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Effects of Pomegranate and Spearmint Syrup on Nausea and Vomiting During Pregnancy: A Randomized Controlled Clinical Trial

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Abstract

Background: Nausea and vomiting during pregnancy (NVP) affects approximately 50% - 80% of expecting mothers. NVP can impose negative effects on the quality of life; therefore, more attention should be paid to improve patients' health outcomes.
Objectives: The purpose of this trial was to evaluate the efficacy of pomegranate and spearmint syrup on NVP.
Methods: In this randomized clinical trial, 74 pregnant women with moderate NVP were divided into 2 groups via block randomization method. A total of 24 and 31 patients were analyzed in the syrup and vitamin B6 groups, respectively. The 24-hour pregnancy-unique quantification of emesis (PUQE-24) scale was used to examine the severity of NVP. The intervention included the use of pomegranate syrup (5 cc/TDS) plus vitamin B6 in the syrup group; on the other hand, the control group only received B6 tablets (20 mg/TDS) for 1 week. The subjects were followed-up for 1 week without any interventions. Data were analyzed, using Chi square test for qualitative variables, t test and Mann-Whitney U test for quantitative variables, and Friedman test for repeated measures.
Results: There was no significant difference between the groups in terms of demographic and pregnancy characteristics. The mean PUQE-24 score in the syrup group was 9.4 ± 1.8 at baseline, 4.6 ± 1.5 on day 7, and 4.8 ± 2.6 on day 14 ($P < 0.001$). The mean PUQE-24 score in the control group was 8.5 ± 1.5 at baseline, 6 ± 2.3 on day 7, and 6.2 ± 2.6 on day 14 ($P < 0.001$). Although a major decline in PUQE-24 scores was observed in both groups, it was more significant in the syrup group ($P = 0.001$). Also, the PUQE-24 score was significantly lower in the syrup group, compared to the control group on days 7 and 14 ($P = 0.02$). The visual analog scale scores also showed a greater reduction in the syrup group, compared to the control group (4.7 ± 2.8 vs. 1.6 ± 3; $P = 0.001$). No significant difference was observed between the groups regarding the duration of nausea, frequency of vomiting, and frequency of retching; also, no complications were reported.
Conclusions: The effectiveness of pomegranate and spearmint syrup in reducing NVP was confirmed in the syrup group versus the control group with significant differences.

Keywords: Pomegranate, Spearmint, Nausea, Vomiting, Pregnancy, Iranian Traditional Medicine

1. Background

The most common, specific, and unpleasant complications among pregnant women include nausea and vomiting during pregnancy (NVP). Approximately 50% - 80% of women experience these complications during pregnancy (1). NVP can impose negative effects on the quality of life; therefore, more attention should be paid to improve patients' health outcomes (2).

Pathophysiology is a combination of genetic, endocrine, gastrointestinal, environmental, and psychosocial factors. Although the exact etiology of NVP remains unknown (3), use of chemical drugs is avoided in early pregnancy as much as possible due to their potential teratogenic effects; therefore, there is an increasing tendency towards alternative therapies (4).

Vitamin B6 is prescribed as the first-line agent in the treatment of mild and moderate NVP (5). Effectiveness of vitamin B6 in NVP has been revealed in some previous studies (6). Moreover, today, use of complementary and alternative medicine (CAM) has become more common in different communities. Traditional Persian medicine (TPM), otherwise known as Iranian traditional medicine (ITM), as part of CAM, has proposed various treatments for NVP (7, 8).

Use of pomegranate (*Punica granatum L.*), which belongs to the Lythraceae family, along with spearmint (*Men-*

tha spicata L.) from the Lamiaceae family, is one of the proposed ITM treatments for NVP (9). Considering the main etiology and management of NVP in ITM, pomegranate juice and spearmint (Anar-Monana syrup in Persian) are assumed to be effective in controlling NVP (10).

Pomegranate, with anti-*H. pylori* and antiulcer activities, has been used as a gastric tonic (7, 11). The therapeutic activities of pomegranate and spearmint have been recorded in the ITM literature (7, 8). Various pharmacological activities, such as cardiovascular protective activities, antihypertensive effects (with inhibition of serum angiotensin-converting enzyme activity), hypoglycemic effects, and increased high-density lipoprotein (HDL)-cholesterol level, have been revealed. Moreover, anticancer, antibacterial, anti-*H. pylori*, antiinflammatory (in the gastrointestinal tract), and antiulcer effects have been recently discovered (11-21).

Furthermore, maternal dietary supplementation with pomegranate juice during pregnancy decreases stimulus-induced apoptosis, placental oxidative stress, and incidence of placental dysfunction in pregnancy (22). However, according to our literature search, no studies have been performed so far on the effects of pomegranate on NVP.

In this regard, in a double-blind randomized controlled trial (RCT), the participants (n, 60) were routinely trained to use a bowel of water with 4 drops of pure mint essential oil (placed on the floor near the bed) for 4 consecutive nights before sleeping, while the control group used 4 drops of normal saline. Based on the visual analog scale (VAS), the mean nausea intensity changed from 4.78 $\pm$ 1.62 to 3.50 $\pm$ 1.95 in the mint group and from 4.85 $\pm$ 1.82 to 4.38 $\pm$ 2.18 in the normal saline group (P = 0.140). Also, the mean rate of vomiting changed from 3.00 $\pm$ 2.19 to 2.23 $\pm$ 1.88 in the mint group and from 2.52 $\pm$ 2.4 to 2.55 $\pm$ 2.55 in the normal saline group (P = 0.577) (23).

Moreover, a double-blind RCT on the efficacy of *M. spicata* and *M. piperita* in the prevention of chemotherapy-induced nausea and vomiting showed a more significant reduction in the intensity and number of emetic events in the first 24 hours in 2 treatment groups receiving *M. spicata* and *M. piperita* ($P < 0.05$), compared to the control group (24). With this background in mind, the present study was conducted to assess the efficacy, safety, and tolerability of pomegranate and spearmint syrup in the treatment of NVP.

2. Methods

The present study was approved by the ethics committee of Kerman University of Medical Sciences, Kerman, Iran (registration number, IR.KMU.REC.1394.232). Consent forms were obtained from all the participants, and the trial was registered in the Iranian registry of clinical trials (IRCT2015022221186N1). This RCT was carried out in prenatal clinics of Shahryar district healthcare centers, affiliated to Iran University of Medical Sciences, Tehran, Iran from September 15, 2015 to March 19, 2016.

To estimate 1.8 differences in 24-hour pregnancy-unique quantification of emesis (PUQE-24) scores between the groups (type I error, 0.05; type II error, 0.2; PUQE-24 score standard deviation, 2.5; and attrition rate, 20%), the sample size was calculated as 37 patients per group. The effect size was considered as 0.72, based on the results of our pilot study. The formula of mean comparison was used to calculate the sample size.

The inclusion criteria were as follows: 1) being pregnant; 2) age range of 18 - 40 years; 3) singleton pregnancy; 4) gestational age of 6 - 16 weeks; 5) moderate NVP (7 - 13 score on the PUQE-24 scale); 6) voluntary participation; 7) possibility of follow-up; 8) ability to read and write; and 9) no intake of antinausea drugs within at least 24 hours before the visit.

On the other hand, the exclusion criteria were as follows: 1) severe NVP requiring fluid therapy and hospitalization; 2) NVP due to secondary causes; 3) presence of pregnancy complications such as bleeding; 4) threatened abortion; and 5) history of chronic diseases, drug addiction, alcoholism, smoking, and drug allergies.

Finally, 74 women were randomized into 2 parallel groups after obtaining the written consent forms. Vitamin B6 was used for the control group, while a general physician administered syrup and vitamin B6 in the syrup group. Block randomization was used for this parallel-group RCT; it should be noted that the study was not blinded. The participants were asked to complete the questionnaires regarding their demographic and pregnancy characteristics.

Vitamin B6 tablets (20 mg) were purchased from Ramopharmin Pharmaceutical Co. (Tehran, Iran). The syrup was prepared from pomegranate juice (2 kg), which was concentrated to half and made consistent with 1 kg of sugar and 0.5 kg of spearmint juice (25). The syrup was prepared at the herbal medicine department of ITM research institute, Iran University of Medical Sciences. It was prescribed in accordance with the ITM guidelines (5 mL after meal for 1 week with a frequency of 3 times per day) (9).

The enrolled women were randomly assigned to receive either 20 mg of vitamin B6 or 5 cc of pomegranate and spearmint syrup 3 times per day, along with 20 mg of vitamin B6 for 1 week. The patients were then visited after 1 week of the intervention (day 7) and 1 week following the end of the intervention (day 14).

The participants were asked to complete the PUQE-24

scale for the assessment of NVP in the past 24 hours. If the subjects' scores ranged between 7 and 12 (moderate NVP), they were enrolled in the study. PUQE-24 scale, which is designed to assess NVP within the past 24 hours, is composed of 3 questions and measures nausea duration, frequency of vomiting, and frequency of retching in the past 24 hours using a rating scale.

In the PUQE-24 scale, the range of scores for each question is 1 to 5, and the total score ranges from 3 to 15; scores ≤ 6, 7-12, and ≥ 13 indicate mild, moderate, and severe NVP, respectively (26). The validity of this questionnaire has been determined in some previous studies (26-28). In the present study, the severity of nausea was evaluated by VAS. VAS consists of a 10-cm line, with 0 representing no symptom(s) and 10 representing the worst symptom(s) (23).

Safety assessments were based on the reports of adverse events and results of routine physical examinations. Pomegranate syrup was well tolerated by most of the participants, and no adverse effects, neither local nor systemic, were reported. Furthermore, no abnormal findings were observed on physical examination in the follow-ups.

Statistical analyses were carried out, using t test (for mean age, gestational age, BMI, age at marriage, duration of marriage, and age at menarche) and Chi square test (for occupation, educational level, impairment in daily activities, history of NVP, family history of NVP, wanted pregnancy, prepartum nausea, history of psychiatric drug use, gravidity, history of abortion, anorexia, history of stillbirth, history of mole and EP, multiple birth, medical history of diseases, and nausea duration). Moreover, Mann-Whitney U test (for PUQE-24 score and severity of nausea), Friedman test, and ANCOVA (for PUQE-24 score, severity of nausea, frequency of vomiting and retching, and nausea duration before, during, and after the intervention) were performed to determine potentially significant associations.

P value ≤ 0.05 was considered statistically significant. SPSS version 17 was used for statistical analysis. Normal distribution of variables was assessed by Kolmogorov-Smirnov test ($P > 0.05$, normal distribution), while the nonparametric method (Mann-Whitney U test) was used for variables without a normal distribution. The results were obtained via per-protocol analysis.

3. Results

The current study included 100 participants, 26 of whom were excluded, as they declined to cooperate (n, 20) or did not meet the inclusion criteria (n, 6). A total of 74 patients with the mean age of 26.6 $\pm$ 5.7 years (range, 18 - 40 years) were screened and randomly enrolled in the groups. During the study, some participants left the study due to unwillingness to continue the interventions; finally, 55 participants completed the study (Figure 1).

The mean PUQE-24 score in patients who left the study was higher in the syrup group in comparison with the control group (10.8 $\pm$ 1 vs. 7.6 $\pm$ 0.8; $P < 0.001$). Attrition in the syrup group occurred after administering only 1 or 2 doses of syrup or before taking the syrup. Therefore, only patients who completed the study were included in the analysis. After eligible subjects were included in the study, per-protocol analysis was performed.

The results demonstrated homogeneity between the groups regarding the following variables: maternal age, gestational age, age at marriage, duration of marriage, age at menarche, occupational status, education, BMI, anorexia, impairment in daily activities, history of NVP, family history of NVP, wanted pregnancy, prepartum nausea, history of psychiatric drug use, history of abortion, anorexia, history of stillbirth, history of mole and EP, multiple birth, and medical history of diseases. Also, there was no significant difference between the groups in terms of demographic and pregnancy information, except gravidity (Table 1).

3.1. PUQE-24 Scores

The mean $\pm$ SD and median (IQR) PUQE-24 scores at baseline and 7 and 14 days after the intervention are shown in Table 2. The decline in PUQE-24 scores from baseline to days 7 and 14 was significant, based on Friedman test results ($P < 0.001$). The decline in PUQE-24 scores was 4.7 $\pm$ 2 vs. 2.5 $\pm$ 2.7 in the syrup and control groups on days 0 - 7 ($P = 0.005$) and 4.5 $\pm$ 2.8 vs. 2.3 $\pm$ 2.6 on days 0 - 14 ($P = 0.001$), respectively. A slight increase was reported in the PUQE-24 scores on days 7 - 14 in both groups (0.2 $\pm$ 2.5 vs. 0.16 $\pm$ 2.0; $P = 0.2$); however, there was no significant difference between the 2 groups (Table 3 and Figure 2).

3.2. Duration of Nausea

Duration of nausea was not significantly different between the groups at baseline ($P = 0.8$); also, there was no significant difference on days 7 and 14 ($P = 0.3$ and $P = 0.2$, respectively). Although the duration of nausea decreased in both groups from baseline to day 7 ($P < 0.001$), the difference was not significant between the groups (Figure 3).

3.3. Frequency of Vomiting

The frequency of vomiting was not significantly different between the groups at baseline ($P = 0.1$); similarly, there was no significant difference on days 7 and 14 ($P = 0.1$ and $P = 0.4$, respectively). Although the frequency of vomiting in the 2 groups showed no significant difference on days 7 and 14, the decline in the frequency of vomiting on days 0

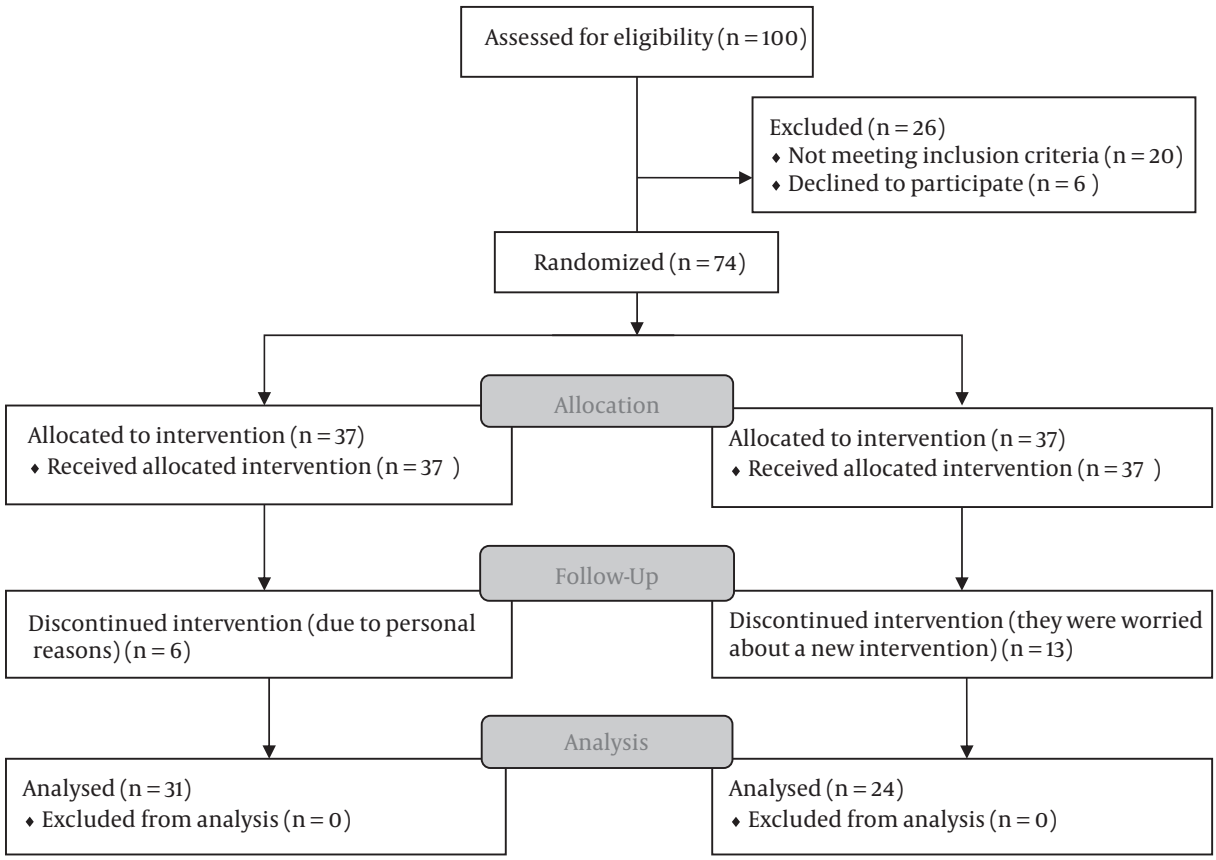

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow Diagram

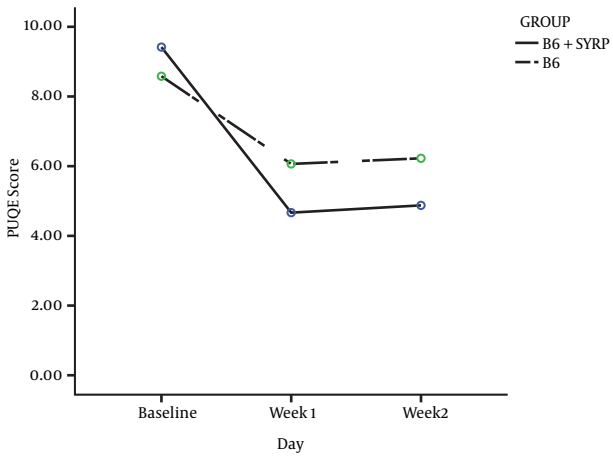

Figure 2. Changes in the Mean PUQE-24 Scores Within 14 days

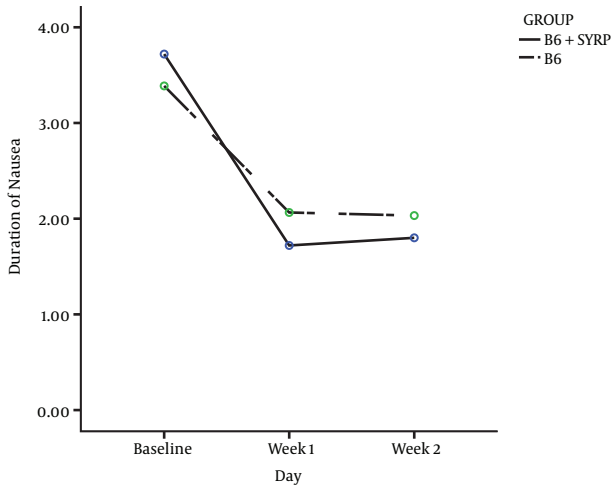

Figure 3. Duration of Nausea Within 14 days

- 7 and 0 - 14 was significant in the syrup group ($P < 0.001$) and insignificant in the control group ($P = 0.4$ and $P = 0.1$,

respectively).

3.4. Frequency of Retching

The frequency of retching in the groups was not significantly different at baseline (P = 0.6); also, there was no significant difference on days 7 and 14 (P = 0.1 and P = 0.2, respectively). Although the frequency of retching in the groups showed no significant difference on days 7 and 14, the decline in frequency within days 0 - 14 was significant in both groups (P < 0.001).

3.5. Analysis of the Severity of Nausea with VAS

The severity of nausea is presented in Table 4. At baseline, the severity of nausea in the syrup group was significantly higher than the control group (P = 0.006), whereas on days 7 and 14, its severity was significantly lower in the syrup group (P = 0.01 and P = 0.04). Changes in the severity of nausea from baseline to days 7 and 14 were more significant in the syrup group, compared to the control group (P < 0.001 and P = 0.001, respectively; Table 5). By considering the baseline severity of nausea as a covariate, ANCOVA test results showed a significant difference between the groups in the reduced severity of nausea from baseline to days 7 and 14 (Figure 4).

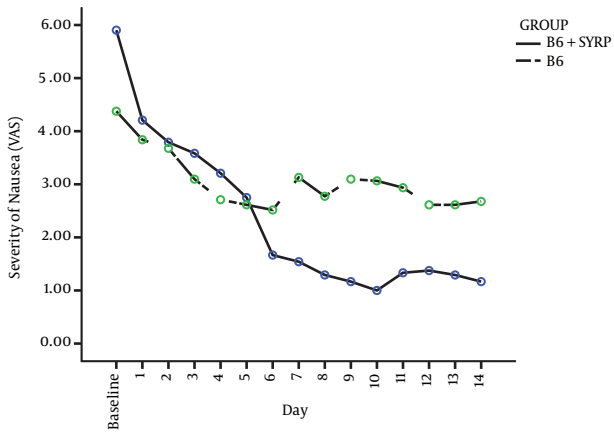

Figure 4. The Severity of Nausea Within 14 Days

4. Discussion

According to the findings of the present study, pomegranate and spearmint syrup is effective in reducing gestational nausea and vomiting. It could lead to a decline in the mean scores of PUQE-24 (Tables 2 and 3, Figure 2) and severity of nausea (Tables 4 and 5, Figure 4). To

the best of our knowledge, this is the first RCT evaluating the effect of pomegranate on NVP.

The etiology of NVP in ITM is attributed to the effusion and accumulation of inappropriate substances in the stomach; in fact, stomach weakness is one of the factors involved in its etiology. Treatment of NVP consists of removing inappropriate substances from the stomach and decreasing their production (29). Use of astringent (Ghabiz) agents, which have the ability to preserve the tonicity of the stomach, is one of the proposed treatments for stomach weakness (30).

P. granatum (pomegranate) is an example of astringent agents, repeatedly mentioned in ITM resources for its effect on the stomach (31). Also, fragmenting (Moghattia), stubbing (Mohallil), and tendering (Mollatif) agents are necessary for removing soft waste materials around the intestinal villi (30) and are found in medicinal plants such as *M. spicata* (spearmint) (31).

One of the limitations of this study was the lack of relevant studies in scientific databases. Another limitation was the higher attrition rate in the syrup group in comparison with the control group, which could produce attrition bias. Considering the decreasing trend of duration of nausea during the intervention (Figure 3) and lower rates of vomiting and retching on days 7 and 14 after the intervention in the syrup group, more definitive findings can be obtained through further analysis and use of a larger sample size.

Application of CAM in Iran has a long history, and midwives and physicians show great interest in this area. Although the therapeutic activity of pomegranate has been mentioned in the ITM literature (32), the findings of this trial showed that pomegranate and spearmint syrup, as a traditional remedy, is effective in reducing NVP (Tables 2 - 5 and Figures 2 - 4). Despite the side effects of long-term use of antiemetic drugs, no serious side effects were reported for the use of pomegranate syrup.

In the present study, pomegranate and spearmint syrup remained effective for 1 week after drug use. This finding might be due to the gastric tonic effects of pomegranate and spearmint, which have been introduced as a treatment for emesis in ITM texts (32). Pomegranate seems to be more effective than vitamin B6 in the treatment of NVP, and there were statistical differences between the treatment groups. Simple preparation, absence of serious complications, and desirable taste can make pomegranate an alternative treatment for NVP.

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Footnote

Conflicts of Interests: We declare no conflicts of interest.

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Table 1. The Participants' Demographic and Baseline Characteristics[a]

Characteristics	Vitamin B6 (N, 31)	Syrup + Vitamin B6 (N, 24)	P Value[b]
Age, y, mean ± SD	27.5 ± 5.6	26.1 ± 5.7	0.37
BMI, kg/m², mean ± SD	24.2 ± 4.4	25.5 ± 3.9	0.23
Anorexia			0.2
No	16 (51.6)	16 (66.7)	
Yes	15 (48,4)	8 (33.3)	
Age at menarche, y, mean ± SD	13.0 ± 1.1	13.4 ± 1.3	0.1
Impairment in daily activities			0.3
Yes	21 (67.7)	19 (79.2)	
No	10 (32.3)	5 (20.8)	
Age at marriage, y, mean ± SD	20.1 ± 3.8	19.4 ± 3.4	0.5
Mother's occupation			0.5
Housewife	29 (96.7)	22 (91.7)	
Employee	1 (3.3)	2 (8.3)	
Education			0.9
Below high-school diploma	18 (60)	14 (58)	
High-school diploma	11 (36.7)	9 (37.5)	
Above diploma	1 (3.3)	4 (4.2)	
Wanted pregnancy			1.000
Yes	28 (90.3)	21 (87.5)	
No	3 (9.6)	3 (12.5)	
Prepartum nausea			0.4
Yes	2 (6.5)	0 (0)	
No	29 (93.5)	24 (100)	
Medical history			0.09
Yes	0 (0)	3 (12.5)	
No	30 (96.8)	21 (87.5)	
0	1(3.2)		
Gestational age, mean ± SD	9.9 ± 2.4	9.8 ± 3.1	0.89
History of consumption of psychiatric drugs			0.4
Yes	0 (0)	1 (4.2)	
No	31 (100)	23 (95.8)	
History of abortion			0.7
Yes	6 (19.4)	3 (12.5)	
No	25 (80.6)	21 (87.5)	
Parity (mean) IQR (min-max)	1 (1 - 2)	0.5 (0 - 1)	0.07
Gravidity (mean)	2 (2 - 3)	1.5 (1 - 2)	0.02

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Table 2. Interquartile Range (IQR) and Mean PUQE-24 Scores at Baseline and 7 and 14 Days After the Intervention

Variables	Mean ± SD			IQR	
	Vitamin B6 (n, 31)	Syrup + Vitamin B6 (n, 24)	P Value	Vitamin B6 (n, 31)	Syrup + Vitamin B6 (n, 24)
Baseline	8.5 ± 1.5	9.4 ± 1.8	0.09	8 (7 - 10)	9 (8 - 11.75)
Day 7	6.0 ± 2.3	4.6 ± 1.5	0.02	6 (4-7)	4 (3-6)
Day 14	6.2 ± 2.6	4.8 ± 2.6	0.02	7 (4-8)	3 (3-7)

Table 3. Changes in PUQE-24 Scores Within 0 - 7, 0 - 14, and 7 - 14 Days

Variables	Days 0 - 7	P Value	Days 0 - 14	P Value	Days 7 - 14	P Value
Syrup + vitamin B6 (n, 24)	4.7 ± 2.0	0.005	4.5 ± 2.8	0.001	-0.2 ± 2.5	0.2
Vitamin B6 (n, 31)	2.5 ± 2.7		2.3 ± 2.6		-0.16 ± 2.0	

Table 5. Changes in the Mean Severity of Nausea Within 0 - 7, 0 - 14, and 7 - 14 Days

Variables	Days 0 - 7	P Value	Days 0 - 14	P Value	Days 7 - 14	P Value
Syrup + vitamin B6 (n, 24)	4.3 ± 2.3	< 0.001	4.7 ± 2.8	0.001	0.3 ± 2.5	0.3
Vitamin B6 (n, 31)	1.2 ± 2.9		1.6 ± 3.0		0.4 ± 2.1	