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Comparison of Vitamin E in Combination with Mafenamic Acid Versus Mafenamic Acid Alone for Management of Primary Dysmenorrhea

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ABSTRACT

Introduction: Painful menstrual cramps, known as primary dysmenorrhea, are a common gynecological condition that affects a great number of women across the globe. Current treatments may include use of a non steroidal anti inflammatory drugs (NSAIDS) as mafenamic acid. Recent research indicated the interaction of vitamin E with NSAIDs may intensify pain relief. **Methodology:** The core objective of the study was to compare the efficacy of vitamin E combined with mafenamic acid versus mafenamic acid alone for the management of primary dysmenorrhea was evaluated in randomized controlled trial. Sixty-six participants were randomly divided into two groups. Before and after treatment, pain intensity was assessed by means of the Visual Analogue Scale (VAS). **Results:** The reduction of pain scores in both groups was found to be significant. While combining vitamin E with mafenamic acid showed highest decrease in VAS score after tuberculosis treatment compared to mafenamic acid alone, these results were interpreted with caution. Demographic and clinical variables were similar between balanced groups. **Conclusion:** The addition of vitamin E to mafenamic acid may be of advantage in relieving the pain of primary dysmenorrhea rather than the use of mafenamic acid alone. These results supported previous findings, suggested that the combination of antioxidants with NSAIDs for the management of menstrual pain can be beneficial for such type of disorders.

INTRODUCTION

Dysmenorrhea is a painful menstrual cramp originating from the uterus and is a common gynecological disorder in women of childbearing age. Although it is widespread, many women do not get the diagnosis because they don't go to the doctor.[1-2] There are two types of primary dysmenorrhea based on the causes, namely primary and secondary. PD is primary dysmenorrhea, pain in the lower abdomen just before or with the start of menstruation although there is no pelvic problem. Rates of this gynecological symptom are between 45 to 95 %, and it is a very common symptom in adolescent and young women.[3-4] Factors such as age, ethnicity, family history, lifestyle (including smoking, alcohol intake, over exercise, diet) and a significant influence from stress can all contribute towards primary dysmenorrhea. Apart from its economic consequences, there are high rates of absenteeism and poor academic performance in the young females.[5] According to most studies, many women had self-medication without consulting with health care professionals.[6-7] This issue can be treated with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) that are usually preferred. However, many women go for the right drug for menstrual pain relief, but the selection of dosage is quite a challenge.[8-9]

Self-medication with over-the-counter NSAIDs for primary dysmenorrhea is common among women but may not be effective, leading to potential health risks like gastrointestinal side effects and drug interactions. Therefore, depending on NSAIDs for primary dysmenorrhea may not be helpful.[10] Prostaglandins play a key role in inducing uterine contractions and causing primary dysmenorrhea. Inhibitors can effectively relieve pain for over 80% of affected women by reducing prostaglandin levels. Decreased progesterone in the luteal phase can trigger arachidonic acid release, leading to increased prostaglandin production and uterine cramps. Vitamin E inhibits arachidonic acid conversion and phospholipid peroxidation, thereby alleviating dysmenorrhea severity. Research showed that Vitamin E reduced the pain severity, duration, and menstrual blood loss in primary dysmenorrhea.[11]

In a study with 100 girls divided into two groups (50 each), showed that the mean pain score decreased more with

vitamin E and NSAID treatment (3.5±1.25) compared to placebo and NSAID (4.3±1.13) after 2 months (p=0.02).[12] The study aims to determine the efficacy of vitamin E in treating primary dysmenorrhea, a distressing condition among females causing anxiety. A well-designed drug regimen can alleviate pain and improve quality of life. The present study was conducted to assess analgesic effect of vitamin E, potentially offering a side-effect-free alternative to medication, particularly for adolescent girls. Unlike a previous study limited to 16 to 18-year-old schoolgirls in Iran,[12] the current study included a broader age range of 16 to 40 years, providing insights into middle-aged women with dysmenorrhea in order to address the limitations of previous studies.

METHODOLOGY

This randomized controlled trial was conducted from 15 October 2024 to 15 April 2025 in the Department of Gynecology and Obstetrics at Lahore General Hospital, Lahore. The study duration was six months following approval of the synopsis by the hospital's Ethical Board. The sample size of 66 (33 in each group) was calculated using the OpenEpi calculator, with a 95% confidence interval, 80% power of the study, and mean pain scores of 3.5±1.25 for the vitamin E group and 4.3±1.13 for the placebo group in combination with Mafenamic acid.[12]

Inclusion criteria included females aged 16–40 years diagnosed with primary dysmenorrhea, defined as cramping pain (VAS ≥4) in the lower abdomen at menstruation onset without pelvic pathology confirmed by normal clinical examination and ultrasound. Exclusion criteria included pregnant females and those with secondary dysmenorrhea.

Primary dysmenorrhea was operationally defined as cramping pain (VAS ≥4) in the lower abdomen at menstruation onset without recognizable pelvic pathology, confirmed by normal clinical examination and ultrasound. The Visual Analogue Scale (VAS) was used to assess pain, ranging from 0 (no pain) to 10 (maximum tolerable pain), and was evaluated on the third day of the menstrual cycle.

After obtaining ethical approval, eligible patients were recruited from the Gynecology Outpatient department. Written informed consent was obtained after explaining the study purpose. Baseline demographic data, including age, educational level, socioeconomic status, and symptom duration, were recorded. A detailed history was taken, followed by a physical examination to confirm eligibility. Baseline VAS scores were assessed on the third day of menstruation.

Participants were randomized into two groups using computer-generated block randomization: Group A received vitamin E (200 mg capsule) combined with Mafenamic acid (250 mg twice daily) for five days at menstruation onset for two consecutive cycles, while Group B received Mafenamic acid (250 mg twice daily) alone for five days at menstruation onset for two consecutive cycles. Patients were followed up after two menstrual cycles, and post-treatment VAS scores were recorded on the third day of menstruation.

Data analyzed with SPSS 22.0. Quantitative variables (e.g., age, symptom duration, pre- & post-treatment VAS) as mean ± standard deviation. Paired t-tests compared post-treatment VAS scores with p-value ≤0.05 significance. Categorical variables (e.g., education, socioeconomic status) presented as frequencies. Stratification employed for potential effect modifiers: age, education, socioeconomic status, symptom duration. Post-stratification independent t-tests examined group differences with significance at p ≤0.05 threshold.

RESULTS

In the combination therapy group, 57.6% were aged ≤25 years, compared to 54.5% in the monotherapy group. More participants aged >25 years were in the Mafenamic Acid alone group (45.5% vs. 42.4%). Mean age was similar in both groups (24.82±3.08 years vs. 25.00±3.21 years). Majority had symptoms for ≤2 months (84.8% vs. 81.8%), with fewer having symptoms >2 months (15.2% vs. 18.2%). Mean symptom duration was comparable (1.70±0.72 months vs. 1.76±0.75 months). Educational levels were similar. Illiteracy was slightly higher in the Mafenamic Acid alone group (21.2% vs. 18.2%). Primary education was reported by 27.3% in combination group and 30.3% in monotherapy group. More low-income participants were in the monotherapy group (33.3% vs. 27.3%). The majority in each group were middle class (63.6% combination, 57.6% Mafenamic Acid alone). Only 9.1% in each group had high socioeconomic status.

The mean VAS score was similar in both groups before treatment (combination therapy group: 7.76±0.93, monotherapy group: 7.70±0.91). Pain scores decreased significantly post-treatment; reduction was greater in the combination therapy group (VAS: 2.15±0.83) compared to the monotherapy group (VAS: 4.15±0.62). Mean change in VAS score was 5.61±0.99 in the combination therapy group, significantly higher than the monotherapy group (3.55±1.03). The p-value for these comparisons was 0.001, indicating statistical significance in pain reduction between the groups.

Table 1

Comparison of Distribution of Different Variables between Groups

Variables		Groups	
		Vit. E plus Mafenamic acid	Mafenamic acid alone
Age groups	≤25 years	19(57.6%)	18(54.5%)
	>25 years	14(42.4%)	15(45.5%)
	Mean±S.D	24.82±3.08	25.00±3.21
Duration of symptoms	≤2 months	28(84.8%)	27(81.8%)
	>2 months	5(15.2%)	6(18.2%)
	Mean±S.D	1.70±0.72	1.76±0.75
Educational level	Illiterate	6(18.2%)	7(21.2%)
	Primary education	9(27.3%)	10(30.3%)
	Secondary education	11(33.3%)	10(30.3%)
	Matric or above	7(21.2%)	6(18.2%)
Socio-economic status	Low	9(27.3%)	11(33.3%)
	Middle	21(63.6%)	19(57.6%)
	High	3(9.1%)	3(9.1%)

Table 2
Comparison of Pain Score on Vas at Different Intervals between Groups

Pain score at intervals	Groups	
	Vit. E plus Mafenamic acid	Mafenamic acid alone
Pre-treatment VAS	7.76±0.93	7.70±0.91
Post-treatment VAS	2.15±0.83	4.15±0.62
Mean change in VAS	5.61±0.99	3.55±1.03
p-value	0.001	0.001

In Table 3, post-treatment VAS scores were compared between age, symptom duration, education level, and socioeconomic status groups. Results showed that using Vitamin E and Mafenamic Acid together significantly reduced VAS scores compared to Mafenamic Acid alone in all subgroups. Younger participants and those with shorter symptom durations experienced enhanced pain relief with the combined therapy. Moreover, regardless of education levels and socioeconomic status, the combination treatment consistently lowered pain scores compared to Mafenamic Acid alone.

Table 3
Stratification of Mean Change in Hemodynamic Variables between Groups with Respect to Different Variables

Variables	Post-treatment VAS	Vit. E plus Mafenamic acid	Mafenamic acid alone	p-value
Age groups				
≤25 years	Post-treatment VAS	2.05±0.78	4.28±0.66	0.001
>25 years		2.29±0.91	4.00±0.53	0.001
Duration of symptoms				
≤2 months	Post-treatment VAS	2.14±0.84	4.22±0.50	0.001
>2 months		2.20±0.83	3.83±0.98	0.017
Educational level				
Illiterate	Post-treatment VAS	1.17±0.40	3.86±0.37	0.001
Primary		2.33±0.70	4.10±0.56	0.001
Secondary		2.45±0.93	4.30±0.67	0.001
Matric or above		2.29±0.48	4.33±0.81	0.001
Socio-economic status				
Low	Post-treatment VAS	2.22±0.83	4.18±0.60	0.001
Middle		2.10±0.88	4.16±0.68	0.001
High		2.33±0.57	4.00±0.01	0.007

DISCUSSION

This study compared the efficacy of vitamin E combined with mafenamic acid versus mafenamic acid alone in managing primary dysmenorrhea. The results showed a significant reduction in pain intensity in both groups, with the combination therapy demonstrating superior outcomes. Specifically, the mean post-treatment VAS score was 2.15 ± 0.83 in the combination group, compared to 4.15 ± 0.62 in the mafenamic acid alone group. These findings highlight the enhanced pain-relieving effects of combining vitamin E with mafenamic acid, likely due to their complementary mechanisms of action.

The combination therapy yielded a greater reduction in post-treatment VAS scores than mafenamic acid alone, suggesting a synergistic effect between vitamin E and mafenamic acid. Vitamin E, as an antioxidant, reduces oxidative stress and stabilizes cell membranes, which may mitigate prostaglandin synthesis and uterine contractions associated with dysmenorrhea. Mafenamic acid inhibits cyclooxygenase enzymes, reducing prostaglandin-mediated inflammation and pain.

Our findings align with several previous studies. Ilyas and Iqbal reported that the combination of vitamin E and mafenamic acid resulted in a mean pain reduction from 6.8 ± 1.2 to 2.9 ± 1.1, compared to a reduction from 6.7 ± 1.3 to 4.1 ± 1.2 for mafenamic acid alone.[13] Similarly, Sadiqa et al. observed a significant reduction in pain scores from 8.5 ± 1.2 to 3.8 ± 1.1 in patients receiving vitamin E plus mafenamic acid, compared to a reduction from 8.2 ± 1.1 to 5.5 ± 1.3 in those receiving mafenamic acid alone.[14] These studies corroborate our findings, supporting the efficacy of vitamin E as an adjunctive treatment for dysmenorrhea.

A study by Roy et al., conducted in Bangladesh, found that VAS scores significantly decreased from baseline to the end of treatment at the third cycle: from 7.40 ± 0.98 to 3.70 ± 0.72 for the vitamin E group and from 7.05 ± 0.75 to 3.52 ± 0.55 for the mafenamic acid group.[15] While both treatments were effective, our study demonstrates that combining vitamin E with mafenamic acid provides even greater pain relief. In addition, Ziaei et al., in a randomized controlled trial, reported that vitamin E reduced pelvic pain severity during the second month of treatment by -2.7 ± 2.1 compared to -1.8 ± 2.4 for placebo.[12] These findings align with our results and further validate the role of vitamin E as a safe and effective option for managing primary dysmenorrhea.

A systematic review and meta-analysis also revealed that vitamin E supplementation significantly reduced dysmenorrhea intensity during both the first month (SDM = -1.16; CI: -2.16 to -0.17) and second month (SDM = -1.83; CI: -2.90 to -0.77) compared to placebo.[16] This supports our conclusion that vitamin E can be an effective adjunctive therapy for reducing menstrual pain.

This study contributes to existing evidence by demonstrating that combining vitamin E with mafenamic acid provides superior pain relief compared to mafenamic acid alone in women with primary dysmenorrhea. The findings highlight a potential therapeutic strategy that targets both oxidative stress and prostaglandin-mediated inflammation, offering improved symptom management for affected women.

Despite its strengths, this study has several limitations: The sample size was relatively small (n=66), which may limit generalizability. The study duration was restricted to two menstrual cycles; longer follow-up is needed to assess sustained efficacy. Potential confounding factors such as dietary antioxidant intake or variations in menstrual cycle characteristics were not controlled. Subjective reporting using VAS may introduce bias despite its widespread use. Future studies should address these limitations by including larger sample sizes, extended follow-up durations, and comprehensive control of confounding variables.

CONCLUSION

Given these findings, it may be suggested that vitamin E in addition to mafenamic acid will offer better pain relief than that achieved with mafenamic acid alone for primary dysmenorrhea. The results for these findings could provide potential advantage of mixing antioxidants with NSAIDs for therapy of menstruation pain.

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