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ORIGINAL ARTICLE

Comparison Between Zinc Sulphate with Mefenamic Acid versus Mefenamic Acid Alone in the Management of Primary Dysmenorrhea

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ABSTRACT

Objective: To evaluate the efficacy of the zinc sulfate plus mefenamic acid versus mefenamic acid alone on the severity of pain score in patients with primary dysmenorrhea using WaLIDD and Wong Baker score.

Methods: This clinical experimental trial was conducted at Department of Gynecology, Lady Willingdon Hospital Lahore from 1st July 2022 to 30th June 2023 over a period of 12 months and 72 patients were enrolled. They were divided into 2 groups by random allocation. In Group A patients were given zinc sulphate (20mg) plus mefenamic acid (500 mg) andmefenamic acid (500 mg)only in Group B. The WaLIDD and Wong Baker score was used to measure the severity of dysmenorrhea, which ranged from 0 to 12. Patients were evaluated for pain using a visual analog score (VAS). Follow-up was done for three menstruation cycles.

Results: The mean ages were 24.36±3.60 years in group A and 24.00±3.76 years in group B respectively. There were 23 (63.9%) in group A and 28 (77.8%) in group B women presented with moderate dysmenorrhea while 13 (36.1%) women in group A and 8 (22.2%) women in group B presented with severe dysmenorrhea. At 1st month and 2nd month no significant difference was seen for pain score between groups**.** At 3rd months mean pain score in group A was 3.38 and in group B was 3.93 which was statistically significant difference (p=0.016). At 1st and 2nd month pain score showed no significant difference between groups. However, at 3rd month 21 (58.33%) women in group A and 12 (33.3%) women in group B had mild pain while 16(44.4%) women in group A and 24(66.7%) women in group B had moderate pain. At 3rd month pain status showed significant difference between groups. Women in group A had better pain control as compared to group B patients.

Conclusion: The addition of zinc supplementation to mefenamic acid is more effective as compared to mefenemic acid alone for treating pain in primary dysmenorrhea patients.

Keywords: Primary dysmenorrhea, Pain, Efficacy, Zinc sulfate, Mefenamic acid

INTRODUCTION

The unique physical phenomena known as menstruation, which occurs once a month in females who are fertile, is associated with the uterine mucous membrane becoming thinner. The process is sparked by the unintentional gestation that occurs when estrogen and progesterone levels fall in the latter stages of the menstrual cycle. Women often report experiencing discomfort and soreness in the lower abdomen either before to or during menstruation. Less women have pain so intense that it prevents them from going about their regular lives and from asking for medical assistance. This phenomenonis referred to as dysmenorrheal.[1] Dysmenorrhea is a Hellenic phrase meaning arduous, aching, and harrowing. Month is denoted by meno and flow by rhoea.[2]

Primary dysmenorrhea is clearly characterized as discomfort with normal pelvic girdle structure and no obvious pathology. It often starts during pubescence, when the ovulation cycle is already well-organized. Pain linked to a gynecological disorder is known as secondary dysmenorrhea; it often manifests a few years after menarche and is more common in women over the age of twenty.[3,4] Between 50 and 80 percent of women have dysmenorrhea of some kind when they are fertile.[5]

Pain symptoms may appear several days before to menstruation and can last for an adjustable period of time.[6] The lower limbs and the low back are often where dysmenorrhea discomfort is felt.[7] In addition, dysmenorrhea may be associated with additional symptoms such as headaches, vomiting, diarrhea, and biliary system issues. Period discomfort may sometimes coexist with giddiness, tiredness, fainting, and lower back pain.[8,9]

Pain management strategies suggested non-steroidal anti-inflammatory medication as the gold standard for the management of primary dysmenorrhea followed by combined oral contraceptive pills.[10] Furthermore, considering the safety, tiaprofenic and mefenamic acid were indicated to be the safest non-steroidal anti-inflammatory drugs (NSAIDs) drugs while indomethacin was likely to cause mild gastrointestinal discomfort. Mefenamic acid is a widely used and easily available drug over-the-counter.[11]

Additionally, zinc is an important nutrient devouring a crucial role in maintaining oxidant/antioxidant stability and precluding oxidative impairment to the cells by the ischemic metabolites. In the endometrial tissue, zinc has also been evidenced to reduce the synthesis of prostaglandins. Zinc has a vital protagonist in improving circulation in the uterus, thus supplementing the blood flow to the uterus and washing away harmful ischemic metabolites. Zinc also has a role in regulating acid-sensing ion channels (ASIC) as well. They are nociceptors and regulate pain by inhibiting these receptors and thus decreasing the pain. In primary dysmenorrhea, all these tools are thought to act together to decrease pain. A study conducted by Rao and Pai[12], reported the combination of zinc sulfate with mefenamic acid versus mefenamic acid alone for pain management in primary dysmenorrhea. The study presented that there is a significant reduction in mean pain scores in the combination therapy group (zinc plus mefenamic acid versus mefenamic acid alone group).

Therefore, the purpose of this study is to evaluate the efficacy of the zinc sulfate plus mefenamic acid versus mefenamic acid alone group on the severity of pain score in patients with primary dysmenorrhea. The incidence of primary dysmenorrhea and the complications of the current medicines used for its management have diverted the public attention to supplementary and herbal medications. There is limited knowledge about the effect of zinc sulfate in combination with mefenamic acid in the management of primary dysmenorrhea. This study is unique in the sense that it engages participants from general hospital setting, uses WaLIDD and Wong Baker Scales for pain scoringwith Zinc Sulphate in syrup form as well as unique dosage schedule and significant in regional context, providing insights to unique genetic and environmental factors of our population. The outcome has the potential to enhance the comprehension of promoting women's health and introduces a low cost remedy to supplement the existing management option.

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MATERIALS AND METHODS

It was a clinical experimental trial conducted at Department of Obstetrics and Gynecology, Lady Willingdon Hospital, Lahore from 1st July 2022 to 30th June 2023 vide IRB letter No.157/RC/KEMU Dated 8-6-23. A total of 72 patients, 36 in each group fulfilling the sample selection criteria were enrolled after gaining an informed written consent by random allocation assigned into 2 groups. Group A (zinc sulphate plus mefenamic acid group = 36 participants; versus Group B: mefenamic acid alone group = 36 participants). The random allocation sequence was generated by using a computerized randomization method. CONSORT 2018 flowchart for randomized control trials was used.[9] The sample size was calculated using 5% level of significance, power of test as 90% and with expected mean value of VAS score for mefenamic acid + zinc sulfate as 3.76±0.65 and mefenamic acid as 4.27±0.66 respectively. The subjects who were16-30 years old having systematic menstrual cycles 28±7 days, a history of at least one day of primary dysmenorrhea each month, candidates of moderate or severe dysmenorrhea and wereenrolled using WaLIDD and Wong baker scale were included. Those who reported with any sign of gynecological disease, substantial medical and surgical history, history of long term antibiotics, those patients of mild dysmenorrhea and with secondary dysmenorrhea were excluded. Participants with a history of consistent menstrual cycles and complaining about primary dysmenorrhea for at least one day per cycle were booked. Primary dysmenorrhea was described as excruciating lower abdominal cramps that occur either before or during menstruation and are not associated with pelvic disease.[12] Efficacy is a technique for the relief of pain in patients with primary dysmenorrhea would be considered efficacious if it would reduce pain efficiently which will be objectively measured by VAS. The pain level was measured using a Visual Analog Scale (VAS), which was ranged from 0 to 10. The following cut points on the pain VAS was proposed based on the distribution of pain VAS scores in patients who characterized their pain severity as none, mild, moderate, or severe. Pain levels: 0 for no pain, 1-3 for mild pain, 4-6 for moderate pain, and 7–10 for severe pain. A scale-type survey, called the Working Ability, Location, Intensity, Days of Pain, Dysmenorrhea (WaLIDD) score, was developed to encompass various aspects of dysmenorrhea, including: The number of anatomical pain locations, categorized as no pain in any part of the body, pain in the lower abdomen, lumbar region, lower limbs, or inguinal region. The Wong-Baker pain range, measured on a scale from "does not hurt" to "hurts a lot more." The number of days experiencing pain during menstruation, grouped into intervals of 0, 1-2, 3-4, or 5 or more days. The frequency of disabling pain affecting daily activities, with options ranging from "never" to "always" was noted. Each parameter in the survey was assigned a specific score between 0 and 3, resulting in a final score range of 0 to 12 points. The SPSS-26 was used for statistical analysis. Where applicable, nominal data was evaluated and compared using the Chi-square test or the Fisher exact test. A statistically significant p-value of less than 0.05 was regarded as significant.

RESULTS

The mean ages were 24.36±3.60 years in group A and 24.00±3.76 years in group B respectively. Mean weight of women in group A was 57.83±6.93 Kg and in group B was 57.94±7.03 Kg respectively. Mean height of women in group A was 5.23±0.16 meters and 5.24±0.20 meters in group B. Mean body mass index of women in group A was 22.96±2.43 kg/m^2 and in group B was 22.61±2.32 kg/m^2 (Table 1).

In group A 23 (63.9%) and in group B 28 (77.8%) women presented with moderate dysmenorrhea while 13 (36.1%) women in group A and 8(22.2%) women in group B presented with severe dysmenorrheal (Table 2).

At 1st month no significant (p=0.384) difference was seen for pain score between groups 4.97 vs. 4.75. At 2nd month no significant (p=0.225) difference was seen for pain score between groups; 3.89 in group A vs. 4.11 in group B. At 3rd month mean pain score in group A and B was 3.38 and 3.93. Difference between groups at this point showed statistically significant (p=0.016) difference (Table 3)

At 1st and 2nd month pain score showed no significant difference between groups. However, at 3rd month 21(58.33%) women in group A and 12 (33.3%) women in group B had mild pain while 16 (44.4%) women in group A and 24 (66.7%) women in group B had moderate pain. At 3rd month pain status showed significant difference between groups. Women in group A had better pain control as compared to group B patients (Table 4).

Table 1: Descriptive statistics of the study participants (n=72)

Variable	Zinc Sulphate + Mefenemic Acid	Mefenemic Acid
Age (years)	24.36±3.6	24.0±3.76
Weight (kg)	57.83±6.93	57.94±7.03
Height (meter)	5.23±0.16	5.24±0.2
Body mass index (kg/m^2)	22.95±2.43	22.61±2.32

Table 2: Frequency of primary dysmenorrhea (n=72)

Primary dysmenorrhea	Zinc Sulphate + Mefenemic Acid	Mefenemic Acid
Moderate	23 (63.89%)	28 (77.78%)
Severe	13 (36.11%)	8 (22.22%)

Table 3: Percentage of pain score at different intervals (n=72)

Pain score	Zinc Sulphate + Mefenemic Acid	Mefenemic Acid
1st Month	4.97	4.75
2nd Month	3.89	4.11
3rd Month	3.38	3.92

Table 4: Pain status in both groups at different follow up intervals

Pain status	1st Month		2nd Month		3rd Month	
	Group A	Group B	Group A	Group B	Group A	Group B
Mild	2 (5.6%)	1 (2.8%)	12 (33.3%)	8 (22.2%)	21 (58.33%)	12 (33.3%)
Moderate	33 (91.7%)	34 (94.4%)	24 (66.7%)	28 (77.8%)	15 (41.67%)	24 (66.7%)
Sever	1 (2.8%)	1 (2.8%)	-	-	-	-
p-value	-		0.293[a]		0.033[b]	

a: Fisher Exact test b: Chi Square test Group A: Zinc Sulphate + Mefenemic Acid Group B: Mefenemic Acid

DISCUSSION

Non-steroidal anti-inflammatory medications (NSAIDs) are the first-line treatment for primary dysmenorrhea. The selection of NSAIDs is dependent on factors such as cost, tolerability, efficacy, and convenience; no one NSAID has been shown to be better than another.[11] Zinc supplementation has emerged as a viable intervention strategy for the management of primary dysmenorrhea, as individuals search for cost-effective alternatives to no steroidal anti-inflammatory drugs or effective supplementary measures with significantly reduced long-term adverse effects.[12] Primary dysmenorrhea patients may effectively manage their discomfort by using zinc sulfate supplements in addition to mefenamic acid.[13]

In the present study mean age of patients ranges between 17-30 years with mean age as 24.36±3.60 and 24.0±3.76 years for study groups. Teimoori et al[5] reported the mean age was 21.4±2.2. Obiagwu et al[13] also reported 21.5±2.5 in experimental group and 21.7±2.2 years in placebo group. Both these studies reported a mean age which was close to ours i.e. young women. Both these studies included participants from university so the mean age is

above 20 years still it was less than that of reported in this study. However, in few studies age range for dysmenorrhea was reported to be less as compared to this study. Obiagwu et al[13] and Kashefi et al[14] in their studies reported mean age of study population as 15.89±1.54 years and 15.2 ±1.7 years respectively. The slightly higher mean age in our study relates to distinct genetic factors related to our population.

In a study by Obiagwu and colleagues[13], pain was assessed with help of VAS at 1st (Group A: 4.97 vs. Group B: 4.75, p=0.384), 2nd (Group A: 3.89 vs. Group B: 4.11, p=0.225) and 3rd month (Group A: 3.38 vs. Group B: 3.92, p=0.016) post treatment. At 1st and 2nd month no significant difference was seen between groups. However, at 3rd month pain score was significantly higher in group B patients as compared to group A patients. As per his findings significant reduction was seen in pain score at 2nd (zinc sulfate: 2.56 vs placebo: 3.80, p=0.014) and 3rd month (zinc sulfate: 1.95 vs placebo: 3.95, p=0.001) in zinc sulfate group when compared with placebo. This study drew a comparison between zinc sulphate and placebo and made a use of Visual Analog Scale, accounting for some difference of result from our study.

Similar findings were reported by Teimoori et al[5] from Iran in his randomized trial. In which he reported higher pain reduction with zinc sulfate+mefenemic acid as compared to mafenemic acid alone. I.e. pain reduction: 4.1 vs. 2.9, p<0.001 but no scale was used for pain categorization in this study which adds novelty to our study.

Obiagwu et al[13] in their double blind randomized controlled trial compared oral zinc supplementation with placebo showed significant reduction in severity of dysmenorrhea, improvement in menstrual bleeding, premenstrual syndrome and complications related to menstruation which were not addressed in our study including physician visits. These advantageous effects of zinc supplementation on reducing dysmenorrhea might be explained by a number of explanations. Prostaglandin and leukotriene-dependent metabolisms are known to produce dysmenorrhea; zinc may inhibit and suppress these metabolisms as well as lower prostaglandin synthesis. In the long run, it may lessen uterine cramps.[15,16] Furthermore, cyclooxygenase 2 (COX-2) activity is decreased by zinc supplementation, according to in vivo research.[17]

Non-steroidal anti-inflammatory drugs have been shown in literature to be quite successful in treating dysmenorrhea. 18% of women who received a placebo reported moderate to excellent pain relief; NSAID users showed a more notable benefit, with 45% and 53% reporting significantly less pain.[18] Ibuprofen and mefenamic acid usage, two NSAIDs often used to treat dysmenorrhea, were shown to be sufficiently correlated with the severity of the condition, according to Motahari-Tabari et al.[19] According to a recently published network meta-analysis mefenamic acid was reported to be the safest NSAIDs.[11] Keeping in mind above discussion regarding effectiveness of mefenamic acid and zinc sulfate supplementation in alone or in combination have shown promising results for treating primary dysmenorrhea in terms of pain reduction.

CONCLUSION

Combination of Zinc supplementation with mefenemic acid is more effective as compared to mefenemic acid alone for treating pain in primary dysmenorrhea patients. Pain severity was well controlled with combination treatment as compared to mefenemic acid alone

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