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Menstrual migraine. Diagnosis, pathogenesis and review of acute and short-term prevention pharmacotherapy

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Abstract

Background

Menstrual migraine describes migraines that occur in alignment with the menstrual cycle, affecting women of diverse age ranges. This condition is relatively common, presenting a unique challenge due to the heightened intensity of pain during these attacks. Additionally, these migraines are often more resistant to standard treatment methods, underscoring the need for specialized approaches to management and relief.

Methods

Review of double-blind, placebo-controlled cohort studies found using PubMed, Google Scholar and Cochrane.

Results

Triptans are considered a primary treatment option for managing acute menstrual migraine episodes, with their effectiveness being the most extensively researched among available therapies. Recently, lasmiditan has emerged as a newer medication showing promising potential for this specific application as well, adding to the options available for menstrual migraine relief. Furthermore, triptans have been validated as effective in the short-term prevention of migraine. The most recent pharmacological advancements that have demonstrated efficacy for this

condition are monoclonal antibodies which target the CGRP receptor: Erenumab and Galcanezumab.
Conclusion
There are effective approaches to both treating and preventing acute migraine attacks. However, menstrual migraine is a condition that requires greater awareness and recognition, as this would allow for the improved and more effective use of existing medications and treatments.

Keywords: Menstrual migraine; Acute treatment; Prevention; Triptans; Lasmiditan; CGRP monoclonal antibodies

Introduction

Migraine is a common disorder that affects 18% of women and 6% of men worldwide [1,2]. It is the first most common cause of years of loss in healthy life in young women, even though it does not shorten survival [3]. It is characterized by severe headaches, photophobia, phonophobia, nausea and vomiting [4]. During seizures neurological symptoms may occur, which are fully reversible [5].

The 3-fold prevalence of women suffering from migraines has led to the association of the disease with female sex hormones. A prevalent trigger causing migraine is menstruation. There are two basic types distinguished - pure menstrual migraine and menstrually related migraine, both with or without aura [6]. The prevalence of menstrual migraine is not well understood, primarily due to the scarcity of data and limitations in population-based studies that differ in case definitions and assessment methods used [7]. This diagnosis may affect even 18-25% of migraineurs [8].

In order to standardize the diagnosis, diagnostic criteria for menstrual migraine were developed. They were published in the 3rd edition of The International Classification of Headache Disorders (ICHD3) [9].

Pure menstrual migraine with or without aura - perimenstrual attacks occurring solely on or between days -2 and +3 of menstruation, in at least two out of three consecutive menstrual cycles, with no migraines experienced at any other time during the cycle.

Menstrually related migraine with or without aura - attacks similar to those in pure menstrual migraine, but they also occur on other days of the cycle [10].

The therapeutic problem is that the attacks are longer and less responsive to standard treatment than in the classic form of the disease [11].

Triptans are the main drugs used to stop migraine attacks. They are selective 5-

hydroxytryptamine 1B/1D (5-HT1B/1D) receptor agonists, cause intracerebral vasoconstriction and inhibit the release of vasoactive neuropeptide [12,13].

Calcitonin gene-related peptide (CGRP) is crucial in the development of migraine headaches. Recent advancements have led to the introduction of medications that target CGRP or its receptors, providing a novel approach to migraine prevention and management. There are two main types of CGRP-targeted treatments: monoclonal antibodies and CGRP receptor antagonists [14].

Lasmiditan is a high-affinity, selective 5-HT1F receptor agonist that can penetrate the central nervous system and does not cause vasoconstriction. Research indicates that lasmiditan's therapeutic effects in migraine management are achieved by reducing neuropeptide release and inhibiting pain pathways, particularly at the trigeminal nerve [15,16,17].

In this research, we would like to discuss the pharmacological treatment of acute attacks and short-term prevention of menstrual migraine.

Pathophysiology

Currently, two basic hypotheses for the pathogenesis of menstrual migraine have been identified. One of them refers to the withdrawal of estrogen, while the other refers to the increased release of prostaglandins. The genetic basis of the condition is also being sought.

The perimenstrual phase in women is associated with a decrease in the amount of estrogen and progesterone levels. The increased number of headaches during this period prompted scientists to conduct research, which led to the development of the hypothesis that estrogen withdrawal in susceptible women contributes to the occurrence of menstrual migraines [18]. The studies involved administering estrogen and progesterone injections. Estradiol successfully postponed the drop in estrogen levels and delayed the onset of migraines. However, while intramuscular progesterone injections delayed menstruation, they were ineffective in preventing migraines [19]. Interestingly, no relationship was observed between estrogen concentration and the day of migraine occurrence [20]. Estrogen levels decline twice during the menstrual cycle: after ovulation and before bleeding, but only the perimenstrual drop was associated with headache onset [21]. The reason for this difference is not yet clear. It is speculated that this may be related to the duration of exposure to estrogen, the effects of progesterone in the luteal phase and the increased release of prostaglandins [22]. One study found a protective effect of progesterone on headache severity. In the mid-luteal phase, where the concentration in urine was the highest, headaches in women were the least severe [23].

Female sex hormones influence the release of neurotransmitters involved in the pathophysiology of pain and migraine. One example is the fact that a decrease in the amount of estrogen contributes to a decrease in serotonin concentration, which may cause the feeling of pain [24]. Another effect of estrogen is its influence on modulation of the μ-opioid system. Reducing its concentration is associated with greater susceptibility to pain in the perimenstrual period [25]. In turn, progesterone and its metabolite allopregalon stimulate GABA-ergic transmission and may therefore have an analgesic effect [26]. A study in guinea pigs demonstrated that allopregnanolone likely reduced activity in the trigeminal nucleus caudalis by acting as a positive allosteric modulator of GABA-A receptors [27]. This is the opposite effect to estrogen, because estrogen contributes to increased activity in the glutamatergic system and reduces GABA-ergic activity [28]. Studies conducted on mice have shown that estrogen contributes to the increased release of analgesic neuropeptides: ghrelin, neuropeptide Y and galanin, which may indicate its analgesic effect [29].

A crucial molecule in the development of migraines is calcitonin gene-related peptide (CGRP), which plays a significant role in both pain transmission and vasodilation, making it a key target for understanding and treating migraines [30,31,32]. In humans, higher concentrations of CGRP were observed in women during pregnancy and while taking combined hormonal contraception [33,34]. However, lower concentrations could be observed in postmenopausal women [35,36].

The role of prostaglandins in the pathophysiology of migraine has not been studied as extensively. It is known that at the beginning of menstruation, the secretion of prostaglandins by the endometrium increases [37]. Painful menstruation is associated with an increase in prostaglandins [38]. It has been noticed that women who experience dysmenorrhea also suffer from migraine more often [39]. Injections of prostaglandins in women suffering from migraines caused migraine-like headaches [40].

Regarding the genetic aspects of menstrual migraine at the moment, no relationship has been found between migraine and polymorphisms in estrogen metabolism genes (COMT, CYP1A1, CYP19A1) or estrogens receptor 1 (ESR1) [41]. However, SNPs in tumor necrosis factor alpha (TNFα) and SYNE1, a gene neighboring ESR1, have been linked to MM. TNFα, as a pro-inflammatory cytokine, may connect estrogen and progesterone to inflammatory processes in MM. Additionally, SYNE1 is linked to other estrogen-related events [42]. The neuropilin 1 gene (NRP1), associated with neurovascular pathways, was also found to be significantly linked to MM, suggesting its role in migraine pathophysiology [43].

Diagnostic criteria

Table 1. Diagnostic criteria of menstrual migraine. International Classification of Headache Disorders, third edition [44].
● **Pure menstrual migraine with or without aura** Migraine attacks during or occurring -2 and +3 days of menstruation, in at least 2 of 3 consecutive cycles, with no migraine attacks in other days of menstrual cycle.
● **Menstrually related migraine with or without aura** Migraine attacks, which are similar to pure menstrual migraine but also occur on other days of the menstrual cycle.

Acute pharmacotherapy

Rizatriptan

In a group of 335 women, a study was conducted with rizatriptan 5 mg and 10 mg compared to placebo. At 2 hours post-dose, 70% of 115 women taking 5 mg and 68% of 135 taking 10 mg had pain relief compared with 44% of 81 patients taking placebo [45].

In the second study, a randomized, double-blind trial from 2007, a study was conducted on 707 patients, obtaining 2-hour pain relief in 70% and 24-hour pain relief in 46% migraineurs taking rizatriptan in 10 mg dose [46].

In the last study using 10 mg rizatriptan, 94 patients participated. The 2-hour pain relief was significantly higher than in the placebo group (63.5% vs. 57.5%) [47].

The above studies show the effectiveness of rizatriptan in treating acute headache attacks. They also indicate a dose of 10 mg as optimal.

Almotriptan

Almotriptan 12.5 mg was used in a double-blind cohort study. Efficacy 2 hours after drug administration was 48.4% compared to placebo at 28.8%. This effectiveness was also found in a longer observation period. It also contributed to reducing nausea and photophobia [48].

The second study, conducted on 275 women, compared the effect of almotriptan in patients with menstrual and non-menstrual migraine. Treatment efficacy outcomes for MRM vs

nonMRM, respectively, were: 2-hour pain relief, 77.4% vs. 68.3%; 2-hour pain free, 35.4% vs 35.9%; and sustained pain free, 22.9% vs 23.8% [49].

In the third study, the efficacy and safety of 12.5 mg almotriptan vs 2.5 mg zolmitriptan were compared in a group of 255 women with MM attacks. Two hours after taking the drug, pain relief was achieved in 67.9% of patients treated with almotriptan vs. 68.6% of zolmitriptan. Meanwhile, 44,9% vs. 41,2% of the respondents did not feel any pain. The relapse rate after 2-24 hours was respectively 32,8% vs. 34,7% and frequency of reporting side effects: 19,8% vs. 23,1% [50].

Data indicate the efficacy and safety of almotriptan 12.5 mg during a pain attack in women with MM.

Zolmitriptan

In a previously discussed study comparing the effectiveness of almotriptan and zolmitriptan, zolmitriptan showed a slight advantage in relieving menstrual migraine pain 2 hours after dosing [50].

In a double-blind, placebo-controlled study of 334 patients, a dose of 2.5 mg zolmitriptan was tested. The results showed a significant advantage of zolmitriptan compared to placebo (65,7% vs. 32,8%) in relieving headache 2 hours after dosing. Additionally, the study demonstrated greater efficacy of zolmitriptan at each time point tested. It also helped reduce the frequency of headache recurrences. Relapses occurred in 29.1% after the drug and in the placebo group in 45.1% [51].

Zolmitriptan 2.5 mg is effective in relieving headaches in migraineurs with MM.

Frovatriptan

There have been several studies testing the efficacy of frovatriptan compared to other triptans in the treatment of MM.

First a double blind, randomized study compared frovatriptan to zolmitriptan. The pain relief rate at 2 hours was 52% for frovatriptan and 53% for zolmitriptan, with no significant difference. The rate of being pain-free at 2 hours was 22% for frovatriptan and 26% for zolmitriptan. After 24 hours, 74% of frovatriptan-treated patients were pain-free, and 83% experienced pain relief, compared to 69% pain-free and 82% with pain relief among those treated with zolmitriptan. The recurrence rate at 24 hours was significantly lower for frovatriptan (15%) compared to zolmitriptan (22%) [52].

The second study compared the efficacy of frovatriptan 2.5 mg with that of almotriptan 12,5 mg. At 2 and 4 hours, the pain relief rates were 36% and 53% for frovatriptan, and 41% and 50% for almotriptan, respectively. The percentage of patients who were pain-free at 2 and 4 hours was 19% and 47% for frovatriptan, compared to 29% and 54% for almotriptan. After 24 hours, 62% of patients treated with frovatriptan experienced pain relief, and 60% were pain-free, while for almotriptan, these rates were 67% for both pain relief and being pain-free. Recurrence rates at 24 hours were significantly lower with frovatriptan (8%) compared to almotriptan (21%), and this trend continued at 48 hours (9% versus 24%) [53].

The third double blind study compared frovatriptan and rizatriptan. The number of patients who experienced pain relief 2 hours after drug administration was 58% for frovatriptan and 64% for rizatriptan. After this time, 31% and 34% were pain-free, respectively. Relapse after 24 hours was significantly lower after frovatriptan treatment (10% vs. 32%) [54].

The latest study tested frovatriptan 2.5 mg alone and in combination with dexketoprofen at doses of 25 mg and 37.5 mg. Pain-free after 2 hours was 29% after frovatriptan, 48% after frovatriptan + 25 mg dexketoprofen and 64% after frovatriptan + 37.5 mg dexketoprofen [55].

The presented results indicate the superiority of frovatriptan in reducing the risk of headache recurrence.

Naratriptan

In a Phase IIIB, double-blind, randomized clinical trial, the effectiveness of a 2.5 mg dose of naratriptan was tested on a group of 275 women. The study showed a significant advantage of naratriptan over placebo in both 2-hour complete pain relief and the maintenance of pain-free intervals over 4-24 hours. Total pain relief at 4 hours was 58% in the naratriptan group compared to 30% in the placebo [56].

Sumatriptan

In a prospective, double-blind, placebo-controlled study, 115 patients participated, who treated each migraine attack with 100 mg of sumatriptan for 2 months. The follow-up point was pain relief 4 hours after dosing. During the menstrual window, headache relief was reported by 67% of patients taking sumatriptan and 33% of those taking placebo. However, outside the menstrual period 79% vs. 31% respectively [57].

In another randomized, double-blind, placebo-controlled clinical trial, the effects of two doses of sumatriptan were compared: 50 mg and 100 mg. Data show that both the 50 mg and 100 mg doses were more effective than placebo at the 1-hour, 2-hour, and 2-24-hour long-term time

points with a slight advantage for the 100 mg dose. This relationship was not supported by statistical data but was noticeable in many measurements [58].

The last two studies used the combination of sumatriptan 85 mg with naproxen 500 mg compared to placebo. In both studies sumatriptan-naproxen was significantly more effective than placebo in providing pain relief at 2 hours, sustaining a pain-free state for 2 to 24 hours.. In Study 1, the 2-hour pain-free rate was 42% for sumatriptan-naproxen vs. 23% for placebo, while in Study 2, it was 52% vs. 22%. The sustained pain-free rates between 2 and 24 hours were 29% vs. 18% in Study 1, and 38% vs. 10% in Study 2 [59].

Lasmiditan

Patients in two double-blind, placebo-controlled studies were divided into groups receiving 50, 100 and 200 mg of lasmiditan. 2 hours after the dose, 33.6% of people taking 200 mg, 16.7% of 100 mg and 50 mg were pain-free compared to 7.6% of placebo [60].

Short-term prevention pharmacotherapy

Naratriptan

In a placebo-controlled study of 206 women with menstrual migraine, 1 mg and 2.5 mg of naratriptan were tested. The tablets were administered twice a day for 5 days in the perimenstrual period (2 days before the expected menstruation). In patients taking 1 mg of naratriptan, a greater number of perimenstruation periods without migraine pain was observed compared to placebo (50% vs. 25%), it also reduced the number of migraines (2.0 vs. 4.0) and the number of days with migraine headache (4.2 vs .7.0). The 2.5 mg naratriptan dose was not statistically superior to placebo [61].

In two identically designed studies examining the efficacy of 1 mg naratriptan, slightly different dosing regimens were used. The women took the drug twice daily starting 3 days before the expected occurrence of MRM for 6 days. 287 women participated in Study no. 1 and 346 women in Study no. 2. The average percentage of perimenstrual periods (PMPs) without MRM per patient was 38% and 34% for those treated with naratriptan who treated at least one PMP, compared to 29% and 24% among those given a placebo in each respective study. Across four perimenstrual periods, the number of menstrual-related migraine days per patient was was notably reduced in the naratriptan group compared to the placebo group in both studies (5.0 days vs. 6.5 days in Study 1 and 5.3 days vs. 6.0 days in Study 2) [62].

Frovatriptan

A placebo-controlled study was conducted on a group of 179 patients taking 2.5 mg of frovatriptan twice or once daily for 6 days during the perimenstrual period. There was a significant advantage of the 2.5 mg twice daily dose over the once daily dose and placebo. Migraines were experienced by 37.7%, 51.3% and 67.1%, respectively [63].

A second study in 546 women also confirms the superior efficacy of 2.5 mg of frovatriptan taken twice daily compared to once daily and placebo. The incidence of headaches in the twice-daily group was 41%, once-daily 52%, and placebo 67%. Both dosing regimens lowered pain intensity, shortened migraine duration, and reduced the need for additional rescue medication [64].

Both dosing regimens were also tested in 410 women with difficult-to-treat menstrual migraine. The average number of headache-free perimenstrual periods was 0.92 for frovatriptan taken twice daily, 0.69 for frovatriptan taken once daily, and 0.42 for placebo. The assumption that frovatriptan contributes to reducing the severity of pain was also confirmed [65].

Zolmitriptan

The efficacy of zolmitriptan in preventing MRM was studied in 244 women. 2.5 mg of the drug was used in a two- and three-dose regimen controlled by a three-dose placebo. Perimenstrual treatment lasted 7 days for 3 consecutive cycles. The 3-dose regimen produced slightly better results. This was assessed by the percentage of patients achieving a ≥50% reduction in menstrual migraine frequency: 58.6% for zolmitriptan three times daily, 54.7% for zolmitriptan twice daily, and 37.8% for placebo [66].

Galcanezumab

In the study conducted in Japanese patients, doses of 120 mg and 240 mg of galcanezumab were used once a month for 6 months. Both doses resulted in a reduction in the number of monthly days of moderate and severe headaches compared to placebo. Pain intensity was significantly reduced in patients taking 240 mg. Galcanezumab played a role in alleviating migraine symptoms, including nausea, vomiting, photo/phonophobia, and aura [67].

Erenumab

Women with menstrual migraine were entered into a placebo-controlled trial with a dose of 70 or 140 mg of erenumab. It was administered subcutaneously once a month for 6 months. Both doses of the drug contributed to the reduction of monthly migraine days. The higher dose was more effective (−2.1 days vs. −1.8 days). The chances of attaining a ≥50% decrease from baseline in monthly migraine days were 2.2 times higher for erenumab 70 mg and 2.8 times higher for 140 mg when compared to placebo [68].

Conclusion

Although menstrual migraine has a poorer response to treatment, there are medications that effectively treat headaches. The beneficial effect of triptans, which are agonists of the 5-HT1B and 5-HT1D receptors, in the treatment of acute headache attacks as well as in the short-term prevention of menstrual migraine has been confirmed. The widespread availability, effectiveness and tolerability of treatment mean that they can be used as a basic line of treatment in women. Lasmiditan as a selective serotonin 5-HT1F receptor agonist also plays a role in acute migraine treatment. This is a newer drug, unfortunately, it has been studied much less extensively in comparison to triptans. More research could determine its place in the treatment of acute MM. Erenumab and galcanezumab are monoclonal antibodies that target the CGRP receptor and block the action of CGRP in the brain. These are the newest drugs approved for migraine prevention. The presented studies indicate that these drugs contribute to reducing the number of migraines and therefore improving the quality of life. Further research is necessary to definitively establish whether they are superior to other medications. Their potential advantage lies in being administered once monthly, eliminating the risk of missing doses, a common issue with daily oral medications. A major challenge with menstrual migraine is its frequent misdiagnosis. Greater attention to accurately diagnosing headache types in patients could lead to improved treatment results.

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Disclosure

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