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Research Paper

The Effect of Magnesium Sulfate on Pain Intensity and Menstrual Blood Loss in Students With Primary Dysmenorrhea: A Randomized Controlled Trial

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ABSTRACT

Background: No evidence exists for the lowest effective dose of magnesium on menstrual pain.

Objective: To determine and compare the effects of two different doses of magnesium on pain intensity and menstrual blood loss in students with primary dysmenorrhea.

Methods: Sixty dysmenorrhea patients were randomly assigned to one of two therapeutic groups and one placebo group (receiving one tablet a day of 300 or 150 mg magnesium sulphate or placebo from the 15th cycle day until no pain existed on the following cycle). Visual analogue scale (VAS) and Hjgham collected data for two cycles before and two cycles after the intervention. The data were analyzed using one-way ANOVA and ANCOVA tests.

Findings: No significant difference was observed between the groups in terms of baseline characteristics. Both intervention groups outperformed the placebo group in terms of pain intensity (adjusted differences of -2.9, 95% confidence intervals of -3.3 to -2.4 and -1.9, -2.4 to -1.5, respectively) and menstrual bleeding (-20.0, -26.0 to -14.0, and -13.0, -19.0 to -7.0, respectively), as well as the secondary outcome, i.e. rest duration and ibuprofen consumption. In terms of pain alleviation and menstrual bleeding, participants in the 300 mg magnesium group outperformed those in the 150 mg magnesium group. No significant difference was observed between intervention groups regarding secondary outcomes.

Conclusion: Both magnesium levels are useful in alleviating pain and reducing menstrual bleeding, although 300 mg of magnesium was more effective.

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1. Introduction

Primary dysmenorrhea is painful menstruation that affects around half of the adult women and 90% of teens [1]. It affects women's quality of life and interferes with their regular tasks [2]. The overproduction of uterine prostaglandins is thought to be the cause of menstrual pain [3, 4]. Although prostaglandin inhibitors can help with menstrual discomfort, long-term use can have some side effects [5]. As a result, most women nowadays seek alternative pain medications that have few or no adverse effects [6].

Evidence shows that various dietary supplements, such as Omega-3 fatty acids, such as fish oil, vitamin B1, vitamin B6, vitamin D, and vitamin E, can help reduce menstrual pain. Magnesium may also aid with menstrual discomfort, but the research is mixed [6]. Several different mechanisms exist through which magnesium can influence dysmenorrhea.It affects serotonin and other neurotransmitters, as well as vascular contraction, neuromuscular function, and cell membrane stability [7]. Some research suggests that magnesium can help reduce premenstrual syndrome symptoms and menstrual discomfort [8-11]. Based on the result of a study, the amount of prostaglandin $F_2\alpha$ in the menstrual blood of women with primary dysmenorrhea who were treated with magnesium reduced compared to before treatment [12]. The researchers demonstrated that lower levels of prostaglandins, a hormone-like molecule, are associated with reduced pain and inflammation [13]. So, magnesium may also influence pain by lowering prostaglandins [14-16]. It may also reduce pain by activating B vitamins, particularly vitamin B6, and influencing muscular relaxation by reducing calcium's effect on muscle contraction [17].

According to our knowledge, this is the first study to examine the effects of 300 and 150 mg magnesium sulfate on menstrual pain severity and blood loss (primary outcome), as well as the number of analgesics used and rest duration due to dysmenorrhea (secondary outcome).

2. Materials and Methods

This double-blind, randomized, placebo-controlled trial with three parallel arms (two intervention groups and one placebo group) was conducted on dysmenorrheal college students living in dorms at Ahvaz Jundishapur University of Medical Sciences, from April to June 2016 (Ahvaz, Iran).

Participants were required to have regular menstrual periods, suffer from moderate or severe primary dysmenorrhea (pain scores of 5 to 9 on the visual analogue scale in previous cycles), and be single. Students with chronic conditions (such as epilepsy, gastrointestinal, cardiovascular, or renal diseases), as well as those using oral contraceptives or vitamin supplements, were eliminated.

We used data from a previous similar study (Mean±SD: 6.8±1.4 of primary dysmenorrhea) to compute sample size, α=0.05, β=0.10, and a dropout probability of 15%, a sample size of 20 was determined for each group [6].

The degree of monthly pain and the amount of menstrual bleeding was assessed using a visual analogue scale (VAS) and a Higham chart, respectively. VAS is a validated 10-cm scale with a 0 on the left end (no pain) and a 10 on the right end (the greatest imagined suffering) [18]. A table was created to record the number of analgesics (ibuprofen) used and the amount of time (hours) spent in discomfort during the two days before and three days after menstruation began.

The Higham chart's validity has been demonstrated in numerous studies and is widely recognized as one of the most effective and reliable indicators of menstrual bleeding. It is a table used to calculate menstrual blood loss. Blood-stained pads are graded as light, moderate, or severe, as well as the excretion of blood clots. A lightly soiled pad receives a score of 1, a highly stained pad a score of 5, and a blood-saturated pad a score of 20. Score 1 is assigned to each little clot and score 5 is assigned to each large clot. Participants make a mark on the chart each time they change the pad. At the end of the menstruation, each sign was multiplied by its score, and the figures were calculated. At the end of the cycle, each sign was multiplied by its score, the resulting numbers were added together, and the overall score was calculated [19, 20].

We distributed the package to each participant in the order decided at the enrollment visit. They were also given 20 ibuprofen tablets (400 mg) and the second diary. The questionnaire had the same pre-intervention entries as well as one extra item concerning the intervention medication history. We asked the participants to take the intervention pills daily, one pill per day, from day 15 of their cycle until the day with no menstrual pain the next cycle, and we kept a record of their pill intake. We then instructed them to take the ibuprofen pills as needed and to complete the remainder of the diary in the same manner as before the intervention for two consecutive under-intervention cycles (both the pills given as intervention and the ibuprofen).

Each tablet contains 300 mg or 150 mg of magnesium sulfate, as well as lactose and microcrystalline cellulose as excipients. Except for magnesium, all of the components in the placebo were the same. The tablets were all the same color, shape, and size. They were created in the industrial pharmacy laboratory of Ahvaz Jundishapur University of Medical Sciences Faculty of Pharmacy under the direct supervision of a pharmacist from our research team.

In this study, the dormitories were randomly selected, while the subjects were recruited using convenience sampling. The researcher visited the students' rooms in the designated dormitories to choose the subjects. She introduced the study's objectives to the students in each room and requested those who were willing to participate and said yes to the question "Are you suffering from painful menstruation?" To fill out a questionnaire designed to determine who was qualified. A total of 99 suitable students were included in the study after signing a written informed consent form. Due to the danger of pill pooling, we did not recruit more than one person from each dormitory room. We gave the subjects 20 ibuprofen (400 mg) tablets and a diary to fill up during the next two menstrual cycles. We told them to only take the medications for menstrual pain and not to take any other pain medicines. Furthermore, they documented every drug consumed in the diary. A list of potential adverse effects was also given in the diary.

Sixty out of 99 cooperative students completed the pre-intervention diaries completely and accurately and were willing to continue participating in the study. They were randomly assigned to one of three groups with a one-to-one allocation ratio to receive two different doses of magnesium or placebo tablets (Figure 1).

The allocation sequence was determined using automated randomized software and block randomization with block sizes ranging from 6 to 9. The individual also made sequentially numbered identical packets containing the 40 intervention pills based on the allocation order (for use across two cycles). The skey outcomes of this study were pain intensity and blood loss. The number of analgesics (Ibuprofen) consumed during two menstrual cycles and the period of rest due to dysmenorrhea was then measured as secondary outcomes. As secondary outcomes, the intensity of premenstrual symptoms was also recorded, and the results are published in the other publication.

The menstrual pain intensity score was calculated twice for each cycle, on the two days (2 days before and 3 days after the start of menstruation) with the highest pain intensity; and on the five days overall. The reported rest due to pain over five days was added to establish the duration of rest at each cycle. The average of the outcomes was used as the baseline value during the two pre-intervention cycles, and the average of those recorded was used as the under-intervention value during the two post-intervention cycles.

Statistical analysis

The baseline values of the groups were compared using one-way ANOVA. The ANCOVA test was performed to compare the groups in terms of under-intervention pain severity, quantity, and menstrual bleeding adjusted for baseline values after correcting for model assumptions. Sidak was utilized to perform multiple group comparisons. All analyses were performed with SPSS software, version 16.0, and a statistically significant difference was defined as $P<0.05$.

3. Results

Nobody was excluded from the analysis of the 60 students who were randomly assigned to groups. None of the subjects in the groups reported any adverse effects. In terms of baseline characteristics, no discernible difference was observed between the groups. Their Mean±SD age was 21.0±1.5, and their Body Mass Index (BMI) was 24.6±2.5. Regular exercise was mentioned by one-third (33.3%) of participants. Three-quarters (75%) had a family history of dysmenorrhea, and around three-quarters (70%) said their menstrual pain interfered with their activities (Table 1).

The characteristics of the groups did not significantly differ from one another. Participants in both intervention groups (300 and 150 mg magnesium) outperformed the placebo group in terms of both primary outcomes, namely menstrual pain intensity (adjusted difference: -2.8 [95% confidence interval: -3.4 to -2.2], and [-2.4 to -1.2], respectively); as well as menstrual blood loss (adjusted difference: -20.- [95% confidence interval:-26.0 to -14.0], and -13.0 [-19.0 to -7.0]), as well as in the secondary outcome, i.e. the rest duration (-0.7 [-0.9 to -0.5] and -0.6 [-0.9 to -0.5], respectively]), and the different number of ibuprofen taken (mean difference [95%CI], -1.7 [-2.4 to -1.1] and -1.8 [-2.4 to -1.1], respectively). In terms of pain reduction, participants in the 300 mg magnesium group did better than the 150 mg magnesium group (-0.9 [-1.4 to -0.5]) and blood loss during menstruation (-7.0 [-13.0 to -1.05]) (Table 2). No significant difference was observed between intervention groups regarding secondary outcomes, resting time (-0.0 [-0.2

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Table 1. Baseline characteristics of the subjects by the study groups (n=20)

Characteristics		Mean±SD/No. (%)			
		Magnesium 300 mg	Magnesium 150 mg	Placebo	P
Age (y)		21.3±0.9	21.0±1.6	20.9±1.9	0.67
BMI (kg/m^2)		24.5±2.3	25.2±2.4	24.2±2.7	0.47
Educational level	Bachelor of science	13(35)	13(35)	17(85)	0.27
	Higher	7(65)	7(65)	3(15)	
Regular exercise		9(45)	6(30)	5(24)	0.39
Age at Menarche (y)	Mean±SD	12.2±0.4	12.4±0.5	12.2±0.7	0.51
	Min-max	12-13	12-13	11-14	
Family history of dysmenorrhea		15(75)	17(85)	13(65)	0.35
Interference with daily activities		16(80)	12(60)	14(70)	0.39
Duration of menstrual bleeding (day)	6, <6	12(60)	8(40)	10(50)	0.27
	>6	8(40)	12(60)	10(50)	
	Min-max	4-7	5-7	5-7	
Amount of menstrual bleeding (CC)	Less than 50	8(40)	2(10)	7(35)	0.51
	50-59	2(10)	9(45)	5(25)	
	60-69	6(30)	4(20)	7(35)	
	70 and more than 70	4(20)	5(25)	1(5)	
	Min-max	37-83.5	36-74	40.5-72.5	

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P for qualitative variables was calculated using chi-square test and in quantitative variables using one-way ANOVA.

SD: Standard deviation; BMI: Body mass index

to 0.2]), and no significant difference was observed in the number of ibuprofen taken (0. [-0.6 to 0.6]) (Table 3).

4. Discussion

The severity of primary dysmenorrhea and menstrual blood loss were examined, and the effects of two different dosages of magnesium sulphate were compared for the first time. The current study showed that both therapies can reduce the severity of primary dysmenorrhea, monthly blood loss, rest length owing to menstrual pain, and the number of analgesics used. The participants reported no side effects. The effect of 300 mg of magnesium sulfate in reducing pain and the amount of menstrual bleeding was greater than 150 mg of magnesium sulfate and placebo.

Menstrual pain is the most prevalent symptom among women with regular periods [21], and the most common treatment for it is nonsteroidal anti-inflammatory drugs, which have a failure rate of about 25% and can produce negative effects in some circumstances [22]; As a result, many researchers are trying to uncover other treatments, such as complementary and alternative therapies, and several studies are being conducted in this area. The genesis and treatment of menstruation problems may be influenced by nutritional and metabolic factors. Dietary treatments are numerous, but more research is needed [23].

Magnesium supplementation has been shown in clinical trials to lessen menstrual discomfort, which is consistent with the results of the current study [8, 11]. In a study conducted by Benassi et al., every woman re-

Table 2. Comparison of the magnesium groups and placebo group with regard to the primary outcomes of study

Primary Outcomes		Mean±SD (n=20 in Each Group)			Comparison					
					Three Groups	Magnesium 300 mg With Placebo		Magnesium 150 mg With Placebo		Magnesium 300 mg With 150 mg	
		Magnesium		Placebo	P	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
		300 mg	150 mg								
Pain intensity (VAS, 0-10)*	Baseline†	6.3±0.6	6.2±0.6	6.3±1.2	0.863						
	Under-intervention‡	2.8±0.7	3.7±0.5	5.7±0.7	<0.001	-3.0 (-2.3 to -3.3)	<0.001	-2.0 (-2.4 to -1.5)	<0.001	-1.0 (-1.4 to -0.5)	<0.001
Amount of menstrual bleeding (Higham chart, CC)	Baseline	58.2±13.2	59.1±2.7	55.1±9.9	0.510						
	Under-intervention	34.4±7.0	41.4±9.2	54.4±11.8	<0.001	-20.0 (-26.0 to -14.0)	<0.001	-13.0 (-19.0 to -7.0)	<0.001	-7.0 (-13.1 to -1.0)	0.023
Duration of menstrual bleeding (day)	Baseline	6.0 ±0.7	6.3±0.6	6.1±0.6	0.278						
	Under-intervention	4.9±0.5	5.6±1.3	6.0±0.8	0.002	-1.1 (-1.7 to -0.5)	<0.001	-0.4 (-1.0 to -0.1)	0.130	-0.6 (-1.2 to -0.1)	0.031

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* Each person reported average of pain intensity during 2 days before and 3 days after starting menstruation during two cycles before and two cycles under intervention, in each cycle, mean pain intensity during 5 days was considered as pain intensity at each cycle and mean of pain intensity during the two pre-intervention cycle considered as baseline pain intensity and mean intensity during two months after starting the intervention was considered as under-intervention pain intensity.

† One-way ANOVA was used for the baseline comparisons.

‡ ANCOVA test was used for the under-intervention pain intensity, amount and duration of menstrual bleeding comparisons adjusted for the baseline values using Sidak for the multiple comparisons between the groups.

Abbreviations: CI: confidence interval; VAS: Visual Analogue Scale

ceived 4.5 mg of oral magnesium pidolate three times a day from the seventh day before menstruation until the third day of menstruation [8]. Dysmenorrhea was reduced in magnesium-treated cycles, with a significant difference compared to the control group. Fontana et al. studied the therapeutic benefits of magnesium on menstrual pain in another investigation. According to the researchers, magnesium had a therapeutic impact on both back pain and lower abdomen discomfort on the second and third days of the cycle [11]. No other study exists that can be directly compared with the current study's findings. Therefore, in the following, other related studies will be discussed.

It has been reported that plasma levels of magnesium in the premenstrual period are lower in people suffering from premenstrual syndrome [24]. This finding can confirm the result of our study. According to Mohammad-Alizadeh et al. (2013), combining 300 mg magnesium stearate with 600 mg calcium carbonate is more beneficial than calcium carbonate alone in lowering menstruation discomfort [25]. According to one study, increasing dietary magnesium intake in women with primary dysmenorrhea can reduce the degree of menstrual discomfort [26]. However, another study found that a daily intake of 500 mg of magnesium did not affect pain reduction when compared to the placebo and vitamin B6 groups [17].

Table 3. Comparison of the magnesium groups and placebo group with regard to the secondary outcomes of study

Secondary Outcomes		Mean±SD (n=20 in Each Group)			Comparison							
					Three Groups	Magnesium 300 mg With Placebo		Magnesium 150 mg With Placebo		Magnesium 300 mg With 150 mg	
		Magnesium		Placebo	P	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
		300 mg	150 mg								
Rest length due to dysmenorrhea at each cycle (h)	Baseline†	0.8±1.1	0.7±0.5	0.9±0.6	0.486						
	Under-intervention‡	0.2±0.2	0.3±0.2	1.0±0.5	<0.001	-0.7 (-0.9 to -0.5)	<0.001	-0.6 (-0.9 to -0.4)	<0.001	-0.0 (-0.2 to 0.2)	0.890
Number of Ibuprofen taken at each cycle[	Baseline	3.3±2.2	2.7±1.5	3.1±1.7	0.652						
	Under-intervention	0.6±1.1	0.6±0.9	2.4±1.1	<0.001	-1.7 (-2.4 to -1.1)	<0.001	-1.8 (-2.4 to -1.1)	<0.001	-0.0 (-0.6 to 0.6)	0.939

† One-way ANOVA was used for the baseline comparisons.

‡ ANCOVA test was used for the under-intervention comparisons adjusted for the baseline values using Sidak for the multiple comparisons between the groups.

[Mean number of Ibuprofen 400 mg taken at each cycle due to dysmenorrhea at the two pre-intervention cycle (baseline) and at two months after starting the intervention (under-intervention).

CI: Confidence interval

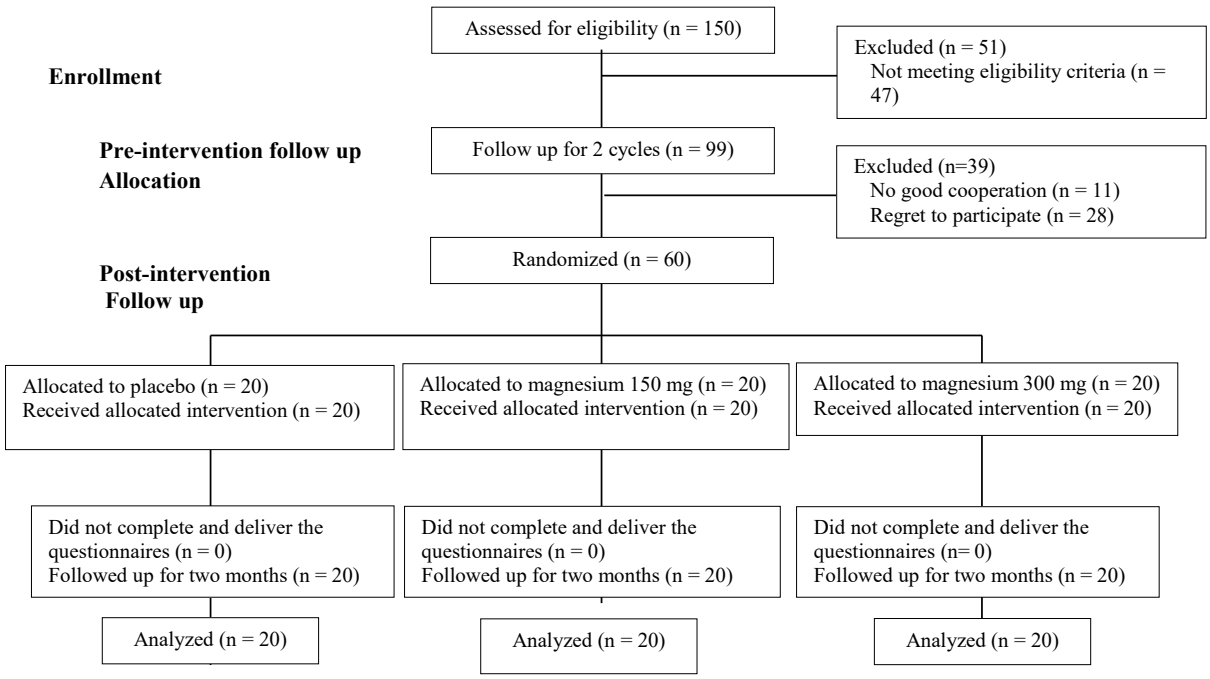

Figure 1. Flow diagram of study

Some reports indicate that college students' dietary status is inadequate. Fiber, vitamin D, vitamin E, calcium, magnesium, potassium, and iron are the most commonly reported nutrients to be deficient in the normal college student's diet [27]. Dietary deficiencies in minerals and vitamins have been reported among Iranian students [28].

5. Conclusion

It has been demonstrated that taking 150 to 300 mg of magnesium per day from the 15th day of the menstrual cycle until the onset of dysmenorrhea of the following cycle significantly reduced menstrual pain severity and flow. Compared to 150 mg of magnesium and a placebo, the effect of 300 mg of magnesium was stronger. Nevertheless, for widespread application of the findings, further study on the efficacy and safety of the results in different contexts with a bigger sample size is recommended.

Limitations of the study

The requirement to take the medications daily can be annoying and lead to a lack of follow-up. We did not measure the participants' magnesium intake in this study. The strong benefits of the therapies on pain alleviation found in this study could be attributed to magnesium insufficiency in the dormitory students, and the findings may not apply to other girls with good diets.

Another limitation of this study is the short period of the investigation and the absence of follow-up following supplementation withdrawal. Based on the outcomes of this study, we cannot estimate the long-term influence of these supplements on menstrual discomfort.

Ethical Considerations

Compliance with ethical guidelines

This trial is registered in the Iranian registry system with a code of IRCT2015080319743N2 and approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences with a code of ethics AJUMS.REC.1394.347 dated October 4, 2015.

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Authors' contributions

Conceptualization and supervision: Parvin Abedi, Masoumeh Yaralizadeh and Salimeh Nezamivand chegini; Methodology, investigation, writing-original draft, and writing-review and editing: All authors; Data collection: Azam Honarmandpour and Masoumeh Yaralizadeh; Data analysis: Saeed Ghanbari and Salimeh Nezamivand chegini; Funding acquisition and resources: Parvin Abedi, Masoumeh Yaralizadeh and Salimeh Nezamivand chegini.

Conflict of interest

The authors declared no conflict of interest.

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