

## ROLE OF MONTELEUKAST IN DYSMENORRHOEA

Mahjabeen Naaz<sup>1</sup>, Juzer Sabuwala<sup>1</sup>, Ayesha Naaz<sup>1</sup>, Heena Farheen<sup>1</sup> and Dr. S. P. Srinivas Nayak<sup>2\*</sup><sup>1</sup>Intern(PharmD), Department of Pharmacy Practice, Sultan-ul-Uloom College of Pharmacy, Aster Prime Hospital, Hyderabad, Telangana, India.<sup>2</sup>Assistant Professor, Department of Pharmacy Practice, Aster Prime Hospital, Sultan-ul-Uloom College of Pharmacy, JNTU-H, Hyderabad, Telangana, India.**\*Corresponding Author: Dr. S. P. Srinivas Nayak**

Assistant Professor, Department of Pharmacy Practice, Aster Prime Hospital, Sultan-ul-Uloom College of Pharmacy, JNTU-H, Hyderabad, Telangana, India.

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## ABSTRACT

Dysmenorrhea is termed as painful menstrual periods which are caused by uterine contractions which often reduce the quality of women's life. Prostaglandins play a major role in the pathomechanism of dysmenorrhea. Leukotrienes have also been postulated to increase the sensitivity of pain fibers in the uterus. Considerable amounts of leukotrienes have been demonstrated in the endometria of women with primary dysmenorrhea. Potent prostaglandins, cyclooxygenase metabolites of arachidonic acid, and leukotrienes, lipoxygenase metabolites of arachidonic acid, are thought to play a key role in the inflammatory process during menstruation. These abnormal uterine contractions cause poor reperfusion and oxygenation, leading to the pain, and also cause prostaglandins and leukotrienes to be released into the systemic circulation, resulting in symptoms such as nausea, vomiting, diarrhea, and headache. The intensity of menstrual cramps and dysmenorrhea-associated symptoms are linked to the amount of prostaglandins and leukotrienes released. Hence, there is a significant role of prostaglandins and leukotrienes in the pathogenesis of dysmenorrhea leading to pain. Therefore, the present work contains a review about the use of leukotriene antagonists in controlling the pain stimulus in women suffering with dysmenorrhea.

**KEYWORDS:** Leukotrienes, dysmenorrhea, pain, leukotriene antagonists.

## INTRODUCTION

Dysmenorrhea also known as painful menstruation is a severe painful cramping sensation in the lower abdomen frequently escorted with other biologic symptoms such as sweating, arrhythmia, headache, nausea, vomiting, and diarrhea occurring just before or during the menstruation.<sup>[1,2]</sup> It is a common gynecological problem among adolescent females.<sup>[3,4]</sup> This pain most times affects their normal daily activity and quality of life depending on its duration and severity.<sup>[5]</sup> International Association for the study of pain postulated that dysmenorrhoea affects 40-90% of girls.<sup>[6]</sup> In developing countries, the most common symptom of all menstrual complaints is dysmenorrhea and poses a greater burden of disease.<sup>[7]</sup> Dysmenorrhea is classified into primary dysmenorrhea and secondary dysmenorrhea. Primary dysmenorrhea, beginning during adolescence frequently is associated with painful menses with normal pelvic anatomy. It is experiential only in ovulatory cycles, frequently developing within 6 to 12 months after menarche with no pathological condition. It is due to excessive quantities of prostaglandin synthesis during the breakdown of premenstrual endometrium. Secondary dysmenorrhea is a menstrual pain involving underlying pathology and its beginning might be years after

menarche. This is due to the partial non-porous hymen or uterus which may lead to obstruction of the outlet.<sup>[8,9]</sup> Potent prostaglandins (PG), cyclooxygenase metabolites of arachidonic acid, and leukotrienes (LT), lipoxygenase metabolites of arachidonic acid, are thought to play a key role in the inflammatory process during menstruation.<sup>[10,11]</sup> Leukotriene (LT) is an eicosanoid involved in a metabolic process of smooth muscle contraction and is produced by the arachidonate pathway.<sup>[12,13]</sup> Prior studies have shown that human uterine tissue can synthesize and metabolize Leukotriene.<sup>[14]</sup> and LT receptor sites have been detected in human myometrial smooth muscles and endometrial cells.<sup>[15]</sup> LTs are vasoconstrictors,<sup>[16]</sup> and are known to stimulate uterine muscle contractions.<sup>[17]</sup> Leukotriene receptors are present in endometrium and uterine smooth muscle. An adult woman with a complaint of dysmenorrhea will have the highest LT values in her uterine tissues and there is a close correlation between menstrual flow LT-C4/D4 levels and the severity of dysmenorrhea symptoms in adult women with primary dysmenorrhea.<sup>[18]</sup>

Leukotriene receptor antagonists, including Montelukast, have been developed by the US Food and Drug

Administration (FDA), to suppress leukotriene activities and used clinically in the treatment of bronchial asthma in both adults and children.<sup>[19,20]</sup> Besides, leukotriene increases vascular permeability and is involved with neutrophil migration, aggregation, and degranulation; thus, it is one of the causative agents of pain. The patients with dysmenorrhea are unresponsive to Nonsteroidal anti-inflammatory drug (NSAID) therapy as the prostaglandin level is not elevated.<sup>[21]</sup> Hence, among such cases, it is thought that leukotriene, not prostaglandin, is involved with the pain associated with dysmenorrhea.<sup>[21]</sup> In this present study, we explored whether blocking leukotriene with a leukotriene receptor agonist (Montelukast) is effective in improving pain associated with dysmenorrhea.

### Etiology

Of adult females, ~40% have painful menstruation and ~10% of these are incapacitated for 1–3 days per month. It is expected that 10–30% of patients with painful periods fail to respond to prostaglandin (PG) synthetase inhibitors and that the concentrations of PGF<sub>2</sub> $\alpha$  and PGE<sub>2</sub> in the menstrual blood from these non-responders are alike to those found in normal controls.<sup>[22]</sup> While lower abdominal cramping is the most familiar dysmenorrheal symptom, many adolescents suffer from other menstruation-associated symptoms. Symptoms classically escort the start of menstrual flow or happen within a few hours before or

after onset, and last for the first 24–48 hours. The severity of dysmenorrheal symptoms completely correlates with early menarche and with improved duration and amount of menstrual flow. Additionally, cigarette smoking also increases the duration of dysmenorrhea, most probably because of nicotine-induced vasoconstriction. Premenstrual symptoms are less common in adolescent girls and are often alleviated by sufficient management of dysmenorrhea. These symptoms include nausea, vomiting, and loss of appetite, headaches, backaches, weakness, and abdominal pain.<sup>[23]</sup>

### Leukotriene Synthesis

The synthesis of leukotrienes from substrate arachidonic acid is initiated by 5-lipoxygenase along with 5-lipoxygenase-activating protein (FLAP).<sup>2</sup> Although FLAP does not have enzymatic activity, it enhances the ability of 5-lipoxygenase to interact with its substrate. Leukotriene A<sub>4</sub> (LTA<sub>4</sub>) is converted by LTA<sub>4</sub> hydrolase to leukotriene B<sub>4</sub> (LTB<sub>4</sub>), or it can be conjugated with reduced glutathione by leukotriene C<sub>4</sub> (LTC<sub>4</sub>) synthase to yield LTC<sub>4</sub>. LTB<sub>4</sub> and LTC<sub>4</sub> are exported from the cell by specific transporter proteins; the released LTC<sub>4</sub> is converted to leukotriene D<sub>4</sub> (LTD<sub>4</sub>), which undergoes conversion to leukotriene E<sub>4</sub> (LTE<sub>4</sub>) by sequential amino acid hydrolysis. The capacity to generate large amounts of leukotrienes from arachidonate is largely confined to leukocytes.<sup>[24]</sup>

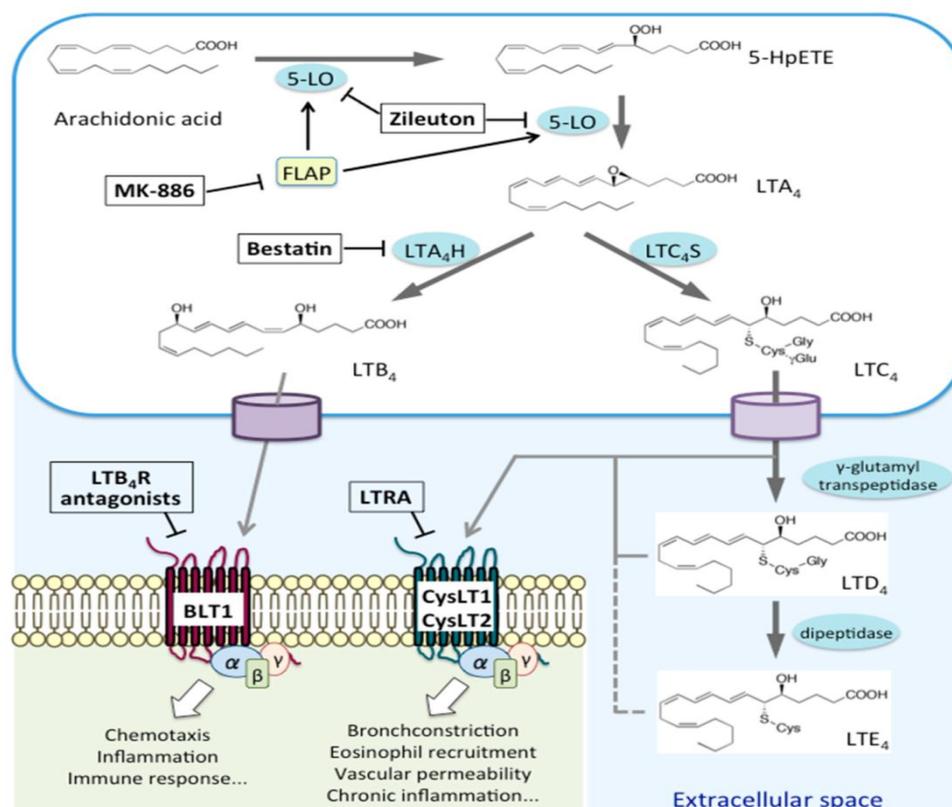


Figure 1: Leukotriene synthesis.

The etiology of dysmenorrhea lies generally in the body's overproduction of prostaglandins and

leukotrienes. Prostaglandin F<sub>2</sub> $\alpha$  (PGF<sub>2</sub> $\alpha$ ) is the cyclooxygenase (COX) metabolites of arachidonic acid

and are responsible for the vasoconstriction, leading to ischemia and myometrial contractions. These abnormal uterine contractions cause poor reperfusion and oxygenation, leading to the pain, and also cause prostaglandins and leukotrienes to be released into the systemic circulation, resulting in symptoms such as nausea, vomiting, diarrhea, and headache. The intensity of menstrual cramps and dysmenorrhea-associated symptoms are linked to the amount of PGF<sub>2</sub> alpha released. Studies have shown that women suffering from dysmenorrhea have prostaglandin levels that are twice as high as women without dysmenorrhea.<sup>[22]</sup>

The function of leukotrienes in the pathogenesis of dysmenorrhea is reliable with the study that human uterine tissue synthesizes leukotrienes and possesses leukotriene receptors. Increased leukotriene levels have been reported both in the urine, uterine tissue, and in the menstrual fluid in patients with dysmenorrhea.<sup>[25]</sup> The corpus luteum (CL) is the major source of progesterone (P<sub>4</sub>) in mammals. P<sub>4</sub> supports the secretory functions of the endometrium, which maintain early embryonic development, implantation, and placentation. Uterine and ovarian PGs are considered to be vital factors for regulating reproductive events such as ovulation, luteolysis, embryo implantation, and maintaining pregnancy. LTs are synthesized by 5-lipoxygenase (5-LO) and are normally known as potential inflammatory factors that cause edema in respiratory tract diseases, but they also have a role in reproduction and may improve the action of PGs.<sup>[26]</sup>

The classical prostaglandins *E<sub>z</sub>* and *F<sub>2a</sub>* can be synthesized in considerable amounts by human endometrium, and these vary with the stage of the menstrual cycle. These prostaglandins are not stored in tissues but result from the rapid metabolism of free arachidonic acid. Most of the arachidonic acid in uterine tissues appears to be covalently bound to cell membrane phospholipids and is not directly accessible for metabolism to prostaglandins. The release of arachidonic acid is catalyzed largely by phospholipase *A<sub>2</sub>*. The uterus also can synthesize thromboxane *A<sub>2</sub>* (*TXA<sub>2</sub>*), prostacyclin (PGI), and some leukotrienes. Both cyclo-oxygenase and lip-oxygenase pathways appear to be active in different uterine tissues. Prostaglandins *E<sub>z</sub>* and *F<sub>2a</sub>*, PGI, *TXA<sub>2</sub>*, the cyclic endoperoxides, and leukotrienes all have functional effects on some of the tissues in the uterus.<sup>[27]</sup>

The majority of cases of dysmenorrhea in adolescents are chiefly related to a normal ovulatory cycle and have clear physiologic etiology. After ovulation, there is an increase in fatty acids in the phospholipids of the cell membranes. The increased ingestion of omega-6 fatty acids in the diet also results in a majority of the omega-6 fatty acids in the cell wall phospholipids. After the onset of progesterone withdrawal before menstruation, these omega-6 fatty acids, mainly arachidonic acid, are released, and a cascade of prostaglandins (PGs) and leukotrienes (LTs) is initiated in the uterus. The inflammatory response,

which is mediated by these PGs and LTs, produces both cramps and systemic symptoms such as nausea, vomiting, bloating, and headaches. In particular, the prostaglandin *F<sub>2a</sub>*, cyclooxygenase (COX) metabolites of arachidonic acid, causes potent vasoconstriction and myometrial contractions, leading to uterine ischemia and pain.<sup>[28]</sup>

Experimental data suggest that leukotrienes might be the alternative pathogenic pathway for primary dysmenorrhoea, especially where there is an abnormally high value of polymorph neutrophils in the menstruum. This high neutrophil concentration may account for the increased synthesis of leukotrienes in this group of women.<sup>[22]</sup>

Leukotriene can be considered as solitary causative agents of pain as it increases vascular permeability and is concerned with neutrophil migration, aggregation, and degranulation. In the gynecologic view, leukotriene receptors are broadly spread in the endometrium and uterine smooth muscles. For patients with menstrual pain, numerous 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.<sup>[29]</sup> Prostaglandins cause contraction of the blood vessels supplying the uterus, abnormal contractile activity of the uterus, which leads to ischemia, hypoxia of the uterus, and increased sensitivity of the nerve endings. Additionally to hormonal changes that occur in the body, other factors, including diet, early age of the menarche, stress, and severity of menstrual periods, and the occurrence of premenstrual syndrome (PMS) may contribute to dysmenorrhea. Prostaglandin *F<sub>2a</sub>* (PGF<sub>2a</sub>) and Prostaglandin *E<sub>2</sub>* (PGE<sub>2</sub>) have specific roles in the inflammatory process. PGF<sub>2a</sub> causes the constriction of arcuate vessels leading to local hypoxia of endometrial tissues. Another task of PGF<sub>2a</sub> is to stimulate the smooth muscle to contract, which in turn supports menstrual bleeding. The action of PGE<sub>2</sub> depends on the type of receptors, but it can include the relaxation of endometrial blood vessels and may work to increase swelling and recruit leukotrienes. Besides, prostaglandins may be involved in the formation of other chemokines and growth factors involved in the inflammatory response or the repair process after menstruation. Prostaglandins may also increase the migration of neutrophils and leukocytes into the endometrium.<sup>[30]</sup> Studies indicate that antenatal montelukast treatment reduces contractile parameters suggesting a tocolytic effect with acknowledged clinical relevance. It might ease the uterine stillness by decreasing the inflammatory syndrome and block the activation of labor by decreasing uterine sensitivity to oxytocin.<sup>[31]</sup> Montelukast, as a leukotriene receptor antagonist, is a very safe medication and does not suppress ovulation or affect hormonal levels, so may

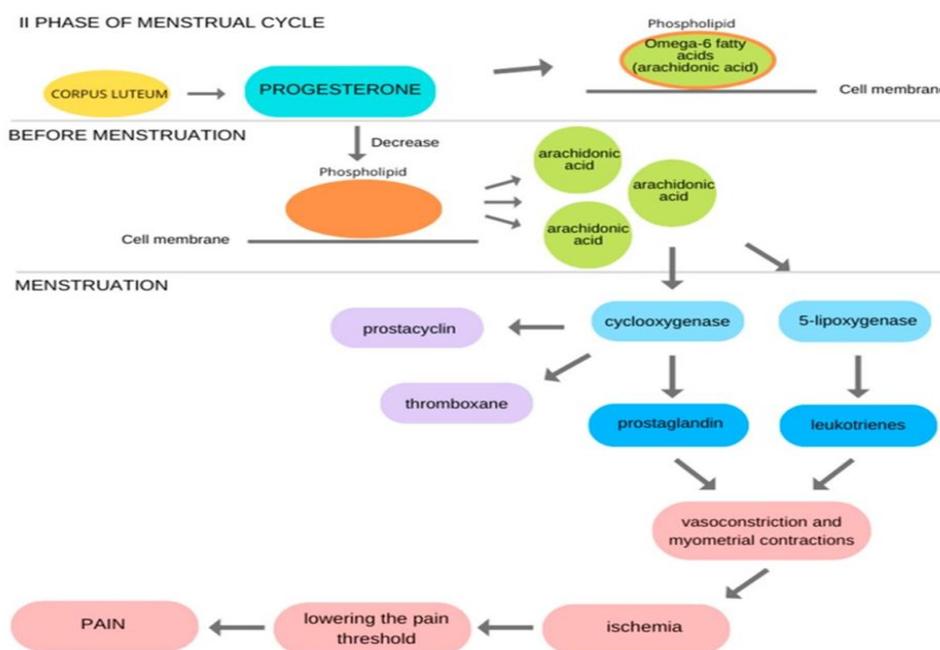
provide some women an alternative option for the traditional treatment of dysmenorrhea, which involves low-dose contraceptive pills and gonadotropin-releasing hormone (GnRH) analogs. These medications do not sufficiently reduce dysmenorrheal symptoms in many women, suppress ovulation, and cause many side effects.<sup>[29]</sup>

**Mechanism of Montelukast in Dysmenorrhea**

Regardless of several studies, the pathogenesis of dysmenorrhea is not clearly understood. Earlier research indicates the complexity of biochemical reactions.<sup>[32]</sup> The menstrual cycle is cyclic changes in ovarian hormone concentrations and these are dependent on prostaglandin level and uterine contractile activity.<sup>[33]</sup> It is explained that one of the factors contributing to dysmenorrhea may be an increase in prostaglandin concentration before menstruation.<sup>[34]</sup> These recommendations were confirmed in subsequent years by other authors who have proved that prostaglandins are overproduced in dysmenorrhea.<sup>[35]</sup> This is also specified by the indications that occur with dysmenorrhea during menstruation.<sup>[34]</sup> Prostaglandins cause narrowing of the blood vessels supplying the uterus, abnormal contractile activity of the uterus, which leads to ischemia, hypoxia of the uterus and increased sensitivity of the nerve endings.<sup>[34-37]</sup> Apart from hormonal changes that occur in the body, other factors, including diet, early age of the menarche, stress, length, and severity of menstrual periods, and the occurrence of premenstrual syndrome (PMS) may also contribute to dysmenorrhea. The publications suggest the role of social, living, and psychological factors have been published.<sup>[38,40]</sup> One of the author suggested that menstruation could be regarded as an inflammatory event, because during menstruation the leukocytic invasion and subsequent production of inflammatory mediators is observed.<sup>[41]</sup>

**Leukotrienes In Uterus**

Leukotrienes have been assumed to intensify the sensitivity of pain fibers in the uterus. Significant amounts of leukotrienes have been detected in the endometrium of females with primary dysmenorrhea that does not respond to treatment or management with prostaglandin antagonists.<sup>[42-45]</sup> Leukotriene receptors were shown to be present in uterus tissues and the number of these receptor sites for the cysteinyl leukotrienes has been found to be as high as that in the lung tissues. Incubation studies revealed that non pregnant women uterine have specific LTC<sub>4</sub> receptor sites in endometrial and myometrial smooth muscle cells. Various experimental studies carried out illustrate that using human endometrium and myometrium has capacity to synthesize leukotrienes. In the menstrual blood from human women with primary dysmenorrhea compared with that in women without significantly higher concentrations of LTC<sub>4</sub> and LTD<sub>4</sub>.<sup>[46-49]</sup> In recent years, lipid mediators such as prostaglandins and leukotrienes have been implicated in the pathogenesis of dysmenorrhea by causing dysrhythmic uterine contractions and decreasing uterine blood flow.<sup>[50-52]</sup> Prostaglandins, especially PGF<sub>2α</sub>, cause uterine contractions by increasing the flow of calcium into the smooth muscle cells. Similarly, the concentration of leukotrienes is increased in the uterine tissue and menstrual fluid samples of patients with Dysmenorrhea.<sup>[53]</sup> In one of the studies it explained that urinary LTE<sub>4</sub> is increased in patients with primary dysmenorrhea. An interventional study by the same group, however, failed to show a beneficial effect of leukotriene receptor antagonism by montelukast on dysmenorrhea.<sup>[54]</sup>



**Figure 2: Possible mechanism of menstrual pain.**

Some of the PGF<sub>2α</sub> is to stimulate smooth muscle to contract, which in turn supports menstrual bleeding. The action of PGE<sub>2</sub> depends on the type of receptors, but it can include the relaxation of endometrial blood vessels and may work to increase swelling and recruit leukotrienes. Hence the leukotriene antagonist such as Montelukast have shown effect in reducing the pain involved during the menses.<sup>[55,56]</sup>

#### Clinical presentation of the montelukast- leukotriene antagonist in the dysmenorrhea

Previous studies have revealed an rise in leukotrienes in the uterine tissue as well as in the menstrual flow of adult females with dysmenorrhea. An increase in leukotriene-E4, the major urinary leukotriene, were reported with dysmenorrhea, additional suggesting a possible involvement of these potent vasoconstrictors and inflammatory mediators in producing dysmenorrhea symptoms.<sup>[57]</sup>

Generally the lipoxygenase products such as leukotrienes have been verified in many mammalian tissues including even the humans. These are widely distributed in the lungs, gut, uterus, kidneys, skin, heart and the liver.<sup>[53]</sup> Their roles as mediators of inflammation have made them therapeutic targets. Substantial amounts of leukotrienes have been found in the endometrium of females with primary dysmenorrhoea who doesn't respond to treatment with prostaglandin antagonists.<sup>[55]</sup> Thereby, in endometriosis, cytokines, which can stimulate the cascade for the biosynthesis of leukotrienes, have been shown to be elevated. It is estimated that around the 10–30% of patients with painful periods fail to respond to prostaglandin (PG) synthetase inhibitors. Some of which is a significantly cause infertility of females. Leukotriene receptor antagonists have been used for many years for the treatment of asthma.<sup>[38-57]</sup>

In this review we represent the use of the leukotriene receptor antagonist- Montelukast in the management of primary dysmenorrhoea especially in patients who doesn't responding to the cultural treatment using PG synthetase inhibitors and perchance also in cases of endometriosis.

Firstly, the dysmenorrhea is the most common condition in the department of gynaecology. Usually begins in few months or years of menarche and also the experimental data implies to understand the leukotrienes might be the alternative pathogenic pathway leading to dysmenorrhea in females. There might be high neutrophil count in the menstruum which account for synthesis of leukotriene in females. In-vitro studies represent that production of leukotrienes by the endometrium from females with dysmenorrhea is higher comparatively to the females without.<sup>[58,59]</sup> In case with this then the Leukotriene receptor antagonists such as Montelukast may provide useful in the monitoring and management of the patients with dysmenorrhea. On the alternative pathogenic basis

of leukotriene pain pathway, we can conclude and treat the female patients suffering with the dysmenorrhea with Montelukast which is primarily used for asthma treatment.

#### CONCLUSION

Leukotriene an eicosanoid involved in smooth muscle contraction and is considered as one of the causative agents of pain as it increases vascular permeability with neutrophil migration, aggregation and degranulation leukotriene receptors are widely distributed in endometrium and uterine smooth muscles. Thus Montelukast a leukotriene antagonist can be used safely and effectively without any adverse effects and can be considered as the primary therapy before starting hormonal therapy.

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