Review Article

Supportive therapy for dysmenorrhea: Time to look beyond mefenamic acid in primary care

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Abstract

Dysmenorrhea is a recurrent and chronic primary health care issue. Mefenamic acid and NSAID based therapy regimens have unwanted side effects on its long-term usage. NSAIDs reduce pain, albeit they do not address the enhanced pain sensitivity and other neuronal symptoms of dysmenorrhea. Hence, there is a need for supportive therapy which can target both pelvic pain and the neuronal symptoms. Historically, European medicinal plants and their extracts such as, valeriana officinalis, humulus lupulus, and passiflora incarnata have been used in menstrual disorders for centuries. The current review is focused on the available evidence for its use as monotherapy or as supportive therapy in combination with other conventional medications.

Keywords: Dysmenorrhea, humulus, mefenamic acid, passiflora, primary care, valerian

Introduction

Menstrual disorders are often ignored in development discourse, despite this condition affecting half of the world's women population. United Nation reports menstrual disorders such as irregular cycles, dysmenorrhea, and menorrhagia, to be common among adolescents and women of reproductive age group.[1] They are responsible for behavioral, physical, and emotional changes during menstruation. Dysmenorrhea has a prevalence rate of 33.5% among adolescent girls while it is prevalent in 87.7% of women of reproductive age group in India.[2] It affects activities of daily living and quality of life which include absenteeism to school, college, or work.[3] Dysmenorrhoea is also a social problem for adolescent girls in middle and low income countries.[4,5]

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In underdeveloped world, use of disposable pads is limited, and cloth is still commonly used as an alternative absorbent which worsens the outcome in management of irregular bleeding and painful menstruation. Of 113 million adolescent girls, 68 million attend about 1.4 million schools, with poor menstrual hygiene management practices and cultural taboos which impedes their social and educational development and proper management of menstrual disorders.[6] An Indian cross sectional study reported varying degree of dysmenorrhea to be prevalent in 84.2% of the participants.[7] In this study 34.2% of girls experienced severe pain, 36.6% moderate and 29.2% had mild pain. Bleeding duration was found to be significantly increased among the subjects with dysmenorrhea.[7] Girls with bleeding duration more than 5 days had 1.9 times more chance of having dysmenorrhea.

Hence the family physician should evaluate bleeding duration, family history of dysmenorrhea and presence of clots while obtaining the medical history. Cultural taboos, add to difficulties of young patients to express, preventing them from seeking help for painful menstruation.[8] From the perspective of

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implementing primary social health care for adolescents or women with menstrual disorders, India has been a country of contrasts, with gender-related disparities, resulting in significant variation in health and social indicators among girls and women.[9] This poses a challenge for the primary healthcare provider in developing nations as there are multiple factors which impede efficient screening of dysmenorrhea patients. Despite the latest advances in the treatment, more than half of women with dysmenorrhea continue to have symptom during every cycle of menstruation. Due to persistence of severe to moderate pain even after treatment, more than half of women continue to have limitation of day to day activities.

In patients with dysmenorrhea, excessive amount of prostanoids and eicosanoids are released from the endometrium during menstruation. There is also an increased prostaglandin synthesis that leads to uterine contractions and vasoconstriction during menstruation. Frequent and dysrhythmical contractions are also associated with increased basal tone and active pressure. Uterine hyper contractility, reduced uterine blood flow, and peripheral nerve hypersensitivity occur at the time when maximal prostaglandins are released into the menstrual fluid. Prostaglandin E2, has been shown to increase psychological stress and impair memory.[10] Therefore, dysmenorrhea is not only a problem of localized pelvic pain, but there is a spillover effect on the central nervous system. Hence, it is imperative to include centrally acting medications to control these symptoms.

In clinical practice, failure of treatment with NSAIDs is not uncommon. Such individuals are treated with Oral Contraceptives (OC).[11] Although suppressing ovarian function with OC improves the symptoms of primary dysmenorrhea, the symptoms recur upon cessation of OC.[12,13] There is also a link between primary dysmenorrhea, endometriosis, and infertility.[14,15] Hence there is need for primary health care physicians to be aware of this link and initiate treatment at the first opportunity.

The existing primary health care therapy for Dysmenorrhea is incomplete. Nonsteroidal anti-inflammatory drug (NSAID) such as Mefenamic acid is the mainstay of treatment for dysmenorrhea. Though NSAIDs improves the symptoms, the benefits aren't long lasting. The pain recurs during every cycle. If mefenamic acid is used for a longer duration, it causes heart burn, constipation, nephro-toxicity, hemolytic anemia, seizures, and diarrhea. Prostaglandins play an essential role in ovulation and NSAIDs such as meloxicam and COX-2 inhibitors are reported to delay ovulation due to inhibition of prostaglandins.[16,17] However, many women are left with no option but to consume NSAIDs despite the adverse effects such as gastric irritation, gastric ulceration, heartburn, drowsiness, and diarrhea.

Dysmenorrhea is a recurrent problem and long-term medication is needed for it. Therefore, it is time to look beyond the conventional treatment options and look for an alternative approach. The alternative therapy should address both neuronal as well as uterine component of dysmenorrhoea. It is also preferred to administer medications that do not alter the menstrual cycle or delay ovulation. In this context, clinicians can choose herbal extracts that have proven benefit in dysmenorrhea and higher safety index when compared to NSAID. Hence, researchers have studied home remedies such as ginger extract and found it to be useful for dysmenorrhea.[18] The other time-tested remedy is *valeriana officinalis* based extracts. *Valeriana officinalis* is reported to be a safe and effective alternative treatment in dysmenorrhea.[19] It reduces the duration of bleeding and has analgesic activity in dysmenorrhea.[20] Hence, the role of herbal extracts is gaining significance in dysmenorrhea. In this review, we selected herbs that have spasmolytic, anxiolytic, and anti-inflammatory action. Medicinal plant extracts from *Valeriana officinalis*, *Humulus lupulus* and *Passiflora incarnata,* either in combination or as a single ingredient have the above-mentioned properties.

Supportive therapy for dysmenorrhea—it's time to put the old wine in new bottle

Since 10th century roots and rhizomes of *Valeriana officinalis* (Valerian) have been used in painful menstruation. The active principle valerinic acid inhibits contraction of smooth muscles resulting from cellular depolarization. *In vitro* and *in vivo* studies have shown its antispasmodic activity on smooth muscles. In this study Valerian and papaverine were equipotent in inhibiting smooth muscle contractions. *Valeriana officinalis* has been widely used for reducing pain, cyclic cramps, dysmenorrhea, anxiety, and stress. No adverse effects or hyper sensitivities were reported in clinical studies, and hence it is safe to use during pregnancy and breastfeeding. It is categorized as a safe drug by Food and Drug Administration. Varied dose of *valeriana officinalis* was studied. In a study, 255 mg of *valeriana officinalis* was administered amongst 49 patients, thrice daily for 2 days at the onset of menstruation for 2 consecutive menstrual cycles. The systemic manifestations associated with dysmenorrhea decreased significantly after the intervention. The possible mechanism may be *valeriana officinalis* inhibited contractions resulting from cellular depolarization.[21] *Valeriana officinalis* blocks calcium channels and opens potassium channels. Potassium channels opening, reduces intracellular calcium concentration, hence it relaxes uterine muscle.[22] Figure 1 depicts mechanism of action of *valeriana officinalis* via $GABA_A$ receptor.

Sub-chronic toxicological studies have shown that, the maximum tolerable dosage of *valeriana officinalis* is 2790 mg/kg/day. In humans, *valeriana officinalis* over dosage leads to mydriasis, headache, cardiac disorders, CNS depression, restless states, and sleeplessness.[23] Increased sleepiness was observed with 900 mg of *valeriana officinalis*, but there was no death reported at this dose. A randomized controlled clinical trial enrolled 39 patients aged between 16 and 42 years diagnosed with primary dysmenorrhea. In the intervention group 18 patients were given 350 mg *v*aleriana officinalis thrice a day, and in controlgroup, 21 patients were given 250 mg Mefenamic thrice a day for 3 days for three cycles, starting from the onset of bleeding or pain. The study

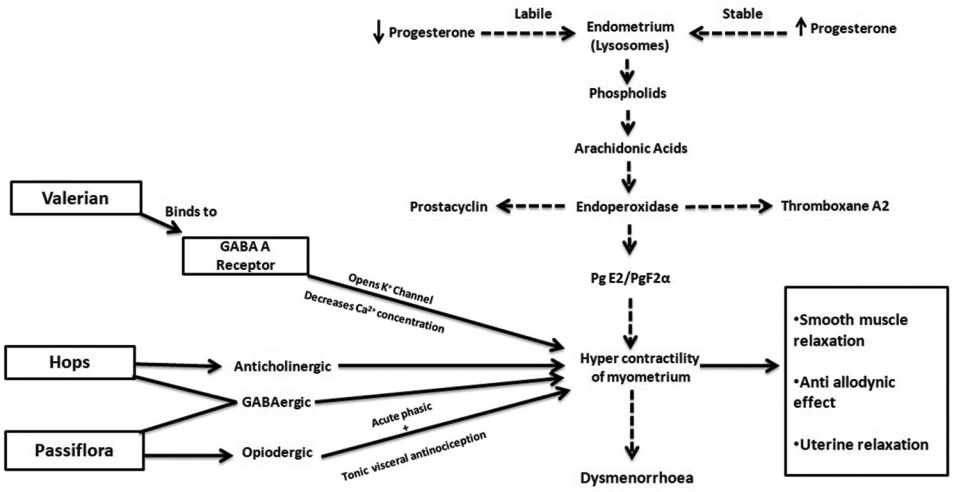

Figure 1: Pathophysiology and treatment of adolescent dysmenorrhoea

revealed statistically significant reductions in mean pain score in Valeriana officinalis ($P < 0.001$). Adverse effects in *Valeriana officinalis* group were fewer compared with mefenamic acid group. Hence, *valeriana officinalis* is non inferior to mefenamic acid in pain reduction with a better safety profile.[24] *Valeriana officinalis* at a dose of 300 mg will be a potent analgesic and spasmolytic based on the available studies.[25]

Humulus lupulus (known as HOPS) is a herb used to treat nervousness, restlessness, and impulsiveness across the globe. The analgesic and anti-anxiety effects of HOPS have been widely stated in various pharmacopoeias around the world. HOPS mainly constitutes flavonoids, terpenophenolics, and phenolic acids. Rutin is the active principle. Apart from alpha acids present in HOPS, rutin also plays an important role in exhibiting its anti-anxiety effect. The analgesic action of HOPS on uterine smooth muscle is via the inhibition of central nervous cholinergic system.[26] The GABAergic arm of Figure 1 demonstrates the mechanism of HOPS in pain management of dysmenorrhea.[27] Isohumolone isolated from HOPS extract is found to have analgesic effect.[28] Isohumolones are effective in reducing inflammatory arthritis pain in clinical trials based on improvement in WOMAC score.[29,30]

The recommended analgesic dosage for *humulus lupulus* is 100 mg/day. The lethal dose for HOPS is 3500 mg/kg for oral formulations. The competitive inhibition on acetylcholine induced contractions by HOPS enables muscle relaxation. Furthermore, smooth muscle relaxant effect pronounced by stimulating the nitric oxide, purinergic or adrenergic modulatory systems. HOPS leads to uterine smooth muscle relaxation in dysmenorrhea by acting on GABA receptors in intestine, ovaries, and uterine smooth muscles.[26]

Passiflora incarnata (known as passion flower) has been extensively used since ages in many countries as a sedative-hypnotic, analgesic, antispasmodic, antiasthmatic, anticonvulsant, antitussive, aphrodisiac, and wormicide. The main constituents of passion flower leaves are flavonoid (0.25%), vitexin, (the active principle), isovitexin, orientin, isoorientin, apigenin, and kampferol. Harman, harmine, harmalol, and harmalineare variousalkaloids present in *Passiflora* leaves. *Passiflora* increases the levels of inhibitory GABA in the brain. Figure 1 illustrates the mechanism in the CNS synaptic cleft. GABA decreases the brain activity thereby reduces anxiety. In a study amongst 36 patients with generalized anxiety disorder, it was found to be as effective as oxazepam.[31] In another study involving 99 patients *Passiflora incarnata* along with other herbs effectively controlled the symptoms of anxiety compared to placebo group. In an animal study *Passiflora* was found to have dose-dependent naloxone and pentylenetetrazole reversible antinociception suggesting an involvement of opioidergic and GABAergic mechanisms. In streptozotocin-induced neuropathic nociceptive model, 200 mg *Passiflora incarnata* unveiled dynamic and static anti-allodynic effects. The paw withdrawal threshold and paw withdrawal latency were increased. At all the tested doses *Passiflora* reduced the incidence of rearing. Also, it decreased locomotor activity equivalent to diazepam in open field test. The anti-allodynic effect of *passiflora incarnata* was also studied in vulval pain and it was found to be effective.[32]

Another study (Ingale, 2012) study reported 150 mg of *passiflora incarnata* to analgesic effect. In the hot plate test and abdominal constriction assay, *Passiflora incarnata* produced dose-dependant naloxone and pentylenetetrazole reversible antinociception suggesting an involvement of opioidergic and GABAergic mechanisms. In the staircase test, 200 mg/kg *Passiflora incarnata* increased the number of steps climbed. The dose 200 mg/kg of *Passiflora*extract exhibited analgesic activity [(13.50 ± 0.43) min] P value < 0.01, at a reaction time of 20 min in hot plate method. The extract at a dose of 100 mg/kg produced a highly significant anti-inflammatory effect [(1.302 ± 0.079) mL, P value < 0.01.[33] The role of *Passiflora* as an analgesic and anti-inflammatory agent is proven.

Valeriana officinalis, Humulus lupulus and *Passiflora incarnata* reduces the contraction of uterine muscle by acting synergistically via GABA. Furthermore HOPS relieves pain in dysmennorhoea by inhibiting the central cholinergic system and Passiflora by agonizing opiod pathways. Tripartate of 300 mg *Valeriana officinalis*, 30 mg of *Humulus lupulus,* and 80 mg of *Passiflora incarnata* aids in relieving dysmenorrheal symptoms. On the basis of the available studies, the herbal combination taken thrice a day for 5 days for three cycles upon onset of bleeding or pain reduces recurrence of dysmennorhoea.

Conclusion

Dysmenorrhea management requires multimodal therapeutic approach. There is evidence in the medical literature for the beneficial and synergistic effects of the herbal extracts such as *valeriana officinalis, humulus lupulus,* and *passiflora incarnata.* These extract have both localized and central action. The safety index is high for these extracts and hence it can be used as first line therapy for dysmenorrhea in primary care. This may be considered as a fixed dose combination having 300 mg of *valeriana officinalis*, 30 mg of *humulus lupulus,* and 80 mg of *passiflora incarnata.* In more severe cases, these extracts can be given as primary therapy and limit the use of NSAID as rescue medication for pain relief.

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Conflicts of interest

There is no conflicts of interest.

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