Rescue Treatment for Migraine Headache in Emergency Department Part 2: Role of Antiepileptic, Magnesium, Corticosteroids, and Discharge Care

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Abstract

Migraine is a common chronic neurological disorder, associated with a high disease-related disability and may lead migraineurs to the Emergency Department (ED). The efficacy of valproate, magnesium sulfate, corticosteroids as the rescue treatment for migraine headaches in ED has been reviewed. Nearly half of patients with migraine headaches discharged from the ED had received neither a specific diagnosis nor appropriate patient education. Hence, discharge planning and a migraine education program at the ED was also highlighted in this article.

Migraine is is one of the most common chronic neurological disorders. It is associated with a high disease-related disability and a significant impact on public health economies.[1-3] Global Burden of Disease studies reported that migraine headache is the third most prevalent disorder in the world. They also ranked migraine as the eighth most burdensome disease, and the seventh highest cause of disability in the world (responsible for 2.9% of all years of life lost due to disability).[4,5] The one year prevalence of migraine in the United States (US) was 11.7% (17.1% in women and 5.6% in men) of the adult population and highest in those aged 30 to 39 years for both men and women.[6] A report from the National Surveillance Studies shows the overall prevalence of migraine or severe headache in adults during the last 3 months was 16.6%. The highest prevalence occurred in females aged 18-44 and the lowest prevalence occurred in males 75 or older.[7] Headaches account for approximately 2.2% of all emergency department (ED) visits.[8] Management of acute migraine in ED is still suboptimal.[9] Migraine-specific medications such as triptans or ergotamine have been used only in few migraineurs who visited ED.[10] Over half of patients used simple analgesics to treat their headache attacks but this is often inadequate.[11] Opioids are commonly prescribed as the first line drug in US and Canadian EDs.[12,13] Rate of opioids prescription for migraine and headaches varied in EDs, ranged from 16% to 72%, which was not only ineffective for migraine headache but also increased risks of abuse, addiction, and contributed to poor clinical outcomes.[14-16]

US Headache Consortium provided the goals for acute migraine treatment as follows 1.) Treat attacks rapidly and consistently without recurrence. 2.) Restore patient's ability to function. 3.) Minimize the use of back-up and rescue medications. 4.) Optimize self-care and reduce subsequent use of resources. 5.) Be cost effective for overall management. 6.) Have minimal or no adverse events.[17]

Specific intravenous (IV) medications for rescue treatment in migraine that are commonly used in ED setting includes dopamine antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, valproate, magnesium, and corticosteroids. We reviewed the efficacy of using dopamine antagonists, NSAIDs, and opioid in the Part 1 entitled The role of dopamine antagonists, NSAIDs, and opioids for rescue migraine treatment in ED (only medications that are available in Thailand)[18] that had been published in

The Bangkok Medical Journal 2014, Volume 7. This is Part 2 and details the efficacy of the other intravenous medications (valproate, magnesium, and corticosteroids) that had been used for rescue treatment of migraine headaches. We also highlighted the importance of appropriate discharge care for migraineurs at the emergence department.

Antiepileptic

Valproate, an antiepileptic medication, had established efficacy for prophylaxis of migraine with and without aura and was also approved by US Food and Drug Administration.[19,20] Intravenous valproate is useful as abortive treatment for acute moderate to severe migraine and even in refractory cases in ED and had been shown to be well tolerated, safe, and with rapid onset of action in several trials.[21-28] Valproate increases gammaaminobutyric acid (GABA) levels, an inhibitory neurotransmitter, by affecting the GABA-ergic enzymatic pathway.[29] This resulted in reduced firing rate of serotonergic cells in the dorsal raphe nucleus, and reduced central activation in the trigeminal nucleus caudalis.[23] Valproate had also been shown to act on the peripheral nerves by reducing neurogenic inflammation through GABA-A receptor antagonism.[30]

A randomized, double-blind study compared the efficacy of 1000 mg IV valproate, 10 mg IV metoclopramide, and 30 mg IV ketorolac for acute migraine treatment in ED. Valproate improved pain score by a mean of 2.8 points (95% CI: 2.3, 3.3) on 0 to 10 scale; those receiving metoclopramide improved by 4.7 points (95% CI: 4.2, 5.2); and those receiving IV ketorolac improved by 3.9 points (95% CI: 3.3, 4.5). IV valproate was less efficacious than IV metoclopramide or IV ketorolac in patients whom presented in ED with acute migraine attack.[31] In a randomized open-label study, valproate 400 mg IV was compared to sumatriptan-metoclopramide (metoclopramide 10 mg IM followed 10 minutes later by 6 mg SQ sumatriptan) in patients with prolonged migraine without aura (more than 4 hours but less than 72 hours). Pain relief at 1 hour (severe or moderate pain to mild pain or none) was observed in 53.3% in the valproate arm and 23.3% in the metoclopramide plus sumatriptan arm ($p = 0.033$), whereas pain relief at 2 hours was reported 60% and 30% respectively ($p = 0$ .037). Dizziness was reported in only one patient in the valproate group.[32]

In a prospective, randomized, double-blind trial in ED that compared 500 mg of IV sodium valproate to 10 mg IV prochlorperazine, the mean change of pain reduction on visual analog scale (VAS) at 1 hour was greater for prochlorperazine (-64.5 vs. -9.0 mm; $p < 0.001$). Median changes over a 60-minute period in VAS for nausea were also significantly different, favoring prochlorperazine over sodium valproate (-35.5 vs. -2 mm; $p < 0.001$). In post hoc analysis, valproate failed to demonstrate significant improvement in pain or nausea over time. In contrast, prochlorperazine showed significant improvement in pain by 30 minutes ($p <0$ .001) and nausea by 15 minutes ($p = 0.002$). Moreover, 79% of patients receiving valproate required rescue treatment compared with 25% of patients receiving prochlorperazine ($p =0$ .001). Sedative side effect was not statistically different between the 2 treatments ($p = 0.603$).[33] Valproate has a favorable side effect profile with lack of sedation, no cardiovascular side effects, no negative interactions with triptans or ergot alkaloids, and no dependence effect. Urine pregnancy test is recommended before use in a woman of child-bearing age. It is contraindicated in pregnancy, hepatic disease, and urea cycle defect.

In summary: IV sodium valproate was substantially less efficacious than IV prochlorperazine, IV metoclopramide, and IV ketorolac.[31,33] IV valproate should not be used as the first-line monotherapy for rescue migraine treatment in ED.[31] Canadian headache society recommended against the use of sodium valproate for the acute treatment of migraine pain in ED (weak recommendation, low quality of evidence).[34]

Magnesium

Magnesium is the second most abundant caution in the intracellular fluids in the human body. It is essential in biochemical and physiological processes especially for neurochemical transmission and muscular excitability.[35] Magnesium may play an important role in both neuronal (cerebral cortex, brainstem) and vascular (the trigeminovascular system) components in migraine pathophysiology and there is a possible relationship between intracellular magnesium levels and the threshold of migraine attacks.[36-38] Magnesium acts on N-methyl-D-Aspartate (NMDA) glutamate receptors to maintain calcium homeostasis, to modulate the release of substance P, and regulate the production of nitric oxide.[39,40] Low magnesium levels can result in opening of calcium channels, increased intracellular calcium, glutamate release, and increased extracellular potassium, which may in turn trigger cortical spreading depression.[38,41-44] In patients with acute migraine headache, 42% reported low intracellular magnesium levels but the total Mg level was normal in most cases.[45] Ionized magnesium levels were low in 45% of women with menstrual migraine attacks, however in menstruating women without migraine only 14% had low ionized magnesium levels.[46]

A case control comparison study in patients presented with a moderate or severe headache of any type reported 80% pain-free within 15 minutes post-infusion with 1 g IV magnesium sulfate ($MgSO_4$) ($p < 0.001$). Migraine-associated symptoms including nausea, photophobia and phonophobia were also completely eliminated. Low ionized magnesium was found in 37.5% of non-responders compared with 89% in those that had sustained pain-free

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at 24 hours. Almost all patients experienced flushing during magnesium infusion.[47] A randomized, single-blind, placebo-controlled trial compared 1 g IV $MgSO_4$ with IV placebo/normal saline (NS) in patients with moderate or severe migraine attacks. Pain-free and symptom-free after treatment with IV $MgSO_4$ was reported in 87% of the patients and 0% for placebo ($p < 0.0001$). Accompanying symptoms disappeared in all patients after IV $MgSO_4$ compared with 20% for placebo ($p < 0.0001$). Mild side effects such as flushing and burning sensation in face/neck were experienced by 86.6% of the patients and asymptomatic slight drop in systolic blood pressure (5 to 10 mmHg) by 13%.[48]

Magnesium sulfate 2 grams IV was compared with placebo/NS IV as an adjunctive medication in randomized double-blind, placebo-controlled study. All patients received 20 mg IV of metoclopramide (repeated up to 60 mg). Pain reduction (measured by VAS) was not different between two groups (magnesium -55 vs. placebo -71), but the proportion that returned to normal function was greater for placebo group (magnesium 8% vs. placebo 17%; $p < 0.05$).[49] The efficacy of magnesium in acute treatment of pain and associated symptoms in patients with migraine with and without aura was performed in randomized, placebo-controlled, double-blind fashion. Magnesium sulphate 1 g IV was compared with placebo/NS IV: in the migraine with aura group, statistically significant improvement of pain, nausea, photophobia and phonophobia compared with controls were reported (50% vs. 13.3%; $p <0 .05$). In the migraine without aura group, there was no statistically significant difference in pain relief and nausea improvement but there was significantly lower intensity of photophobia and phonophobia. Greater response in all symptoms in the migraine with aura group than in the migraine without aura group was observed.[50]

A randomized, placebo-controlled, double-blind study compared the effectiveness of $MgSO_4$ 2 g IV with metoclopramide 10 mg IV and with placebo/NS IV for acute migraine treatment in ED. Mean pain reduction was similar for metoclopramide vs. magnesium vs. placebo (mean VAS -38 vs. -33 vs. -24), but a smaller percentage in the metoclopramide and magnesium groups required rescue medications vs. the placebo group (38% vs. 44% vs. 65%; $p = 0.04$). The recurrent rate in 24 h was not statistically significant between the groups. However, the placebo group required rescue medication more than the others. Dystonia was reported in 3% of metoclopramide group, and flushing was reported in 8% of magnesium group.[51] A prospective study compared $MgSO_4$ 2 g IV with prochlorperazine 10 mg IV in ED patients with acute headache. VAS was obtained at 30 minutes after infusion, mean pain reduction was greater for prochlorperazine than for magnesium (47 mm vs. 24 mm, t = 0.208, $p = 0.045$). Prochlorperazine provided greater headache relief than magnesium (90% vs. 56%; $p = 0.038$). Dysphoria was reported in 1 patient (5%) with prochlorperazine, and IV burning pain in 4 patients (25%) with magnesium.[52] Magnesium has a minimal side effect profile. The common adverse effects were flushing, loose stool, and temporary blood pressure lowering. Magnesium is safe to use in children and pregnant women who have acute migraine attack.

In summary: IV magnesium sulfate can be an effective agent in migraine treatment, either alone or in combination with other medications, especially in patients who have aura.[53] Photophobia, phonophobia, and nausea can be reduced with IV magnesium in all migraineurs.[50] However, a recent meta-analysis failed to demonstrate the statistically significant pain relief of intravenous magnesium over placebo, metoclopramide or prochlorperazine for the treatment of acute migraine in adult patients. This meta-analyses also showed no benefit in terms of the need for rescue medication and patients were more likely to report significant adverse events when treated with magnesium.[54]

Corticosteroids

Intravenous or oral corticosteroids are typically used as rescue therapy for migraine headaches.[55] Corticosteroids have been used in the management of status migrainosus, bridging therapy during the detoxification in patients with medication overuse headache, and treatment of immunosuppressant-induced headache in organ transplant recipients.[17,56,57] The role of corticosteroids in acute migraine is limited. Evidence from meta-analysis of randomized controlled trials (RCTs) suggested that parenteral dexamethasone, a potent anti-inflammatory corticosteroid with almost no mineralocorticoid effect, did not significantly reduce pain scores before discharge from ED; however it could reduce the rate of headache recurrence within 72 hours of initial abortive therapy.[58] Recurrence of headache after ED treatment is one of the major concerns in migraine management. The rate of moderate or severe recurrent headache was reported up to 70% of all patients within 24-48 hours after ED discharge.[10,59,60] Neurogenic inflammation had been proposed as a one of the important mechanisms in migraine generation and relapse.[61-63] Corticosteroids can suppress the sterile neurogenic inflammation and reduce trigeminal sensitization in underlying pathophysiology of migraine.[64,65] Steroids are frequently used in ED to reduce the likelihood of headache recurrence and ED revisit.[66]

Pooled data meta-analysis and systematic review from 8 high-quality RCTs with a total of 905 patients suggested a significant benefit of corticosteroids compared with placebo in addition to standard abortive therapy for acute migraine management in ED (RR = 0.71; 95% CI: 0.59, 0.86). The estimated number needed to treat (NNT) to prevent one moderate or severe recurrent headaches were 10 (95% CI: 6, 22). Adverse events of steroids are benign

and not significant except for dizziness (RR = 2.78; 95% CI: 1.02, 7.61). Subgroup comparison between those who received parenteral versus oral dexamethasone treatment showed no significant difference between patients who received oral steroids and parenteral steroids treatment for the primary outcome of moderate or severe migraine headaches (RR = 0.82; 95% CI: 0.53, 1.27; p = 0.37). A trend of dose-dependent effect of dexamethasone was observed, dosage of greater than 15 mg showed higher efficacy than those less than 15 mg. However, this is not statistically significant.[67]

Side effects of single dose corticosteroids were relatively mild and not significant except for dizziness. However dexamethasone should be used with caution in the elderly, in patients who have diabetes, congestive heart failure, and a history of gastrointestinal ulcer or perforation.

In summary: the data of using corticosteroids for acute migraine headache treatment was limited. However, meta-analysis showed the benefit of added-on intravenous or oral dexamethasone to standard headache abortive therapies in terms of reducing the rate of headache recurrence at 24-48 hours after ED discharge. Side effects were mild and not significant except for dizziness.

Discharge care

Discharge planning and management of migraine in the ED seems to be ineffective due to underdiagnosis, inappropriate prescription of acute and prophylactic medications, or lack of patient education.[9-12] Forty two percent of patients were discharged from the ED without a proper and specific diagnosis[68] and only 20% of patient was headache-free on discharge from ED.[10] In patients who left ED with residual headache, 60% experienced persistent headache.[60] Up to 73% of all patients reported that the headache returned within 24-48 hours after ED discharge.[59] Moreover, at the time of discharge, 24% of patients received no prescriptions and 33% received no follow-up appointments.[68,69]

Effective migraine management requires accurate diagnosis, initiation of appropriate acute and prophylactic medications, patient education, and follow up plan. Migraine educational programs can help decrease headache frequency, reduce migraine-related disability scores, improve quality of life, and improve in cognitive and emotional aspects.[70,71] Active intervention programs including intensive patient education (involving the topics of migraine biogenesis, acute treatment of migraine, and prevention of migraine) can decrease migraine frequency, migraine disability, increase quality of life, and reduce their utilization of headache resources.[72]

Screening for psychiatric conditions is considered in all headache patients because of the high prevalence of psychiatric comorbidity in migraine populations, especially depression and anxiety.[73-77] A prospective cohort study in the Women's Health Study reported in the association between migraine and depression. The adjusted relative risks of incident depression were 1.53 (95% CI: 1.35, 1.74) for migraine with aura, 1.40 (95% CI: 1.25, 1.56) for migraine without aura, and 1.56 (95% CI: 1.37, 1.77) for persons who had past history of migraine compared to no history of headache.[78] Severity of depression was also associated with an increased risk of transformation from episodic to chronic migraine.[79] Migraine and psychiatric comorbidity are in bidirectional association, treatment of the psychiatric comorbidity will improve migraine and vice versa.[80,81]

Conclusion

The ideal rescue therapy for migraine in ED is to administer medicines which provide rapid, complete relief of headache and associated migraine symptoms, restore functional ability, with minimum adverse effects and without recurrence of headache after ED discharge.[82,83] Dopamine antagonists (chlorpromazine and metoclopramide) and parenteral NSAIDs (ketorolac) are recommended as the first line rescue medications for migraine in emergency setting.[34,84] Adequate hydration will promote rapid recovery. Healing environments such as a quiet room with suitable light should be provided to migraineurs with photophobia and phonophobia. Discharge planning, patient education and early detection of psychiatric comorbidity play crucial roles for enhancing treatment outcomes and for preventing transformation from episodic to chronic migraine.

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