pelvic inflammatory disease, chronic pelvic pain, metrorrhagia, ovarian cysts, obstructive vaginal or uterine congenital anomalies, adenomyosis, and other pelvic pathologies); and nosystemic diseases (i.e. inflammatory bowel disease, irritable bowel syndrome, cholecystitis, gastroesophageal reflux, severe liver disease, peptic ulceration, any gastrointestinal bleeding, thyroid, kidney and liver disease, coagulation disease, asthma, malignant diseases, inflammatory joint disease, diabetes mellitus, autoimmune diseases, history of hypersensitivity to NSAIDs, neurologic or psychiatric disease). The students who underwent a surgery during the past eight weeks and hormonal therapy during the last six months were not eligible for inclusion into the study. Moreover, the Students who used contraceptives, hormonal therapy, and analgesics to overcome dysmenorrhea or other pain–48 h before the study onset or during the study–were excluded. Additionally, the students who married during the study, or had

Table 1
Comparison the demographic and menstrual characteristics in salix and mefenamic acid group.

Characteristic	Category	Received salix followed by mefenamic acid (N = 48)	Received mefenamic acid followed by salix (N = 48)	P
Age (year)	–	20.48 ± 1.64	21 ± 1.85	0.145
Age at menarche (year)	–	13.52 ± 1.54	13.58 ± 1.16	0.82
Age at onset of dysmenorrhea (year)	–	15.48 ± 1.51	14.87 ± 1.53	0.053
Duration between two menstruations (day)	–	28.26 ± 1.33	28.45 ± 1.73	0.527
Bleeding duration (day)	–	6.26 ± 0.9	6.62 ± 0.95	0.055
Dysmenorrhea duration (day)	–	2.52 ± 0.78	2.75 ± 0.43	0.077
BMI (kg/m^2)	–	21.7 ± 2.93	21.65 ± 2.09	0.918
Onset of dysmenorrhea				0.876
	One day before or simultaneously	40 (80)	39 (81)	
	More than one day before	10 (20)	9 (20)	
Family history of dysmenorrhea				0.845
	Yes	26 (52)	24 (50)	
	No	24 (48)	24 (50)	
Frequency of painful menstruation				0.699
	Always	23 (46)	19 (39.6)	
	Most times	24 (48)	27 (56.3)	
	Sometimes	3 (6)	2 (4.2)	
Medical aid				
	Physician	17 (34)	17 (35.5)	0.019
	Nurse/midwife	27 (54)	15 (31.2)	
	Never	6 (12)	16 (33.3)	
PMS history				0.419
	Yes	23 (46)	26 (54)	
	No	27 (54)	22 (56)	
Family history of dysmenorrhea				0.843
	Yes	26 (52)	24 (50)	
	No	24 (48)	24 (50)	
Absence from work/school				
	Never	11 (22)	2 (4)	0.041
	Occasional	22 (44)	30 (62.5)	
	Sometimes	9 (18)	6 (12.5)	
	Always	8 (16)	10 (21)	
Physical activity				
	Never	44 (88)	40 (86)	0.76
	Often	4 (8)	6 (10)	
	Always	2 (4)	2 (4)	
Analgesics use				
	Never	2 (4)	4 (8.3)	< 0.001
	Often	44 (88)	18 (57.5)	

developed allergic reactions to salicylates, and those received other types of complementary therapies, were also excluded. Participants who had not completed all the visits were excluded from the analysis as well.

Due to the effects of nutrition on dysmenorrhea severity, students were sampled from the same dormitory to reduce selection bias.[5]

During the first two cycles, the severity of dysmenorrhea was measured–without any intervention. The students were randomly allocated into two groups of A and B, using a randomized block design of size four in the two next consecutive cycles. In cycle 3, group A received salix capsule as the intervention and group B received mefenamic acid capsule as the active control. Reversely, in cycle 4, group A received mefenamic acid capsule and group B received salix capsule. The duration between two consecutive menstrual cycles was considered as a washout period. Note that for mefenamic acid, the half-life is approximately 2 hours[23] and salicylic acid delivered from willow bark has a half-life of approximately 2.5 h.[24]

Mefenamic acid capsules were 250 mg, produced on order by the Razak pharmaceutical company, Tehran, Iran, and salix extract capsules of200 mg, produced on order by the Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran. Either mefenamic acid or salix were packed into three capsules for daily use. Note that one of the salix capsules in each pack was a placebo. The extracts was provided from cultured salix species by 70% ethanol at a ratio of 8–14:1, 15% salicin, which allows for the administration of salicin 240 mg for daily use.[19,20] All the capsules were produced with a same appearance. The students were administered to use the capsules, one hour after the onset of dysmenorrhea. The participants were instructed to use either the allocated treatment every eight.[25] The students were also instructed to continue the medication only while the dysmenorrhea and its symptoms are present. To ensure an accurate follow-up, a trained designated resident was responsible for distributing the questionnaires to the students, in every menstrual cycle and gathering them at the end of each cycle. Furthermore, she was responsible for administering the medicine to the students–in each cycle, according to the randomization list. In addition, it was her responsibility to ensure that the students have answered all the questions; however, when there was a problem, she should refer it to the project director.

2.1. Outcomes

The outcomes of the study were as follows: The 10-point visual analogue scale (VAS) was used to evaluate pain level, as the primary outcome measure.[26] Systemic dysmenorrhea symptoms, including abdominal and back pain, breast pain, headache, vomiting, nausea, diarrhea, cramp, fatigue, muscle stiffness, and faint, were assessed, as the secondary outcomes via the multidimensional verbal scoring system (0 = none to 3 = severe).[27]

The amount of bleeding was measured using a pictorial blood

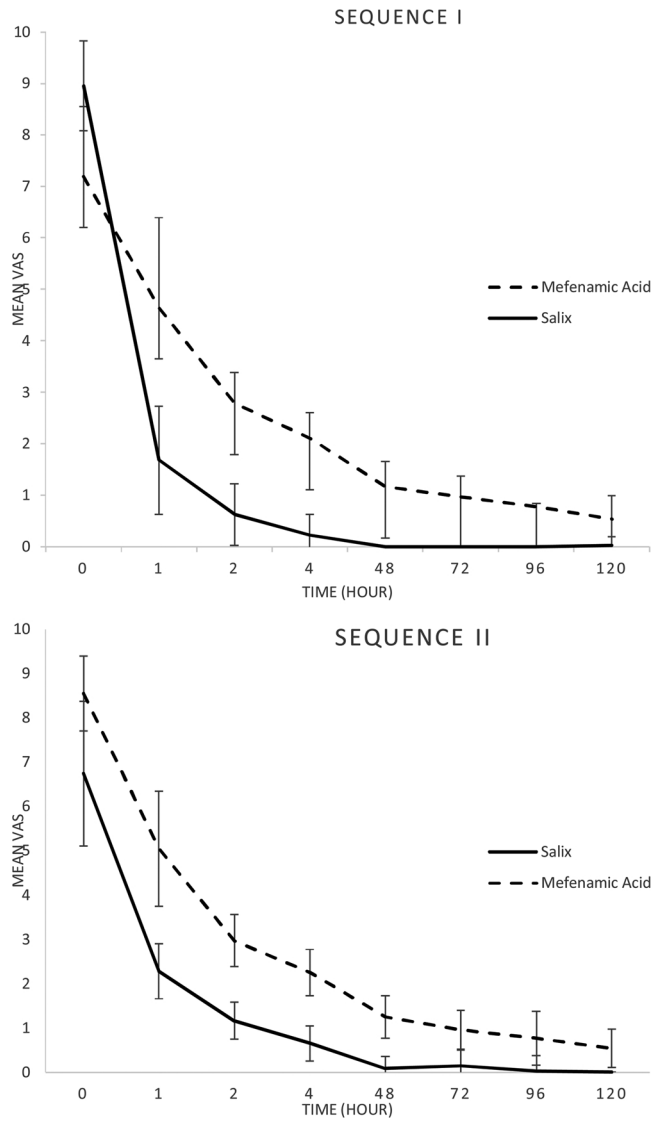

Fig. 2. Mean ± SD VAS for salix and mefenamic acid groupsequence I (above) and sequence II (below) over five days.

assessment chart. The chart was completed for first 10 menstrual days such that 1 point for each lightly stained towel, 5 points for each moderately soiled towel, 20 points for the completely saturated towel. No one used tampons. Finally, 1 point for small clot or 5 points for large clot was recorded.[28,29] An adverse events checklist was used to carefully record scalding, rash, nausea, vomiting, and cough in each cycle. The Ethics Committee of Shahrekord University of Medical Sciences approved the study (code IR.SKUMS.REC.92-10-23). Written informed consent was obtained from all the participants.

2.2. Statistical analysis

Qualitative variables were described using frequency (%), and quantitative variables were reported using mean ± standard deviation (SD). Chi-square test and independent samples *t*-test were used to compare qualitative and quantitative variables between the groups, respectively. Generalized estimating equations (GEE) method was used to assess the treatment effect on outcomes, controlling for time and covariates. The results are presented in terms of mean difference with standard error (SE) and odds ratio (OR) with 95% confidence interval. If the effect of the treatment in the first sequence was persistent into the second sequence, the data from only sequence I was analyzed. SPSS 22 was used for data analysis. P-values less than 0.05 were considered statistically significant.

3. Results

Out of a total 275 dormitory residents, 233 students volunteered to participate in the study. Finally, 106 students who met all the inclusion criteria were recruited. Fifty-one students (in the mefenamic acid group) and 49 students (in the salix group) completed sequence I. Fifty students (in the salix) and 48 students (in the mefenamic acid group) completed sequence II. Finally, 96 students were included in the analysis: 48 students in the treatment group in sequence I who completed sequence II, and 48 students in the control group in sequence I who completed sequence II. Fig. 1 shows the study flowchart. The mean ± SD age of the students was 20.73 ± 1.76 yr. Table 1 shows that the groups were homogeneous in terms of demographic and menstrual characteristics ($P > 0.05$).

3.1. VAS

Fig. 2 illustrates that the mean VAS for the salix group is lower than the mean VAS for the mefenamic acid group over five days in both sequences. The results in Table 2 shows that the students in the mefenamic acid group experienced a significant higher level of pain, according to the VAS, than the students in the salix group (1.61 ± 0.06, $P < 0.001$) controlling for time and the baseline VAS.

3.2. Bleeding

Fig. 3 shows the frequency of the students experiencing dysmenorrhea bleeding levels in the salix and the mefenamic acid group in sequence I and II. Table 2 demonstrates that there was no significant difference in the estimated odds of the bleeding level between the salix and mefenamic acid group [OR: 1.48 (0.69, 3.17), P = 0.31].

3.3. Dysmenorrhea symptoms

The frequency of dysmenorrhea symptoms among the students in each level of symptom is presented in Fig. 4. In average during both sequences, 77.39% ± 16.18 of the students who consumed salix capsules showed no symptoms followed by 22.18% ± 14.08 of the students

Table 2
The effect of treatment on dysmenorrhea mean VAS (over 120 h) and odds of bleeding (over ten days).

	VAS		Bleeding	
Effect	Mean difference (SE)*	P	OR (95%CI)**	P
Treatment (Mefenamic acid vs Salix)	1.61 (0.06)	< 0.001	1.48 (0.69, 3.17)	0.31
Time	−0.03 (0.0009)	< 0.001	0.3 (0.23, 0.37)	< 0.001
Baseline	0.75 (0.03)	< 0.001	2.97 (2.05, 4.31)	< 0.001
Treatment*Time	−0.009 (0.0006)	0.001	1.43 (1.14, 1.8)	0.002

* Standard error.
** Odds ratio (95%Confidence interval).

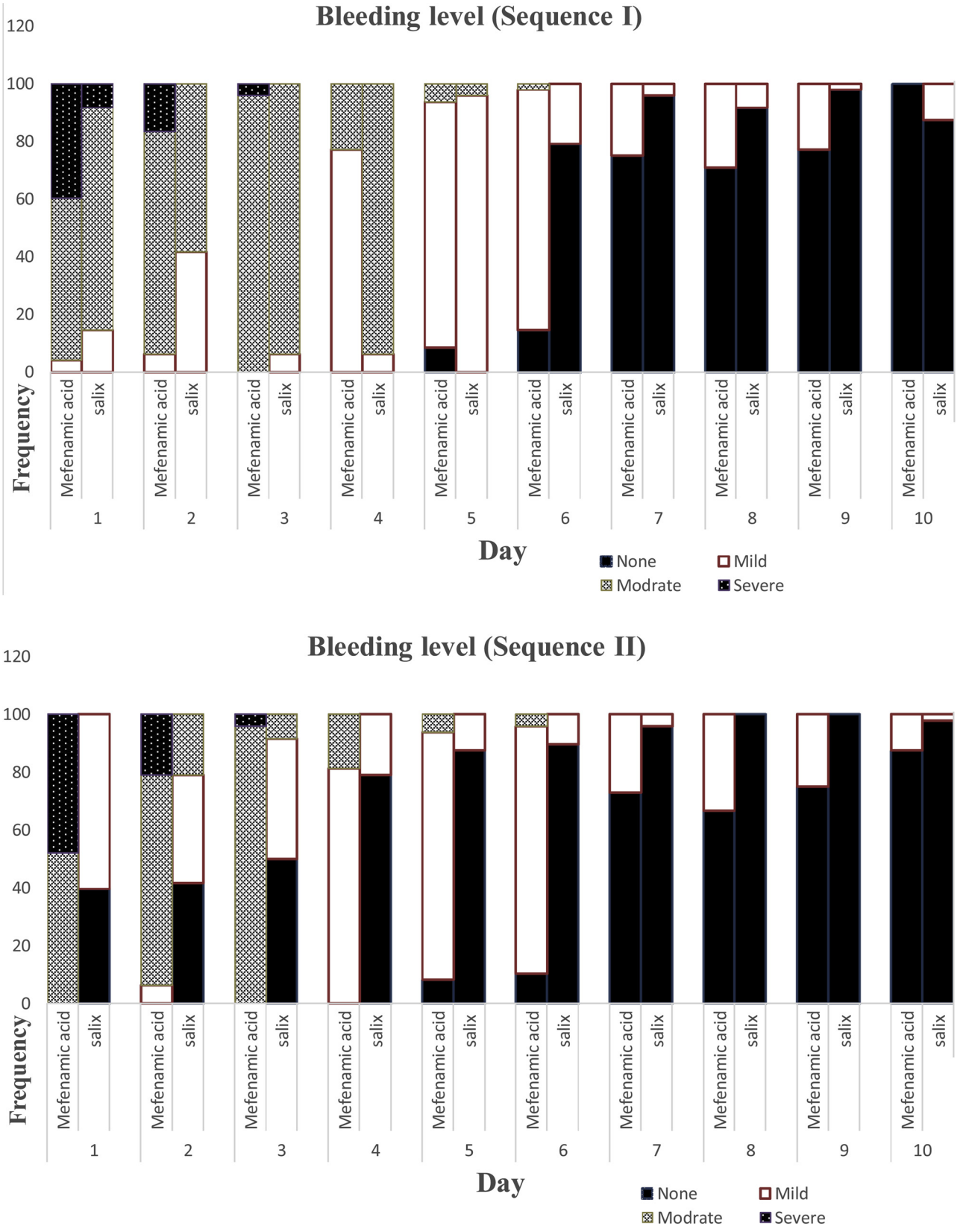

Fig. 3. The frequency of the students in dysmenorrhea bleeding level in the salix and mefenamic acid group in sequence I (above) and II (below).

who experienced the level of mild symptoms. In contrast in average, 44.58% ± 20.16 of the students in the mefenamic acid group had mild symptoms followed by moderate symptoms (28.12% ± 15.29). Due to high zero frequency (60%) in moderate and sever levels, no regression model is fitted.

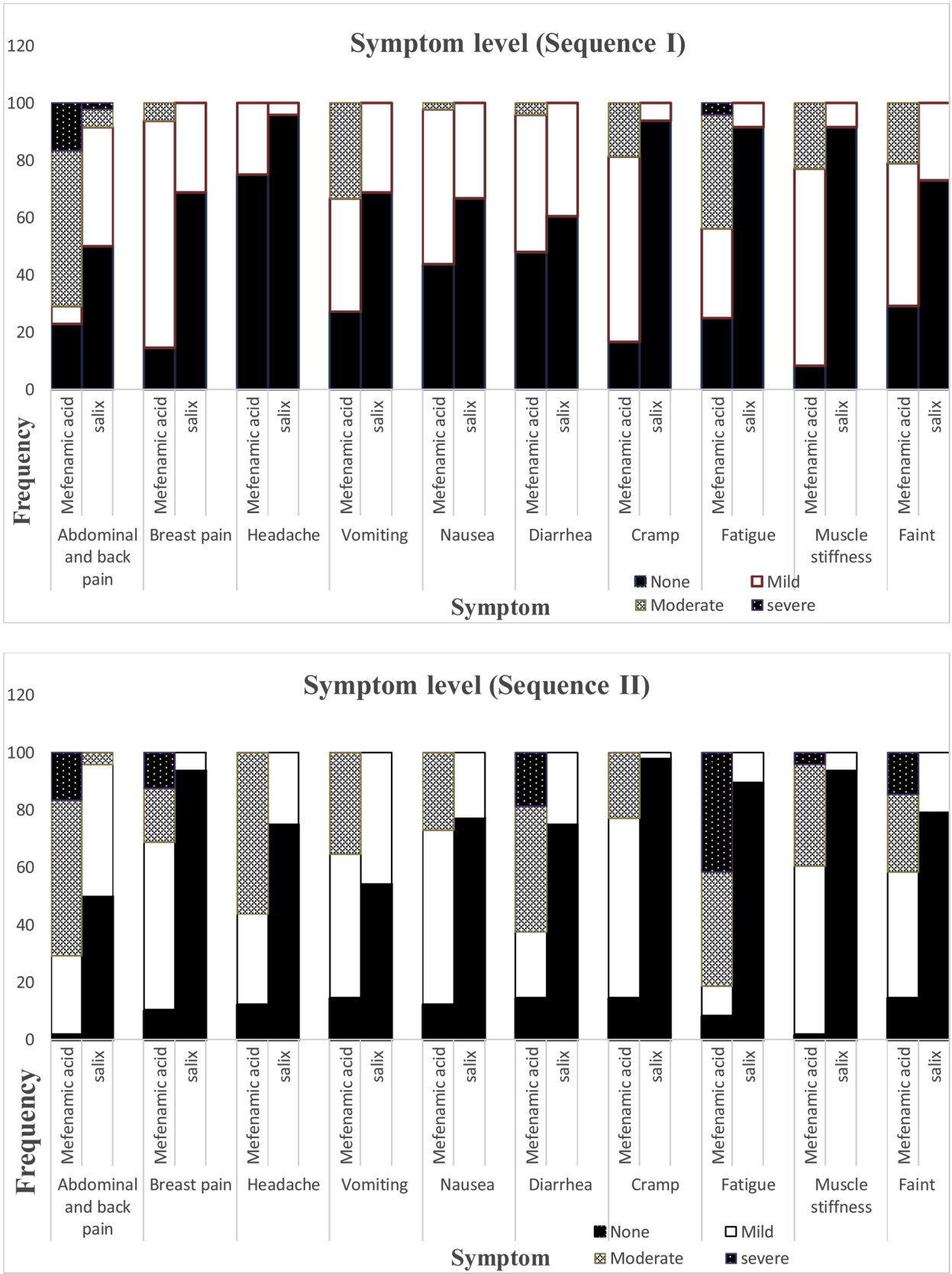

Fig. 4. The frequency of the students in dysmenorrhea symptoms in salix and mefenamic acid group in sequence I (above) and II (below).

3.4. Blood clots

The odds of blood clot in students in the mefenamic acid group was 7.25 (3.51, 10.1) times that of those in the salix group (P = 0.004).

4. Discussion

Traditionally, salix has been used for various medical purposes, including to alleviate menstrual pain, headache, acute back pain, and general pain.[21,30] Moreover, salix extract has anti-inflammatory and analgesic activities, so that it is extensively used in sport performance.[21] The present study demonstrated that salix extract more significantly reduced dysmenorrhea compared with mefenamic acid. Similar to our results, Uehleke et al found that salix had an adequate analgesic effect on rheumatic pain. In addition, it has been suggested that salix can be used as a basic treatment in long-term therapy for painful musculoskeletal disorders–in combination with NSAIDs and opioids, if necessary– which has relevant drug interactions and an acceptable tolerability.[31] Gagnier et al. showed that a daily dose of 240 mg of salicin reduced pain, and was effective as 12.5 mg of NSAIDs rofecoxib in patients with acute back pain.[32] Other study by Nieman et al. also indicated that salix reduced joint pain.[33]

Several factors, including increased the production of PGs, may be involved in menstrual pain.[34] The effect of salix on dysmenorrhea reliefis likely because of salix inhibition COX and lipooxygenase pathways in PG synthesis.[35] which In addition, the anti-inflammatory property of salix can be attributed to inhibition of PG synthesis.[36] However, the effect of salix on dysmenorrhea reduction depends on the inhibition PGs activity as a key mechanism.[37] PGs are produced by COX and lipoxygenase from arachidonic acid.[38] Salix extract and its co-active constituents inhibit COX-2.[19] Additionally, NSAIDs such as mefenamic acid inhibit PGs synthesis through inhibition of COX activity.[39] Salicin has been traditionally used as a biological marker for the activity of salix, and is even considered as a major active constituent. Little attention has been paid to the role of polyphenols and flavonoids in salix preparations.[40] Salix's effect on pain relief can be through its compounds flavonoids and polyphenols by COX inhabitation and lipoxygenase activity.[35] These compounds have a significant anti-inflammatory activity[36] and inhibit PG production.[37] Thus, it seems that salix leads to decreasing dysmenorrhea intensity similar to mefenamic acid with antiprostaglandin effects.

The current research, found no significant difference between the amount of dysmenorrhea bleeding in the salix and mefenamic acid group. However, the risk of blood clotting was significantly lower in the salix group than the mefenamic acid group. Vlachojannis et al. reported that salix extract with a dose of 240 mg salicin had no significant effect on blood clotting.[18]It has been found that salicin in salix could convertd to salicylate, which helps to reduce platelet aggregation and prevent from blood clotting.[41]

The present study revealed a lower level of severity of dysmenorrhea symptoms, including abdominal and back pain, breast pain, headache, vomiting, nausea, diarrhea, cramp, fatigue, muscle stiffness, and faint in the students who received salix in comparison with mefenamic acid. Studies have been shown that treatment with salix preparations is more tolerated than that of synthetic derivatives; therefore, it can be used for treating a range of fevers,[42,43] infections, and chronic pain syndromes. Palliative effect of salix extract on rheumatic complaints, headache, leucorrhea, humid asthma, diarrhea, and dysentery has been also demonstrated in some studies. Furthermore, because of its ability to scavenge free radicals, salix has been used as a natural substitute for aspirin.[44,45]

No adverse event was reported in this study. Compared to NSAIDS, salix extract did not produce undesirable side effects, such as gastric erosions, compared with NSAIDs, likely because of COX1 and COX2 mRNA expressions in salix. In contrast to salicylic acid and aspirin, there is no evidence that salix produces stomach irritation.[30]

Because of its cost-effectiveness, safety, tolerability, as well as an absence of adverse effects,salix can serve as an alternative agent to NSAIDs in the management of primary dysmenorrhea. The student's self-report of endometriosis, which is the most common cause in secondary dysmenorrhea, is one of the limitations of the study. The strength of this study was its crossover design in which each case was considered as its own control. It is highly recommended that future research study the effects of various doses of salix.

5. Conclusion

In summary, based on our findings, salix extract can decrease dysmenorrhea significantly, regarding VAS score in the students with primary dysmenorrhea. In addition, salix extract can reduce severity of dysmenorrhea symptoms compared with the mefenamic acid. Moreover, use of mefenamic acid can lead to a higher blood clot than salix. Regarding amount of bleeding, we found no significant difference between treatment with salix and mefenamic acid. Our study showed that salix extract had no adverse effect; therefore, this herb is recommended to be safely administered to manage primary dysmenorrhea.

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Author's contribution

All authors have approved the final manuscript.

The conception and design of the study, or acquisition of data, or analysis and interpretation of data: Ziba Raisi Dehkordi, Mahmoud Rafieian-kopaei, Fatemeh Sadat Hosseini-Baharanchi

Drafting the article and revising it critically for important intellectual content: Ziba Raisi Dehkordi, Mahmoud Rafieian-kopaei, Fatemeh Sadat Hosseini-Baharanchi

Final approval of the version tobe submitted: Ziba Raisi Dehkordi, Mahmoud Rafieian-kopaei, Fatemeh Sadat Hosseini-Baharanchi

Declaration

Study sponsor had no role in the study design, in the collection, analysis and interpretation of data.

Competing interest statement

No competing interest to declare.

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