



MIGRAINE PREVENTIVE THERAPY; FOCUS ON B-BLOCKERS; LITERATURE REVIEW

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ABSTRACT

Migraine is an unpleasant neurological disorder characterized by frequent severe headache attacks associated with nausea, phonophobia, or photophobia with or without aura. Preventive treatment is an essential part of migraine management if it is indicated in certain circumstances. β -blockers are widely used for reducing migraine attacks frequency and severity for a long time with favorable adverse effects profile. The prevalence of migraine is approximately 12% in the general adult population, and 18% in women, 6% in men in the US population-based studies. Almost 90% of migrainous patients experience moderate or severe pain, three quarter have reduced functional capacity during attacks of headache, and one-third require bed rest during the attacks with performing daily chores, and maintain active family, the inability to work, social, and community relationships. This literature review summarizes the principles of migraine preventive therapy, particularly the efficacy of β -blockers. We did a search in the PubMed database looking for relevant articles on the topic. We used MeSh words: β -blockers, β -adrenergic antagonist, Migraine, and Migraine prevention. β -blockers are highly effective in migraine prevention and provide different classes with a preferable safety profile.

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Introduction

Migraine headaches are characterized by frequent or infrequent intermittent attacks of unilateral, pulsating, and moderate to severe headaches with nausea, photophobia, or phonophobia [1]. Typically, these attacks started before the age of 40, often in adulthood or childhood, and occur most commonly between the second to the fourth decade of life [1]. The diagnosis of chronic migraine is considered when attacks of headache are more than 15 days monthly [1, 2]. Ordinarily, diagnostic tests are used to exclude secondary causes of headaches [2]. However, due to the uncertainty and broadness of the clinical manifestations of migraine headaches, the headache community faced difficulties reaching a consensus on the diagnostic criteria of chronic migraines in clinical practice [2].

The prevalence of migraine is approximately 12% in the general adult population, and 18% in women, 6% in men in the US population-based studies [3]. Almost 90% of migrainous patients experience moderate or severe pain, three quarter have reduced functional capacity during attacks of headache, and one-third require bed rest during the attacks with performing daily

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chores, and maintain active family, the inability to work, social, and community relationships [2, 3]. Moreover, migraine headache is associated with an increased risk of physical and psychiatric comorbidities [4]. Headache is among the top 20 causes of outpatient healthcare visits and the top 5 causes of emergency department visits [4].

Regarding the chronic migraine incidence in the general population, it has not been thoroughly studied yet [2]. Nevertheless, according to the American Migraine Prevalence and Prevention (AMPP) study, the migraine incidence in the United States population in a subsequent year was 2.5% [5]. A prospective German study concluded that the chronic headache incidence was 14% [2]. Chronic migraine evolution is triggered by certain risk factors, including modifiable, non-modifiable, and putative factors [2]. Non-modifiable risk factors include the Caucasian population, female sex, older age, low educational level, poor socioeconomic status, and genetic factors [2]. On the other hand, modifiable risk factors are essential in targeting medical intervention, for instance, attack frequency, life stressors, depression, snoring, obesity, medication overuse, and anxiety [2]. Putative factors, or factors currently being investigated, including proinflammatory and prothrombotic states [2].

The Pathophysiology of Migraine

The exact pathophysiological mechanism of migraine is still unknown, but there are three main theories proposed with regards to the clinical condition [6-8]. Firstly, the vascular theory, which stated that migrainous pain attacks induced by vasodilatation since experimental observation showed that the diameter of the extracranial arteries in migraine patients found dilated [6]. Secondly, the neurological theory considers migraine attacks induced by an alteration in the neurotransmission system [6]. This theory was thought to be related to cortical spreading depression: the main mechanism for aura [6, 9]. The third theory combined the vascular and neuronal theories, for which a release of inflammatory neuropeptides from the trigeminal system cause dilatation of meningeal vessels [6]. Migraine comprehension is essential to reduce the burden and improve the quality of life for migrainous patients [9].

Results and Discussion

Migraine Prevention; Principle and Indications

Migraine prevention is multifactorial, including lifestyle modifications, avoidance of migraine triggers, modifiable risk factors, pharmacological interventions, nutraceuticals, neurostimulation, and behavioral therapies [10]. Migraine prevention aims to reduce the frequency of the attacks, days affected by migraine, symptoms severity, frequency of receiving medical therapy, migraine-related disabilities, and improve daily functional ability [10, 11]. Additionally, migraine prevention resulted in healthcare cost reduction [11]. Recent European and the US guidelines have published certain circumstances that might assure preventive therapy: 1) recurrent migraine attacks that significantly interferes with a patient's quality of life and daily chores despite active treatment; 2) four or more attacks monthly; 3) failure of, contraindications, or suffering side effects from acute treatment; 4) frequent, remarkably long, or distressing auras [11].

Migraine preventive therapy can be short-term, maintenance, or preemptive [12]. When a trigger is identified and avoided, preemptive therapy is used, like sexual activity or exercise [12]. The patient can be notified to pretreat before the trigger exposure; for instance, to prevent exercise-induced migraine, a single dose of indomethacin can be used [12]. When a patient is undergoing time-limited exposure to a migraine trigger, short-term prevention is used, such as rise to menstruation or high altitude [12]. A daily medication before or during the trigger can be used in those patients; for instance, triptan for 3 to 5 days or a perimenstrual use of a non-steroidal anti-inflammatory drug (NSAID) may help in menstrually-related migraine prevention [12]. On the other hand, when patients need continuous treatment, prevention of maintenance is used [12].

When migraine preventive therapy is initiated, one of three outcomes can be expected; the treatment may show a substantial benefit, characterized by a 50% reduction of headache frequency [13]. While the primary outcome of preventive therapy is the reduction of the frequency of the attacks, some patients reported a reduction in migraine intensity and improved response to symptomatic medications while taking prophylactic medication [13]. The second probability is that the patient may not tolerate the adverse effects, such as somnolence, nausea, cognitive slowing, or weight gain, and subsequently, omitting therapy might be needed [13]. The third probability is that the prophylactic medication's efficacy may insufficiently achieve [13]. Most prophylactic medications show remarkable effectiveness within one month of therapy initiation, and therapeutic effects may subsequently increase for several months [13]. Nevertheless, if the patient shows no improvement after two months of therapy initiation at the target dose, prophylactic treatment should be stopped and replaced by alternative preventive medication [13].

β -blockers and Its Role in Migraine Prevention

β -blockers were the first used prophylactic medication for migraine since 1959, and it is a widely used drug class in clinical practice that works by antagonizing adrenergic receptors [14, 15]. β -blockers can be distinguished by their selectivity to β_1 and β_2 receptors, the presence of intrinsic sympathomimetic activity, the variation in lipid solubility that influences penetration into the central nervous system (CNS), the properties of inverse agonist, the ability to induce vasodilatation, and finally, by their pharmacokinetic properties [14, 15]. Moreover, β -blockers are widely used medications in migraine preventive therapy and are highly effective in reducing migraine attacks frequency by 50% [15]. However, the mechanism of action of β -blockers in the prevention of migraines is still uncertain [15]. Migraine is predominantly a neurogenic disorder rather than a vascular, and β -blockers, such as metoprolol, propranolol, and timolol, showed high efficacy because they cross the blood-brain barrier

(BBB), utilizing their lipid solubility and alter neuronal excitability [14, 15]; nadolol, however, does not cross the BBB and still effective in migraine prevention [14].

Furthermore, the β_1 -mediated effect inhibition might consider the primary mechanism of action in migraine prevention [16]. Certainly, blockade of β_1 receptors inhibits the release of hydroxylase activity and noradrenaline (NA), which is the rate-limiting step in NA synthesis [16]. Besides, propranolol decreases the neuronal firing noradrenergic neurons rate in the locus coeruleus [16]. Importantly, β -blockers also regulate the firing rate of periaqueductal grey matter neurons through a GABA-mediated activity [16]. Both of these actions may participate in the antimigraine activity of β -blockers [16]. Also, the sympathetic nervous system inhibitory effect has been exhibited in various measures of cortical information processing that are abnormal in migrainous patients [14]. This is evidenced by alters visual evoked potentials (VEP), cognitive negative variation (CNV), and auditory evoked potentials (AEP) [14]. Furthermore, various studies have found increased VEP amplitudes in migrainous patients; this can be interpreted as increased occipital cortex excitability [14].

Nonetheless, although all β -blockers are β -receptors competitive inhibitors, those with sympathomimetic properties, such as oxprenolol, pindolol, acebutolol, and alprenolol, are ineffective for migraine prevention [16]. Evidence-based support the propranolol use (80mg-240mg/day), timolol (20-30mg/day), bisoprolol (5mg/day), and metoprolol (200mg/day) in migraine preventive therapy [16]. In addition, nadolol and atenolol provide a moderate effect in migraine frequency reduction [16]. Interestingly, nebivolol has shown in a double-blind, randomized clinical trial to be effective as metoprolol in migraine attack prevention [17]. Based on the American Headache Society (AHS) and the American Academy of Neurology (AAN), β -blockers (propranolol, metoprolol, and timolol) are considered one of the level-A drugs in migraine prevention [18]. Level-A drugs are considered if at least two high-quality randomized controlled trials confirm efficacy [18]. β -blockers are the first choice for migraine prevention in patients with hypertension and the preferred option in patients with essential tremors, anxiety, and panic attacks [19].

In meta-analyses comparing different agents for migraine preventive therapy, atenolol, metoprolol, propranolol, and timolol were superior to placebo for episodic migraine headaches [20]. Contrarily, acebutolol, alprenolol, bisoprolol, oxprenolol, pindolol were found with no superior to placebo in preventing migraine attacks [20]. Common side effects of β -blockers include depression, dizziness, and insomnia [20]. Importantly, contraindications to β -blockers include asthma, Raynaud's disease, congestive heart failure, and preferable avoidance in diabetes mellitus and depression [19]. Ordinarily, preventive therapy is considered successful when certain aspects are accomplished: before initiating prophylactic therapy, the patient must be instructed to record the migraine attacks severity, duration, and frequency in a diary, which may help to determine the drug efficacy [21]. Initially, the drug should be started with a low dose (e.g., propranolol 20mg per day) and gradually increase since side effects may occur before impairing patient adherence and prophylactic effects [21]. The preventive therapy must be kept for a minimum of 3 months to allow efficacy maintenance in a specific patient [21]. Discontinuation can be tried when successful therapy is continued for 12 months, but drug dose should be gradually decreased, especially β -blockers, to avoid reflux tachycardia or hypertension [21]. Optimally, patients undergoing prophylactic therapy must be assessed every 2-3 months [21].

Conclusion

Migraine headache is a prevalent, disturbing, and uncomfortable disease which cause significant burden on patient quality of life and healthcare cost. Preventive therapy is targeted to decrease the frequency and attacks severity and improve the patient's functionality and quality of life. Several methods play a significant role in migraine prevention, including identifying potential triggers and avoid them, if possible. Of note, pharmacological intervention might be required in certain circumstances, and multiple drug options are available. β -blockers have been extensively studied in migraine preventive therapy and showed high efficacy with favorable adverse effects profile. However, specific types of β -blockers are commonly used due to their pharmacokinetic properties. Other classes of β -blockers must be studied to establish their efficacy and safety in migraine prevention.

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