Comparison Of Efficacy of IV Ketorolac Vs Valproate Vs Metoclopramide in Patients Presenting to Emergency Department for Acute Migraine Attack

ABC

123456

MPhil Thesis

In

Department of Medical Education

Shaheed Zulfiqar Ali Bhutto Medical University,

Islamabad

CANDIDATE DECLARATION FORM

I, ABC S/O of ABC, Registration # 000000, a candidate of Master of science (Management Sciences) at Shaheed Zulfikar Ali Bhutto Institute of Science and Technology, Islamabad do hereby declare that the Thesis Comparison of Efficacy of IV Ketorolac vs Valproate vs Metoclopramide in Patients Presenting to Emergency Department for Acute Migraine Attack submitted by me in partial fulfillment of MS degree is my original work, and this work contains no material which has been previously accepted for the award of any degree or qualification in any institution and, to the best of my knowledge and belief, contains no material published by another party, except where due reference is made in the text.

_____

Signature

06.04.2023

Date

ABC

Name

DEDICATION

I dedicate this thesis to my parents and siblings who always encourage me to prosper in life and career.

ACKNOWLEDGEMENTS

All praise is to Allah, the most passionate and the merciful. There is just too much of His blessing in this life to count. Peace and blessings be on His Prophet.

I would like to thank everyone who helped me out during the time. First and foremost, I want to say thank to my family. I am indebted to express my deep gratitude to my parents and siblings. They always showed an interest in what I was doing, and invariably showed patience and understanding when my time at home was filled with research work-related activities instead of family time. Without their kind support, encouragement and dedication, this thesis would not have been fully realized. And my little naughty niece and nephews can never be ignored; whose mischievous yet innocent smile always refreshed me during my work.

I am indebted to my Supervisor, Dr. ABC. I really appreciate his sound academic support and the ability to let me see "the bigger picture". Most importantly, thanks for setting high standards that drove me to work harder in order to attain my goals. He always encouraged me to "go the extra mile".

Abstract

Objective

Adults who have migraines suffer from a persistent, incapacitating ailment. Valproate has been studied for its usefulness in treating acute migraines, but it is yet unknown how well it works and is tolerated as an abortive medication. In this study, the effectiveness of intravenous Ketorolac, Valproate, and Metoclopramide in the management of acute migraine was examined.

Methods

The sample size was 109 individuals in each group, and a total of 327 patients with acute migraine headaches, ages 18 to 60, were included in a double-blind, random clinical experiment that we performed. Patients were randomly allocated to receive Valproate (500 mg), Metoclopramide (10 mg), and intravenous IV ketorolac (30 mg), all diluted into 4 mL of ordinary saline. Pain alleviation at 30 mints, one, Two, or three hours after administration was the primary outcome gauge. The secondary outcome criteria were symptom improvement, headache recurrence after 24 hours, and adverse drug reactions. The t-test and Pearson's chi-square were both used in the data analysis.

Results

The results demonstrate that Metoclopramide showed superior efficacy compared to IV Ketorolac and Valproate.

Conclusion

This trial shows that IV valproate or Ketorolac is less effective than Metoclopramide in enhancing headache outcomes in ED patients with acute migraine.

Keywords: Migraine disorders, IV Ketorolac, Valproic acid, Metoclopramide, Acute, Therapeutics

Table of Content

CHAPTER 1

INTRODUCTION

An intracranial vasculature illness called migraine is defined by central, peripheral, and neural system malfunction [1]. The intense and incapacitating pain that acute prodromal symptoms of episodic & chronic migraines generate frequently leads to trips to the emergency department (ED) and lost efficiency, including missed periods from work, class, and other actions [2]. Due to missed productivity, migraines and other associated medical conditions cost the US economy over $13 billion annually. Due to medical plus indirect expenditures, this cost has already been calculated at $3,025 per patient in Canada [3]. The general quality of life is negatively impacted by migraine [4]. It is connected with medical and psychological comorbidities, including severe depressive illness, anxieties, bipolar disorder, phobia, cardiovascular risk [5], and stroke [6]. Poor migraine treatment is frequent; only 56% of sufferers receive a proper diagnosis, and 49% manage their headaches with multiple remedies instead of prescribed ones.

Acute headaches brought on by migraine usually last 4–3 days if left untreated and necessitate bed rest, painkillers, and time absent from work and other obligations. Although most migraine sufferers operate properly in between episodes, migraine is a widespread condition affecting many people's relationships with their families, jobs, and social lives. Most migraine sufferers can manage severe attacks at home, although this approach isn't always practical. Additionally, any additional attempts was likely fail if the oral medication acute therapy does not work [7]. In the preceding 12 months, % of Americans through migraines reported visiting an ER or urgent care facility to treat a severe headache [8]. Headaches amounted to 2.15 & visits, or 2.1 million ED visits annually, in a cohort of adult Emergency department visits in the United States [9]. Five-month research conducted by an American health maintenance organization indicated that ambulatory ED visits by migraine patients were higher than those by asthma patients (1.9 vs 1.0 percent) 10.

Furthermore, numerous ED visits were shown to be more frequent among migraineurs [11]. Although headaches are a frequent reason for patients to visit the emergency department, emergency practitioners' practises vary greatly in the USA and Canada [12]. In U.S. EDs, twenty

different parenteral medications are utilized to treat acute migraines [13]. There is a lot of variation amongst EDs. For instance, compared to just 20% of visits in other EDs, 60% of visits in other EDs employ dopamine antagonists [14].

Adults with migraine headaches experience a persistent and incapacitating primary headache that accounts for 1 to 2 percent of all admissions to emergency rooms [15]. The prevalence of migraines varies globally and is not known with precision. According to reports, the prevalence of migraines in Iran ranges from 18.11 percent in grownups in Tehran to 6 percent in Yazad, with primary school students in Shiraz reporting the lowest frequency (1.7%) [16]. This condition manifests as episodes of moderate towards severe unilateral sore headaches accompanied by nausea, photophobia, vomiting, and phonophobia [17].

Triptans, nonsteroidal anti-inflammatory medicines, Ergotamine, intravenous fluids, antiemetics, opioids, neuroleptics, & IV Ketorolac [18] are among the medications used to treat acute assaults. IV Ketorolac therapy for migraine headaches has been demonstrated to have a variety of outcomes in studies [19]. Due to its anti-inflammatory properties and lack of harmful side effects, several studies found that IV Ketorolac is highly beneficial for giving acute migraine and lowering the likelihood of initial headache recurrence, even when administered as a single high dosage of 20 mg [20]. Studies have examined the effectiveness of Valproate in treating acute migraines at various dosages, and its efficacy has been contrasted with that of other medications, including sumatriptan, Ketorolac, Metoclopramide, and even IV Ketorolac [21].

Different findings have been obtained from these studies and many other surveys [22]. Two investigations comparing IV Ketorolac and intravenous Valproate to relieve acute migraines in various parts of Iran used different samples and doses [23]. A recent development in acute migraine care is using Valproate, an anti-epileptic drug, as a preventative measure. Valproate lowers serotonergic cell firing rates while raising -amino butyric acid levels in the brain's central nervous system. The sodium and calcium current's rate of repeated firing is lowered by this medication, which directly impacts the neuronal cell membrane. This quick-acting action helps to explain Valproate's role in abortive treatment [24].

Although the US Food and Drug Association just newly accepted Valproate's usage for abortive therapy, studies have shown that the drug can have various effects when administered

intravenously for managing pain migraines [25]. This study compared the effects of IV Ketorolac, another widely used medication for treating acute migraines, with intravenous Valproate.

After the opioid problem increases and up to 77 percent of patients enter with pain as their primary grievance, operating in the emergency room may be difficult [26]. Treatment for acute migraine headaches involves over $700 million a year and accounts for 2-3% of visits to emergency rooms. Acute migraine headaches impact 13% of people in the United States; as a result, medical professionals must know the medications available to treat migraines swiftly and efficiently. Migraine headaches are characterized by pulsing on one lateral of the brain, making a person feel ill, lightheaded, and especially sensitive to stimuli like light and sound [27]. Using the acronym POUND, which stands for groups on the surface, one-day period, unilateral vomiting and nausea and debilitating number [28], it is possible to identify an acute migraine headache. How should medical practitioners approach the treatment of migraines? How does one determine when choosing an opioid could be necessary? When selecting the best course of treatment for these individuals, these concerns must be considered.

In the emergency room, there are multiple pharmacologic choices for treating an acute migraine headache, including occasionally a "wide spectrum strategy" of medications that target several channels may be employed. If the patient has received prior treatment, it is crucial to determine which medications were effective for them. The NSAID ketorolac (Toradol) is one common therapeutic choice. A daily limit dose of 120 mg is advised to treat acute migraine headaches. The recommended doses are 15–30 mg intravenously; otherwise, 60 mg intramuscularly. Patients with severe asthma, peptic ulcers, and pregnancy are prohibited from using ketorolac [29]. Acute renal damage patients must also avoid Ketorolac. According to the American Headache Association, Ketorolac is very effective for individuals whose migraine has expanded to their shoulders and full head and those whose headache developed throughout into a migraine upon rising [30].

A unilateral pounding headache, with or without an aura, is an acute migraine. Acute migraine attacks have been treated with a variety of medication types. This study was compare the effectiveness of Ketorolac, Metoclopramide, and Valproate in treating acute migraine attacks.

The term "migraine" refers to a benign, recurrent condition of headaches with varying duration and accompanying nausea, vomiting, or Based on the presence or absence of an aura. The

International Headache Society (HIS) has divided migraine into two main types [31]. When not accompanied by an aura, it frequently suffers from headache bouts that last 4–72 hours. Most headaches are unilateral and have a throbbing character. It is linked to experienced nausea and photophobia and phonophobia, ranges in intensity from mild to severe, and is made worse by normal physical activity. Another subtype associated with an aura may cause speech difficulties, loss of vision, and visual symptoms such as flashing lights, dots, or lines[32]. A migraine is another of the most common symptoms among patients who visit the emergency room. The World Health Organization has ranked it as the sixth most debilitating disease; its one-year prevalence ranges from 15 to 18 percent globally. Without regard to socioeconomic position, it is three times more prevalent in the female population [33].

Although the pathophysiology of migraine is not entirely known, trigeminal innervation of the meningeal vasculature is thought to be involved, and the symptoms are considered to be brought on by cranial blood vessel vasodilatation and surrounding nerve irritation. [34]

NICE guidelines state that IV metoclopramide is preferable for specific age groups who cannot take oral migraine medication. Using IV metoclopramide, a non-oral NSAID can also be added [35]. The research was conducted to determine the ideal dose of intravenous Metoclopramide, and it showed that 10 mg of Metoclopramide is superior to either 20 or 40 mg of Metoclopramide for treating acute migraine attacks [36]. Another study showed that Metoclopramide, rather than opioids, should be taken more commonly as first-line treatment for acute migraine. The American Headache Society has advised against using opioids, particularly as a migraine therapy, claiming "insufficient evidence" as the primary justification. The same recommendations state that Metoclopramide, precisely 10 mg IV, is "very likely helpful". The potential for misuse of opioids is another significant problem. [37]

Metoclopramide, a prokinetic dopaminergic receptor blocker, is now often utilized in emergency rooms as the first-line treatment for acute migraines. Numerous research studies have found that Metoclopramide is more effective than Valproate and Ketorolac in treating acute migraine attacks. [38] According to the logic behind this study, Metoclopramide is preferable to Ketorolac & Valproate in treating patients that report than the emergency room with an acute migraine episode.

Ultimately, migraine sufferers' daily operations are hampered by their headaches, lowering their well-being. Before using opioids, healthcare professionals should be informed of the numerous therapeutic alternatives available and make use of them. Utilizing therapy alternatives like Ketorolac combined with Metoclopramide is essential, as is providing patient education after discharge. The frequency of relapses and the period patients take in the emergency room through migraine headaches may be considerably decreased if all medical providers were informed about the different migraine medications.

One nonsteroidal anti-inflammatory medicine, Ketorolac, treats migraine headaches' acute discomfort. Ketorolac is an effective analgesic in emergency rooms due to its quick mechanism of action. In several trials, Ketorolac has proved to be an effective pain reliever during acute migraine attacks. Ketorolac was shown to be more effective than Valproate in one of Friedman BW's studies on acute migraine. Compared to IV Ketorolac, IV Metoclopramide Plus diphenhydramine significantly reduced headache symptoms in people who visited the ED with tension-type or non-migraine, non-cluster recurring headaches [39]. Valproate is an anti-epileptic agent used for acute migraine prophylaxis for a long time and has been tried in acute migraine attacks recently. It raises gamma-aminobutyric acid levels in the brain and functions as an inhibitory neuropeptide, which slows down serotonergic cell firing. This characteristic has enabled its use in the abortive treatment of acute migraine. The efficiency of IV valproate in treating headaches, particularly those with aura, and in lowering the frequency of migraine attacks has been revealed by Karimi et al. [40].

The emergency physician must be familiar with the variety of available therapies and be able to apply them thoughtfully and intelligently. The most crucial action that emergency physicians can take to help their headache patients is to put them in touch with outpatient doctors experienced in headache management. These doctors was then give these headache patients suitable acute therapeutics, start preventive therapy, and give them advice about one's patient's condition.

Yearly, 1.2 million people in the US attend emergency departments (ED) for acute migraines [41]. In US emergency departments, over than 20 different parenteral medications, including migraine-specific drugs like sumatriptan and dihydroergotamine (DHE), antidopaminergic like Metoclopramide as well as the neuroleptic Prochlorperazine, corticosteroids, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), as well as antihistamines like diphenhydramine and promethazine, are administered to treat migraine [42]. The reasons for this variation in emergency

practise have not been well investigated. Still, they are likely multifaceted and include the following: clinician satisfaction and acquaintance with a particular medicine, worry about temporary side effects, effectiveness beliefs, and patient requests.

The ideal parenteral medicine would allow patients to quickly return to work or their daily activities while providing immediate and consistent headache relief without short- or long-term side effects. Unfortunately, there isn't such a drug. According to published clinical research, less than 25 percent of those who received acute migraine therapy in the ED reported continuing headache freedom [43]. Numerous of the drug mentioned above classes have been linked to rare but irreversible side effects, such as medication dependence on opioids and ischemic vascular difficulties with migraine-specific drugs, tardive dyskinesia to antidopaminergic, avascular osteonecrosis with corticosteroids, gastrointestinal haemorrhage with NSAIDs, as well as tardive dyskinesia through antidopaminergic. Rarely have patients in ED-based clinical studies been tracked for a considerable time.

Few of these investigations had sufficient sensitivity and specificity to identify these unusual downstream effects. Knowing which parenteral drugs should be used as first-line therapy is crucial given the enormous number of migraineurs who visit US emergency departments each year, the variability of existing emergency care, and the regular use of possibly dangerous medications.

Migraine is a common neurological disorder characterized by severe headache episodes that often require immediate treatment in emergency departments. Managing acute migraine attacks poses a significant challenge, and understanding the efficacy of different pharmacological treatments is crucial for improving patient outcomes. This study aims to evaluate the effectiveness of three major pharmacological classes, NSAIDs, neuroleptics, and valproic acid, in treating acute migraine attacks in the emergency department. Specifically, we was assess the efficacy of Ketorolac, Metoclopramide, and Valproate in relieving pain during acute migraine attacks. By comparing the efficacy of these medications, we seek to identify any differences in their effectiveness and determine if one medication outperforms the others. The research hypothesis proposes that Metoclopramide was demonstrate superior efficacy compared to ketorolac and valproate one hour after drug administration in managing acute migraine attacks in the emergency department. Understanding the comparative effectiveness of these medications was contribute to

our knowledge and assist in developing targeted treatment approaches for migraine patients in emergencies.

CHAPTER 2

LITERATURE REVIEW

2.1 Definition of Migraine

Migraine is a clinical disease for which no conclusive laboratory or neuroimaging results have been found. Migraines are characterized as recurring headaches (at least five migraines in a lifetime), lasting four to seventy-two hours, and having at least two of the following characteristics [44]:

- Unilateral location
- Pulsating quality
- Moderate/severe intensity
- Aggravated by physical activity

Additionally, photophobia, phonophobia, or nausea and vomiting are required to diagnose migraine. Recognizing the unique, subjective character of each patient's overall presentation and treating it safely and efficiently using the best available research data is essential for effective pain management. Furthermore, a proper diagnosis was give patients access to the right care as outpatients and at subsequent ED visits. The necessity to identify migraine-specific headaches from other headache subtypes in an emergency is sometimes questioned. Although "severe headache" and "migraine" differ, individuals with mild to moderate headaches frequently benefit from the same analgesic regimen. All medium to severe headaches may be treated with a migraine regimen whenever the diagnosis is murky and serious headache causes have been safely ruled out.

Nearly 4% of all ED admissions involve headaches, making them frequent appearance in emergency departments (EDs) [45]. Although migraine is the primary headache disorder most patients have when they first arrive at the hospital, the emergency physician's job requires that they simultaneously rule out any serious or existence pathology while giving the patient wise and efficient symptom relief [46]. It is noteworthy that current research suggests that this dual mission works effectively, removing more than 99 percent of illnesses that cause significant unfavourable neurologic sequelae, albeit at the expense of using high-frequency and low-yield sophisticated

imaging [47]. This review is primarily meant to explain the remedy of primary migraine and the wide range, efficacy, and indications of those interventions, even though the emergency clinician must have full knowledge of the clinical diagnosis and foundational disease pathogenesis associated with headache disorders. Although identifying the specific kind of headache might aid in focusing treatment, diagnosis in an emergency room can be challenging because most primary headaches are frequently treated similarly.

Most people who present to an emergency hospital with primary acute headaches have migraines, which is an interesting result; yet, most patients only receive a less precise test and a similarly ambiguous treatment [48]. However, because different migraine appearances in the ED are dynamic, variable, and unique, an algorithmic or step-by-step approach to headache care is not advised. The emergency room doctor must know the range of treatments offered and be able to use them wisely and deftly. But after providing adequate analgesia, the most crucial thing that emergency physicians can do for their patients with headaches is to put them in touch with outpatient doctors who are experienced in managing headaches. These doctors was then give these headache patients the right acute therapeutics, start preventive therapy, and guide them on how their disease is advancing.

2.2 Migraine Differential Diagnosis

Although anchoring bias may draw attention to a typical migraine presentation, particularly in individuals with a history of migraines, alternative benign and potentially fatal causes of migraine-mimics must be considered.

With migraines, benign headache conditions comprise muscle spasms, migraine headaches, nerve pain, post-lumbar punctured headaches, bronchitis, coital headaches, drug overuse headaches, and low/high CSF pressure headaches like post-dural puncture headaches.

The following are more severe and potentially fatal causes of headaches (along with related can't-miss red flags): carbon monoxide poisoning (relatives with migraine), sequential septic arthritis (sequential sensuality, jaw claudication, age > 50), subarachnoid and other types of intracranial haemorrhage ('terrible migraine of my life,' found that taking there at emergence, anti - coagulant

have been using), periapical artery evisceration (neck trauma, preemptive face pain (weight loss, history of malignancy).

2.3 NSAIDs USED FOR TREATING MIGRAINES

A migraine may frequently be quite painful. First-line oral pain relievers like acetaminophen (975 mg PO) & ibuprofen may not work well on it (400 mg PO). Various non-opioid options are available for treating migraines that are refractory to oral acetaminophen/ibuprofen combinations. The ideal migraine treatment should be risk-free, quick to take action, highly effective, have few side effects, and provide long-lasting headache relief. This combination is not yet the best one. Opioids are still a standard part of treatment strategies for the 1 million patients who visit our ED annually for migraine therapy, despite hydromorphone being the preferred analgesic in around one-fourth of those situations [49]. However, studies have indicated that non-opioid alternatives provide more significant analgesic relief [50], and many other options have been proved to safely and efficiently treat migraines. Below is a proof list of migraine treatment alternatives that can be used in an emergency [51]. The fundamental methods of therapy are as follows.

Nonsteroidal anti-inflammatory medications (NSAIDs) and acetaminophen are the cornerstone of the analgesic strategy for treating primary headaches in the emergency department. Patients typically appear before usage, even if they routinely try these treatments at home without success. Ibuprofen (400–800 mg orally), acetaminophen (500–1000 mg orally), or a mixture of the two, might be administered to people with moderate symptoms. Numerous studies have shown that these popular drugs are highly effective, with acetaminophen's number that must be taken (NNT) for comprehensive treatment within two hours being 12 and ibuprofen's being just 7.2 [52].

According to comparative dosing studies, higher doses are expected to be more beneficial. However, these tests excluded significant numbers of headache sufferers. [53] Limited data show that therapy with an alternate NSAID may still be helpful in patients who have already tried ibuprofen (or naproxen) from home without relief or in patients who cannot take oral medications due to nausea or vomiting. [54]

Although all NSAID subclasses interact with prostaglandin production and inhibit COX, each group exhibits various traits independent of arachidonic acid metabolism. The enhanced patient

response to multiple subclasses is physiologically based on these distinctions. While acetic acid derivatives (such as Ketorolac and diclofenac) are likely to have different impacts on pathways for signal transduction and inflammatory cytokine concentration, propionic acids (such as ibuprofen or naproxen) may more significantly prevent the superoxide stage of evolution and neutrophil aggregation [55].

Parenteral Ketorolac is often given intravenously or intramuscularly. The prescribed amount of Ketorolac for patients diagnosed is still 30mg IV and 60mg IM, despite recent ED-based research suggesting that doses greater than 15mg IV don't provide better analgesia. These trials excluded migraine patients [56]. Ketorolac injections work through pathways beyond cyclooxygenase inhibition, possibly explaining why this NSAID is so good at treating acute pain. The potential of Ketorolac to block peripheral N-methyl-Daspartate (NMDA) receptors at doses obtainable with the injectable product is an important mechanism that may be relevant in migraine and headaches [57].

2.3.1 Ketorolac

The only nonsteroidal anti-inflammatory medicines (NSAIDs) that may be administered intravenously are Ketorolac and ibuprofen. Ketorolac is strongly advised by the Canadian Headache Society's recommendations for migraine treatment in urgent situations. There are doses between 30 and 60 mg [58]. An appropriate substitute is IV infusion of 400–800 mg ibuprofen. Individuals with severe artery disease or renal failure should avoid using these drugs. Since oral naproxen sodium has been demonstrated to have a reduced heart disease risk than other NSAIDs, it may be an option for people with cardiovascular disease [59]. Any NSAID should be used cautiously in individuals with renal impairment since cyclooxygenase is required for normal glomerular function.

30-mg ketorolac IV boluses, repeatable every 6 hours. Acetaminophen 1000 mg, naproxen sodium 550 mg, or aspirin 325 mg should be given orally instead to those with coronary artery disease, untreated hypertension, acute renal failure, or cerebrovascular illness. We recommend a combination of intravenous fluids together with parenteral drugs such as Ketorolac and a dopamine receptor blocker (e.g., prochlorperazine, Metoclopramide, chlorpromazine) for patients with status migrainosus (i.e., a crippling bout lasting more than 72 hours) (Grade 2C). Other alternatives

include Valproate and dihydroergotamine. However, some patients might need to be admitted for long-lasting, incapacitating symptoms.

Parenteral dihydroergotamine was as effective as or more successful as meperidine, Valproate, and Ketorolac in treating migraine headaches and avoiding relapses, together with an antiemetic (most frequently metoclopramide). In comparison to other medications like nebulized sumatriptan, IV hydrochlorothiazide, IV chlorpromazine, as well as IV dihydroergotamine combined with Metoclopramide, a 2013 systematic review of eight randomized clinical trials discovered that parenteral ketorolac (30 mg intravenous IV as well as 60 mg intramuscular) seemed to be effective for acute migraine [60].

Despite the sparse data, indomethacin may be beneficial as an abortive migraine medication. It is a potent NSAID that is furthermore offered in suppository form, which can be helpful in queasy people. Indomethacin suppositories include a 50 mg dose of the medication; for individuals who experience recurring episodes, the suppositories can be divided in half or third. Studies assessing the relative effectiveness of various NSAIDs are lacking. A different NSAID may be attempted if the first one is unsuccessful.

Individuals may well be given a combination of intravenous fluids and parenteral drugs, including Ketorolac as well as a dopamine receptor blocker treating severe intractable migraine episodes, also known as status migrainosus (i.e., a crippling attack lasting longer than 72 hours) [61]. Other parenteral drugs might also be necessary depending on how well the first therapy [62], which could include Valproate and/or dihydroergotamine, works. The choice of medicine depends on patient-level considerations rather than high-quality evidence, as is the case with treatment choices.

2.4 Neuroleptics Used For Treating Migraines

Dopamine antagonist neuroleptic medication has become a cornerstone in treating primary headache problems in emergency departments. These medications block postsynaptic mesolimbic D1 and D2 receptors in the brain, resulting in fast analgesia and alleviating nausea and vomiting that cover pages of migraine and other primary headache symptoms in the ED [63]. It is now understood that these frequently employed dopamine antagonists likewise mediate proinflammatory cytokine production, potentially contributing to their observed effectiveness.

This is due to the revelation of the crucial function of Calcitonin gene-related peptide (CGRP) for migraine aetiology [64].

Prochlorperazine (10mg IV) and Metoclopramide (10mg IM/IV) are the most often recommended drugs for treating primary headaches in emergency departments. Numerous studies, including significant randomized trials & meta-analyses, have consistently shown that around 2/3 of patients have symptom alleviation after 2 hours of treatment [65, 66]. Metoclopramide, especially the 10 mg dosage, has been highlighted in American Headache Society recommendations as being "very likely to be helpful" in the acute treatment of migraine in emergency rooms [67]. According to several research, Metoclopramide should be taken more commonly as the initial treatment for severe migraine headaches [68]. While treating patients with acute migraines, additional trials found no difference in effectiveness or safety between intravenous Metoclopramide and placebo [69]. Prochlorperazine has demonstrated a slight edge in some difficulties in terms of energy, but this advantage comes at the cost of increased costs of health consequences (sedation, extrapyramidal symptoms). Therefore, the drugs are administered equally often, subject to the provider's judgement or familiarity. Diphenhydramine is frequently given simultaneously with Prochlorperazine to prevent side effects since slow infusions of Metoclopramide, but not Prochlorperazine is known to avoid the development of akathisia. [70]. The use of first-generation antipsychotic drugs to immediately relieve headache symptoms has drawn more attention due to an expanding body of literature and inconsistent pharmaceutical availability. Like Metoclopramide & Prochlorperazine, droperidol and haloperidol elicit widespread central dopamine blocking, which results in analgesia and efficient management of nausea and vomiting. Although black box cautions of QT-prolonging (despite later debunking of any significant danger) and manufacturing limitations have hampered or restricted acceptance, these medicines have beaten their more widely used counterparts in small studies [71].

2.4.1 Metoclopramide

Dopamine receptor antagonists are commonly thought to alleviate nausea in migraine sufferers. However, they also work independently to stop migraines. Thus, they should be taken into consideration whether or not nausea is present. Prochlorperazine and Metoclopramide are the two most often utilized medications. According to the American Academy of Neurology recommendations, Prochlorperazine is advised as the first-line treatment for acute migraine. The

rating for Metoclopramide is a little lower and is regarded as having a modest benefit [72]. Prochlorperazine and Metoclopramide are supported by a high degree of evidence, according to the Canadian Headache Association [73]. Prochlorperazine and Metoclopramide receive a level B recommendation of "should offer" in the American Headache Society's evaluation of parenteral pharmacotherapies (a request that is only also given to subcutaneous sumatriptan) [74]. Thus, any agent may be applied. Before beginning a dopamine receptor antagonist, diphenhydramine with benztropine may be used to lessen the chance of post-treatment akathisia. There is minimal evidence that diphenhydramine is individually helpful in treating migraines.

Metoclopramide (10 mg IV), Prochlorperazine (10 mg IV), chlorpromazine (12.5 mg IV), haloperidol (5 mg IV), & droperidol are common first-line migraine treatments for moderate-to-severe pain (2.5 mg IV or IM). Metoclopramide (10 mg IV) was regarded as the best, evidence-based first-line medication, while the precise frontline analgesic varies on the patient's prior success and current symptoms. Prochlorperazine has also proven to be more effective than opioids at treating acute migraines, although it must be taken with 25 mg of diphenhydramine to prevent extrapyramidal side effects [75]. Metoclopramide & Prochlorperazine should be infused gently over 15 minutes to prevent akathisia. It has been demonstrated that chlorpromazine (12.5 mg IV) is just as efficient as Metoclopramide. In addition, it needs to be given gradually over 20 to 30 minutes. The antidopaminergic medications haloperidol and droperidol might also be regarded as first-line treatments for individuals with an average cardiac QT interval. It has been demonstrated that droperidol (2.5 mg IV) is at least as helpful as Prochlorperazine for reducing acute pain for severe benign headaches in emergencies. Although it causes more agitation, haloperidol (5 mg IV) has been demonstrated to be equally effective for treating acute headaches in emergency rooms as Metoclopramide (10 mg IV). [76].

After a 30- to 60-minute review, individuals with persistent headaches should have all possible diagnoses thoroughly considered, including the fatal can't-miss diagnosis. Consider a different first-line analgesic choice from those mentioned above for further analgesic relief. Additionally, individuals who do not have a contraindication to nonsteroidal anti-inflammatory drugs may get Ketorolac (15–30 mg IV) [77]. Patients who seem dehydrated or have vomited may be given intravenous fluids, although there is no evidence that this may boost migraine relief. Second-line treatments, including Valproate, sumatriptan, & acetylsalicylic acid, may be explored for

individuals who continue to experience migraines despite repeated tries with first-line medications. Patients who have already responded well may be evaluated for Valproate (1 g IV). But studies have revealed lower effectiveness than other first-line remedies (Metoclopramide) [78].

2.5 Valproic Acid

It has been demonstrated that valproic acid can reduce headache discomfort with few negative effects. Following a valproate infusion of 900–1200 mg, 75% of participants in one experiment reported a decrease in pain from moderate or moderate to light or none at all [79]. The inhibitory neurotransmitter gamma-aminobutyric acid is increased after Valproate is transformed to its active form (Valproate), which occurs after administration (GABA). Valproic acid is a frequent second-line drug despite regularly underperforming when contrasted to neuroleptic treatment due to its comforting side effects profile and broad therapeutic window [80]. Usually, valproic acid is given as a steady iv drip lasting 30 minutes in dosages ranging from 500 mg to 1 g [81].

2.5.1 Valproate

Status migrainous has been successfully treated with IV anti-epileptic medications valproate & levetiracetam (migraine more than 72 hours). The most effective treatment for migraines, Valproate has a solid reputation, is well tolerated, and works quickly [82]. Although its usage is anecdotal and no study has evaluated its effectiveness, IV volume repletion is frequently used in acute migraines because most headache specialists believe it is beneficial, particularly in patients with persistent nausea or vomiting.

Antiemetics are reportedly benign. However, butyrophenone droperidol contains an amount of the drug risk of extrapyramidal health consequences, and the entire class bears a black box warning for proarrhythmic threat. Antiemetics may provide an alternative to traditional migraine preventatives such as painkillers, triptans, and ergots. They may also be a better choice in the ED than opioids. Magnesium sulphate may be used to treat migraines due to low serum levels and their link to migraine episodes. Small studies have had mixed results, but the AHS believes IV formulations are probably helpful in treating migraine with aura and provide a non-sedative option for a subset of individuals. [83]

small multicenter case studies Series using Valproate (VPA) IV had demonstrated similar or even less efficacy compared to comparators, decreases in HA intensity, and other migraine symptoms.

VPA should be avoided in fertile women, while it could be an option for some individuals. Although synergy has been observed to lessen migraine severity when taken with antiemetics or NSAIDs, limited trials of IN lidocaine have had mixed results [84]. As just a constituent of nerve blocks, several forms of lidocaine are being employed to treat migraines. In limited studies and case reports, the advantages and acceptability of glucocorticoids for acute migraine were described as dose-dependent effects. One study noted less HA recurrence than with opioids, providing a possibility for use in emergency departments. There is little evidence to support using calcium channel blockers, including granisetron, diphenhydramine, trimethobenzamide, or complementary treatments like feverfew, ginger, or peppermint oil to prevent migraines.

According to limited research, acute migraine therapy with intravenous (IV) valproate could be helpful. In a short study, individuals who received a single 800 mg IV dosage of Valproate were more likely to get pain control by 2 hours than those who got 800 mg of ibuprofen in 99 adults with acute migraine without aura [85]. The benefits were similar whenever Valproate was tested with sumatriptan & IV Ketorolac in limited trials [86]. However, some studies have found that valproate rescue treatment, used at higher rates than antiemetics and analgesics, only offers short-term benefits [87]. Because it acts more quickly, intravenous Valproate is favoured over oral forms for treating acute migraines. The usual dosage is 500 to 1000 mg between 5 to 10 minutes, up to 10 mg/kg per minute. Valproate side effects include tremors, nausea, and vomiting. Due to a higher risk of teratogenicity, pregnant individuals should not take Valproate to treat migraines.

2.6 Different Levels of Migraine Treatment

Early headache therapy is typically more successful than later treatment, and a single high dose is generally more effective than several smaller ones. A non-oral (eg, intravenous, intramuscular, or subcutaneous) agent may be preferred for patients with significant nausea or vomiting.

The abortive (symptomatic) treatment of migraine includes the use of triptans, antiemetics, calcitonin gene-related peptide (CGRP) antagonist, lasmiditan, and dihydroergotamine in addition to more basic analgesics such as nonsteroidal anti-inflammatory medications (NSAIDs) or acetaminophen. Patients who do not react to or tolerate pharmacological therapies well and those who want to avoid drugs frequently employ noninvasive neuromodulation devices. Early headache therapy is typically more successful than later treatment, and a single high dose is usually more

effective than several smaller ones. Oral medications may be less effective for some individuals due to poor absorption brought on by vomiting and stomach stasis brought on by migraines.

The following are general suggestions for managing acute migraine [88]:

- Inform migraineurs about their disease and available treatments, and motivate them to take charge of their care.
- For those with more severe migraines and those whose headaches don't react well to NSAIDs or combination analgesics, use migraine-specific medications (such as triptans, CGRP antagonists, lasmiditan, and dihydroergotamine).
- Patients who have severe nausea or vomiting at the beginning of their migraines should choose a non-oral mode of administration.
- Consider using a self-administered rescue medicine for individuals suffering from severe migraines that do not react well to previous therapies.
- Prevent medicine-overused headaches by warning patients about the danger and giving preventive drugs to headache sufferers.

In a randomized controlled study of 835 migraine adults, the early administration of migraine-specific medicines for severe episodes had the most outstanding results [89]. Aspirin (800–1000 mg) and Metoclopramide (20 mg) were given to patients in one category (stepped care within attacks) as the first treatment for all attacks; those who did not react to treatment following 2 hours in each attack had their treatment advanced to zolmitriptan (2.5 mg). For a second group (step care throughout attacks), aspirin (800–1000 mg) and Metoclopramide (10 mg) were used as the initial treatments. Patients who did not react in at least 2 of the first three attacks were then moved to zolmitriptan (2.5 mg) in the subsequent three episodes. Patients in a third category (stratified care) received zolmitriptan treatment for more severe headaches, while those with milder headaches received aspirin with metoclopramide treatment. While individuals in the stratification group experienced the most adverse effects, the last two groups considerably outperformed the first group regarding headache response and impairment duration. The intensity of the attacks, the prevalence of accompanied nausea & vomiting, the treatment location (ambulatory care or medical care facility), including patient-specific characteristics, for instance, the prevalence of coronary risk factors and medication choice, all influence the pharmacologic method used to treat migraine.

2.6.1 Mild to moderate attacks

Patients in a third category (stratified care) received zolmitriptan treatment for more severe headaches, while those with milder headaches received aspirin with metoclopramide treatment. While individuals in the stratification group experienced the most adverse effects, the last two groups considerably outperformed the first group regarding headache response and impairment duration. The intensity of the attacks, the prevalence of accompanied nausea & vomiting, the treatment location (ambulatory care or medical care facility), including patient-specific characteristics, for instance, the prevalence of coronary risk factors and medication choice, all influence the pharmacologic method used to treat migraine.

2.6.2 Moderate to severe attacks

Oral migraine-specific medications, such as oral triptans and a combination of sumatriptan and naproxen, are first-line treatments for moderate-to-severe migraine episodes not accompanied by vomiting and severe nausea [91]. A calcitonin gene-related peptide (CGRP) antagonist or lasmiditan may be helpful for people who are ineligible for triptans or who cannot tolerate them. Severe migraine episodes that are accompanied by vomiting or intense nausea may be treated with an antiemetic medicine, non-oral migraine drugs such as subcutaneous sumatriptan, nasal sumatriptan, & zolmitriptan, or parenteral dihydroergotamine.

2.6.3 Status migrainosus

Individuals may be treated by a combination of iv fluids and parenteral drugs, including Ketorolac and just a dopamine receptor blocker for extreme intractable migraine episodes, also known as status migrainosus (i.e., a crippling attack lasting longer than 72 hours). Depending on the effectiveness of the first therapy, other parenteral drugs, such as Valproate & dihydroergotamine [92], might also be necessary. The choice of medicine is influenced by circumstances specific to the patient and is not founded on high-quality research, as are treatment choices.

2.6.4 Variable attacks

Numerous migraine sufferers experience episodes that differ in intensity, timing of onset, and relationship with vomiting and nauseousness [94]. For the conscience of acute migraine, these people may need two or more alternatives, such as oral drugs for mild to moderate bouts and non-oral medications (such as subcutaneous, nasal triptans) for much more severe episodes or those connected to vomiting or intense nausea.

2.6.4 Emergency settings

When a patient with a migraine presents to an emergency room, their attacks are sometimes powerful, and their regular acute migraine medication frequently hasn't successfully relieved their symptoms [95]. The concepts used in managing migraine episodes in non-urgent settings described above are also used in emergency rooms and other urgent care facilities.

- • An injection of sumatriptan 6 mg under the skin.
- • Dopamine receptor blockers that are antiemetic.
- Prochlorperazine 10 mg intramuscularly or intravenously (IM)
- Chlorpromazine is given as a single dosage as a slow IV infusion at a maximum rate of 0.1 mg/kg (or 12.5 mg); the maximum cumulative dose is 25 mg.
- Metoclopramide (1 mg IV) with dihydroergotamine (10 mg IV).
- Ketorolac 15 mg IV or 30 mg IM for individuals under 65 years of age; 30 mg IV or 60 mg IM;
- Metoclopramide — Peer - reviewed and meta-analyses have shown that intravenous Metoclopramide helps treat acute migraines.
  - The NNT required one patient to have a meaningful pain decrease; Metoclopramide was four.
  - Regarding reducing pain and nausea, Metoclopramide is much less efficient than chlorpromazine and Prochlorperazine. However, the variations weren't always statistically significant.
  - According to one study, metoclopramide therapy did not significantly differ from sumatriptan regarding frequencies of total migraine resolution or considerable pain or nausea reduction.

2.7 Comparison of Metoclopramide vs Valproate vs Ketorolac

Valproate was even less efficient than Ketorolac or Metoclopramide. Metoclopramide outperformed Ketorolac on some outcomes. Evidence classification This experiment offers Class I evidence that enhancing migraine results in ED patients suffering from acute migraine requires Metoclopramide or ketorolac rather than IV valproate.

In double-blind research, the efficacy of 1000 mg IV valproate, 10 mg IV metoclopramide, plus 30 mg IV ketorolac therapy treating acute migraine in the ED was compared. Metoclopramide decreased pain by 4.7 points (95 % confidence interval [CI]: 4.2, 5.2), IV Ketorolac by 3.9 points, and Valproate by a mean of 2.8 points (on a scale of 0 to 10). (95 percent CI: 3.3, 4.5).

IV valproate was fewer efficacious than IV ketorolac or IV Metoclopramide in treating patients who presented to the emergency room including an acute migraine episode. 31 In a randomized open-label research, valproate 50 mg IV was associated to sumatriptan-metoclopramide (metoclopramide 10 mg IM with 6 mg SQ sumatriptan) in patients with chronic migraine deprived of aura (more than 4 hours but fewer than 72 hours). As opposed to 60 percent and 30 percent, respectively, who reported pain reduction after two hours ($p = 0.037$), 53.3 percent in the valproate arm and 23.3 % in the metoclopramide + sumatriptan arm experienced pain alleviation after one hour (from severe or moderate pain towards mild pain or none).

In the valproate group, just one patient with dizziness was noted. The US Food and Drug Agency also approved the anti-epileptic drug valproate for the prophylaxis of migraines with and without aura [96].

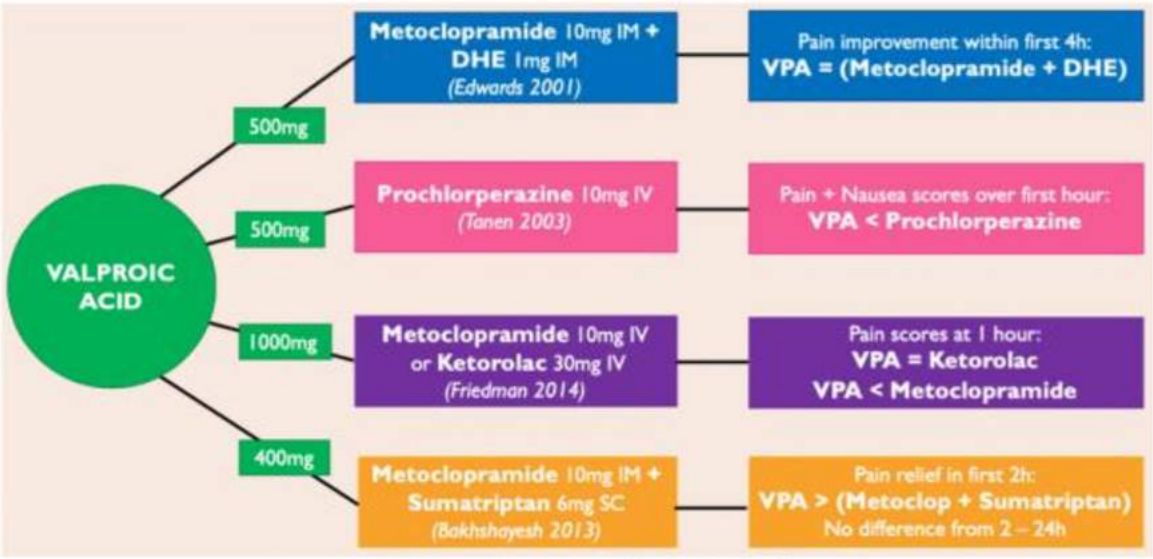
In several trials, intravenous Valproate was discovered to be safe, well tolerated, and had a rapid onset of Effect. It is helpful as an abortive treatment for acute severe to moderate migraine and situations when patients are resistant to the emergency department [97]. Valproate increases inhibitory neurotransmitter gamma amino butyric acid (GABA) levels by changing the GABA-ergic enzymatic pathway [98]. This caused in reduced serotonergic cell firing rate in the dorsal raphe nucleus and decreased central activation in the trigeminal nucleus caudalis [99]. By lowering neurogenic inflammation through GABA-A receptor antagonistism, Valproate has also been demonstrated to affect peripheral neurons [100]. In randomized, double-blind research, the effectiveness of 1000 mg IV valproate, 10 mg IV metoclopramide, and 30 mg IV ketorolac for treating acute migraines in the emergency department was contrasted.

After 30 mints- to 1-hour review, individuals with persistent headaches should have all possible diagnoses thoroughly considered, including the fatal can't-miss diagnosis. Consider a different first-line analgesic choice from those mentioned above for further analgesic relief. Additionally, individuals who do not have a contraindication to nonsteroidal anti-inflammatory drugs may get Ketorolac (15–30 mg IV). Patients who seem dehydrated or vomited may be given intravenous fluids. Still, there is no evidence that this was help them experience more relief from migraines when combined with other first-line treatments. Second-line treatments, including Valproate, sumatriptan, and acetylsalicylic acid, may be explored for individuals who continue to experience migraines despite repeated tries with first-line medications. Individuals who have previously responded well may be evaluated for Valproate (1 g IV). But studies have revealed lower effectiveness than other first-line remedies (Metoclopramide).

IV valproate was substantially less productive than intravenous Prochlorperazine, Metoclopramide, and Ketorolac [101]. IV valproate shouldn't be used as first-line monotherapy in the emergency room to treat rescue migraine. The Canadian Headache Society did not advocate using Valproate for the immediate therapy of migraine headaches in the emergency department (poor recommendation, low quality of evidence) [102]. It was shown that intravenous administration of Ketorolac at the analgesic ceiling dose (10 mg) effectively relieved pain in ED patients with moderate to severe discomfort without producing more side effects. Ketorolac had comparable analgesic effectiveness at intravenous dosages of 10, 15, and 30 mg. Effectiveness-wise, Valproate was less effective than Metoclopramide or Ketorolac.

Comparison Of Usage and Route of Administration of Drugs with Category

Generic Name	Category	Dosage	Route of Administration
Ketorolac	NSAIDs	30-60 mg 60 mg 10 mg	IV IM PO
Metoclopramide	neuroleptic	10 mg	IM/IV
valproate	Valproic Acid	500mg 1g	IV



Combination Of Valproic Acid with Other Drugs in Treatment

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research design

This research was utilizing a randomized controlled trial (RCT) design to compare the efficacy of intravenous (IV) ketorolac, Valproate, and Metoclopramide in patients presenting to the emergency department with acute migraine attacks. An RCT design is appropriate for this study as it allows for comparing different interventions while minimizing bias and providing a high level of evidence.

3.2 Study Settings

The study was conducted at the Department of Emergency, Pakistan Institute of Medical Sciences, SZABMU Islamabad.

3.3 Sample size and randomization

A total sample size of 327 was estimated in the respective group using the consequences of prior clinical studies with 80% power and a 95% confidence interval. When 327 patients had signed up for the trial, participation was ended. A flow diagram created using CONSORT (Consolidated Standards of Reporting Trials) depicts the procedure for recruiting research participants (Fig. 1). Participant recruitment was carried out using block randomization. After being physically examined by a neurologist and completing the qualifying requirements, the patients were chosen by a general physician and enrolled in the research. All patients provided written informed permission, and the Regional Ethics Committee of Islamabad University of Medical Sciences accepted the study plan (code no. 92.12.14). Before taking the medication, each participant finished a questionnaire asking about their demographics, the frequency, duration, and intensity of their headaches, and any accompanying symptoms (photophobia, nausea, phonophobia, and vomiting).

Calculated by using WHO (world health organization) sample size calculator taking the following parameters:

Level of significance = 5%

Power of test = 80%

Population standard deviation = 5.0

Test value of the population. The mean value of improvement in pain score at I hour in the valproate group= was 2.8

Test value of population, mean value of improvement in pain score at I hour in metoclopramide group = 4.7

The sample size was 109 patients in each group, and 327 patients were included in the final study.

Sampling Technique: Non-probability consecutive sampling.

3.3.1 Inclusion Criteria:

• All 15 - 65-year-old patients visiting the emergency department with complaints of moderate to severe headache diagnosed as having "Migraine without aura" or "Migraine with aura" according to the International Headache society (IHS) criteria. Pain score of more than 5 (based on visual analogue scale (VAS)).

• Both genders were included in the study,

3.3.2 Exclusion Criteria:

• Patients had allergies to any medications included in this study.

• Endocrine diseases, i.e., Hypothyroidism, Cushing's syndrome, Addison's disease

• Malignancy • Systemic lupus erythematosus

• Psychiatric disorders, i.e., Schizophrenia disorders and dementia

• Neurological disorders i.e., Epilepsy, Stroke, Parkinsonism, Multiple sclerosis

• Traumatic brain injury

• Patients using these drugs: Corticosteroids, Beta blockers, Calcium channel blockers, Tricyclic antidepressants, Anti-epileptic drugs, Serotoncrgic nor-epinephrine reuptake inhibitors, Ergotamine, triptan, opioid, or combination medication intake for >10 days per month.

• Uncontrolled hypertension (i.e., sitting systolic blood pressure >I60 mm Hg or sitting diastolic blood pressure >90 mm Hg) at the screening visit or randomization.

• History of hypersensitivity to the drugs being studied.

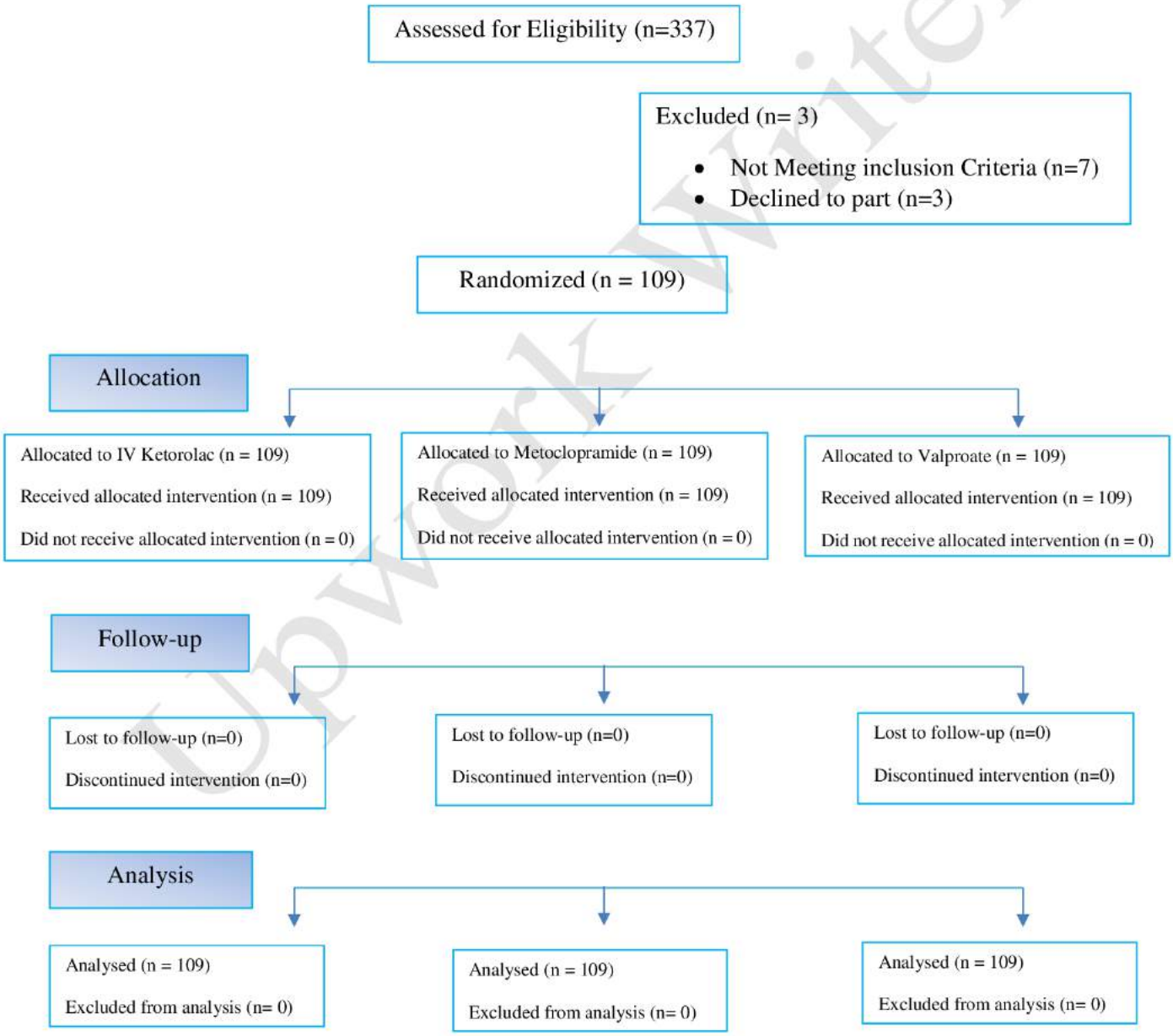


Figure 1: Model diagram of study

3.4 Data Collection Procedure

An electronic random number table was used to provide randomization. Using Excel's Rand between function, the medications were randomly distributed into envelopes and marked with serial numbers ranging from 1,000 to 2,000. (Microsoft, Redmond, WA, USA). A nurse not involved in the research administered the medications by injecting them into the same syringe. The patient and the investigator (an emergency physician and a neurologist) were unaware of the drug given until the study's conclusion.

3.5 Intervention and outcomes

Before initiating study enrollment, ethical approval was gained from the hospital's ethical review committee. All patients, already diagnosed and new cases, fulfilling the inclusion criteria were included in the study through the Emergency Department or referred to the Emergency and Neurology Department from other units of PIMS Hospital Islamabad. The purpose and benefits of the study were explained to the first-degree relatives, who were assured that the study was done purely for data publication and research purposes, and informed consent was obtained (Annexure C). History was taken in detail and thorough examination. Patients with acute migraine were divided into groups A, B and C by lottery method. Group A patients have treated with an intravenous injection of Ketorolac 30 mg. Group B patients have treated with an injection of Metoclopramide 10 mg through an intravenous route.

In comparison, Group C received an Injection of Sodium Valproate 500mg through the IV route. The brand name of drugs used shall be kept the same in all the patients. Treatment was given IN, and VAS scores were assessed abler 30 minutes. I and 2 hours of aller drug administration. The data wase collected on a pre-designed proforma attached as Annexure -A.

3.6 Statistical analysis

The IBM SPSS 23v statistical tool entered patient demographic information and the previously listed factors (IBM Corp., Armonk, NY, USA). The independent t-test and chi-square test were used to assess the degree of post-treatment pain in the three groups, while the t-test and Pearson's chi-square test were used to determine the link between demographic data and medicines. We estimated the period of headache alleviation and treatment effectiveness among the three groups

during the first Three hours using Kaplan-Meier survival analysis and the log-rank test. Success in the treatment was measured by reduced pain intensity (VAS score 3) and the absence or presence of pain. P 0.05 was used as the statistical significance level.

3.7 Ethical consideration:

The patients' data were private, secured, and only used for research. Only those enrolled patients who signed the informed consent for the same purpose. The treatment given to both groups is part of the protocol, and either group is not neglected. All three drugs are free of cost in the hospital's Emergency department, and no patient bears any cost of medications.

CHAPTER 4

RESULTS

This chapter focuses on the results from 327 cases included in the study. The frequency, Mean, Standard Deviation and percentages were calculated for the demographic variables. The result section closes with the study's main results presenting group-specific pain ratings on the visual analogue scale before and after therapy and the Effect of apiece drug on headache relief through visual analogue scale score.

To participate in this study, 337 individuals with acute migraine headaches underwent screening. Seven patients were omitted because they did not match the inclusion criteria. Three participants failed to provide their consent on time. Three hundred twenty-seven patients in all were enrolled and examined. These patients were all still being followed up on. In the control group (IV ketorolac), there were 91 females and 18 males (mean age: 33.3 ± 9.3 years), 88 females and 21 males (mean age: 33.8 ± 9.6 years) in the intervention group (Valproate), and 92 females and 17 males (mean age: 32.2 ± 9.4 years) in the intervention group (Metoclopramide). Table 1 displays the demographic data regarding the patients. The demographic characteristics of the two groups were comparable, and there were no significant intergroup variations. Only one patient in the valproate group did not remark phonophobia, while all patients acknowledged photophobia and phonophobia. 15 (12.5%) patients in the valproate group, 19 (17.5%) patients in the IV ketorolac group and 14 (12.5%) patients in the metoclopramide group did not experience vomiting. There was no intergroup variation in the symptoms that were present.

Table 1 shows the demographics of the patients. Values are displayed as the mean, standard deviation, or percentage (%).

Characteristics	IV Ketorolac group	valproate group	Metoclopramide
Age	33.3 ± 9.3	33.8 ± 9.6	33.2 ± 9.4

Male	18 (16.5)	21 (19.2)	17 (15.5)
Female	91 (83.4)	88 (80.73)	92 (80.7)
Level of education			
Illiterate	0	2 (1.8)	1 (0.91)
Elementary	22 (20.18)	14 (12.84)	18 (16.51)
Under diploma	9 (8.25)	18 (16.51)	30 (27.5)
Diploma	43 (39.44)	35 (32.1)	32 (29.35)
Collage education	35 (32.11)	40 (36.69)	28 (25.68)
Duration of disease (yr)			
1-2	16 (14.7)	15 (13.8)	22 (20.1)
3-5	28 (25.7)	45(41.2)	56 (51.4)
>5	65 (59.6)	49 (45.0)	31 (28.5)
Marital Status (hr)			
Married	40 (36.7)	38 (34.8)	41 (37.6)
Single	51 (46.8)	52 (47.8)	55 (50.45)
Widowed	4 (3.7)	8 (7.3)	5 (4.58)
Divorced	9 (8.3)	11 (10.09)	8 (7.33)
Family history of migraine			
Yes	81 (74.3)	85 (78.0)	91 (83.4)
No	28 (25.7)	24 (22.01)	18 (16.51)
New cases			

Yes	14 (12.8)	15 (13.76)	20 (18.3)
No	95 (87.1)	94 (84.23)	89 (86.7)
Already Diagnosed			
Yes	95 (87.1)	94 (84.23)	89 (86.7)
No	14 (12.8)	15 (13.76)	20 (18.3)

The mean VAS pain severity scores before medication administration were 8.950.79 (95% confidence range, 8.68 to 9.18), 8.990.89 (95% confidence interval, 8.76 to 9.34), and 8.950.79 (95% confidence interval, 8.68 to 9.18), respectively, in the IV Ketorolac, Valproate, and metoclopramide groups. The IV Ketorolac (3.112.71), Valproate (3.93.07), and metoclopramide (3.73.01) groups all saw a substantial decrease in pain intensity 30 minutes after the therapeutic intervention, but there was no discernible intergroup difference (Table 2).

Table 2 shows group-specific pain ratings on the visual analogue scale before and after therapy.

	valproate group	**IV Ketorolac group**	**Metoclopramide**	**P-value**
Before treatment	9.05 ± 0.90	8.95 ± 0.79	8.99 ± 0.89	0.514
After treatment				
30 mints	3.76 ± 3.07	3.11 ± 2.75	3.19 ± 2.79	0.280
1 hr	2.72 ± 3.21	1.84 ± 2.55	2.70 ± 3.10	0.175
2 hr.	2.02 ± 3.13	0.95 ± 1.96	0.94 ± 1.93	0.053
3 hr.	1.35 ± 2.60	0.54 ± 1.38	1.32 ± 2.64	0.081

Values are presented as mean ± standard deviation.

Age, illness duration, sex, or headache enhancement differences across groups were not statistically significant. The Kaplan-Meier curve showed the three groups' success rates and the time it took for pain alleviation to start (Fig. 1).

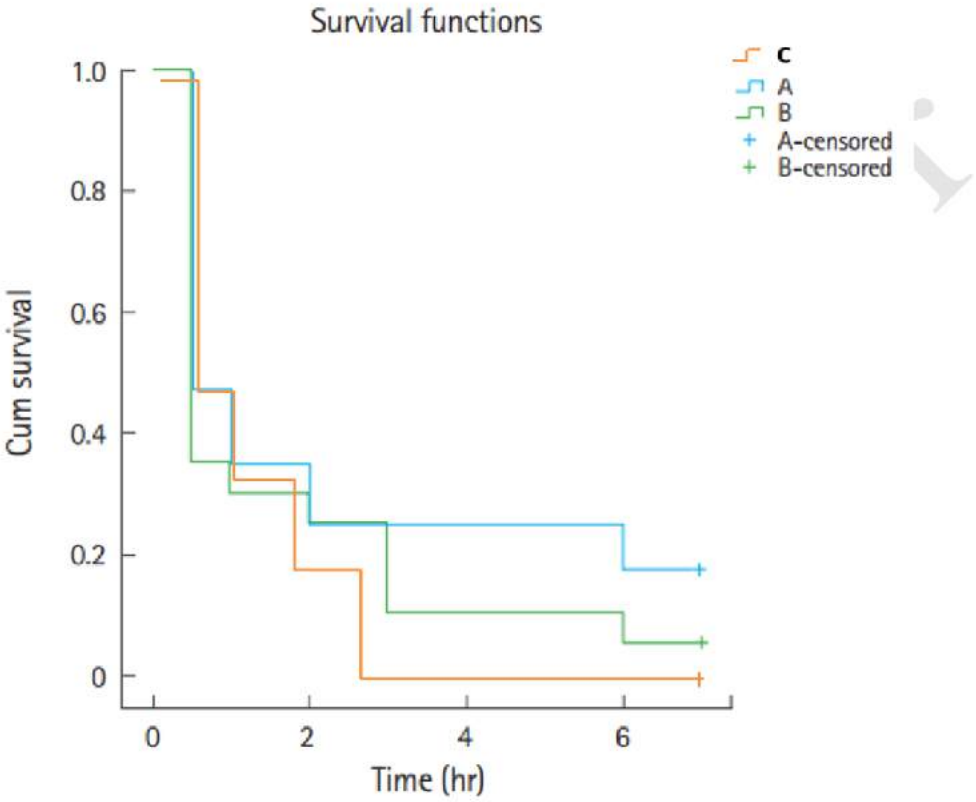


Figure 1: The Kaplan-Meier curve showed the three groups' success rates and the amount of time it took for pain alleviation to start

Table 3 compares the change in pain intensity from before to after therapy using a 4-point scale. The IV Ketorolac, Valproate, and metoclopramide groups successfully reduced the degree of pain in 21 (50.5%), 25 (62%), and 27 (67%) of the patients, respectively, at 30 mints after administration, however there were no significant inter-group differences (P=0.15).

Table 3. Significant pain improvement after treatment grounded on a four-point scale a)

After treatment	Valproate group	IV Ketorolac group	Metoclopramide group	95% CI	P-value
30 mints	54 (50.0)	68 (62.5)	74 (67.0)	0.68-4.21	0.15
1 hr.	81 (75.0)	99 (90.0)	104 (95.0)	0.84-10.54	0.07
2 hr.	90 (82.5)	99 (90.0)	106 (97.5)	0.63-10.95	0.14
3 hr.	101 (92.5)	104 (95)	106 (97.5)	0.47-40.60	0.15

Values exist as numbers (%).

CI, confidence interval.

a) No or mild pain.

Any patient receiving therapy with a VAS score below three was deemed a success. The log-rank test found no evidence of a therapeutic effect difference between groups (2 value [1, 80] =2.018; P=0.155). Complete pain relief was seen up to 6 hours after medication administration in 101 patients (92.5%) in the IV valproate group, 104 patients (95%) in the IV ketorolac group, in addition, 106 patients (97.5%) in the metoclopramide group. The individuals stayed at the emergency room for 24 hours under monitoring. Two hours after treatment, rescue therapy was needed for 19 patients (17.5%) from either the IV valproate group, eight patients (7.3%) from the IV ketorolac group, and six patients (5.5%) from the metoclopramide group.

Three hours after treatment, none of the patients in the valproate group (14 patients, or 12.8%), the IV ketorolac group (6 patients, or 5.5%), or the metoclopramide group (one patient, or 0.91%) exhibited improvement. Both groups saw the same 7.5% frequency of recurring headaches 24 hours after treatment. Photophobia, phonophobia, and nausea or vomiting, which are migraine-related symptoms, considerably decreased in both groups. In contrast to the valproate group, where only one patient experienced an adverse reaction of anxiety, restlessness, and shortness of breath that subsided two hours after therapy, the IV ketorolac group saw no side effects.

CHAPTER 5

DISCUSSION AND CONCLUSION

5.1 Discussion

Numerous research employed Ketorolac. Therefore, both pro and con arguments have been put out. In pilot research, twelve individuals experiencing a headache crisis received 30 mg of intramuscular Ketorolac. All patients' McGill pain questionnaire scores improved statistically significantly, and the authors suggested this medication as a potential therapy option for such individuals [104]. In a prospective, double-blind trial including individuals who complained of migraine headaches, intravenous Ketorolac and Valproate were contrasted. According to the authors, despite both medications significantly decreasing pain, intravenous Ketorolac was superior to Valproate in this respect [105].

IV ketorolac was contrasted to Valproate + Metoclopramide and normal saline as a placebo in a controlled experiment for tension headaches. According to the authors, Ketorolac was better than valproate at 0.5 and 1 hours and better than Metoclopramide at 2 hours [105]. Interestingly, these authors' previous study on acute headache crises revealed that all three treatments might result in considerable pain management. Still, the quantity did not vary among them [106].

In a non-interventional, non-randomized study on pain treatment, oral ibuprofen and injectable Ketorolac were contrasted. The authors concluded that both options provided comparable pain alleviation while treating acute pain in the emergency department. They believed that Ketorolac did not necessarily outperform ibuprofen for this purpose [107]. Another research on migraine sufferers found that most individuals saw a substantial reduction in headache symptoms after an hour after receiving a single injection of Ketorolac [108].

A randomized experiment evaluating the efficacy of intravenous Ketorolac, Metoclopramide, and valproate sodium for treating acute migraine headaches concluded that the former was more successful than the latter [109].

To treat inevitable primary headaches, intravenous Ketorolac was contrasted with intravenous diphenhydramine with Metoclopramide. The study found that intravenous Ketorolac + Metoclopramide is more effective than intravenous Ketorolac for treating people who present to an ED with non-migraine, non-cluster primary headaches [110]. The study's advantages might be using a recognized measurement method like the VAS and careful patient selection. On the other hand, one of the restrictions is the brief follow-up period. Future studies should consider a control group, increasing dosages, a broader population, and documenting individuals who did not react to Ketorolac.

According to this randomized clinical study, acute migraine headaches were successfully treated with IV ketorolac, Valproate, and Metoclopramide. The IV Ketorolac, Valproate group had a higher recovery rate than the Metoclopramide group, but the difference wasn't statistically significant. In other words, the medications showed the same effectiveness for treating severe migraines. The results of comparable studies conducted in Iran in 2017 and 2012 revealed that the three medications had similar effects on headache alleviation [111-112]. In the current trial, the Valproate, IV Ketorolac, and metoclopramide groups all had a reduction in headache frequency during the first 0.5 hours at 50%, 62%, and 67%, respectively. In other investigations, the percentage of pain alleviation after an hour was found to be 75.0% in patients getting Valproate, 90.0% in patients receiving Ketorolac, and 95.0% in patients receiving metoclopramide [113]. There was no statistically significant difference between the three groups regarding demographic variables and the recovery rate in the first 0.5 hours.

According to Foroughipour et al. [24], 292 and 270 minutes of headache relief were seen by 26%, 29%, and 33% of patients in the Valproate, IV Ketorolac, and metoclopramide groups. The patients in that trial got therapeutic doses higher than those in our study, and the sample size was tiny. Regrettably, Valproate's therapeutic dose for acute migraine headaches is yet unknown. Valproate was diluted in normal saline (50 to 200 mL) in various investigations, where the therapeutic dose ranged from 400 to 1,200 mg [115]. To prevent the confounding impact of normal saline, which can relieve headaches by hydrating the body, both medications were given in this trial as a single dosage diluted in a tiny amount of normal saline (4 mL). In treating epilepsy, Limdi et al. [41] documented the security of a quick infusion of undiluted Valproate. The findings of the current

study showed that a low dose of IV ketorolac (30 mg), Valproate (500 mg), and Metoclopramide (10 mg), diluted in 4 mL of ordinary saline, can effectively reduce headache discomfort.

While Rahimdel et al. [115] observed that subcutaneous sumatriptan and IV valproate have comparable attributes to controller acute migraine attacks, Bakhshayesh et al. [117] stated that IV valproate was further efficient than Ketorolac and Metoclopramide at supplying headache relief throughout the 120 minutes post-treatment. When Valproate was used as a headache therapy, Edwards et al. found it was as effective as Metoclopramide and dihydroergotamine. Tanen et al. comparison of the effectiveness of Prochlorperazine against intravenous Valproate showed that the latter was less successful at reducing nausea or pain. Patients were only monitored for the first 60 minutes and established rescue medication, introducing a confounding factor.

In this study, both groups experienced meagre headache recurrence rates after 24 hours. Foroughipour et al. research's [112] showed that within 72 hours of injection, relapses of headache happened in 67.4% of the valproate collection, 64.7% of the IV Ketorolac group, and 65.3% of the metoclopramide group. Additionally, Ghaderibarmi et al.'s research [116] showed that Valproate is superior to sumatriptan in minimizing pain and avoiding headache recurrence. One trial found that IV ketorolac was less effective than oral Ketorolac in preventing acute migraine headache recurrence. In contrast, another found that IV ketorolac infusions were associated with a lower frequency of severe recurrent headaches. Both trials surveyed their participants for 72 hours; however, the number of cases in both was fewer than ours. The patients in this research underwent a 24-hour assessment period. A longer follow-up appears necessary to assess recurrence.

In our study, Valproate and IV Ketorolac significantly reduced migraine-related symptoms. At the same time, all of our patients reported reduced discomfort post-infusion. While Foroughipour et al. [112] observed that IV ketorolac was more successful than Valproate and Metoclopramide at treating the related symptoms, this conclusion is similar to previous trials. The degree and length of the accompanying symptoms before therapy influence how well they respond to treatment. It is necessary to look at this matter more. Only one patient in the valproate group in the current trial complained of a minor adverse effect.

Additionally, additional trials found no significant harmful effects following therapy with Valproate, Metoclopramide, or IV Ketorolac. Numerous studies [118-122] have shown the

effectiveness and safety of intravenous Valproate, Metoclopramide, and IV Ketorolac in treating acute migraine episodes. To our knowledge, only the trial by Shahien et al. [123] has reported substantial adverse effects of intravenous Valproate, likely caused by the large dosage utilized (900 to 1,200 mg).

5.2 Conclusion

In this study comparing the efficacy of IV Ketorolac, Valproate, and Metoclopramide in patients presenting to the emergency department with acute migraine attacks, the results demonstrate that Metoclopramide showed superior efficacy compared to both IV Ketorolac and Valproate. The outcome measure, reduction in pain intensity one hour after drug administration, favored the metoclopramide group, indicating that patients receiving Metoclopramide experienced greater pain relief than those receiving IV Ketorolac or Valproate. This finding suggests that Metoclopramide may be a more practical option for managing acute migraine attacks in the emergency department.

Furthermore, outcome measures also favoured the metoclopramide group, including the proportion of patients achieving pain relief at different time points, the need for rescue medication, and patient satisfaction scores. These additional findings support the conclusion that Metoclopramide offers superior efficacy in relieving pain and improving patient outcomes compared to IV ketorolac and Valproate.

Based on the results of this study, healthcare providers in the emergency department should consider Metoclopramide as a first-line option for pain management in patients presenting with acute migraine attacks. Further research and larger-scale studies are warranted to confirm these findings and explore potential mechanisms underlying the superior efficacy of Metoclopramide compared to IV ketorolac and Valproate. Overall, this study contributes to the body of evidence regarding treating acute migraine attacks and provides valuable insights for clinicians in making informed decisions about medication choices in the emergency department, ultimately improving the care and outcomes of patients suffering from acute migraines.

Reference

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. N Engl J Med 2002;346(4):257-70. PMID: 11807151.
2. Bamford CC, Tepper SJ. Migraine – current understanding and treatment. Techniques Reg Anesth Pain Manage 2009;13(1):20-7.
3. Lambert J, Carides GW, Meloche JP, et al. Impact of migraine symptoms on health care use and work loss in Canada in patients randomly assigned in phase III clinical trial. Can J Clin Pharmacol 2002;9(3):158-64. PMID: 12422253.
4. Lipton RB, Hamelsky SW, Kolodner KB, et al. Migraine, quality of life, and depression: a population-based case-control study. Neurology 2000;55(5):629-35. PMID: 10980724.
5. Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: a population-based study. Neurology 2010;74(8):628-35. PMID: 20147658.
6. Schurks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339: b3914. PMID: 19861375.
7. Diamond S, Bigal ME, Silberstein S, et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache 2007;47(3):355-63. PMID: 17371352. Erratum in Headache 2007;47(9):1365.
8. Friedman BW, Serrano D, Reed M, et al. Use of the emergency department for severe headaches. A population-based study. Headache 2009;49(1):21-30. PMID: 19040677.
9. Goldstein JN, Camargo CA, Jr., Pelletier AJ, et al. Headache in United States emergency departments: demographics, work-up and frequency of pathological diagnoses. Cephalalgia 2006;26(6):684-90. PMID: 16686907. Goldstein JN, Camargo CA, Jr., Pelletier AJ, et al. Headache in United States emergency departments: demographics, work-up and frequency of pathological diagnoses. Cephalalgia 2006;26(6):684-90. PMID: 16686907.
10. Becker WJ, Christie SN, Mackie G, et al., for the Canadian Headache Society Migraine Strategy Task Force. Consensus statement: the development of a national Canadian Migraine Strategy. Can J Neurol Sci 2010;37(4):449-56. PMID: 20724251.
11. Friedman BW. Migraine and other primary headache disorders. In: Rowe BH, ed. Evidence-based emergency medicine. 1st ed. Wiley-Blackwell; 2009. p. 493-502.

12. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. Ann Emerg Med 2002;39(3):215-22. PMID: 11867972.
13. Colman I, Rothney A, Wright SC, et al. Use of narcotic analgesics in the emergency department treatment of migraine headache. Neurology 2004;62(10):1695-700. PMID: 15159464.
14. Richer LP, Laycock K, Millar K, et al. Treatment of children with migraine in emergency departments: national practice variation study. Pediatrics 2010;126(1): e150-e155. PMID: 20530076.
15. Talabi S, Masoumi B, Azizkhani R, Esmailian M. Metoclopramide versus sumatriptan for treatment of Metoclopramide migraine headache: a randomized clinical trial. J Res Med Sci 2013; 18:695-8.
16. Momayyezi M, Fallahzadeh H, Momayyezi M. Pr evalence of migraine and tension-type headache in Y azd, Iran. Zahedan J Res Med Sci 2015; 17: e966.
17. Headache Classification Committee of the Internat ional Headache Society (IHS). The International Cla ssification of Headache Disorders 3rd edition (beta v ersion). Cephalalgia 2013; 33:629-808.
18. Tfelt-Hansen P, Block G, Dahlof C, et al. Guidelin es for controlled trials of drugs in migraine: second e dition. Cephalalgia 2000; 20:765-86.
19. Rowe BH, Colman I, Edmonds ML, Blitz S, Wal ker A, Wiens S. Randomized controlled trial of intra venous IV Ketorolac to prevent relapse in acute mi graine headache. Headache 2008; 48:333-40.
20. Soleimanpour H, Ghafouri RR, Taheraghdam A, et al. Effectiveness of intravenous IV Ketorolac ve rsus propofol for pain relief in the migraine headach e: a prospective double blind randomized clinical tria l. BMC Neurol 2012; 12:114.
21. Friedman BW, Garber L, Yoon A, et al. Randomi zed trial of IV valproate vs Metoclopramide vs ketor metoclopramide olac for acute migraine. Neurology 2014; 82:976-83.
22. Friedman BW, Greenwald P, Bania TC, et al. Ra ndomized trial of IV IV Ketorolac for acute migrai ne in the emergency department. Neurology 2007; 6 9:2038-44.
23. Mazaheri S, Poorolajal J, Hosseinzadeh A, Fazlia n MM. Effect of intravenous Valproate vs de xamethasone on acute migraine headache: a double b lind randomized clinical trial. PLoS One 2015; 10: e0 120229

24. Norton J. Use of intravenous valproate sodium in status migraine. Headache 2000; 40:755-7.
25. Tanen DA, Miller S, French T, Riffenburgh RH. I ntravenous Valproate versus prochlorperazin e for the emergency department treatment of acute m igraine headaches: a prospective, randomized, doubl e-blind trial. Ann Emerg Med 2003; 41:847-53.
26. Knox TH. A Review of Current and Emerging Approaches to Pain Management in the Emergency Department. Pain Ther. 2017 Dec; 6(2):193-202. DOI 10.1007/s40122-017-0090-5.
27. Najjar M, Hall T, Estupinan B. Metoclopramide for Acute Migraine Treatment in the Emergency Department: An Effective Alternative to Opioids. Cureus. 2017 Apr; 9(4): e1181. DOI 10.7759/cureus.11
28. Gupta S, Oosthuizen R, Pulfrey S. Treatment of acute migraine in the emergency department. Can Fam Physician. 2014 Jan; 60(1):47-49.
29. Gelfand AA, Goadsby PJ. A Neurologist's Guide to Acute Migraine Therapy in the Emergency Room. Neurohospitalist. 2012 Apr; 2(2):51-59.
30. Tepper D, Nonsteroidal Anti-Inflammatories for the Acute Treatment of Migraine. J Headache Pain. 2012 Dec; 53(1):225-226.
31. Tarantino, Samuela, Alessandro Capuano, Roberto Torriero, Monica Citti, Catello Vollono, Simonetta Gentile, Federico Vigevano, and Massimiliano Valeriani. "Migraine equivalents as part of migraine syndrome in childhood." *Pediatric neurology* 51, no. 5 (2014): 645-649.
32. Linde, M. "Migraine: a review and future directions for treatment." *Acta Neurologica Scandinavica* 114, no. 2 (2006): 71-83.
33. Badran, Mohammad, and Ismail Laher. "Obesity in Arabic-speaking countries." *Journal of obesity* 2011 (2011).
34. Moskowitz, Michael A. "The neurobiology of vascular head pain." Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society 16, no. 2 (1984): 157-168.
35. Diener, Hans-Christoph, Dagny Holle-Lee, Steffen Nägel, Thomas Dresler, Charly Gaul, Hartmut Göbel, Katja Heinze-Kuhn et al. "Treatment of migraine attacks and prevention of migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology." *Clinical and translational neuroscience* 3, no. 1 (2019): 2514183X18823377.

36. Friedman, Benjamin W., Laura Mulvey, David Esses, Clemencia Solorzano, Joseph Paternoster, Richard B. Lipton, and E. John Gallagher. "Metoclopramide for acute migraine: a dose-finding randomized clinical trial." *Annals of emergency medicine* 57, no. 5 (2011): 475-482.
37. Diener t al., (2019).
38. Najjar, Mejdi, Tyler Hall, and Blanca Estupinan. "Metoclopramide for acute migraine treatment in the emergency department: an effective alternative to opioids." *Cureus* 9, no. 4 (2017).
39. Friedman, Benjamin W., Leonid Garber, Andrew Yoon, Clemencia Solorzano, Andrew Wollowitz, David Esses, Polly E. Bijur, and E. John Gallagher. "Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine." *Neurology* 82, no. 11 (2014): 976-983.
40. Kacperski, Joanne, Marielle A. Kabbouche, Hope L. O'Brien, and Jessica L. Weberding. "The optimal management of headaches in children and adolescents." *Therapeutic advances in neurological disorders* 9, no. 1 (2016): 53-68.
41. Friedman BW, West J, Vinson DR, Minen MT, Restivo A, Gallagher EJ. Current management of migraine in US emergency departments: An analysis of the National Hospital Ambulatory Medical Care Survey. Cephalalgia. 2015; 35:301-309.
42. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. Ann Emerg Med. 2002; 39:215-222
43. Friedman BW, Bijur PE, Lipton RB. Standardizing emergency department-based migraine research: An analysis of commonly used clinical trial outcome measures. Acad Emerg Med. 2010; 17:72-79.
44. Pitts SR, Niska W, & Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. Natl Health Stat Report. 2008 Aug;(7):1-38. Pubmed.
45. Friedman BW, Hochberg ML, Esses D, et al. Applying the International Classification of Headache Disorders to the emergency department: an assessment of reproducibility and the frequency with which a unique diagnosis can be assigned to every acute headache presentation. Ann Emerg Med. 2007 Apr; 49(4):409-419.

46. Dubosh NM, Edlow JA, Goto, T, Camargo Jr CA, Hasegawa K. Missed Serious Neurologic conditions in emergency department patients discharged with nonspecific diagnoses of headache or back pain. Ann Emerg Med. 2019 Oct; 74(4):549-561.
47. Blumenthal HJ, Weisz MA, Kelly KM, Mayer RL, Blonsky J. Treatment of Primary Headache in the Emergency Department. Headache. 2003 Nov-Dec;43(10):1026– 31.
48. International Headache Society Classification ICHD-3: Migraines Without Aura. 2018 [cited 2018; Available from: https://www.ichd-3.org/1-migraine/1-1-migraine-without-aura/ (https://www.ichd3.org/1-migraine/1-1-migraine-without-aura/).
49. Friedman BW, West J, Vinson DR, Minen MT, Restivo A, Gallagher EJ. Current management of migraine in US emergency departments: an analysis of the National Hospital Ambulatory Medical Care Survey. Cephalalgia. 2015;35(4):301-309.
50. Friedman BW, Irizarry E, Solorzano C, et al. Randomized study of IV prochlorperazine plus diphenhydramine vs IV hydromorphone for migraine. Neurology. 2017;89(20):2075-2082.
51. . Friedman BW. Managing Migraine. Ann Emerg Med. 2017;69(2):202-207.
52. Rabbie R, Derry S, Moore RA. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD008039.
53. Codispoti JR, Prior MJ, Fu M, et al. Efficacy of nonprescription doses of ibuprofen for treating migraine headache. A randomized controlled trial. Headache. 2001 Jul-Aug;41(7):665-679.
54. Derry S, Moore, RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD008040.
55. Pescatore R. What to DO: When Ibuprofen Fails, Naproxen Isn't the Answer. Emerg Med News.
56. Motov S, Yasavolian M, Likourezos A, et al. Comparison of intravenous Ketorolac at three singledose regimens for treating acute pain in the emergency department: a randomized controlled trial. Ann Emerg Med. 2017 Aug;70(2):177-184.
57. Cairns BE, Dong XD, Wong H, Svensson P. Intramuscular ketorolac inhibits activation of rat peripheral NMDA receptors. J Neurophysiol. 2012 Jun;107(12):3308-15.
58. Rozen TD. Emergency department and inpatient management of status migrainosus and intractable headache. Continuum (Minneap Minn). 2015; 21:1004–1017. doi:10.1212/CON.0000000000000191 2. Dodick D. Headache as a symptom of ominous

disease. What are the warning signals? Postgrad Med. 1997; 101:46-64. doi:10.3810/pgm.1997.05.217

59. Farkouh ME, Greenberg BP. An evidence-based review of the cardiovascular risks of nonsteroidal anti-inflammatory drugs. Am J Cardiol. 2009; 103:1227-1237. doi: 10.1016/j.amjcard.2009.01.014
60. Gungor F, Akyol KC, Kesapli M, et al. Intravenous dexketoprofen vs placebo for migraine attack in the emergency department: A randomized, placebo-controlled trial. Cephalalgia 2016; 36:179.
61. Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. Neurology 1986; 36:995.
62. Rozen TD. Emergency Department and Inpatient Management of Status Migrainosus and Intractable Headache. Continuum (Minneap Minn) 2015; 21:1004.
63. Isah AO, Rawlins MD, Bateman DN. Clinical pharmacology of Prochlorperazine in healthy young males. Br J Clin Pharmacol. 1991 Dec;32(6):677-684.
64. Yuan H, Chen AY, Silberstein SD. CGRP Therapeutics for The Treatment of Migraine – A Narrative Review. Ann Head Med. 2020; 01:03.
65. Ellis GL, Delaney J, DeHart DA, Owens A. The efficacy of Metoclopramide in the treatment of migraine headache. Ann Emerg Med.1993 Feb;22(2):191-195.
66. Coppola M, Yealy DM, Leibold RA. Randomized, placebo-controlled evaluation of Prochlorperazine versus Metoclopramide for emergency department treatment of migraine headache. Ann Emerg Med. 1995 Nov;26(5):541-546.
67. Orr SL, Friedman BW, Christie S, et al. Management of Adults with Acute Migraine in the Emergency Department: The American Headache Society Evidence Assessment of Parenteral Pharmacotherapies. Headache. 2016 Jun;56(6):91-40.
68. Najjar M, Hall T, Estupinan B. Metoclopramide for acute migraine treatment in the emergency department: an effective alternative to opioids. Cureus. 2017 Apr 20;9(4): e1181.
69. Doğan NÖ, Pekdemir M, Yılmaz S, et al. Intravenous Metoclopramide in the treatment of acute migraines: A randomized, placebo-controlled trial. Acta Neurol Scand. 2019 Apr;139(4):334-339.
70. Parlak I, Atilla R, M. Cicek M, et al. Rate of metoclopramide infusion affects the severity and incidence of akathisia. Emerg Med J. 2005 Sep;22(9): 621-624.

71. Miner JR, Fish SJ, Smith SW, Biros MH. Droperidol vs. Prochlorperazine for benign headaches in the emergency department. Acad Emerg Med. 2001 Sep;8(9):873-879.
72. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidencebased review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000; 55:754-762. doi:10.1212/WNL.55.6.754
73. Swidan SZ, Lake AE 3rd, Saper JR. Efficacy of intravenous diphenhydramine versus intravenous DHE-45 in the treatment of severe migraine headache. Curr Pain Headache Rep. 2005; 9:65-70. doi:10.1007/s11916-005-0077-5
74. Orr, Serena L., Benjamin W. Friedman, Suzanne Christie, Mia T. Minen, Cynthia Bamford, Nancy E. Kelley, and Deborah Tepper. "Management of adults with acute migraine in the emergency department: the American Headache Society evidence assessment of parenteral pharmacotherapies." *Headache: The Journal of Head and Face Pain* 56, no. 6 (2016): 911-940.
75. Long, Brit J., and Alex Koyfman. "Benign headache management in the emergency department." *The Journal of emergency medicine* 54, no. 4 (2018): 458-468.
76. Li, Peinan, Haokun Li, Xiaohong Shu, Moli Wu, Jia Liu, Tangna Hao, Hongxia Cui, and Lianjie Zheng. "Intra-articular delivery of flurbiprofen sustained release thermogel: improved therapeutic outcome of collagenase II-induced rat knee osteoarthritis." *Drug delivery* 27, no. 1 (2020): 1034-1043.
77. Long, Brit J., and Alex Koyfman. "Benign headache management in the emergency department." *The Journal of emergency medicine* 54, no. 4 (2018): 458-468.
78. Shahien R, Saleh SA, Bowirrat A. Intravenous valproate aborts migraine headaches rapidly. Acta Neurol Scand. 2011 Apr;123(4):257–65.
79. Tanen DA, Miller S, French T, Riffenburgh RH. Intravenous Valproate versus Prochlorperazine for the emergency department treatment of acute migraine headaches: a prospective, randomized, double-blind trial. Ann Emerg Med. 2003 Jun;41(6):847–53.
80. Dodson H, Bhula J, Eriksson S, Nguyen K. Migraine Treatment in the Emergency Department: Alternatives to Opioids and their Effectiveness in Relieving Migraines and Reducing Treatment Times. Cureus. 2018 Apr 6;10(4): e2439.
81. Lewis, Donald W. "Headaches in children and adolescents." *Current problems in pediatric and adolescent health care* 37, no. 6 (2007): 207-246.

82. Sun-Edelstein, Christina, and Alexander Mauskop. "Role of magnesium in the pathogenesis and treatment of migraine." *Expert review of neurotherapeutics* 9, no. 3 (2009): 369-379.
83. Vécsei, László, Zsófia Majláth, Délia Szok, Anett Csáti, and János Tajti. "Drug safety and tolerability in prophylactic migraine treatment." *Expert opinion on drug safety* 14, no. 5 (2015): 667-681.
84. Orr, Serena L., Michel Aube, Werner J. Becker, W. Jeptha Davenport, Esma Dilli, David Dodick, Rose Giammarco et al. "Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings." *Cephalalgia* 35, no. 3 (2015): 271-284.
85. Nurathirah, Mohd Noor, Mohd Boniami Yazid, Mohd Noor Norhayati, Kamarul Aryffin Baharuddin, and Mimi Azliha Abu Bakar. "Efficacy of ketorolac in the treatment of acute migraine attack: A systematic review and meta-analysis." *Academic Emergency Medicine* (2022).
86. Orr SL, Friedman BW, Christie S, et al. Management of adults with acute migraine in the emergency department: the American Headache Society evidence assessment of parenteral pharmacotherapies. Headache. 2016; 56:911-940. doi:10.1111/head.12835.
87. Sarchielli, Paola, Franco Granella, Maria Pia Prudenzano, Luigi Alberto Pini, Vincenzo Guidetti, Giorgio Bono, Lorenzo Pinessi et al. "Italian guidelines for primary headaches: 2012 revised version." *The Journal of Headache and Pain* 13, no. 2 (2012): 31-70.
88. Silberstein SD, Rosenberg J. Multispecialty consensus on diagnosis and treatment of headache. Neurology 2000; 54:1553.
89. Lipton RB, Stewart WF, Stone AM, et al. Stratified care vs step care strategies for migraine:the Disability in Strategies of Care (DISC) Study: A randomized trial. JAMA 2000; 284:2599.
90. MacGregor EA. In the clinic. Migraine. Ann Intern Med 2013; 159: ITC5.
91. Becker WJ. Acute Migraine Treatment in Adults. Headache 2015; 55:778.
92. Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. Neurology 1986; 36:995.
93. Rozen TD. Emergency Department and Inpatient Management of Status Migrainosus and Intractable Headache. Continuum (Minneap Minn) 2015; 21:1004.
94. Taylor FR, Kaniecki RG. Symptomatic treatment of migraine: when to use NSAIDs, triptans,or opiates. Curr Treat Options Neurol 2011; 13:15.

95. Kelley NE, Tepper DE. Rescue therapy for acute migraine, part 1: triptans,dihydroergotamine, and magnesium. Headache 2012; 52:114.

96. Klapper JA. Divalproex sodium in migraine prophylaxis: A dose-controlled study. Cephalalgia 1997; 17:103-8.

97. Shahien R, Saleh SA, Bowirrat A. Intravenous valproate aborts migraine headaches rapidly. Acta Neurol Scand 2011;123:257-65.

98. Cutrer FM, Moskowitz MA. The actions of valproate and neurosteroids in a model of trigeminal pain. Headache 1996; 36:265.

99. Mathew NT, Kailasam J, Meadors L, et al. Intravenous valproate sodium (depacon) aborts migraine rapidly: a preliminary report. Headache 2000; 40:720-3.

100. Cutrer FM, Limmroth V, Moskowitz MA. Possible mech- anisms of Valproate in migraine prophylaxis. Cephalalgia 1997; 17:93-100.

101. Friedman BW, Garber L, Yoon A, et al. Randomized trial of IV Valproate vs Metoclopramide vs Ketorolac for acute migraine. Neurology 2014; 82:976-83

102. Orr SL, Aube M, Becker WJ, et al. Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings. Cephalalgia 2014.

103. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013; 33:629-808.

104. Meredith JT, Wait S, Brewer KL. A prospective double-blind study of nasal sumatriptan versus IV ketorolac in migraine. Am J Emerg Med 2003; 21(3): 173-5. doi: 10.1016/S0735-6757(02)42256-5.

105. 105. Harden RN, Rogers D, Fink K, Gracely RH. Controlled trial of Ketorolac in tension-type headache. Neurology 1998; 50(2): 507-9. doi: 10.1212/WNL.50.2.507.

106. Harden RN, Gracely RH, Carter T, Warner G. The placebo effect in acute headache management: Ketorolac, meperidine, and saline in the emergency department. Headache 1996; 36(6): 352-6. doi: 10.1046/j.1526-4610.1996.3606352. x.

107. Wright JM, Price SD, Watson WA. NSAID use and efficacy in the emergency department: single doses of oral ibuprofen versus intramuscular Ketorolac. Ann Pharmacother 1994; 28(3): 309-12.

108. Davis CP, Torre PR, Schafer NC, Dave B, Bass B. Ketorolac as a rapid and effective treatment of migraine headache: evaluations by patients. Am J Emerg Med 1993; 11(6): 573-5. doi: 10.1016/0735-6757(93)90003-T.

109. Friedman BW, Garber L, Yoon A, Solorzano C, Wollowitz A, Esses D, et al. Randomized trial of IV Valproate vs Metoclopramide vs Ketorolac for acute migraine. Neurology 2014; 82(11): 976-83. doi: 10.1212/WNL.0000000000000223.

110. Friedman BW, Adewunmi V, Campbell C, Solorzano C, Esses D, Bijur PE, et al. A randomized trial of intravenous Ketorolac versus intravenous Metoclopramide plus diphenhydramine for tension-type and all non-migraine, noncluster recurrent headaches. Ann Emerg Med 2013; 62(4): 311-18.e4. doi: 10.1016/j.annemergmed.2013.03.017.

111. Mazaheri S, Poorolajal J, Hosseinzadeh A, Fazlian MM. Effect of intravenous sodium valproate vs dexamethasone on acute migraine headache: a double blind randomized clinical trial. PLoS One 2015;10:e0120229.

112. Foroughipour M, Ghandehari K, Khazaei M, Ahmadi F, Shariatinezhad K, Ghandehari K. Randomized clinical trial of intravenous Valproate (orifil) and dexamethasone in patients with migraine disorder. Iran J Med Sci 2013; 38:150-5.

113. Friedman BW, Greenwald P, Bania TC, et al. Randomized trial of IV dexamethasone for acute migraine in the emergency department. Neurology 2007; 69:2038-44.

114. Rahimdel A, Mellat A, Zeinali A, Jafari E, Ayatollahi P. Comparison between intravenous sodium valproate and subcutaneous sumatriptan for treatment of acute migraine attacks: doubleblind randomized clinical trial. Iran J Med Sci 2014; 39:171-7.

115. Ghaderibarmi F, Tavakkoli N, Togha M. Intravenous valproate versus subcutaneous sumatriptan in acute migraine attack. Acta Med Iran 2015; 53:633-6.

116. Bakhshayesh B, Seyed Saadat SM, Rezania K, Hatamian H, Hossieninezhad M. A randomized open-label study of sodium valproate vs sumatriptan and Metoclopramide for prolonged migraine headache. Am J Emerg Med 2013; 31:540-4.

117. Frazee LA, Foraker KC. Use of intravenous valproic acid for acute migraine. Ann Pharmacother 2008; 42:403-7.

118. Donaldson D, Sundermann R, Jackson R, Bastani A. Intravenous dexamethasone vs placebo as adjunctive therapy to reduce the recurrence rate of acute migraine headaches: a

multicenter, double-blinded, placebo-controlled randomized clinical trial. Am J Emerg Med 2008; 26:124-30.

119. Foroughipour M, Petramfar P, Saeidi M, Akbarnezhad MA, Ebrahimzadeh S. Efficacy of intravenous Dexamethasone in treatment of acute migraine headache: a randomized clinical trial running title. Iran J Otorhinolaryngol 2008; 19:27-31.

120. Limdi NA, Knowlton RK, Cofield SS, et al. Safety of rapid intravenous loading of Valproate. Epilepsia 2007; 48:478-83.

121. Innes GD, Macphail I, Dillon EC, Metcalfe C, Gao M. Dexamethasone prevents relapse after emergency department treatment of acute migraine: a randomized clinical trial. CJEM 1999; 1:26-33.

122. Shahien R, Saleh SA, Bowirrat A. Intravenous sodium valproate aborts migraine headaches rapidly. Acta Neurol Scand 2011; 123:257-65