



Non-opioid Intravenous Drugs for Pain Management in Patients Presenting with Acute Migraine Pain in the Emergency Department: A Comprehensive Literature Review

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Abstract

Context: Migraine is one of the most common causes of disability worldwide and the sixth cause of loss of life years due to disability. Migraine is reported mainly in young and middle-aged people, so it can cause a person to face many problems in doing daily tasks. The emergency department annually accepts 1.2 million patients with migraine. Therefore, timely diagnosis of the disease, knowledge of valuable drugs in an emergency, knowing how to use them, and finally, early treatment can play an essential and decisive role in improving patients' symptoms and reducing the disability caused by the disease. An essential and valuable drug category in the emergency department to manage pain is non-opioid intravenous (IV) drugs. Therefore, this study aimed to evaluate non-opioid IV drugs to manage pain in patients with acute migraines in the emergency department.

Method: This study conducted a comprehensive literature review to access the latest scientific studies and documents using keywords (acute migraine, non-opioid IV drugs, pain management) in reliable databases such as PubMed, Scopus, Web of Science, Cochrane, and Google Scholar. We reviewed 87 articles, 53 of which were evaluated and compared.

Results: A review study considers intravenous acetaminophen as a suitable option for the first-line treatment of acute migraine in the emergency department if the patient does not tolerate aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Various studies have obtained positive effects of NSAIDs and dihydroergotamine (DHE) in treating acute migraine. Prescribing anti-dopaminergic drugs can effectively reduce associated symptoms such as nausea and vomiting. Dexamethasone and magnesium sulfate are effective in preventing migraine and severe attacks. Intravenous sodium valproate is effective in moderate to severe migraine attacks or treatment-resistant migraines. In the emergency department, prescribing intravenous haloperidol, lidocaine, and propofol can help manage migraine and improve other associated symptoms, such as nausea or vomiting.

Conclusions: Non-opioid IV drugs are essential to manage pain and improve other migraine symptoms in the emergency setting. Knowing the above drugs and their optimal use has a decisive role in managing patients with acute migraine in the emergency department.

Keywords: Acute Migraine, Emergency Department, Pain Management

1. Context

Migraine is a primary headache disorder classified as one of the most common causes of disability worldwide and the sixth cause of loss of life years due to disability. According to the available data, 18 - 26% of women and 6 - 9% of men have experienced a migraine at least once (1).

According to a study conducted in the United States, one out of every six people is affected by migraine (2). Migraine affects mainly apparently healthy and middle-aged people. It is estimated that 1.2 million visits to the emer-

gency department occur annually due to migraine (3). This disease is considered the fourth or fifth reason for emergency department visits.

The highest prevalence of migraine has been reported in people aged 18 to 44, and 17.9% of such people have experienced an acute migraine at least once in the last three months. Migraine prevalence decreases with age so that its prevalence is reported to be 15.9% in the age range of 54 - 64 years, 7.3% in the age range of 65 - 74 years, and 5.1% in the age range of 75 years or older (2, 4).

Considering that the highest prevalence of migraine occurs in the age group when people are most active and influential in society, we need timely and correct treatment that has a positive and fast effect and, at the same time, does not raise the concern of abuse. Therefore, this study aimed to evaluate non-opioid intravenous (IV) drugs to manage pain in patients with acute migraine pain in the emergency department.

2. Migraine Diagnosis

Migraine is a primary headache disorder usually characterized by frequent attacks. Sometimes, due to its many differential diagnoses, diagnosing and identifying migraine are challenging. In this case, in addition to the patient's pain tolerance, his treatment approach varies such that some first-line treatments will no longer be effective (5). Therefore, it is essential to identify the symptoms and make a timely diagnosis.

One of the crucial ways to diagnose this disease is based on the word POUND (6). The heading of the word POUND and the corresponding table are (Table 1):

P: Pulsatile quality of headache

O: One-day duration of the headache

U: Unilateral headache

N: Nausea or vomiting

D: Disabling intensity of the headache

Table 1. Probability of Migraine Diagnosis Based on Number of Symptoms in Patients According to the Keyword POUND

| Number of Existing Symptoms | Possibility of Migraine (%) | |
|-----------------------------|-----------------------------|-------|
| | Men | Women |
| 4 - 5 symptoms | 60 | 81 |
| 3 symptoms | 18 | 38 |
| 0 - 2 symptoms | 2/5 | 6/7 |

In discussing migraine diagnosis, other differential diagnoses should also be considered. The presence of accompanying comorbidities such as depression can make the diagnosis difficult in many cases and change the treatment approach. Taking a detailed history and clinical examinations can help reach the final diagnosis and choose the appropriate treatment method (7, 8).

3. Migraine Treatment

The evidence-based guidelines of the United States, Canada, and Europe consider lifestyle changes, increasing physical activity, and drug recommendations as the principles of acute migraine treatment (8, 9). Consuming nutritious and timely meals, reducing the consumption of food

additives and artificial sweeteners, and managing and controlling caffeine consumption are nutritional principles that should be considered in treating and preventing migraine attacks (10). Walking daily for at least 30 minutes and increasing physical activity are the measures that, in addition to direct effects, can be effective in managing migraine attacks by managing stress and mental tension (11).

Drug recommendations are one of the essential principles of migraine treatment. It is better to start drug therapy early in a headache attack to prevent disabilities, side effects, and high costs and preserve the person's daily function. In the meantime, for better treatment effectiveness and patient confidence, the patient should know about his condition, treatment strategy, side effects of drug overuse, and the possibility of acute migraine turning into chronic (8).

Different drugs with different administration methods and pharmacokinetics are used to treat migraine. Among these drugs, we can mention acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), sumatriptan, rizatriptan, zolmitriptan (which belong to the triptan family), dihydroergotamine, antiemetic drugs (dopamine antagonists), ketorolac, promethazine, dexamethasone, intravenous magnesium sulfate, and sodium valproate.

Another category of drugs in treating migraine are opioids, including butorphanol, codeine, tramadol, and meperidine. Due to the high possibility of abuse, respiratory depression, and the reduced response to treatment, this category of drugs is not recommended as a routine treatment method, especially in the emergency department (12).

As migraine complaints are one of the most common reasons for going to the emergency department, this study reviews non-opioid IV drugs to manage pain in migraine patients. Choosing the right treatment strategy for each patient should be done according to the symptoms, disease history, and available facilities.

4. Migraine Treatment in Emergency Departments

4.1. Intravenous Fluid (IVF)

Various studies show that intravenous fluid (IVF) has not significantly affected treating patients with acute migraine. Richer et al. showed that using IVF alone has few effects, and even if the symptoms are reduced, the probability of migraine attack recurrence after discharge from the emergency department is about 33% (13). In another study of 570 patients, IVF injection alone could not reduce the pain severity or relieve the symptoms (14, 15).

4.2. Acetaminophen

Different findings have been reported regarding the administration of intravenous acetaminophen. In a study, acetaminophen 1000 mg alone intravenously was not superior to placebo in patients with severe acute migraine (16). A systematic review study recommends intravenous acetaminophen 1000 mg as a suitable option for the first-line treatment of acute migraine in the emergency department if the patient does not tolerate aspirin or NSAIDs. In terms of effectiveness, pain reduction, and response to treatment, acetaminophen combined with metoclopramide is far better than acetaminophen alone. However, other treatment approaches are more effective in the absence of contraindications (17).

4.3. NSAIDs

Various studies have obtained positive results from using NSAIDs to treat acute migraine (18).

4.3.1. Dexketoprofen

Administration of dexketoprofen with a dose of 50 mg/50 mL of saline is an effective treatment option that improves symptoms within 48 hours and reduces the duration of hospitalization in the emergency department and the need for rescue drugs. Due to the low side effects of this drug, its use is recommended to manage the pain of patients with acute migraine in the emergency department (19-21). Gastrointestinal disorders and bleeding are more in dexketoprofen than in other NSAIDs (22). The first line for preventing dexketoprofen-induced gastrointestinal bleeding is proton pump inhibitor (PPI) (23).

4.3.2. Aspirin

Intravenous aspirin with a dose of 1000 mg has effectively reduced pain and improved other associated symptoms in acute migraine attacks. However, this drug should be used with great caution in people with blood problems such as thrombocytopenia, bleeding disorders, or digestive problems (24-27).

4.3.3. Ketorolac

Intravenous ketorolac is an influential factor in reducing patients' symptoms. This drug is much more effective than samaritan and has less potentially addictive effects than other drugs (28). No significant difference was found between ketorolac, dexamethasone, metoclopramide, and chlorpromazine in the reduction of symptoms and pain relief one and 24 hours after the start of treatment (29). Despite these benefits, ketorolac, with a dose of 30-60 mg intravenously or intramuscularly, is classified as an injectable NSAID with level C evidence (30).

4.4. Dihydroergotamine (DHE)

One of the effective drugs in treating acute migraine, especially with associated symptoms such as nausea and vomiting, is intravenous dihydroergotamine (DHE). The European Federation for Neurological Sciences (EFNS) and the American Headache Society (AHS) have recommended using DHE in patients with acute migraine. It can be administered intravenously with a dose of 0.5 - 1 mg every eight hours for 3 - 5 days of hospitalization. According to studies, using DHE in the emergency department as a single drug is less effective than sumatriptan, but if combined with antiemetic drugs, especially metoclopramide, it can be more effective in reducing symptoms (31, 32).

Several issues should be noted regarding DHE. First, due to the prohibition of this drug during pregnancy, it is better to do a beta human chorionic gonadotropin (β hCG) test in case of suspicion of pregnancy. Second, the doctor must ensure that the patient has not taken any medicine from the Triptan family in the last 24 hours. Third, it is better to prescribe intranasal DHE for three days or an analgesic such as acetaminophen during discharge to prevent migraine recurrence. Fourth, DHE can lead to side effects such as leg cramps and tingling of the limbs (due to its vasoconstrictive properties). Therefore, in case of overdose symptoms, the drug's dose should be reduced, or its use should be stopped altogether (7, 33). However, dihydroergotamine may cause nausea, lightheadedness, previous headache exacerbation, and new-onset headache. A combination of dihydroergotamine with metoclopramide controls the symptoms and the side effects of DHE, like nausea (34).

4.5. Anti-dopaminergic Drugs

Prescribing anti-dopaminergic drugs, in addition to improving migraine headaches, can also effectively reduce associated symptoms such as nausea and vomiting. Therefore, it is a suitable option for prescribing in the emergency department. However, at the same time, its extrapyramidal side effects, such as akathisia or tardive dyskinesia, should be noticed. Prophylactic use of diphenhydramine can be effective in reducing its extrapyramidal side effects (35, 36).

4.5.1. Metoclopramide

Intravenous metoclopramide with a dose of 10 - 20 mg is a suitable option for managing patients in the emergency department. Friedman et al. showed that the therapeutic effects of intravenous metoclopramide are much greater than those of sodium valproate injection. Metoclopramide outperformed ketorolac due to the improvement of headaches and other accompanying symptoms such as nausea and vomiting (37).

On the other hand, using IV metoclopramide is preferable to some non-pharmacological treatment approaches, such as greater occipital nerve blocks (GONB), so using these modalities is generally recommended after IV metoclopramide (38, 39). In general, intravenous metoclopramide is widely used in the pain management of patients in the emergency department due to its appropriate and rapid effectiveness, low side effects, and managing other symptoms associated with acute migraine (37).

4.5.2. Chlorpromazine

Chlorpromazine IV 10 mg is a good choice for acute migraine management. The administration of this drug has significantly led to pain relief one and 24 hours after the start of treatment (29). In clinical trials, it has been suitable for managing patients' pain with acute migraine attacks. The vital point is that the prescription of this drug in borderline hypotensive patients should be done with great caution (40).

4.5.3. Prochlorperazine

Administering prochlorperazine IV with a dose of 10 mg effectively reduces pain and the need for administering rescue drugs (41, 42). This drug is placed in level B evidence (30). Prochlorperazines' most important side effects are extrapyramidal disorder and skin diseases with unknown pathology (43).

4.5.4. Droperidol

Droperidol is a dopamine receptor antagonist, which can also have antagonistic properties for serotonin and α_2 histamine receptors. Despite the low use of this drug in the past years, intravenous droperidol with a dose of 2.5 mg is recently recommended as one of the appropriate treatment options to improve patients with acute migraine attacks in the emergency department (44, 45).

In Wang et al. study, IV droperidol with a dose of 2.5 mg every 30 minutes led to pain relief in 72% of patients with acute migraine and 90% of patients with refractory migraine. Other studies have been in line with these results (46).

The critical point is paying attention to the side effects of this drug, such as low blood pressure and the possibility of a prolonged QT interval. In the case of any of the above side effects, it is better to reduce the drug dose or stop it if necessary.

4.6. Magnesium Sulfate

Intravenous magnesium sulfate is primarily used in pregnancy, heart disease, and acute pulmonary disease (47). Magnesium deficiency is one of the essential pathophysiologicals in the occurrence of migraine. Prescribing

intravenous magnesium sulfate with a dose of 1 - 2 g is effective in pain relief after one hour, reducing the period of aura and the need to take painkillers (48).

The studies have considered this drug preferable to ketorolac, intravenous caffeine, dexamethasone, and metoclopramide in the emergency department (49). On the other hand, studies such as Baratloo et al. have found magnesium sulfate effective in managing patients' pain in the emergency department (50).

American Headache Society (AHS) has considered intravenous magnesium sulfate in level B evidence for treating acute migraine (48). Therefore, considering the low side effects, this drug can be used in a wide range of patients (51-53).

4.7. Dexamethasone

Intravenous dexamethasone 10 mg as a single dose is used to manage the pain of patients with acute migraine in the emergency department. This drug effectively prevents migraines and severe attacks (54) and is more effective than morphine in managing the symptoms of patients (55). Repetitive IV dexamethasone therapy with a dose of 10 - 20 mg can prevent the prolongation of migraine attacks in non-hospitalized patients (56).

Some studies classify dexamethasone as level B evidence for preventing and managing pain in patients with acute migraine (30). Using intravenous dexamethasone and adding it to the treatment regimen is also recommended in chronic and prolonged migraines (more than 72 hours) (57). Notably, this drug should not be used for a long time due to the high side effects of its systemic use.

4.8. Sodium Valproate

Sodium valproate IV with a dose of 500 - 1000 mg is a safe drug that patients will tolerate. Prescribing this drug in the emergency department can quickly manage the patient's symptoms. Intravenous sodium valproate is effective in moderate to severe migraine attacks or treatment-resistant migraines. In addition to its therapeutic effects, the FDA has approved this drug for migraine prophylaxis (58). In the meantime, two symptoms of migraine, photophobia, and phonophobia, which can disrupt a person's daily functioning, are well managed by this drug and are resolved within 30 minutes to one hour.

Bakhshayesh et al. compared the effectiveness of valproate, sumatriptan, and metoclopramide in managing acute migraine symptoms. Meanwhile, injectable sodium valproate more effectively manages patient symptoms (59).

4.9. Haloperidol

Intravenous haloperidol with a dose of 5 mg is an effective drug in an emergency. In addition to reducing headaches in acute attacks, prescribing this medicine can improve other associated symptoms, such as nausea or vomiting. Gaffigan et al. showed that in comparison between intravenous haloperidol with a dose of 5 mg and intravenous metoclopramide with a dose of 10 mg, the need for rescue medication was less in haloperidol (60).

Due to side effects such as postural hypotension, the prescription of this drug in patients with cardiovascular problems should be done with many considerations (61). In psychiatric patients, the prescription of this drug should be done in consultation with the relevant doctor. Considering the small number of studies in this regard, designing and implementing clinical trial studies can be instrumental in clarifying the different aspects of prescribing this drug in the emergency department.

Side effects were reported after haloperidol injection, such as intraventricular hemorrhage, some EKG changes like long QT and torsade's de points, catatonia, and extrapyramidal disorder (62). Cardiac monitoring is recommended to prevent and control the cardiac disorder of haloperidol. Nevertheless, an intravenous haloperidol dose of less than 2 mg can be injected without EKG monitoring (63).

4.10. Ketamine

There is a disagreement regarding administering intravenous ketamine to manage migraine symptoms in the emergency department. Some studies, such as Etchison et al., show that not only the administration of low-dose intravenous ketamine in the emergency department (0.2 mg/kg) did not have a significant difference with placebo in reducing symptoms but also the generalized discomfort 30 minutes after the start of treatment was more in the group that received ketamine (64). At the same time, some other studies show that administering this drug in the emergency department, in addition to being well tolerated by patients, is effective in reducing symptoms (65-69).

There is also a disagreement regarding the dosage of this drug, but it is usually started with a dose of 0.2 mg/kg IV, and the dose can be increased every 1-4 hours by 0.05-0.1 mg/kg/h to reach the maximum dose of 1 mg/kg/h. Ketamine has side effects such as nystagmus and hallucination, which can be managed by reducing the drug dose or prescribing lorazepam (65, 66). Compiling clinical trial studies can help clarify all aspects of using intravenous ketamine in the emergency department and determine its appropriate and effective dose.

4.11. Lidocaine

Using intravenous lidocaine, like its other pharmaceutical forms, can help manage patients' symptoms in the emergency setting (70-72). Intravenous lidocaine with a dose of 1 mg/kg bolus and then 2 mg/min as an infusion can effectively manage patients' pain. Some studies show that administering intravenous lidocaine to reduce patients' pain has a moderate and incomplete effect (73, 74).

4.12. Propofol

Propofol is a fast-acting intravenous drug. Using propofol with a dose of 40-60 mg in the emergency department as a bolus or repeated doses can improve the pain and other symptoms of patients and ultimately accelerate the discharge process of patients. Propofol can reduce migraine attacks in patients after discharge from the emergency department. The most common complication of IV propofol is mild sedation in patients, which resolves without special measures (75).

Overall, propofol can be an effective treatment, especially in patients with contraindications to receiving other drugs or people with recurrent or treatment-resistant migraine (76, 77).

For a better summary, the non-opioid IV drugs used in the emergency department for pain management in patients with migraine attacks are summarized in Table 2.

5. Conclusions

Non-opioid IV drugs are essential to manage pain and improve other migraine symptoms in the emergency setting. Knowing the above drugs and their optimal use is decisive in managing patients with acute migraine in an emergency. This study assessed 16 non-opioid IV drugs used in the emergency department to manage patients' pain with acute migraine. The drug selection can vary depending on the patients' symptoms, drug records, and previous diseases. However, it should be considered that the right choice of medicine and the timely start of treatment, especially in the emergency department, can play a decisive role in the recovery of patients and prevent disability and depression in the years of life.

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Footnotes

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Table 2. Intravenous and Non-opioid Drugs for Pain Management in Patients with Acute Migraine in the Emergency Department

| Medicine Name and Authors | Year of Study | Type of Study |
|--------------------------------|---------------|--------------------------------------|
| IVF (intravenous fluid) | | |
| Balbin et al. (14) | 2015 | Analysis of clinical trial |
| Jones et al. (15) | 2018 | RCT |
| Acetaminophen | | |
| Derry and Moore (17) | 2013 | Systematic review |
| Leinisch et al. (16) | 2005 | RCT |
| Dexketoprofen | | |
| Yang et al. (19) | 2019 | Meta-analysis |
| Gungor et al. (21) | 2014 | RCT |
| Aspirin | | |
| Leniger et al. (25) | 2004 | RCT |
| Taneri and Petersen-Braun (24) | 1995 | RCT |
| Ketorolac | | |
| Khazaei et al. (29) | 2019 | RCT |
| Taggart et al. (28) | 2013 | Systematic review |
| Dihydroergotamine | | |
| Scherl and Wilson (31) | 1994 | RCT |
| Colman et al. (32) | 2005 | Systematic review |
| Metoclopramide | | |
| Friedman et al. (38) | 2020 | RCT |
| Cameron et al. (39) | 1994 | RCT |
| Chlorpromazine | | |
| Khazaei et al. (29) | 2019 | RCT |
| Hodgson et al. (40) | 2021 | RCT |
| Prochlorperazine | | |
| Golikhathir et al. (41) | 2019 | Systematic review and meta-analysis |
| Hodgson et al. (40) | 2021 | RCT |
| Droperidol | | |
| Wang et al. (46) | 1996 | Open-label pilot study |
| Gaw et al. (45) | 2020 | Observational cohort study |
| Magnesium sulfate | | |
| Demirkaya et al. (51) | 2001 | RCT |
| Baratloo et al. (50) | 2017 | Prospective quasi-experimental study |
| Dexamethasone | | |
| Singh et al. (54) | 2008 | Systematic review and meta-analysis |
| Taheraghdam et al. (55) | 2011 | RCT |
| Sodiumvalproate | | |
| Ghaderibarmi et al. (58) | 2015 | RCT |
| Bakhshayesh et al. (59) | 2013 | Randomized open-label study |
| Haloperidol | | |
| Gaffigan et al. (60) | 2015 | RCT |
| Fisher (61) | 1995 | Case series |
| Ketamine | | |
| Etchison et al. (64) | 2018 | RCT |
| Lauritsen et al. (65) | 2016 | Case series |
| Lidocaine | | |
| Reutens et al. (73) | 1991 | RCT |
| Jauslin et al. (74) | 1991 | Uncontrolled retrospective study |
| Propofol | | |
| Soleimanpour et al. (77) | 2012 | RCT |
| Mitra et al. (76) | 2020 | RCT |