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EFFECTIVENESS OF PHARMACOLOGICAL MANAGEMENT OF MIGRAINE IN ADULTS

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Abstract:
Migraine headache is considered to be a common and complex neurovascular disorder with a characteristic of recurrent episodes. It affects one side of the head (unilateral) and it is associated with other symptoms including, nausea, vomiting, photophobia, tiredness, neck stiffens, and throbbing pain that increase with movement. Types of migraine are migraine with aura, migraine without aura, retinal migraine, and chronic migraine. Choosing the best and the most effective treatment for migraine are based on diagnosis according to different criteria and migraine phase. The treatment is classified into two categories; treatment that stops the headache from progressing including nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin receptor agonists (triptans) and analgesics and the other one is prophylactic treatment that prevents headache onset such as tricyclic antidepressants, calcium channel blockers, beta-blockers and antiepileptic drugs. Chronic migraine (CM) has different lines of treatment: invasive, oral prophylactic agents, and Botox.

Key words: *Migraine headache, trigeminovascular system, calcition gene-related peptide (CGRP), serotonin, substance P.*

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INTRODUCTION:

Migraine headache is a common disorder, recurrent episodes are one of it is characteristics. Mostly it is unilateral and associated with other symptoms. It affects majority of adults aged between18-65. The prevalence among adults was estimated 50% worldwide [2]. It is more common in women than men [1]. Migraine headache has subtypes: migraine with aura, migraine without aura, retinal migraine and chronic migraine [3]. It has serious impact on individuals' life, health and psychosocial state.

headache comes from a Greek word "hemicrania" which means "half of the head". Also, the pain is felt in back and front of the head bilaterally and rarely in the face. This pain is characterized by throbbing nature and worsens with movement. It is associated with other symptoms like: photophobia, nausea, dizziness, loss of appetite, bowel function disturbance, and sensitivity to smells and noises[5]. Migraine is considered to be a complex neurovascular disorder and has a lot of different causes: first, in the past it was explained by a vascular theory; vasoconstriction of intracranial and extracranial vessels, then rebounding vasodilation occurs resulting in migraine. But now the neurovascular theory took more attention; migraine is predominantly neurogenic followed by secondary changes in the brain perfusion and associated with neurogenic inflammatory process [1]. So, it occurs due to vasodilation of intracranial and extracranial vessels associated with stimulation of trigeminal nerve. This 'trigeminovascular system' stimulation triggers release of many vasodilators particularly calcitonin gene-related peptide (CGRP) that stimulates pain sensation resulting in headache. Furthermore, it was found that the individuals suffering from migraine has low level of neurotransmitters particularly serotonin [6]. Genetics also play a role in migraine as about 70% of patients showed that they have at least a first degree relative having history of migraine headache [1]. Multiple environmental and other factors including behavior may trigger attacks of migraine in individuals predisposed to it. Among these triggers are stress, smoking, weather changes, hormonal changes as occurring with menstruation, ovulation, pregnancy, medications (vasodilators), fasting, lack of sleep and red wine. Also, food including caffeine, artificial sweeteners and citrus fruits can trigger it [1]. In addition, exposure to bright or fluorescent lighting, strong odors (e.g., perfumes, petroleum distillations), head trauma, motion sickness, cold stimulus (e.g., headaches associated with taking ice cream) and deficient exercise are possible precipitating factors.

Although migraine is common in families, genetic mutations were rarely found. Mutation of the gene encoding the enzyme casein kinase 1δ (CK1δ) was found in only two families. It may be also associated with a syndrome called "familial advanced sleep phase syndrome". Migraine is also considered a circadian rhythm disorder in which person's sleep and waking hours becomes earlier than usual [7].

PATHOPHYSIOLOGY:

The first thing in pathophysiology is to know that the source of pain is produced from the trigeminal nerve. A plexus of mostly unmyelinated fibers arising from the ophthalmic branch of the trigeminal ganglia and from the upper cervical dorsal roots in the posterior fossa surrounds the main cerebral vessels, dura mater, pial vessels and main venous sinuses which make these structures pain sensitive. Substance P and calcitonin gene-related peptide (CGRP) were found in the trigeminal fibers innervating cerebral vessels. When the trigeminal ganglia are stimulated, both these substances are raised in humans [8]. Dural nerves of humans innervating the cranial vessels are small sized unmyelinated and myelinated fibers and have nociception role. Convergence of cervical and trigeminal ganglia together may explain the common primary headache and neck stiffens associated with pain in migraine.

There are some phases that patients go through; premonitory or warning phase, aura (not always present), main attack stage, resolution and finally recovery or postdrome stage. The premonitory phase begins 72 hours before the characteristic pain of margarine. The symptoms of this phase originate from the hypothalamus and include changes in appetite, mode, and sleep associated with yawing. The function of the superior salivary nucleus is to regulate the autonomic function, but when it is activated by the hypothalamic descending projection it causes autonomic symptoms. Also hypersensitivity of the hypothalamus to dopamine or its agonists produces these symptoms including nausea, vomiting and yawing [9].

Serotonin, also called 5-hydroxytrypaimne (5-HT), has implications in migraine pathogenies. Serotonergic neurotransmission is controlled by serotonin receptors which have 7 types, but those receptors involved in migraine are; 5-HT1, 5-HT2, 5-HT3 and are found in trigeminal nerve ending [1]. The serotonin receptor (5-hydroxytryptamine [5-HT]) is thought to be the main receptor in the control of "serotonergic neurotransmission" and obviously in numerous functions related to behavior and also headache pathway. 5-HT1 has subtypes; 5-HT1D and

5-HT1B. 5-HT1D is found in sensory division of trigeminal nerve and in solitary tract[6]. 5-HT1B is found in smooth muscle cells of meningeal vessels. Also, it can be found in coronary vessels. It is produced at dorsal raphe which is the site of emergence of trigeminal nerve and trigeminal ganglia. It causes vasoconstriction at nerve endings, so it affects nociceptors and induces pain. So, in migraine, serotonin level is low and causes vasodilatation. Migraine patients reported that vomiting relieves headaches. Vomiting raises serotonin level and stimulates intestine motility [8].

PET scanning for the brainstem in acute migraine patients exhibits stimulation of the contralateral pons, even post-therapy for relieving pain. In addition, once the "cortical spreading depression (CSD)" arises on the brain surface, H+ and K+ ions diffuse to the pia matter and activate C-fiber meningeal nociceptors, releasing a pro-inflammatory neurochemicals such as calcitonin gene–related peptide (CGRP) leading to transudation of plasma. This induces inflammation of the trigeminovascular complex. The throbbing headache occurs after activation of trigeminal system, which stimulates carinal vessels to dilate [1].

DIAGNOSTIC CRITERIA OF MIGRAINE HEADACHE:

An acute migraine is diagnosed according to the severity of pain. Attacks from mild to moderate may be associated with vomiting and severe nausea or without. Attacks from moderate to severe may be associated with vomiting and severe nausea or symptom-free. Patients coming to the emergency are commonly having rigorous attacks. Variable attacks depend on the time of onset and severity of pain with the association of vomiting and nausea [10]. Diagnosing chronic migraine is in steps: recognizing the pattern of headache, recognizing the disorder, taking history in details and investigations. Chronic migraine is defined as headache persisting for at least 15 days/month. The typical pattern is two patterns; the first one is headache starts and never stops. This syndrome is called "new daily persistent headache" (NDPH). In the second pattern, the patient has primary headache disorder but not migraine exclusively. They have a stage of headache attacks with no freedom days in between; it is called "transformed migraine". Taking history in detail is an important issue in diagnosis of migraine. Firstly, start with asking the patient about the pain pattern (when and how it started), is it episodic or continuous? Are there any triggers or factors that cause headache? Then ask about the location of pain, severity, and characters. Also ask about the associated symptoms of chronic pain including yawing, neck stiffens, tiredness, visual disturbance, photophobia, sensitivity to smells and noises and vertigo. Also, it is so important to ask about previous depression, sleep disturbance, and anxiety. Regarding family history, you should ask about a relative with migraine and finally ask about smoking, caffeine, and alcohol consumption [5].

TREATMENT:

Management of a migraine is classified into two categories: the first category is medication used to treat acute migraine and stop the headache from progressing. It includes the following: Paracetamol, Nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin receptor agonists (triptans) and analgesics. The most effective way to stop headache from progression and to manage acute attacks is to take the medication 15 minutes after the onset of pain. Second category is prophylactic medications like tricyclic antidepressants, calcium channel blockers, beta- blockers and antiepileptic drugs [1].

Paracetamol and Nonsteroidal anti-inflammatory drugs (NSAIDs):

Paracetamol is a worldwide used drug because it is inexpensive, available and has analgesic effect. It is preferred more than any NSAIDs because it has better tolerance. Indication of paracetamol in an acute migraine for adults and the dose is 2 tablets at onset of attacks, followed by 2 tablets every 4 hours, and the maximum dosage per day is 6 tablets only [12]. An overdose of paracetamol can cause hepatotoxicity [9]. Mechanism of action of NSAIDs is by inhibiting cyclooxygenases; COX-1 and COX-2 through metabolism of peroxide enzyme. It has a selective inhibition of COX-2 more than COX-1. So, this leads to inhibition of phenoxyl radical formation from critical tyrosine residue which is essential for synthesis and activity of prostaglandins (PG), cyclooxygenase COX-1 and COX-2. In addition, NSAIDs inhibits another peroxidase enzyme called myeloperoxidase. Inhibition of this enzyme results in reduction of halogenating oxidation formation. Decreased halogenating oxidation is associated with multiple inflammatory diseases like rheumatic fever and atherosclerosis. Also, NSAIDs inhibits many endogenous neurotransmitter systems (cannabinoid, opioid, and serotonergic systems) [11].

Selective serotonin receptor agonists:

Triptans are selective 5-HT1B/1D receptors agonists. Its mechanism of action is much different; one of these mechanisms is direct action on the smooth muscle of intracranial vessels causing vasoconstriction. Also, causing the distribution of 5-$HT_{1B/1D}$ receptors in the intracranial vessels more compared to peripheral and coronary vessels.

Another mechanism is inhibiting the release of CGRP, by blocking it from peripheral afferent of the trigeminal system into dural vessels. This can help ending the feedback mechanism of headache due to persistent high CGRP [13]. Triptans acts on a number of sites in central and peripheral nervous system. Sumatriptan is subtype of triptans and has good outcome in migraine treatment. It stimulates second-generation agent development like zolmitriptan, almotriptan, naratriptan, and rizatriptan [3]. In a randomized double-blinded crossover study comparing the effectiveness and tolerance of 6mg and 3mg subcutaneous sumatriptan in treating acute migraine attacks, there was no difference between both doses in their tolerance, but 3mg SC dose was more effective in relieving pain and associated symptoms of a migraine than 6mg [14]. The side effects of triptans are fatigue, paresthesia, dizziness, nausea, and chest tightness and sensation of myocardial infarction pain. The chest tightness is the major effect of sumatriptan and 3-5% of patients had this side effect, but no changes in ECG were recorded. Also, sumatriptan is a risk factor for cardiovascular diseases, so it is contraindicative for patients with coronary disease to use [3].

PROPHYLACTIC MEDICATIONS:

1-Tricyclic antidepressants:

Tricyclic antidepressants (TCAs) first use was in1950s to treat depression. But, appearance of selective serotonin reuptake inhibitors (SSRIs) side effects limited their usage. Although they are used lesser nowadays in depression, still patients who don't respond to treatment of antidepressants are using it. Now it is used in prophylaxis of migraine, treating obsessive-compulsive disorder and neurological pain [15]. In 1964 (TCAs) showed for the first time its effectiveness for prevention of migraine [16]. Its mechanism showed that it works by blocking norepinephrine (NE) and (5-HT) presynaptic reuptake in CNS [17]. It causes sometimes seizures. Also, blocking the receptors of histamine, alpha1 adrenergic and muscarinic, but this may lead to a lot of side effects. Toxicity from tricyclic antidepressants causes hypotension because of blocking alpha1 adrenergic receptors. Also, blocking histamine receptors causes changes in mental state, changes in bowl sound, tachycardia, and dryness of both skin and mouth. All these side effects are caused by blocking muscarinic receptors. It is absorbed rapidly in GIT tract. In toxicity, GIT motility decreases which causes more toxicity and delayed absorption. Toxicity sings appears two hours after taking the drug [15]. A long duration of treatment showed more efficiency in improving the outcome of migraine. Patients who were treated for 6 months had better outcome than who were treated only for one mouth. There was no significant difference between serotonin-norepinephrine reuptake inhibitors (SNRIs) or (SSRIs) and amitriptyline in responding rate and frequency of migraine. But (SNRIs) or (SSRIs) are better because amitriptyline showed less tolerance [18].

2-beta- blockers:

Beta-blockers are used for treatment of hypertension, angina pectoris, anxiety and some type of tremor. It is prescribed worldwide for prevention of migraine. Propranolol is the most effective drug in treating acute migraine. The beta-blockers' exact mechanism in the prevention or treatment of migraine is unknown. It works primarily by blocking adrenaline's activating effect or stimulation. Also, it decreases the inherited excitability property of the nervous system. Because migraine runs in families, patients who have migraine have more excitable nerve system than who don't have. The eye drops of beta-blockers are rapidly absorbed, it enters the lacrimal duct then pass through the nasal cavity after that it is absorbed into the blood rapidly. After absorption, it passes into the blood blocking the adrenaline activating effect, so migraine can be reversed by the nervous system. The eye drops have another beneficial effect, it is not metabolized by the liver, and so small does are affective in the treatment. Also, it works on reduction of nerve cells' electrical excitability; may be this effect is part of cells' potential mechanism. The eye drops are more effective than oral beta-blockers in treating migraine during the attacks due to its rapid absorption. Oral beta-blockers are slowly absorbed into the blood which will reduce its effectiveness. Not all the patients can tolerate beta-blockers; oral or eye drops, as it causes bradycardia and hypotension [19].

Botox in treatment of chronic migraine:

Onabotulinumtoxin A (Botox) is used to treat chronic migraine. Its mechanism is not clearly understood, but it is hypothesized that it may inhibit releasing substance P and (CGRP) from the trigeminovascular system. In a randomized clinical trial, intramuscular injection of onabotulinumtoxin A for a long time (155-195U) fixed-dose and fixed-site showed that onabotulinumtoxin A has good tolerance and effectiveness in preventing chronic migraine [20]. Onabotulinumtoxin A effectiveness has been reported in the prospective analysis of 254 patients; it significantly improved quality of life for patients, increased days without migraine headache (crystal days) and decreased attacks. But, it is not recommended as first-line of treatment. Patients who don't benefit from invasive options like occipital

nerve stimulation or greater nerve blocking, or from oral prophylactic agents can benefit from Botox [21].

CONCLUSION:

In conclusion, the best and the most effective treatment in migraine depend on the type of migraine and the associated symptoms.

Regarding the searched article results, it was found that for managing acute migraine, paracetamol is the most effective drug in decreasing inflammation immediately and reducing the associated symptoms. Also, when comparing it to beta blockers, it has better tolerance. Beta blockers are effective during acute attacks, but are not suitable for everyone as it causes hypotension and unwanted side effects. SSRIs have better and faster outcomes than TCAs, but it has risks for cardiovascular diseases.

Chronic migraine (CM) has different lines of treatment: invasive, oral prophylactic agents, and Botox. Botox has great effect in treating CM especially in patients who had poor outcomes from other lines of treatment, but it's not the first choice of treatment because it is an expensive option.

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