Original Article

Comparison of efficacy and safety of zinc gluconate versus placebo for treatment of Primary Dysmenorrhea

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[1,4] Experimentation/Study conduction
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Abstract

Introduction: Dysmenorrhea is a common gynecological complaint in women of reproductive age. Primary dysmenorrhea is defined as painful menstruation in the absence of any pelvic pathology and occurs in response to increased prostaglandin release from the ischemic endometrium. Conventional treatments include NSAIDs and oral contraceptive pills. Zinc is an essential micronutrient with anti-inflammatory properties. We conducted this study to evaluate the efficacy and safety of zinc supplementation in the treatment of primary dysmenorrhea in our target population as it presents as a very common gynaecological issue in young adolescent females.

Materials and Methods: 100 participants with primary dysmenorrhea were enrolled in the study from the outpatient department via non-probability consecutive sampling. They were randomized into two groups. The intervention group (Group A) received zinc gluconate 50mg once daily and the control group (Group B) received a placebo drug once daily, for 5 days before and 2 days after the onset of menstruation. After three and six months of treatment severity of primary dysmenorrhea was assessed and compared in both groups using a visual analogue scale for pain, along with the side effect profile.

Results: The treatment with Zinc gluconate reduced the mean pain score in females with primary dysmenorrhea after 3 months with a further reduction after 6 months of treatment ($P<0.001$) as compared to placebo. Very few (4% after 3 months & 6% after 6 months) participants experienced the side effects of Zinc supplementation.

Conclusion: Zinc gluconate 50mg daily for 5 days before and 2 days after the onset of menstruation can effectively treat primary dysmenorrhea. The drug has very few side effects at this dose and duration of use.

Keywords: Primary dysmenorrhea, zinc gluconate, pain severity, visual analogue scale.

Introduction

A women's reproductive health is reflected by a regular menstrual cycle. Irregular menstrual cycles, heavy menstrual bleeding, and pain during menstruation are common gynaecological problems experienced by many women.[1] Dysmenorrhea is cramping pelvic pain during menstruation.[2] When no cause is detectable for painful menstruation, the condition is classified as primary dysmenorrhea.[3,4] Secondary dysmenorrhea is defined as painful menses due to some underlying pelvic disease. The estimated prevalence of primary dysmenorrhea in adolescent girls is 16-93% and 2-29% experience severe pain.[5] It usually starts before 20 years of age and many patients also have a family history.[1] It not only has a negative effect on activities of daily living like inability to attend school, and absence from the job but also overburdens the economy.[6-10] Psychological symptoms like depressed mood and anxiety also coexist with dysmenorrhea[7,11,12]

The etiology of primary dysmenorrhea is not very clear. Many research studies have shown that during a menstrual cycle there is a rise in serum concentration of prostaglandins F 2α and leukotrienes, produced mainly from the endometrial lining during the secretory phase. There is hypercontractility and decreased perfusion of uterine musculature. This ischemia leads to cramps and pelvic discomfort.[8,13]

Traditional options to relieve dysmenorrhea include dietary modifications, herbs, vitamins, warm drinks, application of heating pads, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and oral contraceptive pills with variable degrees of success. Most studies compared pain scores using a visual analogue scale (VAS) with scores of 0 signifying no pain and higher scores showing the increasing intensity of pain.[1,3,14,15,16] NSAIDS still effective and commonly used, but have many adverse effects on the gastrointestinal and nervous systems.[17]

Zinc is an intracellular micronutrient vital for the reproductive system. In polycystic ovarian disease with insulin resistance and lipid profile abnormalities, zinc supplements provide symptomatic relief. This metal has anti-oxidant and anti-inflammatory actions. It reduces the production of prostaglandins, cytokines and relieves spasms.[18,19]

Dysmenorrhea is a common and distressing condition. There are limited numbers of human studies on the therapeutic benefits of zinc in relieving menstrual pain. The rationale of the present study was to evaluate the efficacy of zinc supplementation in relieving primary dysmenorrhea. We also studied the adverse effects, to establish drug tolerability in women with dysmenorrhea.

Materials and Methods

A randomized controlled study was performed comparing the efficacy of zinc gluconate and placebo in pain management of primary dysmenorrhea over six consecutive menstrual cycles. Ethical approval was taken. The duration of the study was 02 years from 1st January 2018 to 31st December 2019. The sampling technique was non-probability consecutive sampling.

All the participants were unmarried and educated at least till grade 10 with a history of primary dysmenorrhea and regular menstrual cycles. They were suffering from dysmenorrhea for the last 4-6 months, for at least 3 days of the menstrual cycle, and $\geq$4 scores on the Pain visual analogue scale (PVAS). We excluded women with a history of chronic systemic disease, known pelvic pathology, previous pelvic surgery, or taking any pain medication or oral contraceptive pills from the study. All study participants had a pelvic ultrasound and none had any organic pelvic pathology. All patients gave written informed consent before inclusion into the study and were randomized by lottery method to receive either zinc gluconate (nutrifactor) 50 mg daily (Group A) or a placebo of one tablet daily (Group B).

A pain visual analogue scale of 0-10 was used to assess the severity of pain in two groups.0 indicated complete analgesia and 10 indicated intolerable pain. The scale was explained to the patients before the study in the OPD by the attending registrar, who ensured their clear understanding of PVAS. The rate of pain was measured at the start of the study before prescribing the drugs. Drugs were taken by the patients in both groups five days before the estimated date of menstruation and two days after the onset of menstruation (for 7 days in total). After three and six months severity of pain was assessed in both groups and compared.

Data was entered and analyzed using SPSS version 19. Mean and standard deviation were calculated for quantitative variables and frequencies were calculated for quantitative variables. Comparison in both groups was done by independent student t-test and chi-square test for quantitative and qualitative variables respectively. The p-value of less than 0.05 was taken as significant.

Results

A total of 100 patients who fulfilled the inclusion criteria were finally analyzed. The mean age of the study population was 21.04±1.94, being 21.30±1.86 in the zinc group and 20.78±2.01 in the placebo group.
Analysis of the treatment effect was done by a mean reduction in pain scores between groups after treatment. The mean pain score was not significantly different in the two groups at the start of the study (p=0.348). There was a remarkable reduction in pain severity in the Zinc group 3 months after treatment. The pain improved further after 6 months of treatment. Analysis of the reduction in pain score is presented in Table 1.

Table 1: Comparison of pain score in zinc and placebo group

Pain visual analogue score (PVAS)	*Zinc group mean±SD*	*Placebo group mean±SD*	*P-value*
Before treatment	7.00±0.947	7.18±0.962	0.348
After 3 months of treatment	4.84±0.710	6.24±0.938	0.001
After 6 months of treatment	2.88±0.824	5.50±1.015	0.001

The drug was easily tolerated as only 2 patients experienced mild gastrointestinal symptoms after 3 months and 4 patients after 6 months in the Zinc group. The results are shown in Figures 1 and 2.

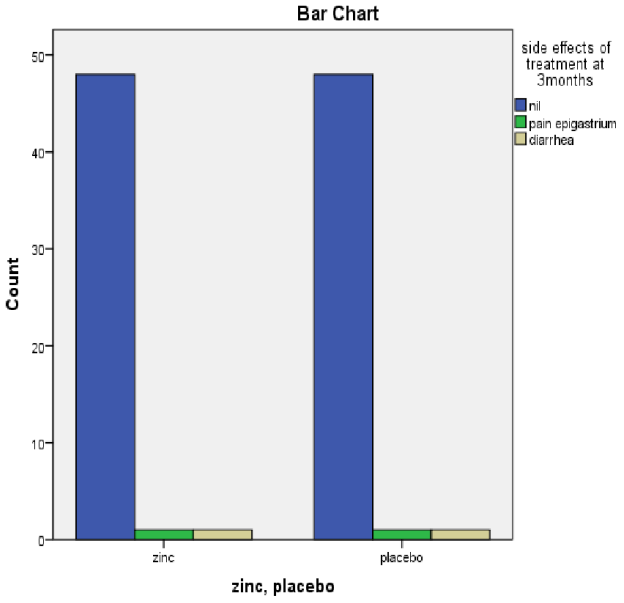

Figure 1: Comparison of side effects of Zinc gluconate and placebo at 3 months

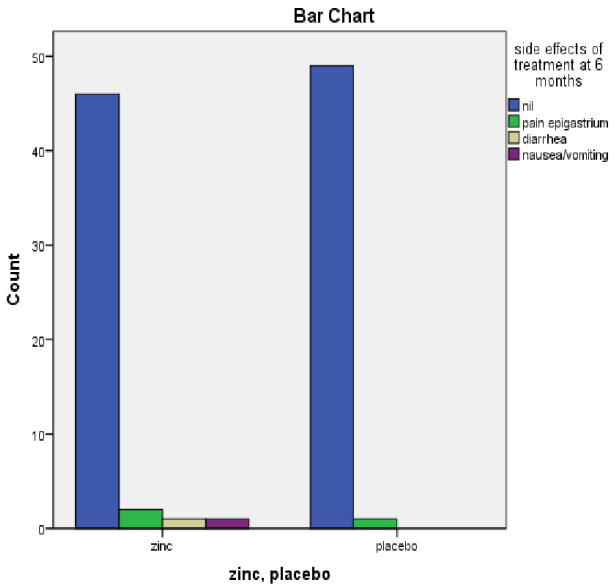

Figure 2: Comparison of side effects of Zinc gluconate and placebo at 6 months

Discussion

The results of our study showed a significant improvement in primary dysmenorrhea in the girls who used Zinc supplements 50mg/day as compared to a placebo group. The Zinc group experienced less pain after three months of use and a further reduction in pain severity was observed after six months. We also evaluated the adverse effects of zinc gluconate and found it to be a highly tolerable drug. Eby G in a case series compared the 15mg/day and 31mg/day zinc supplementation one to four days before menstruation and found that 31mg/day Zinc supplementation was effective in reducing pain and premenstrual tension syndrome. ($p<0.001$) so he suggested 30mg 1-3 times daily usage of Zinc for primary dysmenorrhea and PMS.[20]
Sangestani G [21] also used a higher dose of Zinc supplement (50mg twice daily) for four days before menstruation and observed that it reduced the use of mefenamic acid (p=0.04 in the Zinc group and p=0.92 in the control group) and thermotherapy (p=0.09 in Zinc versus p=1 in the control group) to cope with primary dysmenorrhea. In her study at Hamadan university, she also noticed a significant improvement in muscular pain (p=0.003), weakness (p=0.02), and ability to perform daily activities (p=0.000) after the use of Zinc. Our study used 50mg Zinc gluconate preparation, but improvement in dysmenorrhea was significant. It may be because of the longer duration of

use for 7 days around menstruation (5days before & 2 days after menses).

Researchers have used different doses and duration of Zinc supplements and even combinations with NSAIDS to treat this debilitating condition. Teimoori B[22] compared the efficacy of Zinc sulphate (220mg) and mefenamic acid (250mg) TDS with a placebo and mefenamic acid combination. After 3 months of use, he calculated that more patients (66% versus 34%, P<0.001) in Zinc and the mefenamic acid group experienced no menstrual pain. This finding indirectly supported the therapeutic benefit of zinc in controlling primary dysmenorrhea. In our study, even a low dose of Zinc 50mg/day without NSAIDs was effective in decreasing pain severity. Sundari LR [23] used even a lower dose of Zinc 30mg capsules in 16 medical students who had primary dysmenorrhea, only for four days before menstruation in one cycle only and showed a significant improvement not only in pain severity but also a significant reduction in PGF2 alpha levels. Farah AM [24] observed a gradual improvement in pain severity after 30mg ZnSO4 for 3 consecutive cycles. There is still no consensus on the dose and duration of treatment. There is still a need for further studies to compare the effect of different doses and duration of use of Zinc for pain relief in primary dysmenorrhea.

In another placebo-controlled trial of 137 teenage high school girls (between 15-18 years) zinc sulphate 220mg three times daily supplementation and ginger capsules 250mg three times daily for seven days (4 days before and 3 days after the onset of menstruation) given for 2 cycles significantly reduced the primary dysmenorrhea.[25]

The reduction in the pain severity was not significant during the first month of treatment in the study by Zekavat et al[26] but was significant in subsequent months so it suggests that the duration of drug intake is also important to get a therapeutic benefit. We also observed that although Zinc treatment was effective after 3 months but effectiveness increased even more after 6 months of use.

Side effects: There is a risk of vomiting with zinc supplementation[27,28] but in our study only one Patient (2%) had vomiting. This may be because of the small dose &short duration of use (for 7 days only). In our study 2% & 4%, of patients had epigastric burning after 3 months & 6 months of use, a finding close to the finding of Kasheif etal[25] 1.9% in the first and second months of use. Only one patient (2%) had diarrhoea after 6 months of use, in contrast to 3.8% in Kasheif'sstudy.[25] Overall, the drug was well tolerated by the patients and no patient discontinued it because of side effects. The effect of dysmenorrhea on quality of life is very distressing for women so its management is very important.[30]

Limitations

The limitations of our study were that it was not a double-blind study. We have not studied the beneficial effects of zinc on other premenstrual symptoms.

Further studies are required to compare the therapeutic benefit of different doses and duration of treatment of Zinc on the severity of primary dysmenorrhea. Pre and post-treatment PGF2α levels should also be studied.

Conclusion

50mg zinc gluconate for 5 days before and 2 days after the onset of menstruation is an effective therapy for primary dysmenorrhea with very few side effects.

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