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The Efficacy of Zinc Administration in the Treatment of Primary Dysmenorrhea

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ABSTRACT

Objectives: Dysmenorrhea is a common complaint in women. Primary dysmenorrhea is defined as painful menstruation in the absence of pelvic disease and is caused by uterine contractions caused by prostaglandins released from the endometrium. Conventional treatments include nonsteroidal anti-inflammatory drugs and oral contraceptives. We sought to evaluate the efficacy of zinc supplementation in the treatment of primary dysmenorrhea. ***Methods***: Two-hundred participants with primary dysmenorrhea were randomized into one of two groups. The intervention group received zinc and mefenamic acid, and the control group received mefenamic acid and a placebo drug. After three months of treatment, changes in the incidence of dysmenorrhea and the degree of pain were measured in both groups. ***Results:*** The mean pain score before administration of zinc and mefenamic acid in the intervention group was 5.3±1.8 and after treatment was 1.2±1.9 ($p < 0.001$). In the control group, the mean pain score before administration of mefenamic acid and placebo was 5.8±2.1 and after treatment was 2.9±2.6 ($p < 0.001$). The difference in pain levels before and after treatment in the intervention group was 4.1±2.8, and in the control group was 2.9±1.7 ($p > 0.050$). We also found that 64% of case group and 33% of the control group did not experience dysmenorrhea after treatment ($p < 0.001$). ***Conclusions:*** The use of a zinc supplement in combination with mefenamic acid was superior in reducing primary dysmenorrhea compared to mefenamic acid alone.

Dysmenorrhea is a common gynecological complaint in both its primary and secondary forms. In the primary form, no definite underlying reason has been identified using patient history, clinical examination or laboratory tests. Primary dysmenorrhea occurs without pelvic pathology while the secondary form is associated with an underlying disorder.[1-3]

Primary dysmenorrhea is defined as painful uterine cramping in the lower abdomen just before or during menstruation.[4] It usually starts before the age of 20 years old and almost always six to 12 months after the first menstruation. If the pain begins three years after menarche or if dysmenorrhea is associated with anovulatory cycles, we have to think about secondary causes. Between 50–80% of women experience some form of dysmenorrhea during their reproductive period.[5] Ten to 20% have symptoms severe enough to prevent them from presenting at work.[1,2] Studies show that in some women dysmenorrhea disappears after the birth of the first child but in many women, it may continue through later life. About 30–40% of women aged between 30 and 40 years suffer from dysmenorrhea.[6]

Increased prostaglandins (PGs) and cyclooxygenases (COX) lead to hypercontractility and increase uterine muscle tone, causing uterine ischemia and subsequently lower abdominal cramps. Inhibition of PG synthase can improve the severity of menstrual pain in women.[7] In primary dysmenorrhea, accumulation of PGF2α and PGE2 is high compared to those women who do not experience dysmenorrhea.

According to treatment guidelines, first-line therapy for primary dysmenorrhea should be the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), which should be used for at least three consecutive months. Among the drugs of this family, mefenamic acid is more effective than others because it reduces the production of PGs by COX enzymes and decreases the activity of PGs in the uterus through inhibition of its receptors.[8] NSAIDs provide medical benefits, although it is shown that they have adverse effects on the gastrointestinal tract, liver, kidney and cardiovascular system. Additionally,

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they overlap with various drugs including warfarin and aspirin.[9,10] Oral contraceptive pills (OCP) are used as a second-line treatment. OCP prevent ovulation and improve dysmenorrhea by reducing the amount of endometrial tissue available for PG and leukotrienes.[11]

Zinc is a trace element essential for human health. It has roles in cellular differentiation and production and is vital in the synthesis of proteins and nucleic acids. It is also involved in many biochemical reactions as a micro element.[12–15] Zinc also plays an important role in the function of RNA enzyme and DNA polymerases, and to over three hundred metalloenzymes. Furthermore, zinc plays a role in the optimal performance of the immune system. The effects of zinc deficiency include growth restriction, iron deficiency anemia, organomegaly, suboptimal repair of wounds, weight loss, impaired immune response, and increased susceptibility to infection.[16–20] Zinc has been demonstrated in the improvement of gastrointestinal infections and diarrhea, and in wound healing by activating enzymes involved in collagen synthesis.[21–24] A recent study examined the role of zinc and micronutrients on pregnancy outcome and found a beneficial effect on infants in reducing low birth weight (LBW) and small for gestational age (SGA).[22]

Some studies have shown that zinc may prevent or improve primary dysmenorrhea. There are several hypotheses on how zinc does this, for example, by promoting microcirculation and preventing ischemia, and inactivating oxygen free radicals. Zinc can also downregulate and reduce inflammatory cytokines and regulate the levels of COX-1 and COX-2 as well as inhibit the metabolism of PG, similar to NSAIDs.[25–31]

Previous studies have shown the role of zinc in reducing PG metabolism, as well as premenstrual pain, cramping and common menstrual disorders, especially dysmenorrhea, which limits womens' activities. Therefore, reducing the symptoms and risk of dysmenorrhea is of high importance. The aim of our study was to evaluate the effectiveness of zinc supplementation in the treatment of primary dysmenorrhea.

METHODS

This randomized, double-blind clinical trial included university students with primary dysmenorrhea and was conducted over three menstrual cycles. Female students were recruited from the dormitory of Zahedan University of Medical Sciences. Females who had similar diets in the three months of the study, regular menstrual cycles (28±7 days), and with a history of primary dysmenorrhea for at least one day per month were included in the study. Any students with a history of chronic and systemic diseases such as gynecological disease and significant medical history or active disease were excluded. A total of 200 students were selected, with 100 students in each group.

Following a complete description of the study methods, the students gave their written informed consent. Using a computer-based random digit generation, they were placed in one of two study groups (intervention or control group). All study participants had a pelvic ultrasound, and none had any obvious pelvic pathology indicated.

The intervention group received zinc sulfate capsules 220 mg once daily and mefenamic acid capsules 250 mg three times daily. The control group received a placebo drug and the same concentration and dosage of mefenamic acid. A nurse registered patients and gave them a number. The drug was delivered to the patients based on the assigned number. Both the patients and doctor were not aware of the received drug.

The pain severity measurement tool used was the pain ruler, a standard ruler used in physiotherapy. It consisted of a horizontal line scaled from zero to 10: zero showed absolute analgesia and 10 indicated intolerable pain. The scaling was explained to the patients before the study.[31]

For each patient, the rate of pain was measured before prescribing the drugs. Drugs were taken by the patients in each group, three-days before (estimated based on the women's cycle) and three-days after menstruation.

After three months, the changes in pain and the incidence of dysmenorrhea were measured, and were compared within and between the groups. The rate of pain was measured for each of the patients in the two groups before and after the administration of the drug, and finally, the mean pain intensity were compared between the groups.

Results were analyzed using the statistical *t*-test and SPSS Statistics (SPSS Inc., Chicago, US) version 18a. If needed, other parametric or non-parametric statistical tests were used, accordingly.

Table 1: Mean pain before and after intervention using paired *t*-test.

Group	Before administration	After administration	Pain reduction	*p*-value
Intervention	5.3±1.8	1.2±1.9	4.1±2.8	<0.001
Control	5.8±2.1	2.9±2.6	2.9±1.7	<0.001

Data presented as mean±standard deviation.

Table 2: Incidence of dysmenorrhea after treatment in both groups using chi-square test.

Dysmenorrhea	Intervention	Control	Total	*p*-value
Yes	36 (35)	67 (65)	103 (51.5)	<0.001
No	64 (66)	33 (34)	97 (48.5)	
Total	100 (50)	100 (50)	200 (100)	

Data presented as n(%).

RESULTS

A total of 200 students were administered a combination of mefenamic acid plus zinc or a placebo drug. The mean age of participants was 21.4±2.2 years (range = 18–26 years). The mean age of participants in the intervention group was 21.6±2.1 years, and 21.3±2.0 years in the control group. There was no statistically significant difference in the mean age between the two groups (p = 0.791). The mean pain intensity score at the start of the study in the intervention group was 5.3±1.8, and after the treatment, it decreased to 1.2±1.9, a decrease of 4.1±2.8 units (p<0.001) [Table 1]. The mean pain intensity in the control group before administration of mefenamic acid plus placebo was 5.8±2.1 and after treatment decreased to 2.9±2.6, a decrease of 2.9±1.7 units (p < 0.001). There was no statistically significant difference in pain scores before and after the intervention between the two groups. (p = 0.346).

The incidence of dysmenorrhea after treatment was evaluated in both groups. The 64 patients in the intervention group (mefenamic acid + zinc) and 33 patients in the control group (mefenamic acid + placebo) did not develop to dysmenorrhea. Statistically significant difference was observed between the two groups (p < 0.001) [Table 2].

DISCUSSION

Our study found that the pain caused by primary dysmenorrhea was significantly reduced in both the intervention and control group. However, the rate of pain reduction was greater in the intervention group but was not statistically significant when compared to the control group. We also evaluated the incidence of dysmenorrhea. The number of patients who suffered from dysmenorrhea in the case group was almost half of those in the control group.

Our findings are in line with the findings of a study conducted in 2012 on adolescent girls, which showed the consumption of zinc in primary dysmenorrhea leads to a decrease in the intensity and duration of pain.[30] In 2014, in a similar study done by Kashefi et al,[32] showed that dysmenorrhea was significantly reduced in the group taking zinc compared to the control group.

According to Kelly and Abel,[33] zinc inhibits the metabolism of PGs. They also stated that 10^{-5} moles per liter of zinc in the uterus can inhibit PG metabolism and prevent uterine cramps.[33]

A study conducted in 1982 by Goei et al,[34] showed that administration of 31 mg zinc compared to a lower dose of 15 mg per day caused no premenstrual tension. However, it has also been demonstrated that prevention of uterine cramps is more effective than treatment.[26]

Prasad and his colleagues[35] studied the therapeutic effects of the zinc on the common cold and showed that patients who used zinc did not experience pain before or during menstruation.

In 2007, Eby suggested that zinc may increase the blood supply to the uterus through the microcirculation system.[29] He also concluded that administration of 31 mg zinc three times a day, one to four days before menstruation had the best possible outcome for pain relief and prevention of uterine cramps.[29]

However, there are few studies regarding the effect of zinc on dysmenorrhea, but all have showed

a positive effect of zinc on the reduction of pain intensity. Thus, we can say that the combination of mefenamic acid plus zinc is effective in the treatment of primary dysmenorrhea and causes more pain relief and more decrease in its incidence.

CONCLUSION

We found that mefenamic acid alone, plus zinc supplementation can cause a reduction in the pain severity of primary dysmenorrhea, but this reduction in the pain severity is more obvious with the inclusion of zinc. Based on the results of this study, we recommended that women with primary dysmenorrhea take zinc supplementation along with mefenamic acid.

Disclosure
The authors reported no conflict of interests. No funding was received for this study.

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