Effects of Vitamin E and Mefenamic Acid in the Treatment of Primary Dysmenorrhoea in Tertiary Care Hospital in Bangladesh

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Abstract

Background: In various research, vitamin E and mefenamic supplementation has been suggested as a viable treatment for primary dysmenorrhea.

Objective: To see the effects of Vitamin E and mefenamic acid in primary dysmenorrhea.

Methods: Sheikh Sayera Khatun Medical College and Hospital, Gopalganj conducted this observational type of prospective study. Where information was gathered between 1st April 2019 to 31st March 2020. During the research, a total of 40 Female OPD patients in Sheikh Sayera Khatun Medical College and Hospital, Gopalganj, who fulfilled the selection criteria were the study sample. Purposive sampling was used to acquire the samples according to the inclusion criteria. All data were coded and entered into SPSS-23 for further analysis. The statistics used were both descriptive and inferential. Statistics used to describe data included frequency distribution, percent, mean, and standard deviation; graphs; tables; and figures; and inferential statistics.

Results: VAS score was significantly decreased from baseline to end of treatment at 3rd cycle (7.40 ± 0.98 to 3.70 ± 0.72) for vitamin E group and (7.05 ± 0.75 to 3.52 ± 0.55) for mefenamic acid group. The percentage reduction of VAS was 49.60% and 49.51% at 3rd cycle. The Cox Menstrual Symptom Scale score significantly decreased from baseline to end of treatment at 3rd cycle (3.88 ± 0.40 to 1.25 ± 0.44). The percentage reduction of CMSS score was 67.50% and 65.83% at 3rd cycle.

Conclusion: As both Vitamin E and Mefenamic acid shows significant reduction in pain intensity in primary dysmenorrhoea without any difference between two treatment groups. So, in clinical practice, Vitamin E may be a useful alternative to Mefenamic acid in primary dysmenorrhoea.

Keywords: Primary dysmenorrhoea, Mefenamic acid, Vitamin E.

Introduction

Every woman's menstrual period is a natural occurrence that occurs throughout her reproductive period. Dysmenorrhea is the term for cramping pain that occurs during menstruation. Pain is most commonly felt in the suprapubic area, but it can also radiate to the backs of the legs or the lower back, and it is frequently accompanied by other biological symptoms such as dizziness, fatigue, sweating, backache, headache, nausea, vomiting, and diarrhoea, all of which occur just before or during
menstruation. Primary dysmenorrhoea is pain in the uterus produced by menstruation but not by any known pelvic ailment\[1\]. It appears 1–2 years after menarche and is associated with normal ovulatory cycles\[2\]. Dysmenorrhoea induced by uterine or pelvic illness is known as secondary dysmenorrhoea\[3\]. The majority of pain is caused by endometriosis and adenomyosis\[5\]. The exact source of pain in primary dysmenorrhoea is unknown. Myometrial contractions, which are induced by prostaglandins produced in the uterine endometrium and occur throughout the first 48 hours of menstruation, cause the pain\[2\]. In dysmenorrhoea, the menstrual fluid has a high concentration of Prostaglandin (PG) F2, which causes uterine blood vessel constriction, ischemia, and increased uterine smooth muscle contraction, resulting in dysmenorrhoeic pain\[6,7\]. Non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, calcium channel blockers, and progesterone, among other things, should be utilized to lower uterine prostaglandin synthesis, given the aetiopathogenesis of primary dysmenorrhoea.\[8\] NSAIDs reduce prostaglandin production by blocking the iso-enzymes of the cyclooxygenase (COX) family, which catalyze the synthesis of prostaglandins from arachidonic acid\[7\]. In addition to their therapeutic effects, NSAIDs can cause side symptoms such as heartburn, blurred vision, dizziness, headache, constipation, diarrhea, lethargy, dysuria, drowsiness, anorexia, nausea, skin acne, vomiting, and gastrointestinal bleeding\[8\].

In 1922\[9\] the role of Vitamin E in nutrition and fertility was established for the first time. Vitamin E works by inhibiting the enzymes phospholipase A2 and cyclooxygenase2 to prevent the production of arachidonic acid and the conversion of arachidonic acid to prostaglandin. Protein kinase C and an increase in intracellular calcium concentration are thought to govern phospholipase A2 activation. In the bovine brain, vitamin E inhibits protein kinase C, resulting in an increase in internal opioids and pain relief\[10,11\]. Vitamin E's antioxidant activity may reduce phospholipid peroxidation, hence inhibiting the release of arachidonic acid and its conversion to prostaglandins\[12\]. Even after intake of 300 mg/day for 23 years\[13\], vitamin E at a dose of 400 units per day for five days helps to significantly reduce the severity of pain in the treatment of dysmenorrhoea\[2,12-14\]. Recently several studies revealed that Vitamin E is effective in reduction of pain in dysmenorrhoea. It has also absence of significant side effects in therapeutic doses.

Mefenamic acid is a conventional and non-selective NSAID. It is easily accessible over the counter and is widely used by most local adolescents and adults for dysmenorrhoea. The dosage is 500mg to be taken orally three times/day after mea\[15\]. Vitamin E has a significant effect on dysmenorrhoea, equal to Mefenamic acid, which is a well-known medication for the treatment of dysmenorrhoea\[16\]. The therapeutic effect of Vitamin E in primary dysmenorrhoea was studied in several countries in the world and these studies inspired to see the effect of same drug in our community. So this study was designed to observe the effectiveness of Vitamin E and Mefenamic acid in the treatment of primary dysmenorrhoea.

**Objective**
To study the effects of Vitamin E and Mefenamic acid in primary dysmenorrhoea among OPD patients.

**Methodology**
Department of Obstetrics and Gynaecology, Sheikh Sayera Khatun Medical College and Hospital, Gopalganj conducted this observational type of prospective study. Where information was gathered between 1st April 2019 to 31st March 2020. During the research, a total of 40Female OPD patients in Sheikh Sayera Khatun Medical College and Hospital, Gopalganj who fulfilled the selection criteria were the study sample. Purposive sampling was used to acquire the samples according to the inclusion criteria. All data were coded and entered into SPSS-23 for further
analysis. The statistics used were both descriptive and inferential. Statistics used to describe data included frequency distribution, percent, mean, and standard deviation; graphs; tables; and figures; and inferential statistics.

Results
In table-1 shows age distribution of the study group where the patients were belong to 19-24 years. Mean ± SD of the age was **20.40 ± 1.46** years. while the mean age of 20.15 ± 1.49 years in Mefenamic acid treated group. The mean age of Vitamin E treated group and Mefenamic acid treated group did not differ significantly (t=0.756; p=0.452) suggesting an age matched study. The following table is given below in detail:

**Table-1:** Age distribution of the study group

| Age Range  | Mefenamic Acid group Mean ± SD | Vitamin E group Mean ± SD | P value |
|------------|--------------------------------|---------------------------|---------|
| 19-24 years | 20.15 ± 1.49                    | 20.40 ± 1.46              | 0.452   |

Table 2 shows the mean height (cm) of the Vitamin E treated group was 156.43 ± 4.73; whereas the mean height of the Mefenamic acid treated group was 155.99 ± 4.79. The mean height of the participants did not differ significantly between Vitamin E treated group and Mefenamic acid treated group (t=0.418; p=0.677).

The mean weight (Kg) of the Vitamin E treated group was 53.97 ± 6.05; whereas the mean height of the Mefenamic acid treated group was 55.90 ± 7.09. The mean weight of the participants did not differ significantly between Vitamin E treated group and Mefenamic acid treated group (t=1.307; p=0.195).

The mean BMI (Kg/M²) of the Vitamin E treated group was 22.09 ± 2.59; whereas the mean BMI of the Mefenamic acid treated group was 22.94 ± 2.42. The mean BMI of the participants did not differ significantly between Vitamin E treated group and Mefenamic acid treated group (t=1.514; p=0.134).

**Table 2:** Distribution of patients by anthropometric status

| Anthropometric status | Vitamin E group Mean ± SD | Mefenamic Acid group Mean ± SD | P value |
|-----------------------|---------------------------|-------------------------------|---------|
| Height (Cm) (Mean ± SD) | 156.43 ± 4.73            | 155.99 ± 4.79                | 0.677   |
| Weight (Kg) (Mean ± SD) | 53.97 ± 6.05             | 55.90 ± 7.09                 | 0.195   |
| BMI (Kg/M²) (Mean ± SD) | 22.09 ± 2.59             | 22.94 ± 2.42                 | 0.134   |

In table-3 shows the visual analogue scale score (mean ± SD) was 7.40 ± 0.98 at baseline before the initiation of treatment which decreased to 6.28 ± 0.72 at 1st cycle, to 5.00 ± 0.91 at 2nd cycle and to 3.70 ± 0.72 at 3rd cycle. In Mefenamic acid treated group, the visual analogue scale score (mean ± SD) was 7.05 ± 0.75 at baseline before the initiation of treatment which decreased to 5.90 ± 0.71 at 1st cycle, to 4.75 ± 0.71 at 2nd cycle and to 3.52 ± 0.55 at 3rd cycle. The Cox Menstrual Symptom Scale score (mean ±SD) was 3.88 ± 0.40 at baseline before the initiation of treatment which decreased to 3.12 ± 0.69 at 1st cycle, to 2.02 ± 0.83 at 2nd cycle and to 1.25 ± 0.44 at 3rd cycle. In Mefenamic acid treated group, the Cox Menstrual Symptom Scale score (mean ± SD) was 3.95 ± 0.22 at baseline before the initiation of treatment which decreased to 3.08 ± 0.42 at 1st cycle, to 2.10 ± 0.50 at 2nd cycle and to 1.35 ± 0.48 at 3rd cycle.
Table-3: VAS scores and CMSS scores of the participants at baseline and different cycles of treatment

|                      | Vitamin E Group Mean ± SD | Mefenamic Acid group Mean ± SD | P value |
|----------------------|----------------------------|--------------------------------|---------|
| Baseline             | 7.40 ± 0.98                | 7.05 ± 0.75                    | 0.077   |
| First Cycle          | 6.28 ± 0.72                | 5.90 ± 0.71                    | 0.021   |
| Second Cycle         | 5.00 ± 0.91                | 4.75 ± 0.71                    | 0.173   |
| Third Cycle          | 3.70 ± 0.72                | 3.52 ± 0.55                    | 0.228   |

| CMSS scores         | Mean ± SD                  | Mean ± SD                      | P value |
|---------------------|----------------------------|--------------------------------|---------|
| Baseline            | 3.88 ± 0.40                | 3.95 ± 0.22                    | 0.306   |
| First Cycle         | 3.12 ± 0.69                | 3.08 ± 0.42                    | 0.695   |
| Second Cycle        | 2.02 ± 0.83                | 2.10 ± 0.50                    | 0.626   |
| Third Cycle         | 1.25 ± 0.44                | 1.35 ± 0.48                    | 0.335   |

Figure -1 shows the percentage reduction of VAS score was in Vitamin E group 14.50% at 1st cycle, to 32.06% at 2nd cycle and to 49.60% at 3rd cycle of treatment. In Mefenamic acid treated group, the percentage reduction of VAS was 15.81% at 1st cycle, to 32.16% at 2nd cycle and to 49.51% at 3rd cycle of treatment.

In figure-2 shows the percentage reduction of CMSS score in Vitamin E treated group was 18.96% at 1st cycle, to 47.08% at 2nd cycle and to 67.50% at 3rd cycle of treatment. The percentage reduction of CMSS score in Mefenamic acid treated group was 22.08% at 1st cycle, to 46.88% at 2nd cycle and to 65.83% at 3rd cycle of treatment.
The recorded adverse effects were heart burn (0.0%) vs (22.5%) which was significantly fewer in Vitamin E treated group in respect to Mefenamic acid treated group; p=0.002, while nausea and or vomiting (12.5%) vs (27.5%); p=0.094 and dizziness (7.5%) vs (2.5%); p=0.615 did not differ significantly between two treatment groups.

**Figure 2:** Percentage reduction of CMSS score estimated at different cycles

**Discussion**

Vitamin E inhibits the release of arachidonic acid and the conversion of arachidonic acid to PG via an action on the enzymes phospholipase A2 and cyclooxygenase\[^{17}\]. Several studies reported that treatment with vitamin E therapy daily significantly reduced the severity of pain in primary dysmenorrhoea\[^{17,18}\]. A single study compared the effect Mefenamic acid and Vitamin E in the treatment of dysmenorrhoea with similar efficacy. In this study the age of the patients ranged from 19 to 24 years with the mean age (Mean ± SD) of 20.40 ± 1.46 years in Vitamin E treated group; while the age of the patients ranged from 17 to 23 years with the mean age of 20.15 ± 1.49 years in Mefenamic acid treated group. The
mean age of Vitamin E treated group and Mefenamic acid treated did not differ significantly (p=0.452) suggesting an age matched study. Ibrahim et al., (2015) reported the age of the female patients 21.40 ±1.4 years. This was consistent with the present study. In another study the mean age of the patients was 19.43 (±3.9) years with variation of participants aged 16 to 24 years. Age at enrolment of patients with dysmenorrhoea was 17.0 ± 0.7 years was also reported in the study of Ziae et al., (2001).

In the present study the mean height of the Vitamin E treated group was 156.43 ± 4.73 cm; whereas the mean height of the Mefenamic acid treated group was 155.99 ± 4.79 cm. The mean height of the participants did not differ significantly between Vitamin E treated group and Mefenamic acid treated group (p=0.677). Masoumi et al., (2016) reported mean height of the patients with dysmenorrhoea was 141.63 ± 3.60 cm.

This study demonstrated that the mean weight of the Vitamin E treated group was 53.97 ± 6.05 Kg; whereas the mean height of the Mefenamic acid treated group was 55.90 ± 7.09 Kg. The mean weight of the participants did not differ significantly between Vitamin E treated group and Mefenamic acid treated group (p=0.195). Mean weight of patients with dysmenorrhoea was 55.09 ± 5.81 kg reported in the study of Masoumi et al., (2016) which was close to the result of present study.

In this study the mean BMI of the Vitamin E treated group was 22.09 ± 2.59 Kg/M2; whereas the mean BMI of the Mefenamic acid treated group was 22.94 ± 2.42 Kg/M2. The mean BMI of the participants did not differ significantly between Vitamin E treated group and Mefenamic acid treated group (p=0.134). Farahani et al., (2017) reported that the BMI of the women with dysmenorrhoea was 21.2 ± 3.8. Ozgoli et al., (2009) found that the BMI of the women with dysmenorrhoea treated with Mefenamic acid was 22.2 ± 2.2 kg/m2.

In this study the visual analogue scale score was decreased from the value recorded before initiation of treatment to first cycle, second cycle and third cycle. The overall reduction of visual analogue scale score from baseline to end of treatment was significant (p<0.001) in Vitamin E treated group. Post hoc analysis revealed that VAS score decreased significantly at first cycle of treatment with Vitamin E from baseline and further decreased in subsequent cycle (baseline vs 1st cycle; p<0.001; baseline vs 2nd cycle, p<0.001; baseline vs 3rd cycle, p<0.001; 1st cycle vs 2nd cycle, p<0.001; 1st cycle vs 3rd cycle, p<0.001; 2nd cycle vs 3rd cycle, p<0.001)

Similarly in Mefenamic acid group, the visual analogue scale score was decreased from the value recorded before initiation of treatment to first cycle, second cycle and third cycle. The overall reduction of visual analogue scale score from baseline to end of third cycle of treatment was significant (p<0.001) in Mefenamic acid treated group. Post hoc analysis revealed that VAS score decreased significantly at first cycle of treatment with Mefenamic acid from baseline and further decreased in subsequent cycle (baseline vs 1st cycle; p<0.001; baseline vs 2nd cycle, p<0.001; baseline vs 3rd cycle, p<0.001; 1st cycle vs 2nd cycle, p<0.001; 1st cycle vs 3rd cycle, p<0.001; 2nd cycle vs 3rd cycle, p<0.001). There was no statistically significant difference found between two groups before initiation of treatment (p=0.077), the 2nd (p=0.173) and 3rd cycle (p=0.228) of treatment; but significant difference was observed at 1st cycle of treatment (p=0.021).

In a study by Vilvapriya and Vinodhini, (2017), 200 units of Vitamin E twice daily were given in the treatment of primary dysmenorrhoea. The treatment began two days before the beginning of menstruation and continued through the first three days of bleeding. The severity of pain and duration of pain before and after the treatment was studied. There was a significant difference between the pre- and post-treatment periods in terms of pain severity by VAS score (p=0.720 and p=0.002, respectively). Nayeban et al., (2014)
found that the pain intensity in the vitamin E was 55.7742 before the treatment started and reduced to 45.1398 after the treatment. The reduction of pain measured by VAS score from before the treatment to after the treatment showed a significant difference (p<0.001). In a study by Ziaei et al., (2001) on the effect of Vitamin E on dysmenorrhea, 500 IU Vitamin E was used for 5 days during the beginning of menstruation and was compared with placebo. They showed that both Vitamin E and placebo reduced the pain of dysmenorrhea but that the reduction was greater in the Vitamin E group. The result of this study is in agreement with the present study, but our dosage of Vitamin E was lower. In another study by Ziaei et al., (2005) 400 IU Vitamin E was used for 4 months. The conclusion was that pain severity in month 4 was less than the pain reported in month 2 after treatment, indicating a positive effect of Vitamin E throughout the treatment and that more prolonged use had a greater effect. This study agreed with our study findings. A study by Kashanian et al., (2013) used 400 IU/day of Vitamin E starting 2 days before the beginning of menstruation and continuing for a total of 5 days, for 2 consecutive cycles revealed a significant reduction in severity of pain (p = 0.046) when 400 units of Vitamin E per day was given for 5 days. Shirvani et al., (2015) found that the pain intensity in the Mefenamic acid was 55.03 ± 14.95 in the onset of the study. It was 39.01 ± 17.77 in the first month and 33.75 ± 17.71 in the second month. Repeated measurement showed a significant difference in pain intensity within the groups by time (p<0.05). Farahani et al., (2017) found that the comparison of variations of pain pre-treatment and post-treatment in the Mefenamic acid group revealed statically significant difference pain severity measured by VAS score with p-value of comparison between the first month and control cycle (p<0.001), comparison between the second month and control cycle (p<0.001); and comparison between the first month and second month (p<0.001).

This study also showed the percentage change in VAS score estimated at first, second and third cycle of treatment in comparison to before initiation of treatment. In Vitamin E treated group, the percentage improvement of VAS score was 14.50% at first cycle, 32.06% at second cycle and 49.60% at third cycle of treatment. The overall difference from baseline to last cycle of treatment was significant (p<0.001). In Mefenamic acid treated group, the percentage improvement of VAS score was 15.81% at first cycle, to 32.16% at second cycle and to 49.51% at third cycle of treatment. The overall percentage improvement of VAS score from baseline to completion of treatment was significant (p<0.001). But when percentage reduction of VAS score of the two treatments were compared, there were no significant percentage reduction of VAS score in Vitamin E treated group compared to Mefenamic acid treated group estimated at first cycle (p=0.555), at second cycle (p=0.955) and at third cycle (p=0.968) of treatment. From the above findings of changes in VAS score it was summarized that pain was reduced in both Vitamin E and Mefenamic acid treated group with significantly more pain reduction in first cycle in Mefenamic acid treated group but similar effect was seen thereafter in both groups. In a study by Vilvapriya and Vinodhini, (2017), 200 units of Vitamin E twice daily were given in the treatment of primary dysmenorrhea. The study showed that there was significant difference in percent of reduction of pain of 57.8±22.8 in Vitamin E group at the end of treatment. Other available studies did not show the percent reduction of pain in Mefenamic acid.

In this study the Cox Menstrual Symptom Scale score was decreased from the value recorded before initiation of treatment to first cycle, second cycle and third cycle. The overall reduction of Cox Menstrual Symptom Scale score from the score of before initiation of treatment to cessation of treatment was significant (p<0.001) in Vitamin E treated group. Post hoc analysis revealed that CMSS score decreased significantly at first cycle...
of treatment with Vitamin E from baseline and further decreased in subsequent cycle (baseline vs 1st cycle; p<0.001; baseline vs 2nd cycle, p<0.001; baseline vs 3rd cycle, p<0.001; 1st cycle vs 2nd cycle, p<0.001; 1st cycle vs 3rd cycle, p<0.001; 2nd cycle vs 3rd cycle, p<0.001). Similarly, Mefenamic acid group, the Cox Menstrual Symptom Scale score was decreased from the value recorded before initiation of treatment to first cycle, second cycle and third cycle. The overall reduction of Cox Menstrual Symptom Scale score from baseline to third cycle of treatment was significant (p<0.001) in Mefenamic acid treated group. Post hoc analysis revealed that CMSS score decreased significantly at first cycle of treatment with Mefenamic acid from baseline and further decreased in subsequent cycle (baseline vs 1st cycle; p<0.001; baseline vs 2nd cycle, p<0.001; baseline vs 3rd cycle, p<0.001; 1st cycle vs 2nd cycle, p<0.001; 1st cycle vs 3rd cycle, p<0.001; 2nd cycle vs 3rd cycle, p<0.001). When change in the Cox Menstrual Symptom Scale score in the two treatments groups were compared, no significant difference was observed before initiation of treatment (p=0.306), at first cycle (p=0.695), second cycle (p=0.626) and at third cycle (p=0.335) of treatment. In a study by Vilvapriya and Vinodhini, (2017), 200 units of Vitamin E twice daily were given in the treatment of primary dysmenorrhoea. The study showed that there was significant difference in percent of reduction of duration of pain of 68.5±28.2 in Vitamin E group at the end of treatment. Other available studies did not show the percent reduction of pain in Mefenamic acid. Safari et al. (2006) showed that Vitamin E has a significant effect on dysmenorrhoea, equal to Mefenamic acid, which is a well-known medication for the treatment of dysmenorrhoea; the results are similar to the findings of the present study. One study shows that Mefenamic Acid is a suitable drug for the treatment of primary dysmenorrhoea, especially in those suffering from moderate pain[20]. In another study, Mefenamic Acid has been proposed as a dominant treatment for dysmenorrhoea[21].
Conclusion
Based on study findings, it can be concluded that Vitamin E is effective in the treatment of primary dysmenorrhoea. Vitamin E is free from adverse effects. The Vitamin E has less side effects. Vitamin E is the effective and the safe option for the treatment of primary dysmenorrhoea.

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