



CODEN [USA]: IAJPBB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.4394916>Available online at: <http://www.iajps.com>

Research Article

**STUDYING AND UNDERSTANDING OF MIGRAINE
MECHANISM AND ITS PATHOPHYSIOLOGY ALONG WITH
EMERGING TREATMENTS.**¹Dr Haider Ali,²Dr Munibah Mughal,³Dr Usman Akhtar¹MBBS, Rawalpindi Medical University, Rawalpindi., ²MBBS, Services Institute of Medical Sciences, Lahore., ³MBBS, Abbottabad International Medical College, Abbottabad.

Article Received: October 2020

Accepted: November 2020

Published: December 2020

Abstract:

Migraine is one of the causes of disability on the Earth and a socioeconomic burden [1]. Due to physical activity, migraine pain becomes worse. It may last from 4 to 70 hours. Pharmacological treatment is based on the characteristics of the intensity of the migraine attack. Pharmacodynamics and Pharmacokinetic is necessary for migraine therapy. Migraine disorder has a poor relation to sleep. Sleep plays a therapeutic role in the discontinuing of migraines. Patients continuously report poor sleep before the migraine attacks and during migraine attacks. Migraine is a neurological disorder that is experienced by 10% of the total population. The current review will point up the contemporary aspects of migraine pathophysiology and comprehend the migraine state's working, and the brain is responsible for them. It was evident that neuromodulator strategies require further investigations to confirm their viability in headache. New medicines are quickly opening up for patients. Many facts of migraine pathophysiology are still unclear. Research has been directed to understand all the phrases included in the Migraine attack.

According to the Global Disease Study, researchers estimated that more than 1 billion people were suffering from this migraine disease [2]. It becomes the most neurological disorder. It is the cause of disability in women between the age of 15 and 49 years [3]. Despite the arrival of new drugs, most patients do not experience relief and relaxation. Most of them are unwilling to use pharmacological treatments. Neuromodulation can define as a drug that restrains the transmission of impulse nerve, but it is not the actual transmission [4]. According to the terminology, many interventional techniques are classified as neuromodulatory. For preventive migraine treatment, non-invasive and invasive neurostimulation methods have been proposed. This technology comes out as a safe alternative for pharmacological therapy of migraines, especially for sensitive patients like pregnant and adolescents [5]. At the same time, non-pharmacological neuromodulatory approaches prove cost-effective.

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Please cite this article in press Haider Ali et al, *Studying And Understanding Of Migraine Mechanism And Its Pathophysiology Along With Emerging Treatments.*, Indo Am. J. P. Sci, 2020; 07(12).

INTRODUCTION:

Migraine involves the brain. It is a primary headache disorder. It is the disabling stage of the brain. It is continuously increasing with time. According to the research, it primarily affects females [6]. These are different ways used to combining two things Aura and headache. Aura is a sensory defect that comes before the headache in human beings. There are three types of migraines:

1. Common Migraine, which is a headache alone in the brain with no presence of Aura.
2. Classic Migraine in which both Aura and Headache are present.
3. In which Aura is present.

Aura is the sensory interruption that occurs with Migraines. It can include vision and movement. 30% of the people with Migraines have Aura. They are related to each other. To understand the mechanism of Migraine, it is essential to understand the lobes of the brain. The human brain is divided into three lobes. The Frontal Lobe, Parietal Lobe, and occipital Lobe. These lobes are specialized to perform particular functions. The Frontal Lobe is responsible for controlling movement. The parietal Lobe serves sensation on the backside of the brain. Occipital Lobe performs vision process. Some symptoms of Migraine are exhaustion,

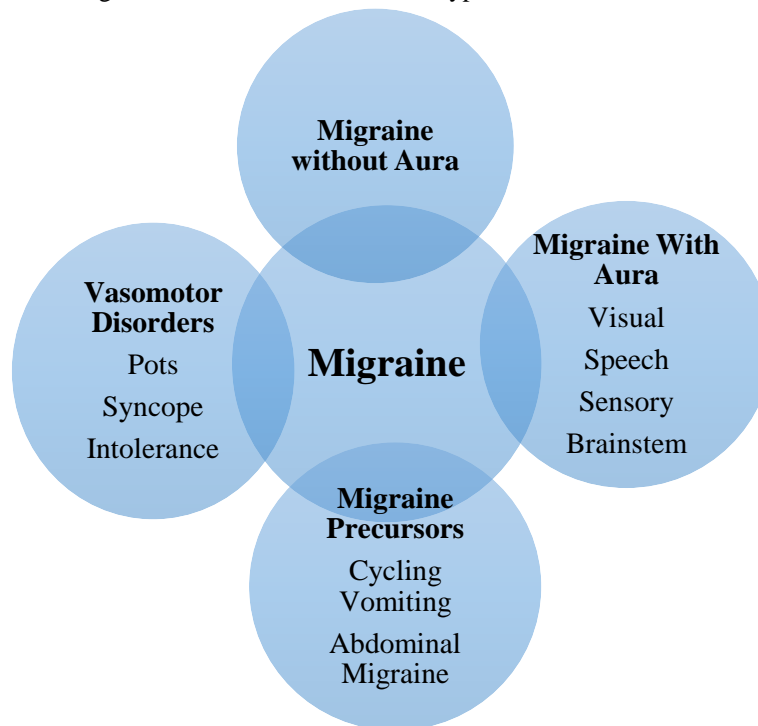
lethargy, drowsiness, Yawning [7]. Due to physical activity, someone feels unwell due to tiredness and is called the postdrome stage. One-third of migraine attacks are correlated with neurological deficits, which is designated as migraine aura.

Historical Background:

It has been known for almost 6,000 years [8]. The discussion over the pathophysiology of migraine has centered mainly on the vascular mechanism linked with attacks. Regarding past events nearly 150 years ago, migraine was considered a disorder by Edward Living. In the 1940s, the study of Wolf on cranial vessels gave the idea of migraine [9] [9]. The concept continued for five decades until the advancement of sumatriptan. Sumatriptan contains both neural and vascular lethal effects.

Disease Mechanism:

Prodromes are symptoms of migraine, which cause the headache by several hours. It is critical to understand their presence triggers a headache. The hypothalamus plays an essential role in the human circadian, and it put effort into maintaining homeostasis. Hypothalamic and brainstem neurons may trigger migraine pain. Hypothalamic neurons activate hypothalamic neurons.

**Classification of Headache Disorders:**

Brain alterations are divided into two categories. Adjustment in brain function and the adjustment in brain structure. Migraine is neurovascular pain. It has

a genetic component. It can be understood in terms of physiology and anatomy. Migraine pathophysiology consists of Migraine aura, Migraine pain, Triggering migraine [10].

ICHD, which is an International Classification of Headache disorder, is a standard tool used to determine primary and secondary migraine headache disorders. There are two criteria for migraine: migraine without aura and the second is migraine with aura. Reversible aura symptoms include brain stem, retinal sensory, visual. Aura symptom lasts 5-60 minutes' maximum. One aura symptom is unilateral. At least two attacks occur in migraine with aura, and At least five attacks occur in migraine without aura. Migraine without aura continuous in between 4 to 72 hours. The postdrome phase has been neglected in migraine [11]. Research shows that the postdrome symptoms are seen only in the arm(placebo) when pain is alleviated.

Migraine Pathophysiology

The enhancement in the concept of migraine Pathophysiology over the last three decades has contributed to many pharmacotherapeutic approaches that can be used in the treatment of Migraine. Research shows that brainstem nuclei and diencephalic nuclei contributed to the modulation of trigeminovascular activation. Many neurovascular hypotheses postulate that Migraine is endogenous pain [12].

Vascular theory and neuronal theory both include the central and peripheral nervous systems. From the genetic point of view, Migraine is considered as a complex brain disorder that involves multiple cortical, subcortical, and brainstem. It enhances our understanding that different areas of the brain are included in the premonitory, aura, and different phases of migraine pain. Migraine affects one side of the head. Other neurological symptoms are changing in sleep patterns, fluctuation of estrogen. Monosodium glutamate age, cheese is also responsible for migraine headaches. It is most common in women than men and children. The cases of Migraine without aura is 85%.

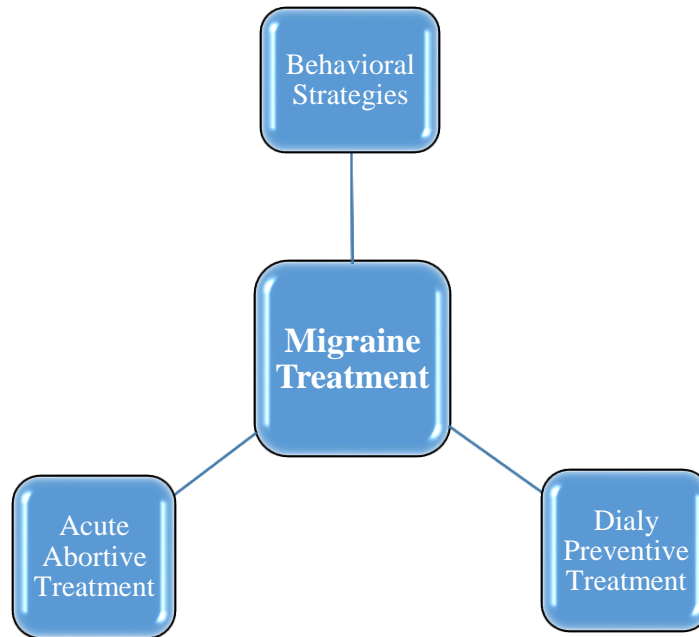
The Trigeminal Vascular System

During the migraine, the trigeminal nerve becomes activated; in this case, neuropeptides release from the cranial nerve. The peptides that cause neurogenic

inflammation are VIP substance P & calcitonin gene peptides [13]. Neural peptides play an essential role in trigeminal vascular pain transmission in migraine pain. Ergots and Triptans are used for the treatment of acute migraine. They decrease the release of neural peptides from cranial nerve five, which decreases cerebral vessel dilation and thus decreasing pain. Decrease neuropeptide release, so less vasodilation, and less pain. Ergots are used in acute migraine treatment. Triptan's function is to inhibit pain pathways in the brain.

Treatment of Migraine:

For the treatment of migraine attack, the medication should match with the patient's needs, and it also depends upon the attack categories, for example, disability, severe headache. Migraine treatment has two objectives. The first is to eliminate acute attacks, and the second is to intercept the next attack from occurring. In respect of eradicating the acute attacks, migraine represents one of the symptoms based on the disease's mechanism. To prevent the migraine from happening, you have to face the challenge that this fatal disease originates in an unknown number of brain areas and is related to structural brain abnormalities. When starting the treatment, the physician should consider the following conditions: Nausea, never use opioids, Headache Intensity, Recurrence of headache, Avoid overuse of medications. If the intensity of migraine is moderate, then nonsteroidal anti-inflammatory drugs may be started first. If this is not a successful strategy and gives no result, then the triptan strategy can be used next. In the starting, less expensive medication is chosen first. Nausea is a common symptom of migraine [14]. The best medication route is selected based on the severity of nausea and vomiting if it is present. For those patients who are severe nausea issues early in the migraine attack, 6mg sumatriptan should be preferred. We can also use triptan. The other options are intranasal sumatriptan and intranasal dihydroergotamine to treat nausea, which is caused due to the migraine. Opiates and barbiturates are not the best options for migraine treatment. These are less effective in many patients.



TREATMENT ARMS IN MIGRAINE:

Methodology:

According to (PRISMA) Preferred Reporting Items for Systematic Reviews and Meta-Analysis, the literature review was carried out [15]. We used a data analysis template for this purpose. RCTs published a full report in a peer-reviewed journal. The database was updated further.

According to the International classification of headache disorders (ICHD), the target patients were children, old, with migraines. Research focuses on other headache types such as tension-type headaches and cluster type headaches. We used the (GRADE) Grading of Recommendations Assessment, Development, and Evaluation system criteria to approach the risk for individual studies and groups of tasks. The overall quality of the research was counted high [16].

We analyzed for this comprehensive systematic study. Meta-analysis was not relevant because the various techniques have a different methods of acting. For preventive treatment, we distinguish headache days/month and a 50% decrease in headache days. For an intense treatment, we consider the pain-free patients at two h, and the Statistical Analysis of the study was performed by using the Stata software. Standard deviations and Mean values were assembled. Heterogeneity results were evaluated by forest plots and the 12 statistics, which is the most normally utilized measurement for estimating the size of

between-study heterogeneity and is successfully interpretable [17]. The pooled analysis recommends a positive effect on PENS. The results of the high-quality trial were considered negative. For acute treatment of migraine REN is effective. CPM is defined as ‘pain inhibits pain’ Other techniques used in meta-analysis. The quantity of efficient surveys and meta-examinations follows up neurostimulation procedure for migraine treatment in humans. Several devices and methods are effective but not in a wider scope. These devices and techniques include PENS, ONS, RTMS for prophylactic treatment, remote electrical neuromodulation for acute treatment. The study has several limitations, and this research includes only migraine patients. The subsequent period was generally short, and in this way, long term advantages of neuromodulation procedures are yet to be demonstrated. Longer, well-conducted research and studies are still needed.

CONCLUSION:

Migraine is an undertreated disease, and it is a cause of disability in humans. It is linked to depression and anxiety. It may lead a person to suicide. Many medications are used for the treatment of acute migraine. The selection of a suitable remedy for the patient is based on the patient's clinical features. Even the current migraine treatment method is appropriate, but still, there are therapeutic needs require as not all patients may benefit from this available treatment for migraine pain. There is a need to focus in-depth on this disease's neurobiology and further innovation of novel

therapies. The biology of migraine is not entirely understood, and this provides the opportunity to continue to improve migraine treatment. Patients and Physicians are looking forward to the enhancement, improvement, and understanding of migraine pathophysiology.

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