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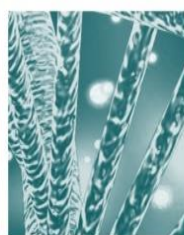
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Vitamin E Combined with Mefenamic Acid versus Mefenamic Acid Alone in Controlling Pain During Primary Dysmenorrhea: A Randomized Controlled Trial

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ABSTRACT

Objective: To compare mean pain scores and pain reduction after treatment with Vitamin E plus mefenamic acid versus mefenamic acid alone in women with primary dysmenorrhea.

Methods: This randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Combined Military Hospital, Multan, from 11 July 2024 to 10th January 2025. Sixty women aged 15–25 years with primary dysmenorrhea were enrolled by non-probability consecutive sampling and allocated to two groups of 30 participants each. Group A received mefenamic acid 400 mg combined with Vitamin E 400 IU, while Group B received mefenamic acid 400 mg alone. Pain intensity was assessed using a 100-mm Visual Analogue Scale (VAS) at baseline and during the second menstrual cycle. The post-treatment assessment was performed by a consultant blinded to treatment allocation.

Results: All 60 participants completed the 4-week follow-up. Mean age was 21.10 ± 3.14 years in both groups. Baseline mean VAS scores were 54.97 ± 7.31 mm in Group A and 53.20 ± 8.12 mm in Group B ($P = 0.374$). At follow-up, mean VAS scores were 18.53 ± 6.13 mm and 34.63 ± 8.10 mm in Groups A and B, respectively ($P < 0.001$). Mean pain reduction was 36.43 ± 5.45 mm in Group A compared with 18.57 ± 1.59 mm in Group B ($P < 0.001$).

Conclusion: In this study, participants receiving Vitamin E in combination with mefenamic acid had greater reductions in menstrual pain than those receiving mefenamic acid alone. Larger, multicenter trials with longer follow-up and prespecified assessment of safety are warranted to determine the reproducibility and longer-term clinical relevance of this finding.

Keywords: Primary dysmenorrhea, Vitamin E, Mefenamic acid, Pain management, Randomized Controlled Trial.

1. INTRODUCTION

Primary dysmenorrhea is characterized by recurrent cramping lower abdominal pain during menstruation in the absence of identifiable pelvic pathology and is particularly common among adolescents and young women¹. Reported prevalence varies substantially, ranging from 20% to 90% among menstruating females². The condition can interfere with educational and occupational activities and may adversely affect quality of life^{3,4}.

The pathophysiology of primary dysmenorrhea is associated with increased uterine contractility and myometrial ischemia. Increased release of vasopressin and subsequent activation of the arachidonic acid pathway have also been implicated. Prostaglandins, particularly PGE₂ and PGF₂ α , contribute to uterine contractions, inflammation, and pain⁵.

NSAIDs are among the principal pharmacological treatments for primary dysmenorrhea because they inhibit prostaglandin synthesis and thereby reduce menstrual pain^{6,7}. Their use, however, may be associated with adverse effects, particularly gastrointestinal symptoms, and not all patients achieve satisfactory pain relief^{8,9}. These considerations have led to interest in adjunctive approaches, including nutritional and antioxidant therapies^{10,11}.

Vitamin E is a lipid-soluble antioxidant that has been investigated as a potential treatment for primary dysmenorrhea¹². Previous studies have suggested that Vitamin E may influence inflammatory and oxidative pathways involved in menstrual pain^{13,14}. Sadiqa et al. reported greater pain reduction among patients receiving Vitamin E in combination with mefenamic acid than among those receiving mefenamic acid alone¹⁵. Ilyas and Iqbal similarly reported lower mean pain scores with

combination therapy than with mefenamic acid alone¹⁶.

Despite these findings, additional studies in different clinical settings may help determine whether the reported benefit is reproducible. The present trial therefore compared pain scores and pain reduction between women receiving Vitamin E plus mefenamic acid and those receiving mefenamic acid alone for primary dysmenorrhea.

2. METHODOLOGY

This randomized controlled trial was conducted over a period of 6 months in the Department of Obstetrics and Gynecology, Combined Military Hospital, Multan, from 11 July 2024 to 10th January 2025 following approval by the institutional Ethics Review Committee.

Women aged 15–25 years presenting with primary dysmenorrhea were assessed for eligibility. Primary dysmenorrhea was defined as pelvic pain with a VAS score of ≥ 4 on a 100-mm scale occurring within two days before the onset of menstruation and continuing for up to three days during the menstrual cycle, with symptoms present for at least 3 months.

Women already receiving Vitamin E were excluded. Patients with secondary dysmenorrhea attributable to underlying pelvic pathology, including fibroids, endometriosis, adenomyosis, or ovarian cysts identified by ultrasound, were also excluded.

A sample of 60 participants, with 30 allocated to each group, was calculated using OpenEpi software based on mean pain-score differences reported in previous literature¹⁶. The calculation was performed using 80% power and a 95% confidence level. Participants were enrolled using non-probability consecutive sampling. After providing informed written consent, eligible participants were allocated to two treatment groups using a computer-generated lottery

method. Participants in Group A received mefenamic acid 400 mg combined with Vitamin E 400 IU at the beginning of the menstrual cycle. Participants in Group B received mefenamic acid 400 mg alone. Pain intensity was assessed using a 100-mm VAS, with 0 representing no pain and 100 representing severe, debilitating pain. Baseline pain scores were recorded before treatment, and pain was reassessed during the second menstrual cycle at the 4-week follow-up.

The post-treatment assessment was performed by a consultant who was blinded to treatment allocation. Data were analyzed using SPSS version 23. The distribution of numerical variables was assessed using the Shapiro-Wilk test. Continuous variables were summarized as mean $\pm$ standard deviation (SD). Between-group comparisons of mean pain scores and pain reduction were performed using an independent-samples t-test. A P-value ≤ 0.05 was considered statistically significant.

3. RESULTS

A total of 60 participants were enrolled, with 30 allocated to each treatment group. All 60 participants completed the 4-week follow-up and were included in the reported analysis. The mean age was 21.10 ± 3.14 years in both groups, with no statistically significant difference between Group A and Group B ($P = 1.000$).

The baseline mean VAS score was 54.97 ± 7.31 mm in Group A and 53.20 ± 8.12 mm in Group B. The difference was not statistically significant ($P = 0.374$). At the 4-week follow-up, the mean VAS score was 18.53 ± 6.13 mm in Group A and 34.63 ± 8.10 mm in Group B. The between-group difference was statistically significant ($P < 0.001$).

Mean pain reduction was calculated as the difference between the baseline and post-treatment VAS scores. The reported mean reduction was 36.43 ± 5.45 mm in Group A and 18.57 ± 1.59 mm in Group B ($P < 0.001$).

The reported pain-reduction value for Group A should be checked against the original dataset because subtraction of the displayed group means ($54.97 - 18.53$) gives 36.44 mm. The manuscript should use the value generated from the original participant-level data and maintain appropriate rounding.

Table 1: Comparison of Pain Scores between Group A and Group B

Variable	Group A	Group B	P-value
Age (years)	21.10 ± 3.14	21.10 ± 3.14	1.000
Baseline Pain (VAS)	54.97 ± 7.31	53.20 ± 8.12	0.374
Post-Treatment Pain (VAS)	18.53 ± 6.13	34.63 ± 8.10	< 0.001
Pain Reduction (VAS)	36.43 ± 5.45	18.57 ± 1.59	< 0.001 *

Figure 1: Mean VAS Pain Scores - Baseline vs Post-Treatment

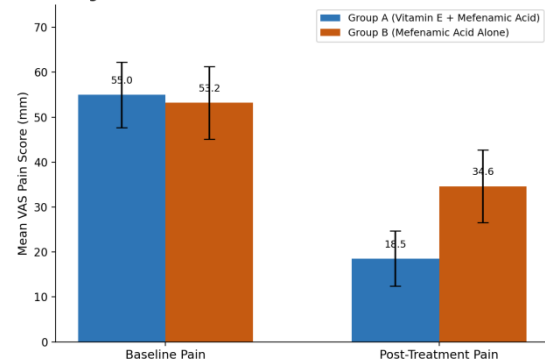
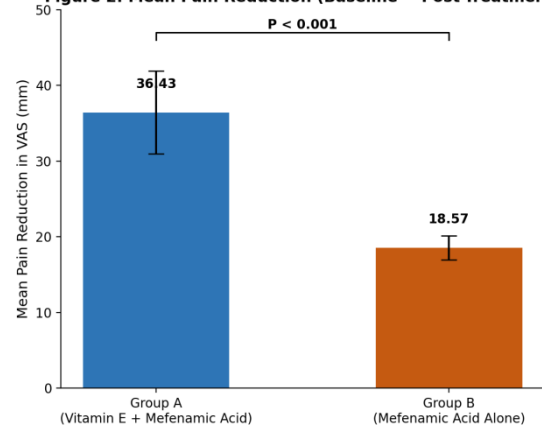


Figure 2: Mean Pain Reduction (Baseline – Post-Treatment)



4. DISCUSSION

This randomized controlled trial found a greater reduction in menstrual pain among participants who received Vitamin E in combination with mefenamic acid than among those who received mefenamic acid alone. At the 4-week assessment, the mean VAS score was 18.53 ± 6.13 mm in the combination group compared with 34.63 ± 8.10 mm in the mefenamic acid-only group ($P < 0.001$). Mean reduction in VAS score was also greater in the combination group (36.43 ± 5.45 mm vs. 18.57 ± 1.59 mm; $P < 0.001$).

These findings are consistent with previous reports. Sadiqa et al. observed a mean pain reduction of 20.50 ± 10.04 in the Vitamin E plus mefenamic acid group compared with 10.92 ± 0.75 in the mefenamic acid-only group¹⁵. Ilyas and Iqbal also reported lower mean pain scores among participants receiving combination therapy than among those receiving an NSAID alone (1.98 ± 0.815 vs. 4.06 ± 0.813)¹⁶. Differences between studies may reflect variation in baseline pain severity, patient characteristics, treatment protocols, adherence, and methods used to assess pain¹⁷. The current study used a 100-mm VAS, whereas categorical pain scales were used in some earlier studies¹⁸.

Several biological mechanisms could potentially explain the observed difference. Primary dysmenorrhea is associated with increased prostaglandin activity and myometrial ischemia, with PGE2 and PGF2 α contributing to uterine contractions and pain^{5,19}. Mefenamic acid inhibits cyclooxygenase-mediated prostaglandin synthesis and is therefore an established treatment for dysmenorrhea²⁰. Oxidative stress has also been investigated in the pathophysiology of primary dysmenorrhea, with previous studies reporting differences in oxidative-stress markers between affected women and asymptomatic controls^{21,22}.

Vitamin E has antioxidant properties and may reduce lipid peroxidation and oxidative damage²³. Previous experimental and clinical literature has also suggested effects on pathways involved in arachidonic acid metabolism²⁴. These mechanisms provide a possible biological rationale for combining Vitamin E with an NSAID. However, the present study did not measure oxidative-stress biomarkers, prostaglandin concentrations, or other biochemical markers. Therefore, the proposed mechanisms cannot be directly established from the present findings.

The clinical significance of improved pain control is potentially relevant because dysmenorrhea can interfere with educational and occupational activities²⁵. Nevertheless, the current study evaluated pain over only one treatment cycle and included a relatively small number of participants from a single center. The findings should therefore be interpreted within these limitations.

The study has several strengths. It used a randomized comparative design, and the post-treatment pain assessment was performed by a consultant blinded to treatment allocation. The eligibility criteria were also designed to select women with primary rather than secondary dysmenorrhea.

Several limitations should be acknowledged. First, the sample size was small and the study was conducted at a single center, which may limit generalizability. Second, follow-up was limited to 4 weeks, corresponding to approximately one subsequent menstrual cycle. The study therefore cannot establish the persistence of the observed treatment effect over multiple cycles or provide evidence regarding long-term safety. Third, the manuscript does not report adverse events, adherence, or treatment discontinuation. If these outcomes were not prospectively collected, conclusions regarding safety should not be made.

Further multicenter randomized trials with larger sample sizes and longer follow-up are needed to determine whether the observed reduction in pain is sustained and clinically meaningful²⁶. Future studies could also incorporate standardized assessment of treatment adherence, adverse events, quality of life, and relevant biochemical markers.

5. CONCLUSION

In this study, participants receiving Vitamin E in combination with mefenamic acid had greater reductions in menstrual pain than those receiving mefenamic acid alone. Larger, multicenter trials with longer follow-up and prespecified assessment of safety are warranted to determine the reproducibility and longer-term clinical relevance of this finding.

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