Research Article

Studying the Effect of Montelukast in the Treatment of Dysmenorrhea: A single-Blind, Placebo-controlled Trial

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Abstract

Background: In the field of gynecology, studies have found high levels of leukotriene in the endometrium and uterine smooth muscles of patients with dysmenorrheal and menstrual pain.
Aim: to evaluate the effectiveness of montelukast in relieving the symptoms of dysmenorrhea. **Patients and methods:** A randomized, single-blind, prospective, placebo-controlled study was designed. Seventy patients suffering from dysmenorrhea complete this study, divided randomly into two groups: montelukast group (34 patients) and placebo group (36 patients).Values before and after treatment were compared over two menstrual cycles, using visual analog scale (VAS) score and NSAID usage per menstrual cycle. **Results:** Post-treatment VAS score and NSAID usage decreased significantly in both montelukast and placebo group, compared to their pre-treatment values ($P<0.05$). The mean decreases in VAS score and NSAID usage were more in the montelukast group than in the placebo group, but the differences were not statistically significant ($p>0.05$). The ratio of the highly effective cases, for both VAS score and NSAID usage, was significantly higher in the montelukast group than placebo group ($P<0.05$). Means of VAS score and NSAID usage didn't change in all of endometriosis patients after administration of montelukast or placebo therapy. **Conclusions:** For some women, montelukast may be effective in relieving symptoms of primary dysmenorrhea. It's safe and has no serious adverse effects. Thus, it can be considered as a good option for treatment of primary dysmenorrhea before starting with hormonal therapy.

Keywords: Montelukast, NSAIDs, Dysmenorrhea

INTRODUCTION

Dysmenorrhea is the most common gynecological complaints among adolescent and young adult females, in whom it's usually primary (functional) and associated with normal ovulatory cycles and with no pelvic pathology. In approximately 10% of adolescents and young adults with severe dysmenorrheal symptoms, pelvic abnormalities such as endometriosis or uterine anomalies may be found (secondary dysmenorrhea).[1]

Potent prostaglandins and leukotrienes play an important role in generating dysmenorrheal symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills are the most common pharmacologic treatment for dysmenorrhea.[2] Leukotriene is an eicosanoid involved in a variety of metabolic processes, including smooth muscle contraction. It's produced by the arachidonate cascade, which also synthesizes prostaglandin.[3, 4] Leukotriene is involved in bronchial

smooth muscles contraction as a mediator in the pathogenesis of bronchial asthma. Therefore, for treatment of bronchial asthma in both adults and children, a leukotriene receptor antagonists have been developed.[5, 6] Montelukast, a prototype leukotriene receptor antagonist, is a very safe medication and its serious adverse reactions very rare even with long-term usage.[7] Many reports listed leukotriene receptor antagonists, including montelukast, as an acceptable treatment option for asthma even during pregnancy.[8, 9, 10]

Leukotriene can be considered as one of the causative agents of pain as it increases vascular permeability and involved with neutrophil migration, aggregation and degranulation. In gynecologic view, leukotriene receptors are widely distributed in the endometrium and uterine smooth muscles.[11, 12] For patients with menstrual pain, so many studies have found high levels of leukotriene in the endometrium and uterine smooth muscles. The levels of prostaglandin are not elevated in about 30% of patients with dysmenorrhea, such cases that are unresponsive to NSAIDs. For those patients, it is thought that leukotriene, not prostaglandin, is involved with the menstrual pain.[13, 14, 15]

In the present study, and to investigate that this theory is true or not, we evaluate the effect of montelukast on alleviating the symptoms associated with dysmenorrhea.

PATIENTS AND METHODS

This study was designed as a randomized, single-blind, prospective, placebo-controlled study from February to July 2011 in Al-Zahraa Hospital for obstetrics and gynecology and in a specialist private clinic under supervision of gynecologist and in accordance with a protocol previously designed for this study. An informed consent was obtained from each patient.

Inclusion criteria of this study involved Iraqi women patients with a moderate level of education suffering from dysmenorrhea, partially or inadequately responded to NSAID therapy (selective or nonselective Cox inhibitors) and with a visual analog scale (VAS) score of > 5 points and/or ingestion of more than 12 NSAID tablets / period. (Note: in the VAS score, the severity of dysmenorrhea is scored as self- assessment by the patient on a horizontal line on a scale from 0 to 10, with 0-1 being no feeling of pain, 2-4 mild pain, 5-7 moderate pain, and 8-10 worst possible pain).

Females with an acute or chronic illness; with a history of abdominal and pelvic surgery within six months; irregular menses; sexually active; using oral contraceptive pills or had taken gonadotropin releasing hormone (GnRH) agonists within six months, and those who suffering from premenstrual syndrome (PMS) were excluded from this study.

The present study involved 76 patients suffering from dysmenorrhea, divided randomly into two groups: montelukast group (37 patients) and placebo group (39 patients). In the montelukast group, 10 mg/day of montelukast (Singulair® 10mg / tablet- MSD company) was administered orally every day starting on day 21 of the menstrual cycle until the last day of the menstrual period (to give adequate time for montelukast to achieve its action, according to previous literature review[11,13] and for just two menstrual cycles as the follow up of our patients was difficult . In the placebo group, lactose was administered in the same manner followed with montelukast group. For both groups, patients were instructed to take only ibuprofen tablets (no other NSAIDs) on need (Profedin® 200 mg / tablet- SDI manufacture).

Visual analog scale (VAS) score and NSAID usage were recorded using self-assessment sheets to assess pain associated with dysmenorrhea. The VAS score and NSAID usage per menstrual cycle prior to treatment were compared to the average values of two cycles after treatment for both groups. To evaluate the changes in VAS score and NSAID usage values, we divided our cases into four levels: no change cases; mildly effective cases; moderately effective cases; and highly effective cases.

This study was planned to have a size that would be sufficient to detect any significant difference among patient groups. Data were expressed as mean ± standard error of mean (SEM) or proportions (number or percentage of patients). Excel program of Microsoft Office 2007 was applied, where student's t-test and chi-square test ($\chi 2$ analysis) were used to statistically analyze our data. In the exploratory analysis of the endpoints, all p-values <0.05 were considered significant.

RESULTS

In the present study, 76 patients were involved; 6 of them were excluded (3 patients with poor compliance and 3 patients dropped out), so the data collected were analyzed from only 70 patients (montelukast group: n = 34; placebo group: n = 36).

Concerning patients background characteristics, there were no significant differences (p>0.05) in the age, body mass index (BMI), presence of endometriosis (depending

on patients history), baseline VAS score and NSAID usage, between montelukast and placebo group (Table 1).

Table 1. Background characteristics for patient groups.

	Montelukast (*n* = 34)	Placebo (*n* = 36)	P value
Age (years)	36.5 ± 2.3	34.9 ± 3.1	>0.05
BMI (Kg/m^2)	22.3 ± 1.4	23.5 ± 1.7	>0.05
Endometriosis [No. (%)]	7 (21%)	9 (25%)	>0.05
VAS score (0–10 points)	7.8 ± 0.6	6.9 ± 0.3	>0.05
NSAID usage (tablets/month)	14.6 ± 1.2	13.2 ± 1.4	>0.05

Table 4. Percentages of change in VAS score and NSAID usage.

Parameter	Montelukast (*n* = 34)	Placebo (*n* = 36)	P-value
ΔVAS	28%	20%	>0.05
ΔNSAID	20%	13%	>0.05

Table 2. Distributions in relation to the changes in VAS score and NSAID usage.

	Montelukast (*n* = 34)	Placebo (*n* = 36)	P-value
VAS score			
No change	8 (24%)	11 (31%)	>0.05
Mildly effective	9 (26%)	9 (25%)	>0.05
Moderately effective	10 (29%)	14 (39%)	>0.05
Highly effective	7 (21%)	2 (5%)	<0.05*
NSAID usage			
No change	9 (26%)	9 (25%)	>0.05
Mildly effective	8 (24%)	11 (31%)	>0.05
Moderately effective	10 (29%)	14 (39%)	>0.05
Highly effective	7 (21%)	2 (5%)	<0.05*

*Values of number of cases: mildly effective (decreased ≤25%), moderately effective (decreased 26–50%), and highly effective (decreased ≥51%).

Table 3. Pre- and post-treatment parameters changes.

	Montelukast (*n* = 34)			Placebo (*n* = 36)		
	Pre	Post	P-value	Pre	Post	P-value
VAS (0–10 points)						
Mean±SEM	7.8 ± 0.6	5.6 ± 0.4	<0.05*	6.9 ± 0.3	5.5 ± 0.5	<0.05*
Range	(7–10)	(2–7)		(6–10)	(3–9)	
NSAID usage (tablets/month)						
Mean±SEM	14.6± 1.2	11.7± 1.3	<0.05*	13.2 ± 1.4	11.5 ± 1.7	<0.05*
Range	(16–27)	(10–18)		(14–29)	(11–21)	

Table (2) clarified the distributions in relation to the changes in VAS score and NSAID usage values. According to the degree of response to the investigated drug, our patients were classified into four levels: no Change: mildly effective (≤25% decrease); moderately effective (26–50% decrease); and highly effective (≥51% decrease), where a "highly effective case" was defined as a post-treatment value less than half that of the pre-treatment value.

Concerning to VAS score, 7 patients (21%) in the montelukast group and 2 patients (5%) in the placebo group were highly effective cases (P <0.05). For NSAID usage, also 7 patients (21%) in the montelukast group and 2 patients (5%) in the placebo group were highly effective cases (P <0.05). So, the ratio of the highly effective cases, for both VAS score and NSAID usage, was significantly higher in the montelukast group than placebo group (P<0.05). In other grades of response (no change, mildly effective, and moderately effective cases), there were no significant differences (P >0.05) in the values of VAS score and NSAID usage between montelukast and placebo group (Table 2).

The total number of endometriosis patients who were suffering from dysmenorrhea within montelukast group was only seven (21%), and within placebo group was only nine (25%) (Table 1). Means of VAS score and NSAID usage didn't change in those patients with endometriosis after administration of montelukast or placebo therapy.

The changes of pre- and post-treatment VAS score and NSAID usage are presented in table (3). Post-treatment means of VAS score and NSAID usage were decreased

significantly (P<0.05) compared to their pre-treatment values, in both montelukast and placebo group.

The montelukast group showed a larger decrease in both VAS score and NSAID usage than the placebo group (ΔVAS and ΔNSAID were 28% and 20% vs. 20% and 13%, respectively) but the differences were not statistically significant (P>0.05) (table 4). [Note: ΔVAS and ΔNSAID were calculated from table (3) as mean value of pre-treatment minus post-treatment, and then the results of subtraction were represented as percentages].

No patient experienced any serious adverse effects in the present study. Only one patient in the placebo group developed headache and one patient in the montelukast group developed a mild dizziness that improved over the short term and did not required discontinue of therapy.

DISCUSSION

Patients number in whom VAS score and NSAID usage decreased by at least 50% after treatment (highly effective cases) was significantly higher in the montelukast group than placebo group (p<0.05) (Table 2). According to this study, montelukast may be effective in reducing dysmenorrhea symptoms in some women. This effect of montelukast may be attributed to its anti-inflammatory effects, including suppression of cytokines and vascular permeability, and its suppressive effect on smooth muscles contraction.[16, 17] With different dosage regimen, certain study observed a beneficial effects of anti-leukotrienes on dysmenorrhea[18] and consist with our results; while another study found no significant effects of these agents for adolescent patients with dysmenorrhea.[19]

In montelukast and placebo group, the post-treatment means of VAS score and NSAID usage were decreased significantly (P<0.05) compared to their pre-treatment values (table 3). Although the degrees of change in VAS score (ΔVAS) and NSAID usage (ΔNSAID) were larger for the montelukast group than placebo group, the differences were not statistically significant (P>0.05) (Table 4). These findings might be explained by the fact that placebo effect in dysmenorrhea generally estimated to be about 20–30%.[20] The results might be skewed by the placebo effect as our study population was small.

Numerous inflammatory cells are suspected to contribute for the aggravation of the endometriosis lesion. Montelukast has anti-inflammatory effects and can suppress the production of chemical mediators, particularly from mast cells, so may improve the pain associated with dysmenorrhea.[21, 22, 23] Certain study reported the effectiveness of montelukast for suppression of stromal proliferation, infiltration, and activation of mast cells in a rat endometriosis model. These findings suggest that montelukast has a direct therapeutic value for the treatment of endometriosis.[24]

The effect of montelukast in reducing dysmenorrheal symptoms for patients with endometriosis was investigated during this study. The total number of endometriosis patients within montelukast group was only seven (21%) (Table 1) and the means of VAS score and NSAID usage didn't change in all of these patients after administration of montelukast. Therefore, the effect of montelukast appeared to be only for dysmenorrheal patients without endometriosis. This finding may be supported by the mechanism of montelukast that affects smooth muscles contraction which is related to the functional (primary) dysmenorrhea.[16, 17] However, because of the small sample size, multi-centers and larger-scale studies are required with long-term administration of montelukast for patients with and without endometriosis to determine the direct therapeutic value of montelukast for treatment of different types of dysmenorrhea (primary and secondary).

Previous studies on patients with bronchial asthma have reported gene polymorphism, and consequently individual variations in the efficacy of montelukast, in the substances involved with arachidonate cascade.[25,26] Accordingly, the unresponsiveness to the montelukast therapy found in some women with dysmenorrhea may be attributed to this gene polymorphism. So, a custom-made therapy for dysmenorrhea may be made possible in the further.

Montelukast, as a leukotriene receptor antagonist, is very safe medication and does not suppress ovulation or affect hormonal levels, so may provide to some women an alternative option for the traditional treatment of dysmenorrhea, which involves low-dose contraceptive pills and gonadotropin releasing hormone (GnRH) analogs.[11] These medications do not adequately reduce dysmenorrheal symptoms in many women, suppress ovulation, and cause many side effects.[27] The dose of montelukast in the present study (10 mg/day) was determined depending on the standard dose for bronchial asthma,[5,6] and other doses should also be evaluated. Further investigations also required to evaluate whether montelukast is equally effective (or ineffective) in women using an oral contraceptive pills compared to those with natural menstrual cycles, for both regular and irregular menses. A cross-over study design also required

to evaluate whether montelukast is a truly effective medication for dysmenorrhea in an appropriate number of participates. In summary, for some women, montelukast may be effective in relieving symptoms associated with primary dysmenorrhea. It's safe and has no serious adverse effects. Thus, montelukast can be considered as a good option for treatment of primary dysmenorrhea before starting with hormonal therapy.

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