



Effectiveness of Magnesium on Menstrual Symptoms Among Dysmenorrheal College Students: A Randomized Controlled Trial

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Abstract

Objectives: The aim of this study was to compare the impact of two different doses of magnesium on severity of menstrual symptoms.

Materials and Methods: In this double-blind placebo-controlled trial, 60 students with moderate or severe dysmenorrhea were randomly allocated to two intervention groups and one control group (receiving 150 mg and 300 mg magnesium stearate, or placebo from the 15th day of menstruation until the following cycle, respectively). All participants reported their menstrual symptoms according to the Symptom Severity Scale 2 cycles before and 2 cycles after the intervention. The main outcomes included menstrual symptoms such as cramps, headache, foot pain, depression, irritability, general pain, and abdominal pain.

Results: According to the results, although both doses of magnesium could significantly reduce all symptoms of dysmenorrhea compared to the placebo ($P < 0.001$), magnesium 300 mg was more effective in decreasing symptoms such as cramps, headache, back pain, foot pain, depression, irritability, and abdominal pain.

Conclusions: The results showed that both doses of magnesium stearate (150 and 300 mg) can reduce severity of menstrual symptoms although the effect was greater with magnesium stearate 300 mg.

Keywords: Magnesium, Menstrual symptoms, Randomized controlled trial, Primary dysmenorrhea

Introduction

Primary dysmenorrhea is a painful menstruation that happens in the absence of pelvic disease (1,2) and affects women's quality of life (3,4). It is often accompanied with headache, diarrhea, fatigue, irritability, depression, insomnia, and a general sense of anxiety. The prevalence of primary dysmenorrhea is estimated to be from 50% to 90%. The exact cause of primary dysmenorrhea is unknown although the widely accepted theory is the overproduction of uterine prostaglandins (4).

Although anti-prostaglandin drugs are effective in the treatment of dysmenorrhea, their long-term use may cause some side effects such as nausea, gastritis, renal papillary necrosis, and decreased renal blood flow (5,6). Thus, most people are now looking for alternative pain relievers (7).

Magnesium deficiency can mimic many disorders including fatigue, irritability, weakness, and dysmenorrhea. Magnesium influences the contractility and relaxation of the uterine smooth muscle and may inhibit the synthesis of prostaglandins (8). The magnesium level in women with primary dysmenorrhea was low (9-13). Therefore, it is possible that magnesium can reduce the severity of menstrual pain and its associated symptoms by decreasing the level of prostaglandins. In addition, it regulates the

entry of calcium into the cell, which acts as a physiological antagonist of calcium. Magnesium is also an *N*-methyl-D-aspartate receptor antagonist, which may be effective in the prevention and treatment of pain (8).

The results of a clinical review showed that using magnesium in some trials could reduce dysmenorrhea and the level of prostaglandins in the blood (14). Although magnesium in combination with calcium can decrease menstrual pain (15), the minimal therapeutic dose of magnesium is unclear yet. Therefore, the present study aimed to investigate the minimum effective dose of magnesium in reducing severity of menstrual symptoms among college students. Based on the null hypothesis of this study, the two doses of 150 and 300 mg magnesium are equally effective in relieving dysmenorrhea.

Materials and Methods

This double-blind placebo-controlled trial with three parallel arms, two intervention groups, and one control group was conducted on students residing in the dormitories of Ahvaz Jundishapur University of Medical Sciences. All participants gave written informed consent before data collection. College students with primary dysmenorrhea were included in the study. On the other

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Key Messages

- ▶ Discomforts related to dysmenorrhea is the most common gynaecologic complaint and affects 50% to 90% of young women.
- ▶ Based on this study, magnesium stearate can reduce severity of menstrual symptoms in female college students with dysmenorrhea.

hand, girls with secondary dysmenorrhea and any other diseases were excluded from the study.

Eligible students were randomly allocated to one of the three groups. Following criteria were also required for the study participants: having regular menstrual periods, having moderate or severe primary dysmenorrhea (pain score of 5-9 using a visual analog scale (VAS) in previous cycles), and being single. On the other hand, students with a history of any chronic diseases or those using oral contraceptive pills or vitamin supplements were excluded from the study. Considering the high prevalence of dysmenorrhea among young people and the usual age for college in Iran (between 18 and 22 years), this study was conducted on this age group.

Considering a mean (standard deviation) of 6.8 (1.4) of menstrual pain intensity based on the results of a study performed with a similar aim (16), $\alpha=0.05$, $\beta=0.10$, and 15% possible drop-outs, the sample size was calculated to be 20 for each group in order to detect at least a 25% reduction in pain intensity after the intervention.

To select the subjects, one of the researchers attended the students' rooms in the selected dormitories. She explained the aim of the study to the students, and those who were willing to participate and gave an affirmative answer to the question "Are you suffering from painful menstruation?" were requested to fill up the questionnaire containing questions to determine eligible persons. A total of 60 eligible students were enrolled in the study after signing a written informed consent form. It should be noted that the researchers did not recruit more than one person from each room due to the possible transmission of information about the intervention.

Then, the young girls were asked to record their pain intensity in the checklist (a diary) during two consecutive cycles and use any medication for relieving pain such as ibuprofen while not taking any other pain relievers, and they had to record every taken pill in the diary. The diary also included a table to record pain intensity and sick leaves (hours) due to pain during menstruation.

Measurements

The questionnaire in this study included three sections. In the first section, the students were asked to state their socio-demographic and medical information, dysmenorrhea status, and personal habits. The second section encompassed the VAS, and the last section dealt

with dysmenorrhea using the somatic symptom scale (SSS).

Using a 10-cm line, the VAS represented the continuum of the student's opinion about the degree of pain. One extreme of the line represented 'unbearable pain' while the other extreme represented 'no pain at all'. The participants were asked to rate the degree of pain by making a mark on the line. The received scores from the scale were classified into mild, moderate, and severe dysmenorrhea if the scores were in the range of 1-3, 4-7, and 8-1, respectively (17).

To evaluate the outcome of the study, the severity of menstrual symptoms was measured by SSS during four continuous cycles (2 cycles before and 2 cycles after the intervention). All participants reported their severity of 8 common menstrual symptoms on a 5-point Likert-type scale (0 = Symptom not present, 1 = Slightly, 2 = Moderately, 3 = Severely, & 4 = Very severely) 2 days before and after the onset of the menstrual bleeding. The SSS is a reliable and valid self-report measure of the somatic symptom burden (18).

Intervention

Out of the 99 students, 60 cases completed the pre-intervention diaries and had consent to continue participation in the study, thus were randomly allocated into three groups with the allocation ratio of 1:1:1 using the random table produced by Excel to receive 300 and 150 mg/d of magnesium or placebo tablets (Figure 1). The person generating the random allocation table was unaware of the purpose of the study.

To preserve allocation concealment, a person who was unaware of the purpose of the study prepared sequentially numbered identical packages containing 40 pills (magnesium 300 mg, 150 mg, or a placebo to be used during the two cycles). Therefore, the researcher who distributed the medications and participants were both blinded to the study.

Each participant received a package based on the determined sequence at the enrolling visit. Moreover, 20 ibuprofen tablets (400 mg) and the second diary were given to them. The diary included the same pre-intervention items in addition to one extra item about the recording of taking the intervention pills.

The participants were asked to take the magnesium (two groups of 150 mg or 300 mg) or placebo pills regularly (one pill a day) from day 15 of their cycle until the day with no menstrual pain in the following cycle and to record the pill taking daily in the diary. In addition, they were instructed to take ibuprofen pills when they needed and record it in the other parts of the diary exactly similar to the pre-intervention period for two consecutive intervention cycles. The completed diaries with the remaining pills (both doses of the magnesium pills, placebo, and ibuprofen) were collected after two months.

Magnesium supplements are available in many types,

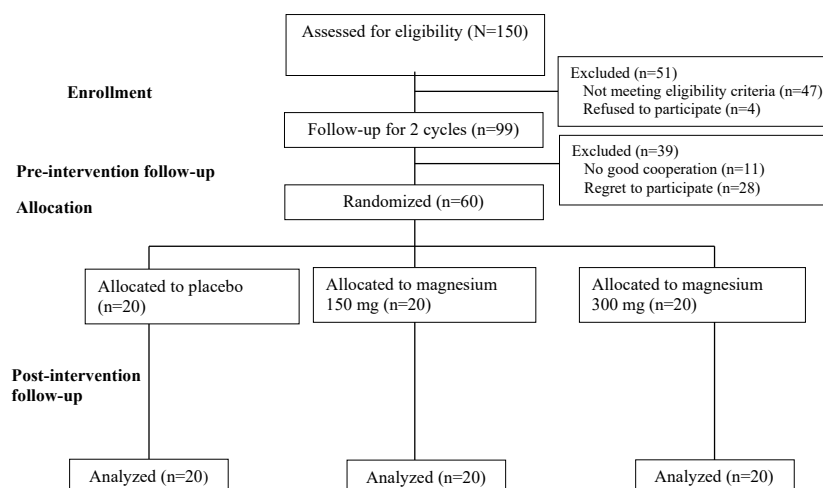


Figure 1. Flow Diagram of the Recruitment and Retention of Study Participants.

but magnesium stearate was used in this study because of its high bioavailability (19). Each tablet contained 150 mg or 300 mg magnesium stearate or some lactose, and microcrystalline cellulose as the excipient to be used by the two intervention groups. The placebo had the same ingredients except for magnesium and contained starch. The tablets were identical in color, shape, and size and were produced in the laboratory of the Pharmacy School of Ahvaz University of Medical Sciences under the direct supervision of the pharmacist from our research team. This study adheres to CONSORT guidelines.

The severity of menstrual symptom scores at each cycle was calculated as the mean score of symptoms two days before and three days after the start of menstruation. The average of the outcomes during the two pre-intervention cycles was considered as baseline values that were compared to the average of those recorded during the two cycles after the intervention.

Statistical Analysis

One-way ANOVA was used for assessing the difference between the groups in terms of continuous data (i.e., age, age of menarche, and severity of menstrual symptoms), the severity of symptoms according to the SSS questionnaire (i.e., cramps, headache, back pain, foot pain, depression, irritability, general pain, abdominal pain, and the total score of symptoms), and the mean differences of dysmenorrhea syndrome before and after the intervention. The post hoc test (Sidak) was applied to identify the variable(s) that caused a significant difference. The Kruskal-Wallis test was employed to compare categorical data (i.e., educational level, exercise, family history of dysmenorrhea, and interference with daily activities). Finally, the ANCOVA test was used to compare between mean differences before and after the intervention. A 95% confidence interval was considered to demonstrate the results. All analyses were conducted

using SPSS (version 16.0), and $P < 0.05$ was considered statistically significant.

Results

Out of a total of 150 initially assessed university students, 99 cases were eligible and gave consent for participation. Of these 99 women, 39 cases were excluded because they were either not cooperative ($n=11$) or regretted to participate in the study ($n=28$). Finally, the remaining 60 students were randomly assigned to three groups, of whom none withdrew from the study (Figure 1). There was no considerable difference between the groups in any of the baseline characteristics. The mean (SD) of the age and their body mass index were 21.0 ± 1.5 and 24.6 ± 2.5 , respectively. One-third of the participants (33.3%) had regular exercise, 75% of cases reported a family history of dysmenorrhea, and 70% of them indicated that their menstrual pain interferes with their usual daily activities (Table 1).

Table 2 presents the mean and SD of dysmenorrhea symptoms in the three groups of magnesium 300 mg, 150 mg, and placebo. Based on the data, magnesium 300 mg could significantly reduce all areas of dysmenorrhea symptoms compared to magnesium 150 mg and placebo ($P < 0.001$).

Table 3 provides the mean differences between magnesium 300 mg in comparison with magnesium 150 mg, and both these doses of magnesium as opposed to placebo. At baseline, there were no significant differences among the three groups. However, magnesium 150 mg was found to significantly decrease all symptoms of dysmenorrhea after the intervention compared to the placebo ($P < 0.05$).

Magnesium 300 mg could also significantly reduce cramps (MD: -2.2, 95% CI: -3.3, -1.0), headache (MD: -1.3 95% CI: -2.5, -0.1), back pain (MD: -1.9, 95% CI: -2.9, -0.8), foot pain (MD: -1.8 95% CI: -2.8, -0.8), depression

Table 1. Baseline Characteristics of the Participants in Three Study Groups

Characteristics	Magnesium 300 mg n=20 (%) Mean ± SD	Magnesium 150 mg n=20 (%) Mean ± SD	Placebo n=20 (%) Mean ± SD
Age (y)	21.3 ±0.9	21.0 ±1.6	20.9±1.9
BMI (kg/m ²)	24.5±2.3	25.2 ±2.4	24.2 ±2.7
Age at menarche (y)	12.2±0.4	12.4 ±0.5	12.2±0.7
Educational level		No. (%)	
Bachelor of science	13 (35)	13 (35)	17 (85)
Higher	7 (65)	7 (65)	3 (15)
Regular exercise	9 (45)	6 (30)	5 (24)
Family history of dysmenorrhea	15 (75)	17 (85)	13 (65)
Interference with daily activities	16 (80)	12 (60)	14 (70)

Note. BMI: Body mass index; SD: Standard deviation.

Table 2. Comparison of the Study Groups With Regard to the Severity of Menstrual Symptoms*

Menstrual Symptoms (SSS:0 -20)	Magnesium 300 mg (n=20) Mean ± SD	Magnesium 150 mg (n=20) Mean ± SD	Placebo (n=20) Mean ± SD	P Value
Cramp				
Baseline	6.5 ±1.8	6.6 ±1.3	6.7 ±2.1	0.91
After intervention	1.7 ±1.5	3.9 ±1.5	6.7 ±2.2	<0.001
Headache				
Baseline	3.9 ±2.3	4.5 ±2.2	4.0 ±2.8	0.70
After intervention	0.5 ±0.8	1.8 ±1.4	3.9 ±2.9	<0.001
Back pain				
Baseline	7.4 ±1.2	6.9 ±1.3	6.8 ±1.1	0.30
After intervention	2.1 ±1.7	4.0 ±1.3	5.8 ±1.9	<0.001
Foot pain				
Baseline	3.8 ±1.8	4.1 ±1.3	4.0 ±1.9	0.80
After intervention	0.2 ±0.6	2.1 ±1.3	3.4 ±2.2	<0.001
Depression				
Baseline	5.9 ±2.1	6.0 ±1.3	5.5 ± (1.5)	0.68
After intervention	1.6 ±0.9	3.0 ±1.2	5.4 ±2.0	<0.001
Irritability				
Baseline	5.8 ±1.6	5.4 ±1.7	6.1 ±1.9	0.51
After intervention	1.4 ±1.3	2.6 ±1.3	5.9 ±1.7	<0.001
General pain				
Baseline	5.0 ±1.4	4.4 ±2.3	5.2 ±2.6	0.51
After intervention	1.0 ±1.2	2.1 ±1.5	4.8 ±2.7	<0.001
Abdominal pain				
Baseline	7.4 ±1.9	7.5 ±2.0	8.0 ± 1.5	0.49
After intervention	2.2 ±1.3	3.7 ±1.6	7.7 ±1.4	<0.001
Total score of symptoms				
Baseline	45.7 ± 6.4	45.6 ± 4.2	46.5 ±6.6	0.85
After intervention	10.9 ±3.7	23.3 ±4.1	43.8 ±8.4	<0.001

Note. *The average scores of two cycles, the total score that can be earned for each symptom in each cycle between 0 and 20, were calculated from the total score of 0-5 over the 4 days (2 days before and 2 days after of menstrual bleeding). SD: Standard deviation.

(MD: -1.3 95% CI: -2.3, -0.3), irritability (MD: -1.2, 95% CI: -2.1, -0.1), abdominal pain (MD: -1.5 95% CI: -2.4, -0.5), and the total score of symptoms (MD: -12.4 95% CI: -16.1, -8.7) compared to magnesium 150 mg. No side effect was reported by any of the participants in the three groups. There was no significant difference regarding the use of analgesics in the three groups.

Discussion

This study was conducted to compare the effect of two doses of magnesium stearate (300 and 150 mg) on the severity of the menstrual syndrome. The results showed that taking both doses of magnesium reduced the severity of menstrual symptoms. However, magnesium 300 mg was more effective than magnesium 150 mg.

Table 3. Mean Differences of Severity of Menstrual Symptoms in Three Groups of Study

Menstrual Symptoms (0-20)*	Comparison of Magnesium 300 mg With Placebo		Comparison of Magnesium 150 mg With Placebo		Comparison of Magnesium 300 With 150 mg	
	MD (95% CI)	P	MD (95% CI)	P	MD (95% CI)	P
Cramp						
Baseline	-0.2 (-1.3, 0.9)	0.67	-0.1 (-1.2, 1.0)	0.85	-0.1 (-1.2, 0.9)	0.80
After intervention	-5.0 (-6.1, -3.9)	<0.001	-2.8 (-3.9, -1.7)	<0.001	-2.2 (-3.3, -1.0)	<0.001
Headache						
Baseline	-0.1 (-1.7, 1.4)	0.84	0.4 (-1.0, 2.0)	0.54	-0.6 (-2.2, 0.9)	0.42
After intervention	-3.5 (-4.7, -2.2)	<0.001	-2.1 (-3.3, -0.8)	0.001	-1.3 (-2.5, -0.1)	0.034
Back pain						
Baseline	0.5 (-0.2, 1.3)	0.15	0.1 (-0.7, 0.8)	0.84	0.5 (-0.3, 1.3)	0.22
After intervention	-3.7 (-4.7, -2.6)	<0.001	-1.8 (-2.8, -0.7)	0.001	-1.9 (-2.9, -0.8)	0.001
Foot pain						
Baseline	-0.3 (-1.3, 0.8)	0.60	0.1 (-1.0, 1.1)	0.92	-0.3 (-1.4, 0.7)	0.54
After intervention	-3.1 (-4.1, -2.1)	<0.001	-1.3 (-2.2, -0.3)	0.009	-1.8 (-2.8, -0.8)	<0.001
Depression						
Baseline	0.3 (-0.7, 1.3)	0.57	0.4 (-0.6, 1.5)	0.39	-0.1 (-1.2, 0.9)	0.77
After intervention	-3.8 (-4.7, -2.8)	<0.001	-2.4 (-3.4, -1.4)	<0.001	-1.3 (-2.3, -0.3)	0.006
Irritability						
Baseline	-0.3 (-1.3, 0.8)	0.61	-0.6 (-1.7, 0.5)	0.25	0.3 (-0.7, 1.4)	0.52
After intervention	-4.5 (-5.4, -3.5)	<0.001	-3.3 (-4.2, -2.3)	<0.001	-1.2 (-2.1, -0.1)	0.013
General pain						
Baseline	-0.1 (-1.5, 1.2)	0.82	-0.7 (-2.1, 0.6)	0.28	0.6 (-0.7, 2.0)	0.38
After intervention	-3.8 (-5.0, -2.5)	<0.001	-2.7 (-3.9, -1.4)	<0.001	-1.1 (-2.3, -0.1)	0.081
Abdominal pain						
Baseline	-0.6 (-1.7, 0.5)	0.27	-0.5 (-1.6, 0.5)	0.37	-0.1 (-1.3, 1.0)	0.82
After intervention	-5.5 (-6.4, -4.5)	<0.001	-4.0 (-4.9, -3.0)	<0.001	-1.5 (-2.4, -0.5)	0.003
Total score of symptoms						
Baseline	-0.9 (-4.6, 2.8)	0.63	-0.9 (-4.6, 2.8)	0.61	0.1 (-3.6, 3.7)	0.97
After intervention	-32.9 (-36.6, -29.2)	<0.001	-20.4 (-24.1, -16.7)	<0.001	-12.4 (-16.1, -8.7)	<0.001

Note. *The average scores of two cycles, the total score that can be earned for each symptom in each cycle between 0 and 20, were calculated from the total score of 0-5 over the 4 days (2 days before and 2 days after of menstrual bleeding). MD (95% CI): Mean difference (95% confidence interval).

Dysmenorrhea and its associated symptoms are the most commonly experienced problems in women with normal ovulatory cycles. The prevalence of primary and secondary dysmenorrhea was 71% and 18% in young females in Iran, respectively (20). Therefore, finding appropriate and effective alternatives for its treatment is important. The most common treatment for relieving symptoms is using non-steroidal, anti-inflammatory drugs whose failure rate is about 20-25%, and side effects can be observed in some cases (21). Therefore, many researchers have been attempting to find other treatments such as complementary and alternative therapies, and numerous studies are being conducted on this subject.

Nutrition is one of the most important factors influencing the quality of life. Nutritional and metabolic conditions may have an important role in the etiology and treatment of menstrual disorders (22). The most lacking nutrients reported in a typical college-student's diet are fiber, vitamin D, vitamin E, calcium, magnesium, potassium, and iron (23,24).

Many nutritional studies have reported lower intake of mineral nutrients such as magnesium among university students in Iran (25). Furthermore, the dietary surveys of people in Europe and the United States revealed that the rate of magnesium intake is lower than the recommendation (26). Low mineral and vitamin intakes have been mentioned in the Iranian students' diet. For example, Saeedian Kia et al indicated that there are lower serum levels of Ca and Mg in women with pre-menstrual syndrome (PMS) compared with their healthy controls (25).

According to the results of the present study, magnesium 150 mg and 300 mg were both effective in reducing the dysmenorrhea symptoms compared to placebo. However, magnesium 300 represented better results when compared to magnesium 150 mg. Although the positive effects of magnesium supplementation on the pain reduction of women with primary dysmenorrhea have been already shown in some clinical trials (26,27), the literature lacks any study comparing the two doses of magnesium.

In their study on 30 young girls with dysmenorrhea, Benassi et al used 4.5 mg oral magnesium pidolate for three days from the 7th day before the onset of menses until the 3rd day of menstruation. The results demonstrated that magnesium could significantly decrease dysmenorrhea on the first day of menstruation and this reduction continued until six cycles (26), which is in line with our findings.

To compare the effect of magnesium with vitamin B6, Ebrahimi et al enrolled 126 young girls and divided them into three groups of magnesium, vitamin B6, and placebo. Their results showed that although magnesium could significantly reduce some symptoms of dysmenorrhea such as craving, water retention, and anxiety, the effect of magnesium in terms of somatic changes and depression was equal to or less than that of vitamin B6 (28). This discrepancy between our results and those of Ebrahimi et al may be because they used magnesium 250 mg and different scales for assessing dysmenorrhea symptoms.

Likewise, Fathizadeh et al reported that a combination of Mg and vitamin B6 was more effective than Mg and placebo for decreasing PMS symptoms (29). In a case-control study, Saeedian Kia et al found that magnesium deficiency was more prevalent in women with PMS (25). In this study, the null hypothesis was rejected because the two doses of magnesium were not the same.

Strengths and Limitations of the Study

To the best of our knowledge, this is the first study to compare the effect of two doses of magnesium on primary dysmenorrhea. The researchers intensively followed the participants for four cycles (two cycles before and two cycles after treatment). However, this study has some limitations. First, the magnesium intake of the participants was not measured in this study. Therefore, the significant effect of the two doses of magnesium on the observed pain relief in this study may be related to magnesium deficiency in the diet of the participants. In addition, this study was conducted only in dormitories in an urban setting, which may not be generalized to other girls from rural populations. Finally, the diagnosis of primary dysmenorrhea was only based on self-report while not using any other diagnostic tests such as sonography.

Conclusions

The results showed that both doses of magnesium stearate (150 and 300 mg) can reduce the severity of menstrual symptoms in students with primary dysmenorrhea with no adverse events. The effect was higher with magnesium stearate 300 mg compared with placebo and magnesium stearate 150 mg. Therefore, the use of magnesium stearate is recommended to reduce dysmenorrhea in young girls. In this study, the researchers did not measure the magnesium intake of the participants. The significant effect of the interventions on the pain relief in this study is probably related to magnesium deficiency in the students' diet, and the results may not be generalized to

women with a sufficient diet. Therefore, further studies with measurement of the nutritional status of participants and on women with no dietary deficiency could provide comprehensive information in this area.

Authors' Contribution

Conceptualization: PA, SNC, and MY. Methodology and data collection: MY, SNC, and FN. Analysis and interpretation of data: MY and PA. Writing, reviewing, and editing the manuscript: PA and MY. All authors read and approved the final manuscript.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This trial was registered in the Iranian Registry for Clinical Trials with the code of IRCT2015080319743N2 and approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Reference No: AJUMS.REC.1394.347).

Availability of Data

The dataset of this study is available upon request from the corresponding author.

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