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# The Positive Effects of Zinc Supplements on the Improvement of Primary Dysmenorrhea and Premenstrual Symptoms: A Double-blind, Randomized, Controlled Trial

Gita Sangestani (PhD)[1,2], Mahnaz Khatiban (PhD)[3]*, Roberto Marci (MD)[4], Isabella Piva (MD)5

[1] Mother & Child Care Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[2] PhD Candidate in Midwifery, Department of Morphology, Surgery and Experimental Medicine ,University of Ferrara, Ferrara, Italy
[3] Associate Professor, Mother & Child Care Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[4] Associate Professor, Department of Morphology, Surgery and Experimental Medicine, Section of Obstetrics and Gynecology, University of Ferrara, Ferrara, Italy
[5] Specialist, Department of Morphology, Surgery and Experimental Medicine, Section of Obstetrics and Gynecology, University of Ferrara, Ferrara, Italy

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**ABSTRACT**

***Background & aim:*** Primary dysmenorrhea can be relieved via some medical and non-medical approaches. In this regard, the probable therapeutic role of zinc supplements has been recently emphasized. The present study was conducted to determine the positive effects of zinc supplements on relieving primary dysmenorrhea and premenstrual symptoms.

***Methods:*** The present double-blind, randomized, controlled trial was conducted on 66 students at Hamadan University of Medical Sciences. Students with the experience of primary dysmenorrhea in at least the last three menstrual cycles (ranging between 21 and 35 days) were included in the study. The participants were randomly divided into experimental and control groups. The experimental group received oral zinc supplements (50 mg) twice daily for four days before the onset of menstruation and the control group received placebo. For data analysis, t-test, Mann-Whitney U test, ANOVA and Wilcoxon test were performed (95% CI).

***Results:*** The intervention led to a decrease in the severity of dysmenorrhea and menstrual bleeding in the experimental group, unlike the control group. The experimental group experienced a lower frequency of some premenstrual symptoms such as headache, vertigo, muscular pain, disability in performing daily activities and general weakness; however, these changes were insignificant in the control group. Lower rates of medicine use for improving dysmenorrhea and its side-effects were reported in the experimental group, compared to the control group. Moreover, the experimental group had a lower tendency to use thermotherapy.

***Conclusion:*** The intake of zinc supplements at therapeutic doses could effectively reduce the severity of dysmenorrhea, improve menstrual bleeding and premenstrual symptoms and prevent other premenstrual symptoms.

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## Introduction

Menstrual cramps during the first days of menstruation are quite common in women and may be accompanied by severe nagging pain and limited disability in daily activities. High levels of prostaglandins and multiple sexual hormones have been reported in these women, which lead to complications such as headache, gastrointestinal disorders and urinary tract problems (1, 2). These contractions may also lead to reduced uterine blood supply and aggravate dysmenorrhea and premenstrual symptoms (3).

Primary dysmenorrhea can be relieved via some medical approaches including the inhibition of the production or release of prostaglandins, use of anti-inflammatory drugs for reducing inflammatory pain and even contraceptives for preventing ovulation, menstruation and cramping (4-6). Besides, some non-medical strategies have been suggested for the treatment

* *Corresponding author:* Mahnaz Khatiban, Mother & Child Care Research Center, Hamadan University of Medical Sciences, Hamadan, Iran. Email: Mahnaz.khatiban@gmail.com

of dysmenorrhea such as thermotherapy, regular physical exercise, psychotherapeutic consultation, surgical interruption of pelvic nerve pathways and even holistic and alternative therapies (7-10).

In recent years, the advantageous effects of zinc supplements for improving the symptoms of dysmenorrhea have been reported. Earlier studies have indicated an association between plasma zinc level and uterine contractibility. Therefore, these supplements have been recommended for women with low zinc levels (11). Moreover, it has been suggested that plasma zinc concentration fluctuates during the menstrual cycle in a phase-related fashion in women with normal menstruation. However, the pattern of this fluctuation might alter during primary dysmenorrhea (12, 13).

Physiological changes in the uterine fluid and blood, caused by zinc supplements, and the association between zinc intake and uterine contractility have been recently more investigated, particularly in animal models (14). In a previous study, zinc sulfate had the same positive effects as ginger on dysmenorrhea (15). However, the efficiency of zinc supplements in dysmenorrhea and other premenstrual symptoms has not been clearly determined in human clinical settings. Therefore, we performed this double-blinded, randomized, controlled trial to determine the positive effects of zinc supplements on relieving primary dysmenorrhea and premenstrual symptoms.

## Materials and Methods

The present double-blinded, randomized, controlled trial was conducted on 66 students at Hamadan University of Medical Sciences. Students with the experience of primary dysmenorrhea in at least the last three menstrual cycles (ranging from 21 to 35 days) were included in the study. The exclusion criteria were as follows: 1) a prior history of zinc supplement intake; 2) sensitivity to supplements; 3) failure to attend the counseling sessions; and 4) withdrawal from the study.

The sample size was estimated at 32 subjects per group, according to the following formula with the effect size of 0.7 (95% CI and power of 0.80):

$$n = 2(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2(\frac{1}{ES})^2$$

However, the researchers invited 34 students to be included in the experimental group. All participants were asked to attend some meetings. During the first consultation session, the study objectives and procedures were explained. The subjects were asked to use only mefenamic acid capsules for medical treatment or local thermotherapy as a non-medical approach for relieving dysmenorrhea during the research period (one menstrual cycle before and one after the intervention). Then, written informed consents were obtained and baseline data were collected, using a self-administered questionnaire.

The second consultation session was held to verify subjects' compliance with the guidelines and routes of drug use in the next cycle. The third session was held after the second menstrual cycle for assessing the subjects' compliance with instructions on the use of supplements (or placebo) and completing the questionnaires after the intervention.

Before the second session, the participants were randomly divided into experimental and control groups. The experimental group received oral zinc supplements (50 mg) twice per day for a period of four days before the onset of menstruation. The control group received placebo medicines with the same shape, color and duration of use as zinc supplements. In order to prevent any physical or mental complications, the subjects were asked to contact the researchers to benefit from their expert advice. There was no attrition in either of the groups.

For the assessment of symptoms and pain severity, the participants were familiarized with a 10-point visual analog scale (VAS), ranging from 0 (no pain) to 10 (the worst imaginable pain). The results were presented as mean±standard deviation (SD) for quantitative variables; for categorical variables, frequency distribution was applied.

The categorical variables were compared, using Chi-square or Fisher's exact test. The quantitative variables were compared, using t-test, Mann-Whitney U test, ANOVA and Wilcoxon test. For statistical analysis, SPSS version 16 was applied (SPSS Inc., Chicago, IL, USA). P-value ≤ 0.05 was considered statistically significant. This study was registered in IRCT (code: IRCT201106186827N1).

## Results

As shown in Table 1, the experimental and control groups were similar in terms of mean age, menarche, educational course, occupational status, regular sports and even drinking tea and coffee (P>0.05). None of the participants in the two groups had a prior history of smoking or alcohol use.

Regarding the improvement of dysmenorrhea and the associated manifestations (Table 2), the use of zinc supplements led to a decrease in the severity of dysmenorrhea (P<0.05) and menstru-al bleeding in the experimental group (P<0.05), unlike the control group. However, the intake of

**Table 1.** Comparison of demographic characteristics between the two groups

| Demographic characteristics | Experimental group (n = 34) | Control group (n = 32) | P-value |
|---|---|---|---|
| **Age (year)** | 21.5±2.5 | 21.7/2.2 | 0.75 |
| **Educational course** | | | 0.36 |
| Nursing | 2 (5.9) | 2 (6.2) | |
| Midwifery | 13 (38.2) | 9 (28.1) | |
| Medicine | 2 (5.9) | 2 (6.2) | |
| Health | 9 (26.5) | 4 (12.5) | |
| Dentistry | 3 (8.8) | 3 (9.4) | |
| Others | 5 (14.7) | 12 (37.5) | |
| **Occupational status** | | | 0.99 |
| Employed | 33 (97.0) | 31 (97.0) | |
| Unemployed | 1 (3.0) | 1 (3.0) | |
| **Age of menstruation (yr.)** | 13.2±1.0 | 13.6±1.3 | 0.23 |
| **Regular sports** | | | 0.92 |
| Yes | 5 (14.7) | 5 (15.6) | |
| No | 29 (85.3) | 27 (84.4) | |
| **Drinking tea** | | | 0.40 |
| Yes | 33 (97.1) | 32 (100) | |
| No | 1 (2.9) | 0 (0) | |
| **Drinking coffee** | | | 0.40 |
| Yes | 2 (5.9) | 4 (12.5) | |
| No | 32 (94.1) | 28 (87.5) | |

**Table 2.** Comparison of dysmenorrhea and its manifestations between the two groups before and after the intervention

| Variables | Before Mean ± SD | After Mean ± SD | P-value |
|---|---|---|---|
| **The duration of menstruation (day)** | | | |
| Control group (n=32) | 5.62 ± 1.3 | 5.59 ± 1.2 | 0.21 |
| Experimental group (n=34) | 6.15 ± 1.3 | 6.06 ± 1.2 | 0.57 |
| P-value | 0.11 | 0.12 | |
| **The interval between menstruations (day)** | | | |
| Control group (n=32) | 27.66 ± 2.8 | 27.56 ± 2.9 | 0.69 |
| Experimental group (n=34) | 28.26 ± 2.6 | 28.32 ± 2.5 | 0.49 |
| P-value | 0.36 | 0.36 | |
| **The severity of bleeding (cc)** | | | |
| Control group (n=32) | 81.2 ± 71.2 | 78.9 ± 60.5 | 0.96 |
| Experimental group (n=34) | 78.2 ± 54.1 | 64.3 ± 32.5 | 0.1* |
| P-value | 0.80 | 0.02* | |
| **The severity of dysmenorrhea (VAS=0-100)** | | | |
| Control group (n=32) | 56.25 ± 15.0 | 54.53 ± 18.1 | 0.44 |
| Experimental group (n=34) | 64.85 ± 16.2 | 41.47 ± 22.3 | 0.000*** |
| P-value | 0.03* | 0.01* | |

* P <0.05

this supplement did not affect the duration of menstruation or the interval between menstrual cycles.

With respect to premenstrual symptoms (Table 3), the experimental group experienced lower rates of some complications such as vertigo (P<0.05), muscular pain (P<0.01), disability in performing daily activities (P<0.001) and general weakness (P<0.01); however, these changes were insignificant in the control group (P>0.05).

A reduction was observed in the rate of physician visit in the experimental group from five before the intervention (14.7%) to zero after the intervention (0.0%). In the control group, the rate of physician visit increased from two (6.2%) to three (9.4%). However, the difference between the two groups was not statistically significant (P=0.07).

**Table 3.** Comparison of premenstrual signs and symptoms between the two groups before and after the intervention

| Variables | Before the intervention | After the intervention | P-value |
|---|---|---|---|
| **Headache** | | | |
| Experimental group | 11 (32.4 %) | 6 (17.6 %) | 0.12 |
| Control group | 6 (18.8 %) | 7 (21.9 %) | 0.11 |
| P-value | 0.19 | 0.68 | |
| **Vertigo** | | | |
| Experimental group | 9 (26.5 %) | 2 (5.90 %) | 0.63 |
| Control group | 8 (25.0 %) | 10 (31.2 %) | 0.04 * |
| P-value | 0.89 | 0.01 * | |
| **Nausea** | | | |
| Experimental group | 21 (61.8 %) | 18 (52.9 %) | 0.55 |
| Control group | 21 (65.6 %) | 20 (62.5 %) | 0.57 |
| P-value | 0.51 | 0.95 | |
| **Vomiting** | | | |
| Experimental group | 6 (17.6 %) | 2 (5.9 %) | 0.50 |
| Control group | 2 (6.2 %) | 4 (12.5 %) | 0.35 |
| P-value | 0.16 | 0.35 | |
| **Constipation** | | | |
| Experimental group | 8 (23.5 %) | 4 (11.8 %) | 0.13 |
| Control group | 3 (9.4 %) | 3 (9.4) | 1.000 |
| P-value | 0.12 | 0.75 | |
| **Diarrhea** | | | |
| Experimental group | 9 (26.5 %) | 11 (32.4 %) | 0.85 |
| Control group | 9 (28.1 %) | 6 (18.8 %) | 1.000 |
| P-value | 0.35 | 0.35 | |
| **Urinary urgency** | | | |
| Experimental group | 18 (52.9) | 19 (55.9) | 1.000 |
| Control group | 11 (34.4) | 11 (34.4) | 0.10 |
| P-value | 0.13 | 0.08 | |
| **Muscular pain** | | | |
| Experimental group | 27 (79.4) | 20 (57.6) | 0.003 ** |
| Control group | 23 (71.9) | 22 (68.8) | 0.31 |
| P-value | 0.06 | 0.43 | |
| **Disability in performing daily activities** | | | |
| Experimental group | 27 (79.4) | 10 (29.4) | 0.000 *** |
| Control group | 29 (90.6) | 26 (81.2) | 0.25 |
| P-value | 0.20 | 0.000 *** | |
| **Weakness** | | | |
| Experimental group | 33 (97.1) | 26 (76.5) | 0.02 * |
| Control group | 26 (81.2) | 21 (65.5) | 0.06 |
| P-value | 0.04 | 0.33 | |

* P <0.05, ** P <0.01, *** P< 0.001

**Table 4.** Comparison of two groups based on the use of mefenamic acid and local thermotherapy before and after the intervention

| Variables | Before the intervention | | | After the intervention | | | Wilcoxon test |
|---|---|---|---|---|---|---|---|
| **Mefenamic acid (Number)** | Yes n (%) | Mean | SD | Yes n (%) | Mean | SD | |
| Experimental group | 31 (91.2) | 2.2 | 1.4 | 20 (58.8) | 1.5 | 1.8 | P= .04* |
| Control group | 27 (84.4) | 2.1 | 1.3 | 28 (87.5) | 2.1 | 1.3 | P= .92 |
| Mann-Whitney U test | P=.80 | | | P=.02* | | | |
| **Thermotherapy (hours)** | | | | | | | McNemar's test |
| Experimental group | 16 (47.1) | 1.50 | .80 | 8 (23.5) | 1.3 | .90 | P= .09 |
| Control group | 16 (50.0) | 1.44 | .63 | 17 (53.1) | 1.41 | 1.1 | P=1.00 |
| $X^2$ | P=.19 | | | P=.01* | | | |

* P< 0.05

The subjects, who received zinc supplements, reported lower rates of medicine use for improving the severity of dysmenorrhea and premenstrual symptoms (P<0.05). They also had a lower tendency to use thermotherapy (P<0.05) (Table 4).

## Discussion

The present intervention, which included the use of zinc supplements, reduced the severity of dysmenorrhea and menstrual bleeding in the experimental group, unlike the control group. Furthermore, the use of these supplements could effectively prevent the presentation of some premenstrual symptoms such as headache, vertigo, muscular pain, disability in performing daily activities and general weakness. Moreover, the use of medical and non-medical regimens in those receiving zinc supplements considerably decreased.

Considering the central role of prostaglandins and potent leukotrienes in causing menstrual cramps, zinc supplements are speculated to inhibit the metabolism of these mediators (16, 17). Some case-series have shown that the daily intake of zinc (1-3 30 mg) four days prior to the onset of menstruation could prevent menstrual cramping (1).

Considering the fact that the activities of prostaglandins in inducing menstrual cramps are mainly mediated by COX-2 precursors, it seems that these precursors contribute to the efficacy of zinc supplements. Furthermore, it is now hypothesized that zinc supplements can limit dysmenorrhea-related inflammation, given the antioxidant and anti-inflammatory effects of these supplements in the uterus; therefore, micro-vascular circulation of the uterus can be improved by zinc consumption (18).

An important concern is that the positive effects of zinc supplements are entirely dose-dependent. According to previous research, consuming 31 mg of zinc per day could effectively prevent the symptoms of premenstrual tension, while the use of 15 mg of zinc (or less) did not seem effective. In our observation, participants consumed 50 mg zinc supplements twice a day, which seemed to be potentially effective in relieving menstrual bleeding and dysmenorrhea. In a similar experiment, use of 30 mg of zinc once to three times a day for a period of 1-4 days immediately before menstruation was recommended for preventing dysmenorrhea (1).

Some guidelines have recommended different doses of zinc for various age groups in order to maximize its efficacy. The Recommended Dietary Allowance (RDA) in the United States for zinc is 9 mg per day for females, aged 14-18 years, and 8 mg per day for females, aged 19 or higher. However, those who use zinc supplements for therapeutic reasons need higher doses. In fact, the tolerable upper intake level for zinc is 34 mg per day for females, aged 14-18 years, and 40 mg per day for women, aged 19 or higher (19).

Recent studies have globally emphasized on zinc deficiency and the essentiality of this element for humans. Zinc deficiency has been reported to affect nearly two billion people in developing countries. This deficiency could lead to some serious abnormalities including growth retardation, hypogonadism, rough skin, impaired immunity, neuro-sensory

disorders and cognitive impairment, especially in developing communities (20, 21). In fact, the high rates of severe dysmenorrhea can be explained by the increasing trend of zinc deficiency. Therefore, enhancing zinc nutrition and promoting its intake at therapeutic dosages are strongly recommended to control zinc deficiency, particularly in young women.

## Conclusion

The consumption of zinc supplements at therapeutic doses can effectively reduce the severity of dysmenorrhea, improve menstrual bleeding and prevent some menstrual complications. However, further longitudinal research with a larger sample size is required.

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### Conflict of Interest

There were no conflicts of interest.

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## References

1. Eby GA. Zinc treatment prevents dysmenorrhea. Medical Hypotheses. 2007; 69(2):297–301.
2. Kelly RW, Abel MH. Copper and zinc inhibit the metabolism of prostaglandin by the human uterus. Biology of Reproduction. 1983; 28(4):883–889.
3. Altunyurt S, Göl M, Altunyurt S, Sezer O, Demir N. Primary dysmenorrhea and uterine blood flow: a color Doppler study. The Journal of Reproductive Medicine. 2005; 50(4):251-255.
4. Livshits A, Seidman DS. Role of Non-Steroidal Anti-Inflammatory Drugs in Gynecology. Pharmaceuticals. 2010; 3(7): 2082-2089.
5. Robinson JC, Plichta S, Weisman CS, Nathanson CA, Ensminger M. Dysmenorrhea and use of oral contraceptives in adolescent women attending a family planning clinic. American Journal of Obstetrics and Gynecology. 1992; 166(2):578-583.
6. Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertility and Sterility. 2008; 90(5):1583-1588.
7. Hong YR. Effects of heat therapy using a far infrared rays heating element for dysmenorrhea in high school girls. Journal of Korean Academy of Nursing. 2011; 41(1):141-148.
8. Mahvash N, Eidy A, Mehdi K, Zahra MT, Mani M, Shahla H. The Effect of Physical Activity on Primary Dysmenorrhea of Female University Students. World Applied Sciences Journal. 2012; 17(10):1246-1252.
9. Latthe PM, Proctor ML, Farquhar CM, Johnson N, Khan KS. Surgical interruption of pelvic nerve pathways in dysmenorrhea: a systematic review of effectiveness. Acta Obstetricia et Gynecologica Scandinavica. 2007; 86(1):4-15.
10. Lloyd KB, Hornsby LB. Complementary and alternative medications for women's health issues. Nutrition in Clinical Practice. 2009; 24(5):589-608.
11. Durá-Travé T, Puig-Abuli M, Monreal I, Villa-Elizaga I. Relation between maternal plasmatic zinc levels and uterine contractility. Gynecologic and Obstetric Investigation. 1984; 17(5):247-251.
12. Deuster PA, Dolev E, Bernier LL, Trostmann UH. Magnesium and zinc status during the menstrual cycle. American Journal of Obstetric and Gynecology. 1987; 157(4Pt1):964-968.
13. Hähn N, Paschen K, Haller J. Serum levels of copper, iron, magnesium, calcium and zinc in women with a normal menstrual cycle, under treatment with oral hormonal contraceptives and in pregnancy. Archiv Für Gynäkologie. 1972; 213(2):176-186.
14. Alavi-Shoushtari SM, AsriRezaie S, Pak M, Alizadeh S, Abedizadeh R, Khaki A. Copper and zinc concentrations in the uterine fluid and blood serum during the bovine estrous cycle. Veterinary Research Forum. 2012; 3(3):199–203.
15. Kashefi F, Khajehei M, Tabatabaeichehr M, Alavinia M, Asili J. Comparison of the effect of ginger and zinc sulfate on primary dysmenorrhea: a placebo-controlled randomized trial. Pain Management Nursing. 2014; 15(4):826-833.

16. Harel Z. Dysmenorrhea in adolescents and young adults: etiology and management. Journal of Pediatric and Adolescent Gynecology. 2006; 19(6):363-371.
17. Hess SY, Lönnerdal B, Hotz C, Rivera JA, Brown KH. Recent advances in knowledge of zinc nutrition and human health. Food & Nutrition Bulletin. 2009; 30(1Supplement):5S-11S.
18. Prasad AS. Clinical, immunological, anti-inflammatory and antioxidant roles of zinc. Experimental gerontology. 2008; 43(5):370-377.
19. Pinkerton JV. Pharmacological therapy for abnormal uterine bleeding. Menopause. 2011; 18(4):459-467.
20. Prasad AS. Discovery of human zinc deficiency: 50 years later. Journal of Trace Elements in Medicine and Biology. 2012; 26(2):66-69.
21. Maret W, Sandstead HH. Zinc requirements and the risks and benefits of zinc supplementation. Journal of Trace Elements in Medicine and Biology. 2006; 20(1):3-18.