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Efficacy of montelukast, a leukotriene receptor antagonist, for the treatment of dysmenorrhea: A prospective, double-blind, randomized, placebo-controlled study

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ABSTRACT

Objective: To investigate the effectiveness of montelukast, a leukotriene receptor antagonist, in alleviating the symptoms of dysmenorrhea.
Study design: This prospective, double-blind, randomized, placebo-controlled study was comprised of 62 patients with dysmenorrhea who were randomly divided into 2 groups (montelukast and placebo). Data obtained from 50 patients were analyzed (montelukast: 24; placebo: 26). Using visual analog scale (VAS) scores and nonsteroidal anti-inflammatory drug (NSAID) usage per menstrual cycle, values before treatment were compared to average scores over two menstrual cycles with treatment.
Results: Both the VAS scores and NSAID usage decreased significantly in both groups. The decreases were greater in the montelukast group compared to the placebo group, but the differences were not statistically significant. Nevertheless, in "highly effective cases," which were defined as having a post-treatment value less than half of the pre-treatment value, the decreases were significantly greater in the montelukast group than in the placebo group (VAS: montelukast, 4 vs. placebo, 0 ($P = 0.029$); NSAID: montelukast, 9 vs. placebo, 3 ($P = 0.031$)).
Conclusions: The present study found that montelukast may be effective in alleviating pain associated with dysmenorrhea in some women. Montelukast is safe and does not influence hormonal levels. Therefore, montelukast is a clinically reasonable management option to consider before prescribing a hormonal agent.

1. Introduction

Leukotriene is produced by the arachidonate cascade, which also synthesizes prostaglandin. It is an eicosanoid involved in a variety of metabolic processes, including smooth muscle contraction [1,2]. In the pathogenesis of bronchial asthma, leukotriene is involved in bronchial smooth muscle contraction. Leukotriene receptor antagonists, including montelukast, have been developed to suppress leukotriene activities and used clinically in the treatment of bronchial asthma in both adults and children [3–6]. Montelukast, which obtained FDA approval in 1998, is a very safe medication. Severe adverse effects appear to be extremely rare even with long-term continuous administration [7]. While there have not been many reports on the use of leukotriene receptor antagonists in pregnant women, some studies found no significant abnormalities [8,9], and a US National Asthma Education and Prevention Program report listed leukotriene receptor antagonists as an acceptable treatment option during pregnancy [10].

In addition, leukotriene increases vascular permeability and is involved with neutrophil migration, aggregation and degranulation; thus, it is one of the causative agents of pain [11]. In the field of gynecology, studies have found high levels of leukotriene in the endometrium and uterine smooth muscle of patients with menstrual pain [12–15]. The endometrium and uterine smooth muscle are known to possess leukotriene receptors [16]. About 10–30% of patients with dysmenorrhea are unresponsive to nonsteroidal anti-inflammatory drug (NSAID) therapy [15,17]; in these patients, the prostaglandin level is not elevated [14]. Therefore, among such cases, it is thought that leukotriene, not prostaglandin, is involved with the pain associated with dysmenorrhea [11,15].

In a pilot study, we reported the beneficial effects of 10 mg montelukast qid on dysmenorrhea [18]. However, one placebo-controlled study found no significant differences in the effects of montelukast for adolescent dysmenorrhea [19]. The patients

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received montelukast from day 21 of one cycle through day 5 of the subsequent menstrual cycle, which was a different regimen from that of our pilot study. To date, no general consensus has been reached in regard to the efficacy of montelukast for the treatment of dysmenorrhea. In this subsequent study, we investigated whether a leukotriene receptor agonist (montelukast) is effective in alleviating pain associated with dysmenorrhea.

2. Materials and methods

A prospective, double-blind, randomized, placebo-controlled study was conducted from October 2003 through March 2006. After obtaining approval from the Institutional Review Board of Jichi University Hospital and Jichi University Saitama Medical Center, written informed consent was obtained from each patient. The subjects were Japanese patients with dysmenorrhea in whom NSAID therapy did not adequately relieve their pain. The criteria for dysmenorrhea included a maximal VAS score of more than 5 points and/or ingestion of more than 10 NSAID tablets per month. Excluded were patients who had taken hormonal agents or a gonadotropin releasing hormone agonist (GnRHa) within six months, patients who had undergone surgery within six months, patients with submucosal myomas, and patients with $\geq$10 cm interstitial myomas.

Calculations for the sample size were set with a significance level of 0.05 and the power of 80%. We assumed that the effective percentage in the treatment group would be 60% and the placebo effect in the control group would be 20%. The assumption of the 60% level is justified by our previous pilot study of montelukast for dysmenorrheal patients [18]; the 20% rate for the placebo effect was estimated by a previous paper, which found that rate for dysmenorrheal patients [20,21].

The patients were randomly divided into two groups (montelukast and placebo). The study was double-blinded, and the allocation was not known either to the patients or to the medical staff who administered the medication. The randomization code was known only to the principal investigator. In the montelukast group, 10 mg/day of montelukast sodium (Singulair®, Banyu, Japan) was administered orally every day starting on day 5 of the menstrual cycle until the end of the second treatment cycle. The patients were allowed to continue taking the NSAIDs that were prescribed prior to the study. To assess pain associated with dysmenorrhea, visual analog scale (VAS) scores and NSAID usage were recorded using self-assessment sheets. As a control, a lactose placebo manufactured by our institute was administered every day in the same manner, and VAS scores and NSAID usage were recorded using self-assessment sheets. Patients who were taking more than one brand of NSAID were instructed to take only loxoprofen sodium (Loxonin®, Daiichi-Sankyo, Tokyo, Japan).

A blood sample was drawn at the time of registration and during the second menstrual cycle after treatment; this was done to measure blood count, hepatic and renal function, and serum CA125 and CA19-9 levels. In patients with measurable organic disease, such as ovarian endometriomas or adenomyosis, ultrasonography was performed at the time of registration and the end of the study to document the size of the endometriomas or degree of adenomyosis (myometrial thickness).

VAS scores and NSAID usage per menstrual cycle prior to treatment were compared to the average values of two cycles after treatment for the two groups. The maximum VAS scores were adopted as the VAS range, and the total amount of NSAIDs used per month was adopted as the NSAID range. A "highly effective case" was defined as a post-treatment value less than half that of the pre-treatment value. The number of highly effective cases was compared between the montelukast and placebo groups. Statistical analyses were performed using the χ^2 test, the Wilcoxon signed-rank test, and the Mann–Whitney *U*-test.

3. Results

During the study period, 62 patients were registered; 12 patients were withdrawn (7 patients dropped out, and 5 patients were excluded due to noncompliance). Data collected from 50 patients were analyzed (montelukast group: $n = 24$; placebo group: $n = 26$).

Table 1 presents the patients' background characteristics. There were no significant differences in age, body mass index, parity, presence of endometriosis, ovarian endometrioma size, degree of adenomyosis, pre-treatment VAS score, and pre-treatment NSAID usage between the montelukast and placebo groups. While the CA125 level was higher in the montelukast group (for no apparent reason), there was no significant difference in the CA19-9 level.

The changes of pre- and post-treatment VAS scores and NSAID usage are presented in Fig. 1. Both the VAS scores and NSAID usage decreased significantly in the montelukast group and in the placebo group. The mean decrease in VAS score (ΔVAS) and the mean decrease in NSAID usage (ΔNSAID) are also presented in Fig. 1. Both the VAS score and NSAID usage decreased more in the montelukast group than in the placebo group, but the differences were not statistically significant.

The distributions in relation to the changes in VAS score and NSAID usage are presented in Table 2. We divided the patients into four groups: increased/no change; mildly effective ($\leq$25% decrease); moderately effective (26–50% decrease); and highly effective ($\geq$51% decrease). The post-treatment VAS scores for the highly effective cases were less than half that of the pre-treatment scores (4 patients (17%) in the montelukast group and 0 patients in the placebo group; $P = 0.029$). In regard to NSAID usage, nine patients (38%) in the montelukast group and three patients (12%) in the placebo group were highly effective cases ($P = 0.031$). The ratio of highly effective cases, in regard to both VAS score and NSAID usage, was significantly higher in the montelukast group than in the placebo group.

Table 1
Patient background factors for montelukast and placebo groups ($n = 50$).

	Montelukast ($n = 24$)	Placebo ($n = 26$)	*P*
Age (years)	34.7 ± 1.7	32.4 ± 1.3	NS
BMI	20.0 ± 0.6	21.4 ± 0.6	NS
Multiparous	9[a]	7[a]	NS
Endometriosis	20[a]	18[a]	NS
CA125 (IU/ml)	103 ± 23.3	50.5 ± 8.1	0.024
CA19-9 (IU/ml)	44.4 ± 12.8	43.9 ± 16.8	NS
Size of ovarian endometriomata (mm)	50.6 ± 6.4	57 ± 12.5	NS
Myometrial thickness of adenomyosis (mm)	46.8 ± 8.5	45.0 ± 7.5	NS
VAS (0–10 points)	7.5 ± 0.4	6.6 ± 0.4	NS
NSAID (tablets/month)	10.8 ± 1.3	12.0 ± 2.2	NS

Mean ± SE; NS = nonsignificant.
[a] Number of cases.