

Comparison of Effects of Ginger, Mefenamic Acid, and Ibuprofen on Pain in Women with Primary Dysmenorrhea

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Abstract

Objectives: To compare the effects of ginger, mefenamic acid, and ibuprofen on pain in women with primary dysmenorrhea.

Methods: This was a double-blind comparative clinical trial conducted from September 2006 to February 2007. Participants were 150 students (18 years old and over) with primary dysmenorrhea from the dormitories of two medical universities who were alternately divided into three equal groups. Students in the ginger group took 250 mg capsules of ginger rhizome powder four times a day for three days from the start of their menstrual period. Members of the other groups received 250 mg mefenamic acid or 400 mg ibuprofen capsules, respectively, on the same protocol. A verbal multidimensional scoring system was used for assessing the severity of primary dysmenorrhea. Severity of disease, pain relief, and satisfaction with the treatment were compared between the groups after one menstruation.

Results: There were not significant differences between groups in baseline characteristics, $p > 0.05$. At the end of treatment, severity of dysmenorrhea decreased in all groups and no differences were found between the groups in severity of dysmenorrhea, pain relief, or satisfaction with the treatment, $p > 0.05$. No severe side effects occurred.

Conclusion: Ginger was as effective as mefenamic acid and ibuprofen in relieving pain in women with primary dysmenorrhea. Further studies regarding the effects of ginger on other symptoms associated with dysmenorrhea and efficacy and safety of various doses and treatment durations of ginger are warranted.

Introduction

Dysmenorrhea is one of the most frequent gynecologic disorders, affecting more than half of menstruating women. Most adolescents experience dysmenorrhea in the first few years after the menarche. Primary dysmenorrhea is defined as pelvic pain around the time of menstruation in the absence of an identifiable pathologic lesion, present from menarche.¹ It is a frequent cause of absenteeism and medical visits, and affects personal as well as economic aspects of life. It is estimated that severe dysmenorrhea results in the loss of 600 million working hours and \$2 billion in lost productivity annually.²

Although the etiology of primary dysmenorrhea is not completely understood, symptoms are generally associated with increased production of prostaglandins (PGs) in the en-

dometrium with menses, and approximately 80% of patients can experience pain relief by taking prostaglandin inhibitors, including propanolol and phenamates.³ Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as first-line therapy in women with primary dysmenorrhea. Evidence-based data support the efficacy of ibuprofen, naproxen, mefenamic acid, and aspirin.⁴ These agents, however, have side effects, of which gastrointestinal disorders such as nausea, dyspepsia, and vomiting are the most common.⁵

Some patients with primary dysmenorrhea do not respond to treatment with NSAIDs or oral contraceptives. In addition, some women have contraindications to these medications. Consequently, researchers have investigated numerous alternative/complementary treatments such as herbal and dietary therapies,⁶ behavioral interventions,⁷ acupuncture,⁸ and aromatherapy.⁹ Ginger, the rhizome of *Zingiber*

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officinale, is a traditional medicine with anti-inflammatory and anticarcinogenic properties.¹⁰ It is a botanical general recognized as safe (GRAS) by the United States Food and Drug Administration (FDA)¹¹ with no report of severe side effects or drug interactions in Germany's Commission E Monograph.¹² Ginger has been widely used in medicine, and has been administered in Traditional Chinese Medicine for more than 2500 years as an anti-inflammatory agent in musculoskeletal disorders.¹⁰ Two compounds in ginger, [6]-Gingerol and Gingerdiones, are potent inhibitors of PGs by blocking cyclooxygenase.^{10,13} Traditional application of ginger to relieve symptoms of dysmenorrhea has been noted in several classical sources¹⁴ such as *Kitab al Qanun fi Al Tibb* by Ibn Sina (*The Canon of Medicine* by Avicenna).¹⁵ However, to the best of our knowledge, there are no reports of a controlled study of the use of ginger in dysmenorrhea. The aim of the present study was to compare the effects of ginger with mefenamic acid and ibuprofen on pain in women with primary dysmenorrhea.

Materials and Methods

This was a double-blind comparative clinical trial conducted from September 2006 to February 2007. Patients included students (aged 18 years and over) with primary dysmenorrhea selected by continuous sampling from the dormitories of Isfahan and Shahid Beheshti Universities of Medical Sciences. The purpose and method of the study were explained and informed consent was obtained from all patients. The ethics committee of Shahid Beheshti University of Medical Science approved the study.

At baseline, the severity of dysmenorrhea, demographic data, and menstrual characteristics were assessed by a self-administered questionnaire. Severity was assessed before and after the intervention by a verbal multidimensional scoring system that has been used in previous studies^{9,16} with four grades: painless menstruation = 0, menstruation with pain but rare use of analgesics or limitation of activities = 1, menstruation with moderate pain with influence on daily activities and use of analgesics with relief = 2, and menstruation with severe pain with significant limitations on daily activities, ineffective use of analgesics, and such symptoms as headache, tenderness, nausea, vomiting, and diarrhea = 3. Patients with moderate to severe dysmenorrhea (score 2 or 3) were included. Exclusion criteria were a pre-existing diagnosed disease, history of gestation or taking oral contra-

ceptives, medicinal or herbal sensitivities, body mass index (BMI) <19 or >26, and mild dysmenorrhea (score 1).

The 150 patients were alternately allocated into three groups. Each group took their medication four times a day for three days from the start of their menstrual period. In the first group, patients received capsules containing 250 mg of ginger rhizome powder (Zintoma; Goldaru Co., Iran). The second group received 250 mg mefenamic acid capsules (Ponstan; Razak Co., Iran) and the third group took 400 mg ibuprofen capsules (Brufen; Roozdaru Co., Iran). The capsules in all groups were similar in shape and package and were administered anonymously with coding by a midwife colleague with no knowledge of the codes. To measure compliance we asked patients to report the number of capsules they have taken.

Final assessment was performed after one menstrual period by another colleague who had no information about the groups. Patients and assessor were blinded to the groups. In addition to the verbal multidimensional scoring system, a 5-point scale was used to assess pain relief (considerably relieved, relieved, unchanged, worse, considerably worse) and patient satisfaction with the treatment was also assessed (satisfied, not satisfied). Analysis of variance (ANOVA) and chi-square tests were used to identify any difference between the groups in baseline characteristics, severity of disease, pain relief, and satisfaction with the treatment; a *p* value < 0.05 was considered significant. A sample size of 150 patients was required assuming 90% power and estimation of improvement for mefenamic acid (80%) and for ginger (at least 50%).

Results

At baseline, no significant differences were found between the groups regarding age, BMI, or menstruation characteristics (Table 1).

There were no significant differences between the groups in severity of dysmenorrhea before or after treatment (Table 2). Also, no significant differences were found between the three groups in relief, stability, or aggravation of symptoms. Compliance in using the capsules was the same in all three groups.

Four students in each group reported a slight increase in bleeding as a menstrual change. One student in the mefenamic acid group and one in ginger group experienced decreased bleeding, and one student in the ibuprofen group reported increased duration of menstruation.

TABLE 1. BASELINE DEMOGRAPHICS

	Mefenamic acid (n = 50)	Ibuprofen (n = 50)	Ginger (n = 50)
Age (years)	21.8 ± 2.3	21.3 ± 2.3	21.5 ± 2.6
Body mass index	22.2 ± 2.2	22.3 ± 2.2	22.2 ± 2.3
Menarche (age in years)	12.9 ± 1.3	13 ± 1.5	12.9 ± 0.9
Duration of menses (days)	6.4 ± 1	6.2 ± 1.2	6.6 ± 1.1
Duration of cycles (days)	28 ± 1.8	28.9 ± 2.9	29.1 ± 2
Interval of cycles (days)	22.4 ± 2	22.4 ± 3	22.6 ± 2.3
Pads used	3.1 ± 1	2.7 ± 0.9	2.8 ± 0.9
Pain in all cycles			
Yes	42 (84%)	44 (88%)	47 (94%)
No	7 (14%)	6 (12%)	3 (6%)

TABLE 2. SEVERITY OF DYSMENORRHEA BEFORE AND AFTER TREATMENT

	Mefenamic acid (n = 50)	Ibuprofen (n = 50)	Ginger (n = 50)
At baseline			
Moderate	31 (62%)	34 (68%)	36 (72%)
Severe	19 (38%)	16 (32%)	14 (28%)
After treatment			
Painless	10 (20%)	13 (26%)	18 (36%)
Mild	12 (24%)	14 (28%)	13 (26%)
Moderate	19 (38%)	20 (40%)	25 (30%)
Severe	9 (18%)	3 (6%)	4 (8%)
Change in pain severity			
Considerably relieved	15 (30%)	18 (36%)	18 (36%)
Relieved	18 (36%)	15 (30%)	13 (26%)
Unchanged	13 (26%)	17 (34%)	15 (30%)
Worse	3 (6%)	3 (6%)	4 (8%)
Considerably worse	1 (2%)	0	0
Rate of satisfaction	20 (40%)	22 (44%)	21 (42%)
Number of capsules used	11.2 ± 1.4	11.1 ± 1.9	11.5 ± 1.5

Discussion

Our findings showed that ginger was as effective as mefenamic acid and ibuprofen in relieving menstrual pain. Mefenamic acid and ibuprofen are the drugs of choice for treating primary dysmenorrhea,¹⁷ with up to 80% efficiency.³ Different theories exist regarding dysmenorrhea-inducing mechanisms, one of which is increased production of PGs in the endometrium. PGs originate from arachidonic acid in cyclooxygenase and lipooxygenase pathways. Studies have shown that the menstrual blood of women with dysmenorrhea has greater amount of two PGs—PGE₂ and PGF₂α. In women with primary dysmenorrhea, pain results from myometrial contractions induced by PGs (mainly PGF₂α) originating in secretory endometrium.³

Anti-prostaglandins such as NSAIDs can relieve dysmenorrheal pain. Mefenamic acid from fenamate groups and ibuprofen from propionic acids act as inhibitors of PGs synthesis.⁵ The question is why ginger has similar effects as the other two drugs. In a search of the literature, we found no study that assessed the effects of ginger on dysmenorrhea; its use has been based on traditional sources.¹⁵ However, the effects of other herbs such as fennel,^{16,18} cumin, and chamomile on dysmenorrhea have been studied.¹¹ Like other herbs, ginger compounds are very complex and include many substances such as carbohydrates, free fatty acids, amino acids, proteins, phytoesters, vitamins (niacin), and some nonaromatic compounds such as gingerols and shogaols.¹¹ Its essence mainly includes sesquiterpene.¹⁴ Altman and Marcussen compared the effects of two ginger species (*Z. officinale* and *Alpinia galangal*; 510 mg twice daily) with placebo in patients with knee osteoarthritis and found that ginger extract had a significant effect on reducing symptoms of osteoarthritis.¹⁹ Salicylate has been found in ginger in amounts of 4.5 mg/100 gm fresh root. Therefore, there was less than 1mg salicylate in the capsule in the study of Altman and Marcussen, and this could not explain the observed effects of ginger.¹⁹ In fact, ginger inhibits cyclooxygenase and lipooxygenase pathways in PGs synthesis.^{10,13} In pharmacopoeias, ginger is indicated for dyspepsia, disten-

sion, colic, vomiting, diarrhea, spasms and other smooth muscle disorders, colds, influenza, and rheumatism as an anti-inflammatory agent.¹⁴ It has been shown that gingerols in ginger have anti-inflammatory effects both *in vitro* and *in vivo*.^{20,21} The anti-inflammatory property of ginger has been attributed to the inhibition of cyclooxygenase and lipooxygenase, leading to reduction of leukotriene and prostaglandin.²²

Considering this evidence, it seems that ginger had anti-prostaglandin effects similar to those of mefenamic acid and ibuprofen, and gingerols may be the principle active ingredient for these effects. Measuring PGs in plasma or menstrual blood throughout the treatment may help to clarify the mechanism of action of ginger on primary dysmenorrhea. Dysmenorrhea is sometimes associated with nausea and vomiting, and ginger also works to alleviate these symptoms. The efficacy of ginger in treatment of chemotherapy-induced delayed nausea²³ and nausea and vomiting in pregnancy and after surgery^{24,25} has been reported, with minor side effects.

It has been reported that more than 6 g of dry powder of ginger can cause desquamation of the epithelial cells in the stomach lining of humans. Therefore, the dosage should be limited to less than 6 g on an empty stomach.²⁶ It can also result in sensitivity reactions, dermatitis²⁷ and, at high doses, in depression of the nervous system as well as cardiac dysrhythmia.²⁸ Although there is no evidence regarding drug interactivity of ginger,¹¹ NSAIDs, particularly aspirin, have the potential to interact with herbal supplements, and further research is needed to confirm and assess the clinical significance of these potential interactions.²⁹

There are some limitations to this study. Because randomization was not easily possible, patients were alternately allocated into the groups. However, all three groups were similar in baseline characteristics. Although participants could not determine whether they received a ginger or other capsule even after examining, smelling, and swallowing it,³⁰ questioning participants whether they thought they had received an active treatment or a placebo could specify a double blind setting. We did not assess other possible symptoms

associated with dysmenorrhea; that is suggested for future studies. Also, using measurements such as the visual analogue scale or the numeric rating scale for assessing symptoms may help to find minimal differences between the groups.

Conclusion

Ginger is as effective as mefenamic acid and ibuprofen in relieving pain in women with primary dysmenorrhea. Further studies regarding the effects of ginger on other symptoms associated with dysmenorrhea, the efficacy and safety of various doses and treatment durations of ginger, and the exact mechanism of action are warranted.

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Conflicts of interest

No competing financial interests exist.

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