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Efficacy and safety of lornoxicam vs ibuprofen in primary dysmenorrhea: a randomized, double-blind, double dummy, active-controlled, cross over study

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ABSTRACT

Objectives: Study was planned to evaluate the efficacy and safety of lornoxicam in moderate to severe menstrual pain due to primary dysmenorrhea.
Study design: This doubled blind, double dummy, randomized, comparable study of lornoxciam versus ibuprofen was conducted at Sir Takhtsinghji General Hospital, Bhavnagar, Gujarat, India. Total 57 primary dysmenorrhea participants having mean age ± standard deviation (SD) of 19.2 ± 2.08 were analyzed. The participants were randomly allocated to either lornoxicam 8 mg or ibuprofen 400 mg two times a day for maximum of three days on two consecutive menstrual periods. The different medication was taken on each cycle. The analgesic efficacy was compared by a total area under pain relief score to 4 and 8 h, pain intensity difference, sum of pain intensity difference to 4 and 8 h, peak pain intensity difference to 4 and 8 h, peak pain relief to 4 and 8 h, total medication consumption, rescue medication and participant global evaluation. Adverse effects were recorded in both groups.
Results: In both treatments, efficacy parameters were significantly reduced at measured time points as compared to baseline. No significant difference was observed between lornoxicam and ibuprofen in terms of efficacy parameters: total area under pain relief to 4 h (8.0 ± 2.6 vs 8.3 ± 2.7), total area under pain relief to 8 h (22.4 ± 4.6 vs 23.0 ± 4.4), sum of pain intensity difference to 4 h (−5.7 ± 1.9 vs −6.0 ± 2.0), sum of pain intensity difference to 8 h (−17.5 ± 3.3 vs −17.8 ± 3.5), peak pain relief to 4 h (3.4 ± 0.8 vs 3.5 ± 0.8), peak pain relief to 8 h (3.9 ± 0.5 vs 3.9 ± 0.4), peak pain intensity difference to 4 h (−2.6 ± 0.7 vs −2.7 ± 0.7), peak pain intensity difference to 8 h (−3.3 ± 0.6 vs −3.3 ± 0.6). Total medication consumption, a requirement of rescue medication and global evaluation of efficacy were comparable in both groups. The incidence of adverse effect was also similar in both groups.
Conclusions: Lornoxicam appears to be a new therapeutic agent for the treatment of primary dysmenorrhea.

Introduction

Dysmenorrhea is characterized by severe uterine pain during menstruation affecting woman's life each month [1]. Dysmenorrhea can be classified as either primary or secondary. The menstrual pain not associated with an underlying cause is known as primary dysmenorrhea [2]. It usually presents within three years of menarche. It lasts for 48–72 h and more severe during first and second day of menstruation. Untreated primary dysmenorrhea affects quality of life, work and school attendance [3]. Primary dysmenorrhoea occurs due to release of prostaglandins (PGF_2) and other inflammatory mediators in the uterus due to the destruction of the endometrial cells [4].

Primary treatment of dysmenorrhea consists of non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptive pills and non-pharmacological measures like acupuncture, diet, exercise, topical heat, etc. [5]. NSAIDs are well established first-line therapy for dysmenorrhea. They provide menstrual pain relief by inhibiting

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synthesis of prostaglandins. NSAIDs such as ibuprofen, naproxen, diclofenac, mefanamic acid are commonly used in primary dysmenorrhea [6,7]. All NSAIDs have been associated with gastrointestinal adverse effects (AEs) such as nausea, dyspepsia, peptic ulcer, and diarrhea. Ibuprofen is the first NSAID to be approved for over-the-counter (OTC) use [8]. It is widely used for mild to moderate type of acute pain (e.g. dysmenorrhea, dental pain, headache, etc) with lower doses ($\leq$1200 mg/day for $\leq$10 days) [9]. It is associated with the low risk of serious upper gastrointestinal complications. Its gastrointestinal tolerability profile was indistinguishable from placebo when administered at the maximum OTC dose of 1200 mg/day for 10 days for headache, dysmenorrhea, and arthritis [10].

Lornoxicam, a NSAID, belongs to oxicam class with an analgesic, anti-inflammatory and antipyretic properties. It differs from established oxicams by a relatively short elimination half-life (3 to 5 h), which may be responsible for reduced incidence of gastrointestinal and renal AEs. It has a better tolerability profile than other oxicams [11–13]. No literature is available about the effect of lornoxicam on dysmenorrhea. To confirm the same we planned its comparative study with ibuprofen for reliving moderate to severe menstrual pain due to primary dysmenorrhea.

Materials and methods

Study protocol was approved by the Institutional Review Board (IRB), Govt. Medical College, Bhavnagar and was conducted in accordance with declaration of Helsinki and Good Clinical Practice guidelines. The protocol was registered at clinical trial registry of India (CTRI/2011/08/002671). The participants were recruited between 2010 and 2012 from Sir Takhtsinghji General Hospital, Bhavnagar, Gujarat, India. The written informed consent in vernacular language was obtained from each participant before enrollment.

Inclusion and exclusion criteria for subject selection

Participants were screened by obtaining medical and gynecological history. The eligibility criteria for enrollment were: age between 18 and 40 years, with a regular menstrual cycle (21–35 days), willingness for non-pregnant status during entire study period, at least four painful periods from previous six menses characterized by pain intensity of moderate or severe on verbal rating scale at screening visit. Moderate and severe menstrual pain were defined as per literature [14,15].

Participants were excluded if they had associated with recurrent pelvic and lower abdominal pain outside the menstrual period such as secondary dysmenorrhea with other diseases of reproductive organs; had mild menstrual pain; had a history of abnormal vaginal discharge; non-responsive menstrual pain to NSAID in the past; had a history of severe gastritis, peptic ulceration, any gastrointestinal bleeding, significant hematological, hepatic, gastrointestinal, genitourinary, cardiovascular, respiratory, metabolic, endocrine, allergic, neurological, rheumatic, immune, psychiatric diseases or surgical procedure. Pregnant and lactating women were excluded from the study. Participants were also excluded if they had history of hypersensitivity to NSAIDs, had used NSAIDs or analgesics before 48 h of study medication, any evidence of substance abuse or addiction, and had used psychotherapeutic drugs, platelet aggregation inhibitors, prostaglandin synthesis inhibitors or any other concomitant drugs.

Trial design

Participants satisfying the inclusion and exclusion criteria were randomized through one block randomization (Random allocation software version 1.0) to allocate study medication. The third person independent of the study generated random allocation sequence. The study was double-blind, double dummy, active control, complete block cross-over trial. Study was 2-sequence crossover design over consecutive menstrual cycles (two treatment periods) (Table 1). The treatment unit included two boxes (one labeled for each treatment period); each containing two medication strips having one capsule and one tablet. Study medications were prepared in double dummy method in such a way that each treatment would appear identical to ensure blinding. The two treatment regimens were assigned to participants comprising an either sequence I (Cap. Lornoxicam 8 mg + Tab. Placebo) or sequence II (Tab. Ibuprofen 400 mg + Cap. Placebo) two times daily for a maximum three day. Participants were allowed to use any analgesics as rescue medication during each treatment period, if study medication was insufficient to control pain. Those who took rescue medication before 1 h of study medication were excluded from the analysis.

Study medication was supplied in a participant specific box with computer generated participant diary and information sheet before a start of each menstrual cycle. Participants were asked to rate an intensity of menstrual pain at each treatment period. The study could be extended if the participant did not medicate for maximum two consecutive menstrual cycles because lack of moderate to severe pain, illness, travel, or any other reason accepted by the investigators. If $>$2 consecutive cycles were missed, the participants were withdrawn from the study.

Participants were asked to take the assigned medication at home and registered the time of intake, pain intensity and pain relief score immediately before and after first dose of study medication for first 8 h in a participant's diary. Those participants who had not completed all the visits and withdrew the consent were excluded from the analysis. Investigator telephoned the participants around expected day of the menstrual period to remind the study procedure. Participants were asked to attend the clinic after each menstrual cycle with their diary and any unused study medications. At every visit during entire study period, an investigator recorded all the observation, AEs, global evaluation and details about concomitant medications from the participants.

Outcome assessment

Primary efficacy variables were total area under pain relief score to 4 h and 8 h after the initial dose of study medication. The pain relief was assessed by using a 5-point scale, where 0 = no pain (0% reduction); 1 = a little relief (25% reduction); 2 = some relief (50% reduction); 3 = a lot of relief (75% reduction); 4 = complete relief (100% reduction) as suggested by Daniels et al. [14].

The pain intensity was categorised on the 5-point scale, where 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe pain [14]. Pain intensity difference, summed time-weighted pain intensity difference to 4 h and 8 h, peak pain intensity difference (maximum difference in pain intensity scores from baseline recorded to 4 and 8 h) and peak pain relief (maximum pain relief score recorded to 4 and 8 h) were also analyzed. Pain relief and pain intensity assessments were made at baseline and 2, 4, 8 h after drug intake.

Table 1
Treatment sequence of crossover design with double dummy technique for two consecutive menstrual cycles.

Cycles	Sequence 1 (n = 35)	Sequence 2 (n = 35)
1	Cap. lornoxicam, Tab. Placebo	Tab. Ibuprofen Cap. Placebo
2	Tab. Ibuprofen Cap. Placebo	Cap. Lornoxicam Tab. Placebo