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**ORIGINAL ARTICLE**

# Effect of Mefenamic Acid on Premenstrual Syndrome in Reproductive age Group

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## ABSTRACT

**Background:** Premenstrual syndrome is a cyclic disorder with symptoms that are severe enough to interfere with some aspect of living. The debilitating symptoms reappear with each cycle, the most common being generalized headache, breast swelling and tenderness, bloating, fatigue, depression and irritability.
**Aim:** To determine the efficacy of mefenamic acid in treatment of premenstrual syndrome women in reproductive age groups.
**Methods:** A quasi experimental study was donein the Department of Obstetrics and Gynecology, Federal Government Services Hospital, Islamabad between November 2020 and April2021. The study was carried out over 75 patients. Mefenamic acid for at least 3 months and followed up for a minimum of 3 months were advised. After follow up the sequel of symptoms and efficacy was noted.
**Results:** Average age of the patients was 26.03±6.27 years. The symptoms of premenstrual syndrome nausea 84%, gastrointestinal tract disturbance 85.3% and headache 80% noted to be the leading symptoms followed by breast tenderness 77.3% and vomiting 74.7%.The efficacy of mefenamic acid in term of relieving of symptoms was observed 70.7%.Statistically significant improvement in symptoms of headache, dysmenorrhea, breast tenderness and mood irritability were noted ($p \leq 0.05$). While no clinically significant distinction found among marital status, occupation, education and duration of symptoms improvement ($p \geq 0.05$).
**Practical implication** of the study is that the effect of mefenamic acid relieving the symptoms of PMS.
**Conclusion:** The study concluded that mefenamic acid is effective in term of relieving symptoms in patients with premenstrual syndrome.
**Keywords:** Mefenamic acid; Efficacy; Premenstrual syndrome; vomiting.

## INTRODUCTION

Premenstrual syndrome (PMS) is a periodic lutealphase condition with the symptoms that are severe enough to impede with some aspect of living and that occur with a typical anticipated relation to menstruation[1]. The debilitating symptoms reappear with each cycle, the most common being generalized headache, breast swelling and tenderness, bloating, fatigue, depression and irritability[2]. The prevalence of PMS symptoms can vary depending on the population studied and the assessment tools used. The estimated range of 70% to 90% represents a general estimate of the proportion of women who experience some degree of PMS symptoms during their reproductive years. It is 37.5% in Arab women, 17.5% in Japanese women, 25.2%-97.2% in Brazilian women and 41% in America, with the lowest incidence in Europe 10%-12%, and in Asia the highest percentage is 98%[3]. Further, approximately 5-8% of women with hormonal cycles experience moderate to severe symptoms[4].

The risk of developing peri-menopausal depression[5] and postnatal depression is greater in women who have PMS[6]. PMS causes a decrease of 27.5% in women's work efficiency, 22% in work relationships, 83% with husbands, 61% with children and 41.5% in social relationships[7].

Bertone-Johnson et al highlights a potential association between the experience of abuse (emotional, sexual, or physical) in early life and an increased risk of PMS in the middle-to-late reproductive years for women[8]. Various non-pharmacological treatments for PMS found to be effective includeschanging dietary habits, reducing salt intake, reducing animal fat, exercise, reducing stress, and having a support system[9]. Pharmacological treatments including GnRH analogues, spironolactone, danazol, alprazolam, mefenamic acid, gamalinoleaic acid and fluoxetine[10]. The anxiolytic drug alprazolam is more effective than placebo for the syndrome, but prolong use of benzodiazepines isundesirable[11]. Varnell et al study found that mefenamic acid, a prostaglandin synthetase inhibitor, relieved many of the symptoms associated with PMS[12]. Mefenamic acid may be especially effective when PMS is associated with dysmenorrhea or menorrhagia[1].

This study objective was to determine the efficacy of mefenamic acid in treatment of PMS as this drug does not have the side effect of dependence.The significance of the study is an appropriate measure being taken to increase awareness among women and provide better ways to alleviate PMS symptoms.

## METHODOLOGY

This quasi-experimentalstudy was done in the department of obstetrics and gynecology, Federal Government Services Hospital (FGSH), Islamabad between November 2020 and April 2021. After approval of Institutional Review Board (IRB) of the hospital and informed written consent, a sample of 75 patients consecutively (WHO calculator of sample size was used; taking CI; 95%, alpha (α) error 5%, and precision rate 5%)[4] were enrolled in this study.Women with age range 14-40 years, had regular menstrual cycle since last 3 months and symptomatic for at least 3 months were included in the study. At least three of the symptoms either psychological and physiological e.g., nausea, vomiting, headache, dysmenorrhea, GIT disturbances, breast tenderness and irritability were included in the study. Pregnant women, premenopausal, women with irregular menstrual cycle, taken hormonal replacement therapy and women who had used oral contraceptive pills were excluded from the study.

The following procedure was done for evaluation of the patients and data collection; complete history and examination were performed to exclude any pathology. Relevant investigations were performed. Symptomatic patients were prescribed 250mg mefenamic acid tablets for at least 3 monthsstarting from 3 days before and for first 3 days of menstrual cycle in two daily servings and followed up for a minimum of 3 months. MINEMAR was applied before treatment and after treatment.A proformaprepared to record the registration number and all the relevant data such as hospital number, bio-data of the patient, duration and severity of symptoms, relief of symptoms and follow-up and effect of treatment noted.

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Data analysis done by using SPSS v 23.Quantitative data variables like age and duration of illness were measured as mean ± SD.Qualitative data variables like PMS symptoms,education, marital status and efficacy were measured as frequency and percentage.The probability p-value ≤0.05 was considered significant. Further, effect modifiers e.g., age, marital status, symptoms at presentation, duration and education measured by stratification. Chi-square test was used after stratification.

## RESULTS

Total 75 women with atleast three of the symptoms (described in methodology section) were enrolled in this study. Majority of the patients were educated, married and housewife. Average age of the patients was 26.03±6.27 year with range 16-41 years. The patient's ageswerecategorized into four groups, mostly common age group ofPMS was less than 25 years. There were 43(57.3%) women of less than 25 years. 11(14.7%) women were 26-30 years, 13(17.3%) were 31-35 years and 8(10.7%) were above 35 years of age. At presentation, the symptoms of premenstrual syndrome nausea, gastrointestinal tract disturbance and headache noted to be the leading symptoms followed by breast tenderness and vomiting (Table 1).

The efficacy of mefenamic acid in term of relieving of symptoms was observed in 53(70.67%), while in 22(29.33%) patients show no efficacy (Fig. 1).

Age wise distribution showed that the efficacy of mefenamic acid in improving symptoms of premenstrual syndrome among women of different age groupwas somewhat alike. The efficacy of 72.1% was noted amongwomenwith age less than or equal to 25 years. While in the women of age 26-30 years, 31-35years, above 35 years, the efficacy reported was of 63.6%, 76.9% and 62.5%, respectively (Table2).Statistically significant improvement in symptoms of headache, dysmenorrhea, breast tendernessand mood irritability were noted (Table 3). While no clinically significant distinction found among marital status, occupation, education and duration of symptoms improvement (Table 4).

Table I: Symptoms of premenstrual syndrome (n=75)

| Symptoms | | Frequency | %age |
|---|---|---|---|
| Nausea | Yes | 63 | 84.0% |
| | No | 12 | 16.0% |
| Vomiting | Yes | 56 | 74.7% |
| | No | 19 | 25.3% |
| Headache | Yes | 60 | 80.0% |
| | No | 15 | 20.0% |
| Dysmenorrhea | Yes | 48 | 64.0% |
| | No | 27 | 36.0% |
| GIT disturbance | Yes | 64 | 85.3% |
| | No | 11 | 14.7% |
| Breast tenderness | Yes | 58 | 77.3% |
| | No | 17 | 22.7% |
| Irritability | Yes | 57 | 76.0% |
| | No | 18 | 24.0% |

Fig. I: Efficacy of mefenamic acid (n=75)

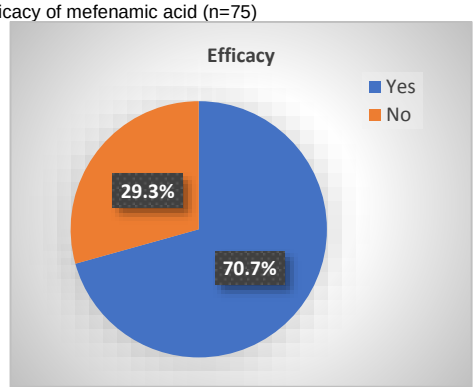


Table II: Age wise distribution of efficacy (n=75)

| Age in years | Efficacy | | Total | p value |
|---|---|---|---|---|
| | Yes | No | | |
| 16-25 | 31 (41.3%) | 12 (16.0%) | 43 | 0.848 |
| 26-30 | 7 (9.3%) | 4 (4.5%) | 11 | |
| 31-35 | 10 (13.3%) | 3 (4.0%) | 13 | |
| 36-41 | 5 (6.6%) | 3 (4.0%) | 8 | |
| Total | 53 (70.7%) | 22 (29.3%) | 75 | |

Table III: Stratification of efficacy over symptoms premenstrual syndrome (n=75)

| | Efficacy | | | | p-value |
|---|---|---|---|---|---|
| | Yes | | No | | |
| | Count | % | Count | % | |
| **Nausea** | | | | | |
| Yes | 45 | 71.4% | 18 | 28.6% | 0.740 |
| No | 8 | 66.7% | 4 | 33.3% | |
| **Vomiting** | | | | | |
| Yes | 41 | 73.2% | 15 | 26.8% | 0.804 |
| No | 12 | 63.2% | 7 | 36.8% | |
| **Headache** | | | | | |
| Yes | 46 | 76.7% | 14 | 23.3% | 0.022 |
| No | 7 | 46.7% | 8 | 53.3% | |
| **Dysmenorrhea** | | | | | |
| Yes | 41 | 85.4% | 7 | 14.6% | 0.007 |
| No | 12 | 44.4% | 15 | 55.6% | |
| **GIT Disturbance** | | | | | |
| Yes | 48 | 75.0% | 16 | 25.0% | 0.204 |
| No | 5 | 45.5% | 6 | 54.5% | |
| **Breast Tenderness** | | | | | |
| Yes | 47 | 81.0% | 11 | 19.0% | 0.002 |
| No | 6 | 35.3% | 11 | 64.7% | |
| **Irritability** | | | | | |
| Yes | 46 | 80.7% | 11 | 19.3% | 0.001 |
| No | 7 | 38.9% | 11 | 61.1% | |

Table IV: Stratification of efficacy over education, marital status and duration of symptoms, (n=75)

| | Efficacy | | p value |
|---|---|---|---|
| | Yes | No | |
| **Marital status** | | | |
| Married | 37 (72.5%) | 14 (27.5%) | 0.602 |
| Single | 16 (66.7%) | 8 (33.3%) | |
| **Occupation status** | | | |
| Employed | 21 (72.4%) | 8 (27.6%) | 0.792 |
| House wife | 32 (69.6%) | 14 (30.4%) | |
| **Educational status** | | | |
| Uneducated | 18 (66.7%) | 9 (33.3%) | 0.541 |
| Primary/basic education | 19 (79.2%) | 5 (20.8%) | |
| Higher/professional education | 16 (66.7%) | 8 (33.3%) | |
| **Duration of symptoms (in weeks)** | | | |
| ≤ 2 | 31 (75.6%) | 10 (24.4%) | 0.302 |
| ≥ 3 | 22 (64.7%) | 12 (35.3%) | |

## DISCUSSION

In this study 75 women were enrolled with symptoms of premenstrual syndrome. The symptoms of premenstrual syndrome nausea 84%, gastrointestinal tract disturbance 85.3% and headache 80% noted to be the leading symptoms followed by breast tenderness 77.3% and vomiting 74.7%. The efficacy of mefenamic acid in term of relieving of symptoms was observed 70.7%. Statistically significant improvement in symptoms of headache, dysmenorrhea, breast tenderness and mood irritability were noted (p≤0.05). While no clinically significant distinction found among marital status, occupation, education and duration of symptoms improvement (p≥0.05). Premenstrual syndrome comprises a blend of psychological, social and physical symptoms that influence the daily routine ofmarried women in their reproductive age. Up to 80% of menstruating women experience premenstrual symptoms[12] and according to the American College of Obstetricians and Gynecologists (ACOG) criteria, the prevalence of PMS is between 20-40%[13].

Mefenamic acid is approved drug for dysmenorrhea and clinically shown meclofenamate is very effective in improving symptoms and changing the underlying pathophysiology[14]. The two-way mechanism of action gives these agents increased effectiveness and a rapid onset of action. In addition, in vitro the ability of meclofenamate inhibit 5-lipooxygenase activity, unlike members of propionic acid group, which have little or no inhibition[15]. Moreover, increased production of prostaglandins derived from cyclooxygenase-2 (COX-2) and other inflammatory mediators has been shown to cause excessive uterine contractions and increased uterine pain and contractions[16]. COX-2 inhibition by specific steroidal anti-inflammatory drugs reduces the synthesis of prostaglandins, contributing to their analgesic, antipyretic and analgesic properties and making them effective in increasing the severity of menstrual pain in women.[17]Use of these drugs is reported to be as high as 75-80%, and adverse effects range from minor symptoms such as diarrhea, abdominal pain, and nausea to more serious conditions such as chronic kidney disease[18]. Similarly, in our study we found efficacy of 72.7% of premenstrual symptoms in subset of psychological and physiological symptoms.

An Indian study observed premenstrual symptoms of headache in 52%, vomiting in 28%, breast tenderness in 30%. Further, the study reported 60% preferred the use of mefenamic acid and dicyclomine combination for symptoms relief as compared to paracetamol, ibuprofen, dicyclomine alone and hyoscine[19]. In our study, symptoms of headache, nausea, vomiting and breast tenderness reported were 80%, 84%, 74.7% and 77.3%, respectively. These symptoms were 70-80% improved with mefenamic acid use only. Moreover, various studies noted mefenamic acid to be the most commonly used and effective among various drugs used for self-medication[20,21]. Also, it was delineated that mefenamic acid had a comparable effect to clecoxib in relieving symptoms[22].

Various studies have reported the dramatic alleviation of dysmenorrhea associated with PMS, either alone or in combination with other complementary therapies[23-24]. However, the effect of mefenamic acid alone on overall symptoms of PMS is not appraised appropriately especially among the people of Pakistan. Moreover, due to less awareness about premenstrual symptoms and its management among people, majority of them suffer from various symptoms without reporting. Therefore, appropriate measures are being taken to increase awareness among women and provide better ways to alleviate PMS symptoms. Appropriate pharmacological and psychological treatment will improve quality of life.

## CONCLUSION

In conclusion, mefenamic acid is effective in women having premenstrual syndrome with the majority of treated women ensuing a favorable outcome. Although there is still no firm treatment algorithm, and the use of mefenamic acid and its dosage in premenstrual syndrome is controversial. According to our study, this may be an effective treatment option that should be considered, but more randomized studies involving large groups are needed to support this argument.

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**Conflict of interest:** Nil

**Authors Contribution: AZ;** provided concept/research design and did data collection. **MS, UN & MJ** did statistical analysis and manuscript writing. **AZ & MT** did edit of manuscript and project management. **AR & MT** did critical revision of the manuscript for important intellectual content. **AZ** takes the responsibility and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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