Migraine Headaches : Acute treatment in Thailand

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Migraine headache is a very common, chronic neurovascular disorder with a prevalence of 11.7% in the United States of America, and 29.1% in Thailand. Females tend to experience migraine more often than males. The common age group is between 30 and 39 years of age.[1, 2] Migraine is characterized by episodes of unilateral, pulsating or throbbing pain which is moderate to severe in its intensity and is often debilitating. It is also associated with nausea, vomiting and hypersensitivity to either light, sound, or smell. Headaches are usually aggravated by routine physical activity and are often alleviated by sleep within appropriate surroundings, such as in a dark, silent and cool place. If untreated or unsuccessfully treated, symptoms can persist from 4 to 72 hours.[3] Approximately 90% of the migraineurs have moderate or severe pain. Approximately 75% of cases said their routine functions deteriorated whilst 53% reported serious impairment or required bed rest during attacks.[2, 4] At least one half migraineurs complained of decreased productivity and one third missed at least one day of work or school in the previous year.[5-7]

Pathophysiology

The pathophysiology of migraine is not fully understood. Copious studies suggest a link between the pathogenesis of migraine and cortical spreading depression (CSD), neurogenic inflammation and vasodilatation.[8, 9] Moreover, surveys in twin populations strongly imply that migraine is a disorder which is the result of a combination between genetic mutations and environmental factors. This is particularly so in sufferers with familial hemiplegic migraine, which involves the voltage-gated calcium channel mutation (CACNA1A), voltage-gated sodium channel mutation (SCN1A), and sodium-potassium pump mutation (ATP1A2).[10-16] These channelopathies produce cerebral hyperexcitability and lower CSD threshold from a variety of triggers.[17] CSD can activate the trigeminovascular system. Several neuropeptides such as calcitonin gene-related peptide (CGRP), substance P (SP), vasoactive intestinal peptide (VIP), and nitric oxide (NO) are released from nerve terminals which led to meningeal neurogenic inflammation, plasma extravasations, and vasodilatation. These peripheral pain mechanisms activate nociceptive afferents in trigeminal nerve and upper cervical dorsal root (C2-C3) and then turn back to activate the central pain pathway including trigeminal ganglion, trigeminal nucleus caudalis in brain stem, thalamus, and finally in the sensory cortex.[18,19]

Clinical features of migraine attack

Migraine attack consists of four phases: (i) prodrome phase (e.g., irritability, food craving), (ii) aura phase (e.g., visual, sensory, language, or motor symptoms that often precede the headache),

(iii) headache phase (usually unilateral, pulsating), and (iv) postdrome phase (e.g., tiredness, head pain).[3, 20, 21]

The prodrome or premonitory phase may occur for hours or up to one day prior to the onset of headache in 70% of migraineurs.[22] It is composed of symptoms which may be psychological (depression, euphoria, irritability, restlessness, hyperactivity, hypoactivity, fatigue, drowsiness); neurological (photophobia, phonophobia, hyperosmia) or general (stiff neck, increased thirst, anorexia, diarrhea, constipation, fluid retention, craving for particular foods, repetitive yawning); there are also other less typical symptoms reported by some patients.[23-25]

Aura symptoms occur in one fifth of migraineurs. Typical aura is characterized by fully reversible focal neurological disturbances such as visual symptoms, sensory symptoms or dysphasia / aphasia that gradually develop over ≥ 5 minutes and last for ≤ 60 minutes.[3] Visual aura is the commonest aura found in 99% of cases, followed by a sensory aura (54%), and aphasic aura (32%).[26, 27] Headaches could start simultaneously or after aura onset. However, most migraineurs (80%) usually developed the headache within 60 minutes after the end of aura.[28]

In 20% of patients, headaches can consistently occur at the same side. However, in 40% of cases headaches may develop bilaterally. Head pain could be aggravated by routine physical activities such as walking or climbing stairs. Headache symptoms usually occur gradually, any sudden onset of headache should raise suspicions of secondary headache.[29-31]

Postdrome phase is reported in 68% of migraineurs. Symptoms include tiredness (71.8%), head pain (33.1%), cognitive difficulties (11.7%), hangover (10.7%), gastrointestinal symptoms (8.4%), mood change (6.8%), and weakness (6.2%). Postdrome is frequently found in females (69.1%) and is associated with a full-blown migraine attack.[32]

The International Classification of Headache Disorders (ICHD-2) criteria were introduced in 2004 for standard diagnosis and research. Migraine was classified into six major categories. Two major sub-types were recognized; (1) Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms, and (2) Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or sometimes accompany the headache. ICHD-2 criteria for diagnosis of the two major types of migraine are shown in Table 1.

Strategies in migraine treatment

There are two approaches in migraine treatment: step care and stratified care.[33] Step care starts treating the attack with general pain-killer medications e.g., acetaminophen, NSAIDs, or combination of simple analgesics. If headaches are not responsive within two hours, migraine-specific medication such as triptan or ergot should be commenced.

In the other approach, known as stratified care, the person with migraine is firstly evaluated for severity of disability by using the Migraine Disability Assessment (MIDAS).[34, 35] This is a 5-item questionnaires which assesses lost time caused by headache over 3 months. A MIDAS score of more than *'10'* indicates moderate to severe disability that requires migraine-specific treatment. Another validated disability tool is the Headache Impact Test (HIT-6). A HIT-6 score more than 60 indicates severe impact from migraine.[36] The Disability in Strategies of Care (DISC) study showed stratified care is superior to step care, resulting in better patient outcomes, and also reduced time loss.[37, 38] Stratified care is recommended in current guidelines for migraine treatment.[33, 39]

Nonspecific acute migraine treatment

Analgesics

NSAIDs inhibit cyclooxygenase (COX) and reduce prostaglandin within the central nervous system (CNS) and outside the blood-brain-barrier. Selective cyclooxygenase - 2 (COX-2) inhibitors, refecoxib and valdecoxib, have been studied and demonstrated their efficacy in acute migraine treatment but they were withdrawn from the market because of increase in cardiovascular risk. Celecoxib, an available selective COX-2 inhibitor, could be used for acute migraine attack with doses between 100 and 400 mg. Since it causes less gastrointestinal side effects, it should be considered in people with gastrointestinal intolerance.[40, 41]

Analgesics such asacetylsalicylic acid (ASA) up to 1000 mg,[42-44] naproxen 500 - 1000 mg,[45] ibuprofen 200-800 mg,[46] diclofenac potassium 50 - 100 mg,[47] and paracetamol 1000 mg[48] are the first medications for mild to moderate migraine. A combination of *"Aspirin-acetaminophen-caffeine (AAC)"* elucidates higher efficacy for acute treatment in those with mild or no disability migraines, when compared to treatment with placebo or other individual analgesic.[49-51] The United States Headache Consortium recommended that NSAIDs and AAC can be effective for non-disabling migraine (Level A).[39, 52]

Table 1 : ICHD-2 criteria for migraine headache.[3]

Migraine

1.1 Migraine without aura
1.2 Migraine with aura
- 1.2.1 Typical aura with migraine headache
- 1.2.2 Typical aura with non-migraine headache
- 1.2.3 Typical aura without headache
- 1.2.4 Familial hemiplegic migraine (FHM)
- 1.2.5 Sporadic hemiplegic migraine
- 1.2.6 Basilar-type migraine

1.3 Childhood periodic syndromes that are commonly precursors of migraine
- 1.3.1 Cyclical vomiting
- 1.3.2 Abdominal migraine
- 1.3.3 Benign paroxysmal vertigo of childhood

1.4 Retinal migraine
1.5 Complications of migraine
- 1.5.1 Chronic migraine
- 1.5.2 Status migrainosus
- 1.5.3 Persistent aura without infarction
- 1.5.4 Migrainous infarction
- 1.5.5 Migraine-triggered seizures

1.6 Probable migraine
- 1.6.1 Probable migraine without aura
- 1.6.2 Probable migraine with aura
- 1.6.3 Probable chronic migraine

Migraine without aura

Diagnostic criteria:

A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not attributed to another disorder

Migraine with aura (Typical aura with migraine headache)

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness:
   1. fully reversible visual symptoms including positive features (e.g., flickering lights, spots or lines) and/or negative features (i.e., loss of vision)
   2. fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
   3. fully reversible dysphasic speech disturbance
C. At least two of the following:
   1. homonymous visual symptoms and/or unilateral sensory symptoms
   2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
   3. each symptom lasts ≥ 5 and ≤ 60 minutes
D. Headache fulfilling criteria B-D for begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

Table 2 : Medications for acute treatment of migraine (Available in Thailand).[39, 52, 76]

Medications	Dose/Route	Level of recommendation*	Comment
Non-Specific Medications			
- Acetylsalicylic acid (ASA)	1000 mg PO	A	Gastrointestinal side effects.
- Ibuprofen	200-800 mg PO	A	Gastrointestinal side effects.
- Naproxen	500-1000 mg PO	A	Gastrointestinal side effects.
- Diclofenac-K	50-100 mg PO	A	Gastrointestinal side effects.
- Paracetamol	1000 mg PO	A	Caution in liver and kidney.
- Ergotamine tartrate and Caffeine	1 mg, 100 mg PO	B	Caution in cardiovascular, liver and kidney diseases.
Specific Medications			
- Sumatriptan	50-100 mg PO	A	Caution in cardiovascular diseases.
- Eletriptan	20-80 mg PO	A	Caution in cardiovascular diseases.
Parenteral Medications			
- Metoclopramide	10 mg IV	A	Risk for extrapyramidal effects and mild sedation. Contraindicated in childhood and in pregnancy; also have analgesic efficacy.
- Chlorpromazine	0.1 mg/kg IV	B	Risk for extrapyramidal effects and mild sedation.
- Ketorolac	15-30 mg IV 60 mg IM	A	Non-sedating, risk for gastrointestinal (GI) bleeding.

Classification of Recommendations.[39, 52]

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies)

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies)

Level C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

Medications for acute migraine treatment

Ketorolac, a parenteral NSAIDs, has not yet been researched in placebo-controlled study to assess it in acute migraine treatment. The efficacy of ketorolac in acute migraine treatment was similar to meperidine and led to headache resolution similar as antiemetic medications.[53, 54] Ketorolac can be administrated intravenously at a dosage of 15 to 30 mg or intramuscularly at 30 to 60 mg per dose. The U.S. Headache Consortium recommended that intravenous or intramuscular ketorolac injection should be considered for acute treatment of migraine for whom requiring parenteral therapy (Level B).[52] Opioid use in acute migraine is generally ineffective.[55-57] The U.S. Headache Consortium stated that enteral and parenteral opioid may be added for acute migraine should the sedative effect not put patients at risk: moreover the risk for abusive use of opioids has been addressed (Level B).[52] Opioid should be limited and reserved for some particular circumstances such as pregnancy, lactation, contraindication to triptans or NSIDs (Level U).[52] Parenteral opioid should be used as a back up for acute migraine when sedation side effects will not increase patient risk and when the risk of abuse has been addressed (Level B).[52]

Antiemetics and Neuroleptics

Nausea and vomiting are common associated symptoms of migraine and can be as disabling as the headache. Antiemetic in acute migraine is recommended to treat these symptoms. It increases gastric emptying times resulting in optimizing absorption and effectiveness of oral medications. However, large prospective, placebo-controlled randomized trials are still lacking.

Intravenous metoclopramide showed superiority over placebo and ibuprofen in acute migraine treatment.[58, 59] Repeated doses of metoclopramide plus intramuscular dimenhydrinate were found to have an effectiveness similar to subcutaneous sumatriptan.[60] However, using oral metoclopramide alone, as monotherapy, is not effective for acute migraine treatment (Level A) but it can still be considered as an adjunctive therapy to NSAIDs or triptans (Level B).[52] Intravenous 10 to 20 mg metoclopramide is recommended for adults and adolescents (Level A).[39, 52]

Intravenous chlorpromazine demonstrated a higher efficacy than meperidine and lidocaine.[61] Dose of 0.1 mg/kg chlorpromazine intravenously achieved a pain free response within 30 minutes compared with placebo.[62] Chlorpromazine should be used for patients requiring parenteral therapy (Level A).[52]

Both metoclopramide and chlorpromazine share common side effects which include drowsiness, sedation, and hypotension. Extrapyramidal side effects such as acute dystonic reaction and akathisia are uncommon.[63]

Specific acute migraine treatment

Triptans

Triptans are selective 5-hydroxytryptamine (5-HT) 1B/1D-agonists and ameliorate headache without sedative effect. Agonist of serotonin-1D receptors inhibit CGRP and inflammatory neuropeptide release in the meninges that cause extravasation of dural plasma protein, and block pain transmission from peripheral trigeminal pathway to the centrally trigeminal nucleus caudalis in brain stem. They also work via the 5HT1B receptor to constrict vessels dilated by CGRP. On the present market, there are seven types of triptans: sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan. In Thailand, however, only two triptans are available, sumatriptan and eletriptan. Non-oral routes are also not available in Thailand. The efficacy of triptans has been proven in large placebo-controlled trials of which meta-analyses have been published.[64-67] Triptans can be effective at any time during a migraine attack. However, there is evidence that the earlier triptans are taken, the better their efficacy. Triptans should be taken when the headache is mild, ideally within less than 30 minutes from onset.[74, 75] Triptans are also effective in about 60% of NSAIDs non-responder. All triptans should be used for acute treatment of mild, moderate, and severe migraine unless contraindicated (Level A).[39, 52]

Sumatriptan was the first triptan to be introduced in 1991. Sumatriptan 100 mg (oral form) is significantly more effective than placebo for complete headache relief at 2 and 4 hours. Doses of 50 mg and 100 mg sumatriptan are more effective than dose of 25 mg. Dose of 50 mg is associated with a lower incident of adverse events than the dose of 100 mg.[62, 68] Sumatriptan is extensively metabolized in liver by monamine oxidase-A (MAO-A) and therefore it should not be used in patients who take MAO-A inhibitors.

Eletriptan is rapidly absorbed and has a higher bioavailability (50% vs. 14%) with longer half-life (5.5 hours vs. 2 hours) than sumatriptan.[69] Eletriptan 20, 40, and 80 mg have been studied in double blind, placebo-controlled trials which revealed that eletriptan provided higher favorable outcome compared with placebo. Eletriptan 40 mg is more effective than 20 mg and causes lower side effect than 80 mg dose.[66, 70-73]

Table 3 : Pharmagology and efficacy of triptans in Thailand.[65, 66, 69, 76]

Pharmacokinetics	Sumatriptan	Eletriptan	
Onset of Efficacy (minutes)	45-60	60	
Bioavailability (%)	14	50	
Elimination Routes	Hepatic, MAO	Hepatic (active metabolite) CYP3A4	
Maximum Daily Doses (mg)	200	80	
Efficacy	Sumatriptan	Eletriptan 40 mg	80 mg
Headache response at 2 hours (%)	50-61	65	65-80
Complete relief of pain at 2 hours (%)	29-36	22-41	30-53
Recurrence rate at 24 hours (%)	29-34	19-23	21-33

Active metabolism of eletriptan, N-desmethyl eletriptan, is catalyzed by cytochrome P-450 system (CYP3A4). Thus eletriptan should not be used with potent CYP3A4 inhibitors such as ketoconazole and clarithromycin.

Triptans are contraindicated in those with coronary artery disease, high risk for occult cardiac disease, cerebrovascular disease, peripheral vascular disease, uncontrolled hypertension, and pregnant woman. The most common adverse effects are fatigue, dizziness, asthenia and nausea. Known as triptans sensations, sensation of flushing, chest pain or chest pressure can occur in some cases and those symptoms are mild and usually transient.[64-66]

Contraindication of Triptans

1. Ischemic stroke.
2. Ischemic heart disease.
3. Prinzmetal's angina.
4. Raynaud's disease.
5. Uncontrolled high blood pressure.
6. Severe liver or renal failure.
7. Familial hemiplegic migraine.
8. Basilar type migraine.
9. Pregnancy and lactation.
10. Ergotic alkaloid used.
11. Monoamine oxidase inhibitors used.
12. Caution in selective serotonin reuptake inhiditos (SSRIs) or serotonin/norepinephrine reuptake inhiditos (SNRIs) used.

Conclusion

Migraine is a common, chronic and mostly debilitating neurovascular disorder, which impairs quality of life. Its pathophysiology is still not fully discovered but cerebral hyperexcitability either from genetic mutation or environmental factors can trigger central and peripheral pain pathway. Stratified care is recommended for migraine treatment. Persons with headaches should establish the correct diagnosis and evaluate their level of disability together with impact of migraine, prior to treatment. NSAIDS and ACC are the drugs of choice for those with mild to moderate migraine headaches. Ketorolac is a solely parenteral NSAID recommended for acute migraine treatment. Opioid should be avoided due to sedative side effect and risk of abuse. Intravenous metoclopramide and chlorpromazine can be used in patients with nausea/vomiting and who require parenteral therapy. Triptans are specific treatment for acute migraine headache and should be used in disabling migraineurs in the absence of vascular contraindications.

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Questions of Migraine Headaches

Q1. Which of the following is not a feature of migraine prodrome?

a. Fatigue
b. Muscle aching
c. Increased thirst
d. Visual blurring
e. Irritability

Q2. Which of the following is not true of migraine aura?

a. Aura can occur in isolation without headache phase.
b. Aura phase can occur suddenly.
c. Visual aura is the commonest symptom of aura phase.
d. Unilateral motor weakness is a part of migraine aura.
e. Aura in migraine can be suppressed by antiepileptic medications.

Q3. Which is the best tool for assessing the severity of a migraine attack that occurred in the last month?

a. MIDAS (Migraine Disability Assessment)
b. HIT-6 (Headache Impact Test)
c. Migraine-ACT (Migraine Assessment of Current Therapy)
d. HART (Headache and Assessment of Response to Treatment)
e. PHQ-9 (Patient Health Questionnaire)

Q4. What is the most appropriate oral medication for patient with acute severe migraine attack that interferes with his or her daily activities?

a. Naproxen sodium (Synflex®)
b. Combination of ergotamine, and caffeine (Cafergot®)
c. Eletriptan (Relpax®)
d. Domperidone (Motilium®)
e. Haloperidol (Hadol®)

Q5. What is the most appropriate intravenous medication for acute migraine attack (rescue therapy)?

a. Metoclopramide (Plasil®)
b. Ketorolac (Acular®)
c. Parecoxib (Dynastat®)
d. Meperidine (Pethidine®)
e. Tramadol (Tramol®)

Answers of Migraine Headaches

Answer 1: d. Prodrome includes symptoms which are: psychological (depression, euphoria, irritability, restlessness, hyperactivity, hypoactivity, fatigue, drowsiness), neurological (photophobia, phonophobia, hyperosmia) or general (stiff neck, increased thirst, anorexia, diarrhea, constipation, fluid retention, craving for particular foods, repetitive yawning), and other less typical symptoms. The most common aura symptoms in migraine are visual symptoms including positive (flickering, zig zag line, bright dot, blurring) and negative (scotoma).

Answer 2: b. Acute onset of aura should cause suspicion of causes other than migraine, such as transient ischemic attack (TIA) or seizure aura. Migraine aura is characterized by gradual onset of symptoms in more than 5 minutes. Visual, sensory, aphasic and motor aura are recognized as transient neurological dysfunction in migraine. Aura can occur in isolation without headache. Cortical spreading depression that clinically represented aura can be suppressed by antiepileptic medications.

Answer 3: b. HIT-6 is an easy and reliable tool with which to assess severity and impact of migraineurs in the last month. MIDAS is another tool for assessing severity and impact in migraineurs in the 3 month follow up period.

Answer 4: c. Triptans (Eletriptan, sumatriptan) are recommended in debilitating migraine, according to stratified strategy (level of evidence A). NSAIDs and combination of ergotamine, and caffeine (Cafergot®) can be used in non-disabling migraine attack.

Answer 5: b. Ketorolac is the only parenteral NSAIDs that is approved for acute migraine treatment. Metoclopramide can be used in acute migraine attack because it is binding in a non-selective fashion on dopamine receptors. However, it can cause dystonic reaction, and akathisia. Opioids, such as meperidine, tramadol should be avoided in migraine and other headache treatment because they can induce central sensitization and also have addictive effect.