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Oral Administration of Zinc Capsule for 4 Days before Menstrual Period Decreases Prostaglandin (PGF2α) Level and Pain Intensity in Women with Primary Dysmenorrhea

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Abstract: ***Background: Dysmenorrhea is the most common gynecologic complaint among women, where 40-70% of women in their reproductive years had this complaint. It is caused by prostaglandin efflux that occurs due to endometrial desquamation. Analgesia treatment is often used to cure dysmenorrhea to date. Zinc reduces cyclooxygenase enzyme activity, which in turn decreases prostaglandin synthesis that can prevent pain. This study is about the effectiveness of zinc to prevent pain in patients with primary dysmenorrhea. Method: The pre-test and post-test control group design study was carried out on thirty-two female college students who had a history of primary dysmenorrhea as samples. Subjects were divided into two groups randomly with sixteen women in each group. Control group were given placebo capsules, and the experimental group were given 30 mg zinc capsules for four consecutive days before the period to start. Prostaglandin (PGF2α) levels and pain intensity were measured before and after treatment, and was analyzed using independent t-test and chi square-test. Results: The average PGF2α level decrease for experimental group was 743.44 pg/ml ± 454.43 and it was 514.49 pg/ml ±226.78 for the control group. The median of pain intensity for the treatment group was grade I, and the control group was grade II in the verbal rating scale. From post-test results comparison, the experimental group shows a significant decrease of PGF2α level and pain intensity (p<0.05). Conclusion: Administration of 30 mg zinc capsules for 4 days before the start of period decreases PGF2α level and pain intensity in women with primary dysmenorrhea.***

Keywords: Zinc, Dysmenorrhea, PGF2α and Pain Intensity

1. Introduction

Menstrual pain or dysmenorrhea is commonly occurred among women, and it can cause inconvenience in daily physical activity. It is correlated to absenteeism at school and workplace, therefore it may have some influence to productivity. Forty to seventy percent of women in reproductive age experiencing menstrual pain, and 10 percent of those women claim that dysmenorrhea interferes daily activities.[1] Approximately 70-90 percent of menstrual pain cases occur in adolescence. The menstrual pain will affect their academic and social activities.[2,3,4] In United States, menstrual pain was reported as the main cause of repeated absenteeism female students at school.[5] In Indonesia, the incidence of mild, moderate and severe dysmenorrhea to be 18%, 62% and 20% respectively.[6]

Menstrual pain divided into two such as: primary and secondary dysmenorrhea. Primary dysmenorrhea is defined as recurrent cramping pain that occurs during menstruation without pelvic pathology. Secondary dysmenorrhea is pain during menstruation is based on pathological abnormalities in the pelvis, ex: endometriosis.[7]Primary dysmenorrhea usually started at adolescence age, a time when ovulation cycle began regularly. Major cause of primary dysmenorrhea is ischemia uterine. Ischemia uterine will produce biochemist mediator, prostaglandins.[8]It will reduce or inhibit blood supply temporarily to uterus, which causes oxygen deficiency causing myometrial contractions and pain.[8, 9]

It has been found that 30-70% of young women cured their menstrual pain with analgesic drugs (NSAIDs).[9] Alternatively, researchers conducted various studies to find a replacement therapy or complementary therapies that are safer than NSAIDs such as: herbal therapy, supplements, acupuncture therapy, behavior therapy, and aromatherapy.[10,11]Zinc inhibit prostaglandin metabolism in human endometrium. [12] Zinc is one of nutrients that can increase conversions of fatty acids essential as anti-inflammatory to prostaglandin.[13] Zinc was studied as a treatment for menstrual pain due to its effect in reducing prostaglandin synthesis through its ability as an endogenous anti-inflammatory and antioxidant catalyst that improving micro-circulation of the blood vessels. In that research, women who consumed 31 mg zinc per day were not complaining menstrual pain, compared with those who consumed 15 mg zinc per day.[14]

Previous study have shown the role of zinc in reducing pain when women got dysmenorrhea. The aim of this study was to evaluate the effectiveness of zinc supplementation in preventing pain on primary dysmenorrhea.

2. Method

Design of this study was true experimental with pre-test and post-test control group design.[15] The research was conducted in School of Medicine Udayana University Denpasar take place during March to June 2016. The inclusion criteria of the population study: The medical students suffering from primary dysmenorrhea, age 17-21 years, experiencing moderate to severe menstrual pain over the past 3 months, never been married and giving birth, having regular menstrual cycles at the last 3 months (28-30 days). Students with history of other complaints in womb and pelvis, pain in other body parts, being treated with pain

medications, had undergone surgery on the abdomen and pelvis , use contraceptives and other medicines and have history of gastritis were excluded. Drop out criteria as follows: can't complete follow the oral administration of 30 mg zinc per day for 4 + 1 days before menstruation, period started before 3rd day of zinc treatment and period started after 5th day zinc treatment. The sample size is determined by the Pocock formula. [16] Total 32 students were selected, with 16 students in each group. They were placed into two groups (experimental and control group) with simple random sampling. All of them had joined the study in voluntarily based and given informed consent.

The experimental group received zinc picolinate capsules 30 mg once daily. The control group received a placebo drug. Patients came approximately 4 days before period started, and nurse registered patients and delivered the drugs to the patients. The blood was collected twice, before and after treatment. Before treatment, it means at first day when period has started without zinc and placebo. After treatment, it means at first day when period has started after taking zinc or placebo. Level of PGF2α in blood and pain intensity were measured at that time. PGF2α were measured with ELISA standard kit and pain intensity were measured with verbal rating scale. Verbal rating scale was categorized as 0 = No pain, 1 = mild pain, were reported to the patient when asked without change behavior, 2 = moderate pain, reported by the patient when asked characterized by spontaneous pain behavior or reported, 3 = severe pain associated with voice response, pull the hand or arm, moaning or crying face, and the result were compared between the groups. Data of prostaglandin analyzed using independent t-test, and data of pain intensity analyzed using Mann-Whitney test. This study had approved by Ethical Committee of the Medical School of Udayana University.

3. Results and Discussion

Analysis of the treatment effect was tested by a mean reduction in PGF2α level between groups after treatment Analysis of the significance test are presented in Table 1.

Table 1: The mean decrease in PGF 2α level between group after treatment

Group	N	Mean of Decrease PGF2α level (pg/ml)	SD	*T*	P
Placebo	16	79,23	277,13	3,32	0,002
Zinc	16	392,12	255,59		

This means that the average reduction in prostaglandin levels in both group is significantly difference ($p < 0.05$).Figure 1 indicates the different levels of prostaglandins before and after treatment in both groups

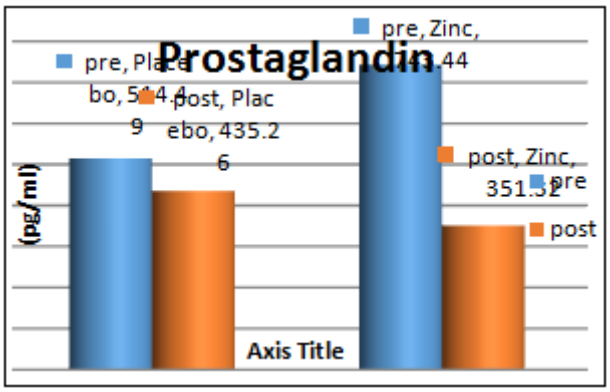

Figure 1: Prostaglandin Levels Before and After Treatment.

Zinc as one of micronutrient may inhibit the PGF2α metabolism where zinc concentration 1x10-5 mol /l in physiological range concentrations in uterus tissues can inhibit prostaglandin metabolism.[12] Other research suggests that mechanism of zinc in uterine smooth muscle similar to the mechanism of zinc in the treatment of angina pectoris by increasing circulation in the capillaries.[14] Zinc also regulates cyclooxygenase-2 (Cox-2), an enzyme that involved in pain and inflammation, zinc reduce the activity of Cox-2, therefore it cause synthesis of prostaglandin were decreasing.[17] In this study found the difference in reduction on PGF2α level in both groups significantly. This is supported by research from Akinola and Odutuga that conducted on rats, found that zinc-deficient mice have high level of prostaglandin metabolite in plasma, compared with mice that did not deficient on zinc.[18] Increased levels of prostaglandins have an important role as a cause of menstrual pain. Dawood found the myometrium spasms triggered by substances in menstrual blood, natural lipid-like that became known as prostaglandins, that increased levels in menstrual pain and found in muscle of the uterus.[7,8] Zinc has effect of reducing of prostaglandins synthesis and as anti-inflammatory and antioxidant that improve micro-circulation in blood vessels.[14,19,20] Zinc is also one of nutrients that increase the conversions of essential fatty acids as anti-inflammatory to prostaglandin. [13] Analysis of the treatment effect is tested based on median intensity of menstrual pain between groups after treatment. The results of the analysis of significance with the Mann-Whitney test are presented in Table 2.

Tabel 2: Median intensity of -group Menstrual Pain After Treatment

Group	n	Median	Quartile (Q1 – Q3)		P
Placebo	16	2	1,25	2	0,017
Zinc	16	1	1	2	

This means that median intensity of menstrual pain in both groups differ significantly ($p < 0.05$).

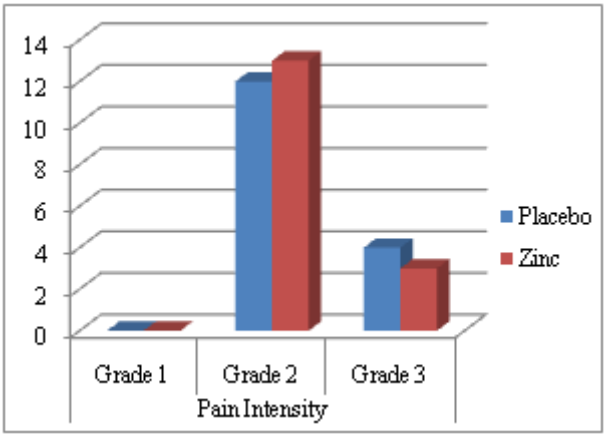

Figure 2: Graph Frequency Menstrual Pain before Treatment in Both group

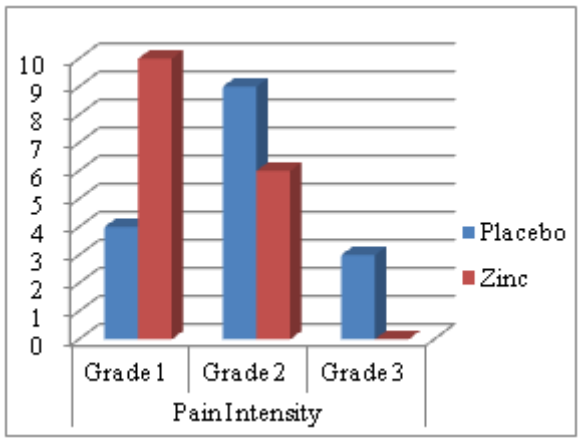

Figure 3: Graph Frequency Menstrual Pain After Treatment in Both group

In this study, a significant reduction in pain intensity in zinc group (Figure 2 and 3). Reduction in pain intensity is supported by research about zinc treatment on primary dysmenorrhea.[14,19,20,21]These study found that women who consumed zinc before and during period were not complaining menstrual pain, compared to those who were not consumed. Giving zinc also reduce levels of Cox-2, an enzyme involved in pain, inflammation and uterine cancer precursors. [17] Supported also by Sieppmann et al (2005), that the primary and secondary menstrual pain will worsen in zinc deficiency. [22,23]

The correlation between the levels of prostaglandins with pain intensity was also analyzed quantitatively by Spearman correlation. The analyze obtained $r = 0.483$ and $p = 0.005$. This means there is a significant positive relationship between levels of prostaglandins and menstrual pain intensity ($p < 0.05$).

There is a correlation between the complaints of menstrual pain and prostaglandin production. Found these substance in menstrual blood, stimulates uterine smooth muscle contraction. The substance containing PGF2α and PGE2, where the ratio of PGF / PGE higher in endometrium and menstrual blood of women with primary dysmenorrhea.[24]PGF2α and PGE2 have vascular opposite effect, leading to vasoconstriction and vasodilation.[25] PGF2α stimulates uterine contractions during all phases of the menstrual cycle, whereas PGE2 inhibits myometrial contractility during menstruation and stimulating time proliferative phase and the luteal phase.

4. Conclusion

Supplementation of zinc during the four days before menstruation can reduce levels of PGF2α and pain intensity in primary dysmenorrhea, and there is a correlation between PGF2α level and menstrual pain in primary dysmenorrhea. This finding support the usage of zinc picolinate 30 mg as a supportive treatment to reduce pain in primary dysmenorrhea

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