Prevention and Management of Menstrual Migraine

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Menstrual migraine occurs in 40% to 60% of women migraineurs. Due to its predictable nature, it is particularly well-suited to be approached in a preventive fashion when acute management alone is insufficient to address the often severe disability associated with menstrual migraine. Acute, mini-preventive, and preventive strategies for menstrual migraine management are discussed in this article. Comments are given regarding the usefulness of such strategies in the clinical setting. A combination of acute and mini-preventive/preventive treatment may be appropriate for many women suffering from menstrual migraine.

Introduction

The high prevalence of menstrual migraine in women is well-established. Among female migraineurs, 40% to 60% report perimenstrual exacerbation [1]. This reflects approximately 12 million women annually. Given the often severe disability associated with menstrual migraine, an aggressive management approach seems reasonable. A trial involving more than 1000 women showed that those with menstrual migraine had significant disability involving social activity (84%), household chores (81%), and work (45%) [2]. A study of 21 women with chronic migraine found that frequency, severity, and disability were all greater in the first 6 days after the onset of menses [3••]. This article explores and discusses preventive and management options for this large population of women who suffer significantly from migraine during a predictable time frame of their monthly cycle.

Definition

According to International Headache Society criteria, menstrual migraine is, by definition, migraine without aura [4]. It is defined as migraine without aura that occurs in at least 66% of menstrual cycles during the 5-day perimenstrual period from day -2 through day +3 (day 1 = first day of flow; also known as day 1 of cycle). Menstrual migraine is then divided into two types: pure menstrual migraine and menstrual-related migraine. Pure menstrual migraine is defined as migraine without aura that occurs exclusively during the 5-day perimenstrual period of day -2 through day +3 and reflects only approximately 14% of female migraineurs. More common is the menstrually related migraine, a migraine without aura occurring perimenstrually in 66% of the cycles but also at other times of the month. This condition applies to approximately 46% of female migraineurs [5].

Why the distinction between women suffering from pure menstrual migraine and menstrual-related migraine? In my opinion, women with pure menstrual migraine can be aggressively treated with mini-preventive regimens targeting their vulnerable time of their cycle; they are less likely to need daily long-term preventive medication. They are more likely to benefit from hormonal management because their predominant migraine trigger is hormonal. They are also, more likely as a group, to have significant improvement in their migraines when they become menopausal. In contrast, the larger group of women with menstrual-related migraine can be more challenging to treat because their headaches are not just hormonal-related; they may have multiple triggers and are less likely to benefit from a single mini-preventive strategy. They are more likely to require daily preventive regimens.

Drawbacks of current definition of menstrual migraine

There are women who have predominately migraine without aura and report worsening around the time of menses but occasionally have migraine with aura; how are these women to be categorized? In my practice, I have taken the history of many women who suffer from menstrual migraine but report that on occasion, they may experience aura. Usually this aura is visual, lasts well under 60 minutes, and often occurs less than 10% of the time with their migraines. If the migraine with aura occurs around the time of menses, are these not women with menstrual exacerbation of their migraines? However, menstrual migraine is defined as migraine without aura by the International Headache Society. In my opinion, the classification system

is too rigid and does not allow for female migraineurs who occasionally have migraine with aura around the time of menses to be classified as having menstrual migraine.

Diagnosis of Menstrual Migraine

The key to making the diagnosis of menstrual migraine is having all female headache sufferers keep a headache calendar for at least 3 months. This should be done in all of our female headache patients, regardless of whether they have a diagnosis of migraine. It is still common for women to think of headache as a normal phenomenon of premenstrual syndrome and not consider their perimenstrual headaches as possible migraine. The headache calendar should reflect the first and last days of the period, as well as all days a headache is experienced. It should be emphasized that all headache days should be recorded on the calendar and not just the severe ones. All too often, women only report their severe headache days. As a result, the frequency of headaches is often underreported, and inappropriate treatment plans may result. This underreporting can also lead to missing the presence of chronic daily headache and medication overuse headache.

The clinician should carefully look at the headache calendar with the patient and not just rely on the patient's interpretation or recollection of the headache days and relation to menses. A careful inspection of the calendar can help to determine if menstrual migraine can be diagnosed by seeing if there is a headache with menses in at least two of three cycles. An assessment of both the duration and severity of the perimenstrual headache is necessary to help with appropriate treatment. In general, the greater the severity and duration of the menstrual migraine, the more important prevention becomes. Looking at the nonmenstrual part of the calendar for the occurrence of other headache days can help differentiate women suffering from pure menstrual migraine versus the more common menstrual-related migraine.

Headache history

In addition to reviewing the headache calendar, additional history should be taken before the prevention and treatment options can be discussed. Importantly, is there ever aura with the perimenstrual headache? Migraine with aura is considered a contraindication to using any estrogen-containing contraception. Therefore, the presence of aura may preclude hormonal treatment with estrogen. An assessment of cardiac risk factors such as smoking, obesity, and hypertension should be made. Past and current treatment regimens should be reviewed. In particular, attention should be paid to past experience with hormonal regimens. It is important to know whether the patient is at risk for getting pregnant, is trying to get pregnant, or is actively using a form of contraception. Migraine peaks in women of child-bearing years; some headache medications can adversely affect the fetus and therefore should not be included in a preventive or management plan for many of these women.

Management of Menstrual Migraine

The management of menstrual migraine can be broken down into acute, preventive, and mini-preventive treatment options; such options can include prescription medications, over-the-counter (OTC) products such as analgesics, NSAIDs, and herbal and vitamin supplements, and hormonal manipulation. Nonpharmacologic strategies can be useful as well. The remainder of this article explores commonly used management strategies. Whenever possible, the usefulness of such strategies from research studies is discussed.

Acute treatment

In general, clinical trials show similar responses of patients with menstrual and nonmenstrual migraines to acute treatment [6]. The clinical desired endpoint of pain-free and back to full function within 2 hours of treatment seems reasonable. Treatment options include both OTC and prescription medication.

Acetaminophen-aspirin-caffeine

The efficacy of acetaminophen-aspirin-caffeine (AAC) in treating both menstrual-related migraines and nonmenstrual attacks in three randomized controlled trials was retrospectively analyzed by Silberstein et al. [7]. For both types of attacks, AAC was superior to placebo in providing headache relief at all post-treatment time points. There was no significant difference in headache response and pain-free rates for the two groups. Specifically, headache response was 61% at 2 hours for the menstrual-related migraine group and 58% for the nonmenstrual-related migraine group. Pain-free rates at 2 hours were 21% for the nonmenstrual group and 25% for the menstrual-related group. Significantly, however, patients with incapacitating headaches were excluded.

Comment

AAC is readily available as an OTC product, is cost effective, and is well-tolerated. It may be a good initial option for women who have mild-moderate menstrual migraine. Educating these patients on limiting AAC to no more than two to three times/week on a regular basis can help prevent overuse and rebound headache from this popular OTC product.

NSAIDs

This class of drugs has long been used to treat dysmenorrhea (pain with menses) but has not been well-studied for the acute treatment of menstrual migraine. A selective cyclooxygenase-2 (COX-2) inhibitor (rofecoxib) was US Food and Drug Administration (FDA)–approved for acute treatment of migraine before it was pulled from the market.

Table 1. Common mini-preventive regimens for menstrual migraine*

NSAID (eg, naproxen) dosed twice daily for 13–14 days
Magnesium 360–400 mg every day for 13–14 days
Triptan twice daily for 5–6 days
Hormonal therapy (add-back estrogen) the week of menses
Increase dose of daily preventive for 7–10 days

*None of these regimens is US Food and Drug Administration–approved for menstrual migraine prevention.

Comment
NSAIDs are readily available both in OTC formulations and as prescription medications. They are cost effective and generally well-tolerated. Women can benefit from reduction of menstrual pain as well as headache relief. However, they are not migraine-specific and are generally less efficacious than the triptan medications in moderate-severe menstrual migraine. However, they can often be used in a mini-preventive regimen perimenstrually, as well as in conjunction with a triptan. Therefore, giving women with menstrual migraine a prescription for an NSAID is, in my opinion, a cost-effective treatment approach. The NSAID can be regarded as one part of the overall management plan.

Triptans
The triptans are routinely used for migraine with and without aura. The labeling of the triptans does not indicate a reference to menstrual migraine; however, as has been discussed, menstrual migraine is migraine without aura. None of the triptans has been FDA-approved for preventive treatment of menstrual migraine. Sumatriptan, zolmitriptan, frovatriptan, eletriptan, and rizatriptan have all been studied in randomized controlled trials to look at their efficacy in acute treatment of menstrual migraine. All are superior to placebo in these studies. A complete overview of all triptan studies relating to menstrual migraine was published by Mannix and Files [8•]. More complete detail of triptans and other acute treatments for menstrual migraine can be found in an article by Tepper in this issue that focuses on acute treatment (page 169).

Comment
The triptans, as a class, can be very effective in the acute management of menstrual migraine, as has been demonstrated in clinical trials. The triptans should be considered as first-line therapy for moderate-severe menstrual migraine. The availability of non-oral formulations is an advantage for this class of drugs. For a woman with only 1 to 2 days of menstrual migraine each cycle, the triptan medication may be all that is needed. Triptans are generally well-tolerated and classified as class C for pregnancy.

Ergots/ergot alkaloids
The ergotamines may be useful for moderate to severe migraine that has not responded to the triptans or to other acute medications. They have not been formally studied for acute treatment of menstrual migraine.

Comment
The ergotamines are category X for pregnancy and should be absolutely avoided in women who are not using a consistent, reliable means of contraception.

Opioids
These agents may be useful for rescue of severe menstrual migraine when other acute measures have failed. However, the addictiveness and sedative side effects are a concern.

Comment
Use of an opioid for severe menstrual migraine on more than a rare occasion should warrant an aggressive preventive approach.

Mini-preventive treatment options
In clinical practice, this is also known as short-term prevention or mini-prophylaxis. Because menstrual migraine is predictable for many women, this gives an opportunity to pretreat and begin preventive medication before the expected onset of the menstrual migraine. Preventive treatment is often begun 3 to 5 days before the onset of menses and continued for 3 to 7 days into menses; this duration can vary depending on the pattern of the individual's menstrual migraine (Table 1).

NSAIDs
This class of drugs can be very cost effective when used in a mini-preventive regimen. Naproxen, 550 mg, was used in a double-blind, placebo-controlled study and was administered twice daily for 13 to 14 days starting 7 days before the expected onset of menses and continued for 6 days after onset. Both pure menstrual migraine and menstrual-related migraine were reduced in frequency, compared with placebo; 33% of patients who took naproxen were headache-free, compared with 0% who took placebo [9]. Both rofecoxib and celecoxib (COX-2 inhibitors) were studied for menstrual migraine prevention; both reduced the number of headache days. However, rofecoxib has been taken off the market.

Comment
Use of an NSAID as a mini-preventive for menstrual migraine can be very effective in some women. The COX-2 inhibitors are not as cost effective, and one (rofecoxib) has been taken off the market. I commonly use naproxen in a generic formulation for my patients for use in a mini-preventive fashion; in addition, they can use this with their triptan for nonmenstrual migraines. In some cases, they also use the naproxen alone for mild migraine headache. Overall, I find it very cost effective for menstrual migraine patients to have a prescription for an NSAID.

Magnesium

In a small study of 20 women, magnesium pyrrolidone carboxylic acid, 360 mg/day, or placebo was administered starting on day 15 of the cycle and continuing until the onset of menses. This was done for two cycles. Women who received magnesium had significantly less pain and fewer number of headache days [10].

Comment

Magnesium is OTC, relatively inexpensive, and generally well-tolerated. The most common side effects are gastrointestinal, especially diarrhea. I think it is a valid option to offer to women who want to try to prevent their menstrual migraine in a natural way and are against prescription medications. It can also be used as an adjunct to other preventive therapies (eg, a woman could take both naproxen, 550 mg twice daily, and magnesium, 360 mg/day, as a mini-preventive regimen). Obstetrician-gynecologists think magnesium is safe during pregnancy, and thus this is an option for women who are trying to get pregnant.

Triptans

Sumatriptan, naratriptan, zolmitriptan, and frovatriptan have all been studied as intermittent preventive therapy for menstrual migraine. Complete details of the study designs and outcomes can be found in a review looking at the use of triptans in the management of menstrual migraine [8•]. Newman et al. [11] conducted a pilot study to look at the efficacy of sumatriptan, 25 mg three times a day taken during the perimenstrual time; 52% of the treated cycles (119 cycles treated) were free of menstrual migraine, and severity was reduced by 50% to 90% in 42% of the cycles. Subsequently, double-blind, placebo-controlled trials were conducted with frovatriptan, naratriptan, and zolmitriptan. Silberstein et al. [12] evaluated frovatriptan in a large study involving 546 women. There were three arms in the study: patients were given placebo, frovatriptan as a loading dose of 5 mg followed by 2.5 mg twice daily, or frovatriptan as a loading dose of 5 mg twice daily followed by 2.5 mg twice daily. Treatment was begun 2 days before the expected onset of the headache. Both dosages of frovatriptan were superior to placebo in reducing the frequency of menstrual migraine; the response was dose-dependent (ie, more women were free of menstrual migraine on the 2.5-mg twice daily regimen than the 2.5-mg every day regimen) [12]. In the naratriptan study, women were randomized to placebo, naratriptan 2.5 mg twice daily, or naratriptan 1 mg twice daily. Naratriptan, 1 mg twice daily, showed superiority over placebo, with less perimenstrual headaches, and when breakthrough menstrual migraine occurred, the duration of pain was reduced [13]. Naratriptan, 2.5 mg twice daily, failed to show statistical significance over placebo; the reason for this is not clear. In addition, zolmitriptan was studied for prevention of menstrual migraine in dosages of 2.5 mg three times daily and 2.5 mg twice daily; a placebo arm also existed. Both regimens were superior to placebo in reducing the number of headache days [14].

Comment

Use of a triptan in a mini-preventive regimen is effective in women who do not optimally respond to acute treatment or to less expensive preventive options. However, most of the studies looking at intermittent preventive therapy with a triptan involved patients taking the triptan for 6 days or more. In some cases, the more effective dosage was a twice-daily regimen. Although potentially very effective in preventing the severity and duration of menstrual migraine, this management approach could be cost-prohibitive for many patients.

Preventive management options

This can be divided into traditional daily preventive medications such as the tricyclic antidepressants, β-blockers, antiepileptic drugs, and calcium-channel blockers, and the less traditional approach of using hormonal therapy. A daily preventive may be needed for women who have menstrual migraines not responding optimally to a combination of acute and mini-preventive regimens. The choice of which preventive may depend on the woman's comorbidities, willingness to put up with certain side effects, and relative risk of pregnancy. Divalproex sodium is category D for pregnancy and has been associated with increased risk of neural tube defects. Therefore, it is a good idea to avoid divalproex sodium in women of child-bearing potential. In some cases, increasing the dose of a currently prescribed daily preventive during the perimenstrual time can help prevent menstrual migraine. This strategy is already used with perimenstrual increase in selective serotonin reuptake inhibitor (SSRI) dose to help with premenstrual dysphoric disorder (PMDD). Although not formally studied, I have several patients who report increasing their dose of topiramate in a perimenstrual fashion with good results. In my clinical practice, I do not find the SSRI class of drugs very helpful for preventing menstrual migraine, although they can be very effective for PMDD and other mood disorders.

Hormonal therapy is a common approach to menstrual migraine prevention. The most common strategy is to try to maintain an even estradiol level throughout the cycle. This can be accomplished using continuous-dose oral contraceptives (eg, a monophasic pill containing 35 μg or less of estrogen); the incidence of headache complaints was reported to be 9.7% in women using extended-regimen oral contraceptives, versus 17.3% in those using standard regimens [15]. The contraceptive vaginal ring (Nuvaring; Organon USA, Roseland, NJ) can be used continuously by leaving the ring in and replacing every 4 weeks. More controversial is the transdermal estradiol patch (Ortho-

Table 2. Common hormonal therapies for menstrual migraine

Continuous oral contraceptives (monophasic/low-dose*)
Transdermal estradiol patch 0.1 mg 7–14 days
Continuous vaginal contraceptive ring (Nuvaring†)
Refractory: medical oophorectomy/add-back estrogen

*Monophasic: constant estrogen/progesterone amount in each active pill; low-dose is considered to be ≤ 35 μg of estrogen content per pill.
†Manufactured by Organon USA, Roseland, NJ.

Evra; Ortho-McNeil Pharmaceuticals Inc., Raritan, NJ); studies have indicated that patch users may be exposed to 60% more estrogen than women using a 0.035-mg estrogen-containing oral contraceptive. In addition, the level of estradiol provided by the patch may not remain steady [16]. For women who do not need contraception, a 0.1-mg transdermal estradiol patch applied perimenstrually can be effective in preventing menstrual migraine. Significantly, lower doses of the patch (ie, 0.05 mg estradiol) were ineffective [17]. These data suggest that it may be necessary to maintain a serum estradiol level more than 45 pg/mL to prevent menstrual migraine. The 0.1-mg patch provides serum estradiol levels of 45 to 75 pg/mL (Table 2) [18••,19].

Contraindications for hormonal therapy with estrogen include migraine with aura and the presence of multiple risk factors for stroke/cardiovascular disease, such as smoking, obesity, and uncontrolled hypertension. Also, estrogen should be avoided in women who have a clotting disorder, a history of deep vein thrombosis, or a high risk for deep vein thrombosis.

Conclusions

Menstrual migraine is very common and is often undertreated and under-recognized in our female patients. Although acute treatment options may help some of these women, increasing attention is now being directed to mini-preventive and preventive management that can greatly reduce the burden of disability associated with menstrual migraine. In most cases, a combination of acute and mini-preventive/preventive treatment is appropriate. A collaborative effort between gynecologists/providers in making decisions regarding hormones and with the headache providers is ideal for optimal management of menstrual migraine.

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