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LITERATURE REVIEW

PREVALENCE OF MENSTRUAL MIGRAINE AND THE EFFICACY OF SUMATRIPTAN ADMINISTRATION

Prevalensi Migrain Menstrual dan Efikasi dari Pemberian Sumatriptan

Aldilla Afifie Putri Maridsky[1], Devi Ariani Sudibyo[2], Ema Qurnianingsih[3], Citrawatri Dyah Kencono Wungu[4]
[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia, 60132, maridskyaldilla@gmail.com
[2]Department of Neurology, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia, 60132, devi.as@fk.unair.ac.id
[3]Department of Biochemistry, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia, 60132, ema-q@fk.unair.ac.id
[4]Department of Biochemistry, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia, 60132, citrawati.dyah@fk.unair.ac.id
Corresponding Author: Devi Ariani Sudibyo, devi.as@fk.unair.ac.id, Department of Neurology, Dr. Soetomo Academic General Hospital, Faculty of Medicine Universitas Airlangga, Surabaya, East Java, 60132, Indonesia

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ABSTRACT

Background: Menstrual migraine is a primary headache that often attacks women of reproductive age. This type of migraine has high severity and is resistant to treatment. Therefore, an effective treatment is needed to treat this menstrual migraine. Sumatriptan has been shown to have a better effect as an acute treatment for menstrual migraine patients. **Purpose:** This study aims to determine the prevalence and effectiveness of sumatriptan as a therapy for menstrual migraine. **Methods**: This research is based on a literature review following predetermined inclusion criteria. First, a literature search was carried out adhering to the PRISMA flow in 4 databases: Pubmed, Science Direct, ProQuest, and ClinicalTrial.co. **Results**: Based on keywords, 267 studies were found in the literature search. However, only three studies covering 845 participants met the predetermined inclusion criteria. The average age of menstrual migraine patients in the three studies was 37 years. These three studies of sumatriptan revealed a significant effect in providing a pain-free response in menstrual migraine patients. These three studies also showed that sumatriptan 100 mg has a higher level of effectiveness in providing a pain-free response in menstrual migraine sufferers and was preferably given during mild attacks. **Conclusion**: These three studies indicate that typically, women who suffer from menstrual migraines are of reproductive age. Additionally, this study shows that using sumatriptan as an acute therapy significantly helps provide a pain-free response in menstrual migraine patients.

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ABSTRAK

Latar belakang*: Migrain menstrual merupakan salah satu nyeri kepala primer yang sering menyerang wanita pada usia produktif. Tingkat keparahannya lebih tinggi dan lebih resisten terhadap pengobatan maka dibutuhkan pengobatan yang tepat untuk mengatasi migrain menstrual. Sumatriptan diketahui memiliki efek yang lebih baik sebagai pengobatan akut pada penderita migrain menstrual.*. ***Tujuan:*** *Penelitian ini bertujuan untuk mengetahui prevalensi dan efektivitas sumatriptan sebagai terapi pada penderita migrain menstrual.* ***Metode:*** *Penelitian ini merupakan tinjauan literatur sesuai dengan kriteria inklusi yang telah ditentukan. Pencarian literatur dilakukan dengan mengikuti alur dari PRISMA pada 4 database yaitu Pubmed, Science Direct, ProQuest, dan ClinicalTrial.co.* ***Hasil:*** *Berdasarkan kata kunci, ditemukan 267 penelitian dalam penelusuran literatur. Namun hanya 3 penelitian yang memenuhi kriteria inklusi yang telah ditentukan dengan jumlah peserta 845 orang. Usia rata-rata dari ketiga penelitian adalah 37 tahun. Ketiga penelitian mengenai sumatriptan ini menunjukkan efek yang signifikan dalam memberikan respon bebas rasa sakit pada pasien migrain menstrual. Ketiga penelitian tersebut juga menunjukkan bahwa sumatriptan 100 mg memiliki tingkat efektivitas yang lebih tinggi dalam memberikan respon bebas nyeri pada penderita migrain menstruasi dan sebaiknya diberikan pada saat serangan ringan.*. ***Simpulan:*** *Ketiga penelitian tersebut menunjukkan bahwa rata-rata wanita yang mengalami migrain menstrual adalah wanita usia reproduksi dan sumatriptan sebagai terapi akut secara signifikan mampu memberikan respon bebas nyeri pada penderita migrain menstruasi.*

INTRODUCTION

Migraine is one of the most common neurological disorders with high prevalence and morbidity, especially in young adults and women (1). Migraines in women vary significantly during puberty, the menstrual cycle, pregnancy, the postpartum period, and menopause. About 18% to 25% of women with migraines experience menstruation-related migraine attacks (2). Migraine often occurs in women during the fertile period and, in one year, can affect around 20–30% of women. Menstrual migraine (MM) most often occurs in the second decade of life around the beginning of menarche and usually without aura. The peak prevalence of migraine in women occurs between the ages of 35 and 45 years (3). A study states that around 42-61% of women suffer from menstrual migraine (4). Hormonal balance in regular ovarian cycles is a migraine trigger that is most often associated with women suffering from this condition (5). Migraine ranks second in causes of disability and first in women under 50 years of age based on the Global Burden of Disease 2019. Migraine prevalence varies substantially with age and gender (6).

Headache is a physical symptom that often appears before or during menstruation (7). Migraine is a primary headache disorder that is multifactorial and episodic. Migraine is characterized by moderate or severe attacks, unilateral and throbbing, accompanied by nausea, vomiting, photophobia (eye discomfort from bright light), and phonophobia (intolerance or hypersensitivity).

MM is a general term used for all types of migraines associated with the menstrual phase. The frequency of migraine attacks associated with menstruation occurs at least two out of three consecutive menstrual cycles (8). This occurs due to decreased natural estrogen levels during the menstrual phase. The two main pathophysiological mechanisms of menstrual migraine recognized to date are estrogen withdrawal and dissociable prostaglandin release (9). The estrogen withdrawal mechanism is the most accepted theory in explaining the pathophysiology of menstrual migraine. Estrogen withdrawal is when somewhat stable estrogen levels are replaced by a more fluctuating pattern (10).

Based on the International Classification of Headache Disorder, 3rd edition (ICHD-3), MM is

included in the classification of migraine with or without aura and is divided into pure menstrual migraine (PMM), menstrual-related migraine (MRM), and non-menstrual migraine. PMM is a migraine without aura that occurs only during the 5-day perimenstrual window, consisting of 2 days before the onset of menstruation and continuing until the first three days of the menstrual phase. It is estimated that around 7-35% of women experience PMM (11). MRM is a migraine attack with or without aura that occurs during the 5-day perimenstrual window and at other times of the menstrual cycle (12).

Menstrual migraine is prevalent in women, especially those of reproductive age. The severity level is higher and more resistant to treatment, so appropriate treatment is needed to treat this condition (13). One acute therapy that is effective in treating MM is sumatriptan. This class of drugs has a mechanism of action as a potent vasoconstrictor and inhibits the release of neuropeptides. Acute therapy is used to treat migraine attacks, while preventive or prophylactic therapy is used to reduce the frequency, severity, and duration of migraine attacks. Acute migraine therapy is divided into specific migraine therapy, such as triptans and ergots, and non-specific migraine therapy, such as NSAIDs. A clinical study shows that triptans are practical for use as menstrual migraine therapy, such as sumatriptan, almotriptan, eletriptan, fravotriptan, naratriptan, rizatriptan, and zolmitriptan. Acute therapies recommended to treat menstrual migraines as first-line therapy are triptans and NSAIDs (14). This study aims to determine the prevalence and effectiveness of sumatriptan as a therapy for menstrual migraine.

METHODS

The design of this study is a literature review. Literature searching was acquired from 4 databases: PubMed, ProQuest, Science Direct, and ClinicalTrial.gov. There is no year limit in the literature search. Researchers also used keywords adapted to Medical Subject Headings (MeSH) and boolean operators OR and AND in literature searches, including ("menstrual migraine" OR "menstrual-related migraine" OR "pure menstrual migraine" OR "menstrual associated migraine") AND (sumatriptan). The inclusion criteria for this study is full-text literature containing menstrual migraine patients according to ICHD-3 diagnostic criteria that were intervened with sumatriptan. The exclusion criteria were menstrual migraine patients who received intervention other than sumatriptan. Assessment of the quality of literature analysis uses the Cochrane Collaboration Risk of Bias Tools for Randomized Trials (RoB 2). RoB 2 is used to assess the risk of bias in assessing the impact of interventions reported from randomized trials. The impact assessed compares two interventions consisting of an experiment and a comparison.

RESULTS

Two hundred sixty-seven works of literature were obtained from a literature search through 4 databases, and only three studies were found in the literature search results that concluded the effectiveness of sumatriptan as a therapy for menstrual migraine. The characteristics table for the three studies is available in Table 1. Two studies used two doses of sumatriptan, namely sumatriptan 50 mg and 100 mg (15,16), while 1 study only used sumatriptan 100 mg (17). These three studies obtained a randomized controlled trial with 845 participants. The average age of menstrual migraine patients in the three studies was 37 years. The literature search flow diagram can be seen in Figure 1.

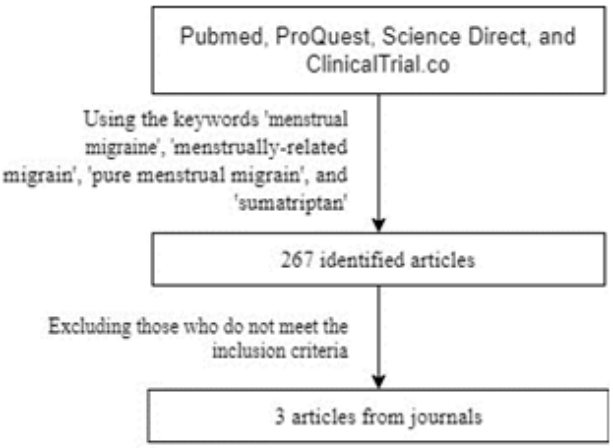

Figure 1. Flow chart of Selected Studies

Table 1
Characteristics of All Studies

Author (Year)	Nett et al (2003)	Landy et al (2004)	Dowson et al (2005)
Title	Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine	Efficacy and tolerability of sumatriptan tablets administered during the mild-pain phase of menstrually associated migraine	Managing migraine headaches experienced by patients who self-report with menstrually related migraine: a prospective, placebo-controlled study with oral sumatriptan
Country	United States, Canada, and Puerto Rico	Europe, Canada, and New Zealand	United Kingdom
Participants	349	403	93
Mean Age	36 years old	37 years old	38 years old
Design	RCT	RCT	RCT
Findings	Percentage of patients showing a pain-free response 2 hours after treatment of menstruation-related migraine • Sumatripan 100 mg group (61%) • Sumatripan 50 mg group (51%)	Percentage of patients showing a pain-free response 2 hours after treatment of menstruation-related migraine • Sumatripan 100 mg group (61%) • Sumatripan 50 mg group (51%)	The proportion of patients who reported a headache-free response within 4 hours of taking the first dose of the study drug, sumatriptan 100 mg (54%)

Table 2
Results of The Cochrane Risk of Bias Tool for Randomized Trials (RoB 2)

Study (Year)	Risk of Bias Checklist																					Overall Judgement
	Domain 1				Domain 2								Domain 3		Domain 4				Domain 5			
	1	2	3	Judgement	1	2	3	4	5	6	7	Judgement	1	Judgement	1	2	3	Judgement	1	2	3	Judgement	
Nett et al (2003)	Y	Y	N	Low	N	N	-	-	-	Y	-	Low	Y	Low	N	N	N	Low	Y	N	N	Low	Low Risk of Bias
Landy et al (2004)	Y	Y	N	Low	N	N	-	-	-	Y	-	Low	Y	Low	N	N	N	Low	Y	N	N	Low	Low Risk of Bias
Dowson et al (2005)	Y	Y	N	Low	Y	Y	Y	Y	Y	N	N	Some Concerns	Y	Low	N	N	N	Low	Y	N	N	Low	Some Concerns

Figure 2. Forest Plot Pain Free Response After Sumatripan 100 mg Therapy

The results of the analysis of the effectiveness of sumatriptan in providing pain-free responses to menstrual migraines in the form of forest plots can be seen in Table 2. Analysis of the third showed significant results, where sumatriptan 100 mg could provide 2x the pain-free response (RR 2.38; 95% CI 1.94-2.93) compared to placebo in menstrual migraine sufferers. Internal research validity quality assessment uses the Cochrane risk of bias tool for randomized trials (RoB 2), having 5 question domains broken down into 22 questions. Both studies received a final rating of low risk, and 1 study received a rating of some concerns in Figure 2.

DISCUSSION

Migraine attacks occur more frequently in women than in men, and this is supported by an imbalance in ovarian hormones that occurs during menstruation as one of the causes of headache symptoms in menstrual migraine sufferers (18). Menstruation is one of the most frequently reported migraine triggers after stress (19). The incidence of migraine in women is related to the reproductive stage, which increases during puberty, reaches its peak during childbearing age, and decreases after menopause (20). Menstrual migraine usually occurs at the beginning of menarche, which on average takes place at the age of 12 - 13 years and has a peak prevalence at around the age of 40 years (21). This is supported by three studies showing that the average age at which menstrual migraines occur is 36-38 years. Research conducted by Chalmer et al (2) showed that 1,532 participants provided validation regarding the diagnostic criteria for menstrual migraine and the average age of all participants was 38.7 years. An observational study also showed that the prevalence of menstrual migraine was around 45.15% of all participants. Moreover, the average age was 20 years (22).

The understanding of menstrual migraine prevalence remains poor, mainly due to the scarcity of data and limitations in population-based studies having varying depths of case definition and assessment methods used. The majority of women with migraines experience migraine attacks either before menstruation or at other times of the month, which is defined as MRM and is estimated to affect around 50-70% of women of childbearing age (11). It is estimated that around 60% of women with migraines experience menstruation-related migraine attacks. The headache impact and functional burden associated with migraine were also more significant compared to those suffering from migraine unrelated to menstruation (23). ICHD 3rd edition (ICHD-3) indicates that the diagnosis of menstrual migraine can occur with or without aura, and studies in the general population with more selective criteria show that 4–8% of all women and 18–25% of women with menstrual migraine experience without aura (9). The prevalence of menstrual migraine with aura is estimated to be less, namely around 1.7-8.1% of female migraine sufferers in the general population. The prevalence of migraine without aura associated with menstruation ranges from 35-51% of women, while PMM without aura varies between 7-19% (24).

Recent research states that hormonal imbalance emphasizes the decrease in estrogen hormone levels that occurs in the early phase of menstruation. A decrease in the hormone estrogen can result in several things, such as increasing the susceptibility of blood vessels to prostaglandins, working through serotonergic and dopaminergic effects, modulating neural excitability and pain perception, suppressing endogenous opioid activity, and increasing allodynia and central sensitization (25). A decrease in estrogen levels occurs in the early phase of menstruation, which impacts reducing levels of monoamine oxidase (MAO), a pain receptor in the brain. Serotonin, as one of the essential neurotransmitters from MAO, also decreases levels in the brain, especially in the cranial blood vessels (12).

Low serotonin levels in the brain lead to vasodilation of cranial blood vessels and cause pain. Sumatriptan is used in this case to stimulate the 5-HT1B/1D receptor, which is a serotonin receptor in the intracranial blood vessels and trigeminal nerve terminals, causing the cranial blood vessels to narrow and reducing neurogenic inflammation by decreasing the release of pro-inflammatory peptides such as CGRP (26).

Acute migraine attacks in menstrual migraine sufferers are often accompanied by symptoms of acute migraine in general. There are no definite studies that state the success of sumatriptan in eliminating symptoms related to menstrual migraine. However, several studies show that this condition may occur due to the secondary action of sumatriptan, which blocks the release of certain natural substances that cause migraine symptoms

in general. The correct dose and preparation during a mild attack are essential in increasing treatment success.

Clinically, sumatriptan can reduce several clinical symptoms in two ways, namely as a 5HT1B vascular receptor agonist, which causes blood vessel contraction in certain parts of the brain and limits the release of vasoactive neuropeptides from perivascular trigeminal sensory neurons as well as reducing trigeminal nerve pain signal transmission (27). Sumatriptan has a plasma half-life of only 2 hours. The oral dosage of sumatriptan is 25 mg, 50 mg, and 100 mg, but the drug's efficacy is preferred at doses of 50 mg and 100 mg for treating acute migraine attacks (28). As ICHD-3 guidelines state, there will be a pain-free response for 2 hours after effective treatment was used as the primary efficacy parameter in treating acute migraine attacks in randomized controlled trials (29). Sumatriptan also could provide a pain-free response for 4 hours after sumatriptan treatment in menstrual migraine (17).

Sumatriptan oral preparations have several side effects, namely non-coronary vasospastic reactions and peripheral vascular ischemia (30). Apart from that, this drug can also provide mild sedative effects such as drowsiness or fatigue in patients. Administration of sumatriptan is contraindicated in patients who have a history of severe liver disorders, ischemic heart disease such as coronary artery vasospasm, myocardial infarction, and angina pectoris, as well as patients with peripheral vascular disease.

Research Limitations

This research needs to be revised because of the limited number of studies discussing menstrual migraines. Thus, it is not easy to get the expected data. Besides, there are few controlled trials related to menstrual migraines, leading to limited samples obtained.

CONCLUSION

These three studies show that, on average, women who experience menstrual migraines are women of reproductive age, and sumatriptan as an acute therapy is significantly able to provide a pain-free response in menstrual migraine sufferers. These three studies also show that sumatriptan 100 mg has a higher level of effectiveness in providing a pain-free response in menstrual migraine sufferers and should be given during mild attacks.

CONFLICT OF INTEREST

The authors declared that there was no conflict of interest on this research.

AUTHOR CONTRIBUTION

AAPM and DAS: Conceptualization, Methodology, Data Curation. EQ and CDKW: Supervision and Reviewing.

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