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Opioids in Pain Management for Acute Gout: Friend or Foe?

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A B S T R A C T

Intense and severe pain is the most common symptom of acute gout arthritis (GA) flare. A recent study revealed that opioids were commonly prescribed for 28% of acute GA flare cases. This paper aims to explain current evidence on opioid use in managing acute gout. This literature review was constructed based on a literature search on PubMed and Google Scholar in June 2022. We included all relevant studies, cohorts, and randomized controlled trial articles published in the last ten years. Meanwhile, pre-print or non-English articles were excluded. The evidence regarding opioid use for acute gout pain was rare. No guidelines recommend opioids as an initial analgesic choice in managing pain for acute gout. Opioids are indicated in acute gout patients with severe kidney dysfunction if oral and intra-articular corticosteroids are ineffective in reducing pain. Opioids should be the last choice in selected cases of acute gout.

INTRODUCTION

Gout arthritis (GA) is inflammatory arthritis caused by uric acid deposit-induced inflammation. It is most common in adults. The estimated global prevalence of GA is 1-4%, with an incidence rate of 0.1-0.3%. Subsequently, each decade of life increased its prevalence (more than 10%) and incidence (more than 0.4%). In addition, males have a higher risk of GA than females, with a comparison of 10:1 (Singh and Gaffo, 2020).

Gout has four clinical spectrums, asymptomatic hyperuricemia, acute gout, Intercritical period, and chronic tophaceous gout. Intense and severe pain is the most prominent symptom of acute gout, followed by cardinal signs of inflammation (Stewart *et al.*, 2020). The flare usually affects the lower extremities in 73% of the cases at the first metatarsophalangeal joints (Stewart *et al.*, 2016). Pain management is essential in acute flare. Current guidelines recommend colchicine, NSAIDs, or corticosteroids as initial pain treatment (Perhimpunan Reumatologi Indonesia, 2018).

Opioids are drugs that regulate opioid receptors, commonly in pain modulation. They frequently manage pain in postoperative, cancer, and chronic disease, especially in moderate to severe pain (Mikosz *et al.*, 2020). A recent study revealed that opioids were commonly prescribed for 28% of acute GA flare cases (Dalal *et al.*, 2020). Therefore, this paper aims to explain current evidence on opioid use in managing acute gout.

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METHOD

This literature review was constructed based on a literature search on PubMed and Google Scholar in June 2022. Keywords were acute gout, pain management, opioid, and analgesic, and its synonym to identify relevant articles. In addition, Boolean operators were used to specify the search. We included all relevant reviews, cohorts, and randomized controlled trial articles published in the last ten years to describe and explain the risk-benefit of opioid usage in managing acute gout flare. Meanwhile, pre-print or non-English articles were excluded.

RESULT AND DISCUSSION

URIC ACID, HYPERURICEMIA, AND GOUT ARTHRITIS

Uric acid (UA) is the end-product of purine metabolism with a molecular weight of 168 Da. Animal proteins are the exogenous source of purine, while nucleic acid from damaged or viable cells is the endogenous source. Adenine and guanine from purine undergo a deamination and dephosphorylation process. Then, both transform into inosine and guanosine. Subsequently, the phosphorylation process by nucleoside phosphorylase converts inosine to hypoxanthine and guanosine to guanine. Finally, a key enzyme, xanthine oxidase, takes the final step by converting hypoxanthine to xanthine, followed by xanthine to UA. In addition, guanine deaminase produces xanthine from guanine and, followed by oxidation by xanthine oxidase, produces UA (El Ridi and Tallima, 2017).

Physiologically, the majority form of UA is urate which is distributed in serum and excreted through the urinary system. The normal level of serum UA is 1.5-6.0 mg/dL in male and 2.5-7.0 mg/dL in female. The regulation of UA concentration is dependent on its production and elimination. Overproduction due to a purine-rich diet or reduced elimination due to kidney diseases leads to increased UA concentration. Despite numerous laboratory definitions, hyperuricemia commonly defines as a serum UA level above 7 mg/dL (Jin *et al.*, 2012; Skoczyńska *et al.*, 2020).

Uric acid has limited solubility in the blood. Serum levels above 6.8 mg/dL would induce UA crystallization in the kidney, soft tissue, and joints. The most common crystal form is monosodium urate (MSU) (Skoczyńska *et al.*, 2020). MSU accumulation in the joints potentially initiates a sterile-inflammatory process and causes arthritis or gout arthritis (GA). However, prior studies hypothesized that MSU accumulation alone could not induce GA (Desai, Steiger, and Anders, 2017; Zhang, 2021). The activation of the immune system also plays a significant role in GA development. The MSU-coated serum protein induces NOD-like receptor P3 (NLRP3) inflammasome activation followed by cleavage of pro-interleukin (IL)-1β maturation and activation. The IL-1 β initiates neutrophil-macrophage recruitment, reactive oxygen species (ROS) production, and other inflammatory substances. The crosstalk between

MSU with these inflammation processes is the leading cause of acute GA (Desai, Steiger, and Anders, 2017; El Ridi and Tallima, 2017).

Gout has four clinical spectrums, asymptomatic hyperuricemia, acute gout, Intercritical period, and chronic tophaceous gout. Intense joint pain is the most prominent symptom during acute gout. A previous study showed pain intensity of acute gout was 6.9-7.1 using a 0-10 scale numeric rating scale (Roddy *et al.*, 2020). In addition, other inflammation signs such as a tumor, rubor, and color were also present in the joint. The flare involved a single joint, and about 73% of cases involving metatarsophalangeal joint or podagra (Stewart *et al.*, 2016; Ragab, Elshahaly, and Bardin, 2017).

CURRENT PAIN MANAGEMENT FOR ACUTE GOUT

The principles in acute gout treatment are pain management and urate-lowering therapy. The Indonesian Rheumatology Association (IRA), American College of Rheumatology (ACR), and European League Against Rheumatism (EULAR) strongly recommend three medications for acute GA flare. The therapies are colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and steroids (Richette *et al.*, 2017; Perhimpunan Reumatologi Indonesia, 2018; FitzGerald *et al.*, 2020).

Colchicine is a drug of choice in managing flares that occur in less than 12 hours. Colchicine binds to tubulin and inhibits microtubule formation. The microtubule disruption leads to less inflammatory activation by leukocytes (Leung, Yao Hui, and Kraus, 2015). An initial dose of colchicine 1 mg is administered during the acute phase, followed by an additional 0,5 mg in the next hour. Subsequently, colchicine is recommended with NSAIDs or steroids (Perhimpunan Reumatologi Indonesia, 2018).

NSAIDs are also effective in managing pain during acute flares independent of its onset. The CONTACT trial is a multicenter study comparing naproxen as an NSAID with low-dose colchicine as the first-line treatment of acute flares in primary care (Roddy *et al.*, 2020). The naproxen was administered by an initial loading dose of 3x250 mg, followed by 250 mg/8 hours for seven days, while colchicine was administered at 0.5 mg/8 hours for four days. The results showed that naproxen and colchicine exhibited similar analgesic effects (adjusted mean difference: -0.18, 95%CI: -0.53─0.17, p=0.32). Interestingly, the study recommended naproxen as the first-line treatment since naproxen was cost-effective and had fewer additional analgesic usage and side effects. In addition, non-selective NSAIDs such as Indomethacin, Meloxicam, Mefenamic Acid, Diclofenac Sodium, and selective NSAIDs such as Etoricoxib and Celecoxib could be prescribed in primary care settings (Low *et al.*, 2022).

The last medication option for acute gout is an oral corticosteroid (OCS). Ideally, OCS is administered when there is a contraindication for Colchicine and NSAIDs, such as kidney disease. The recommended OCS is Prednisolone 30-35 mg/day or equivalent for 3-5 days (Richette *et al.*, 2017).

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OPIOIDS

Opioids are a type of analgesic derived from *Papaver somniferum*. Generally, there were two classifications of opioids based on synthetic processes and the effect on opioid receptors. There are three classes of opioids based on the process: natural extract (Morphine, Codeine, and Papaverine); semi-synthetic (Heroine, Buprenorphine, and Oxycodone); and synthetic (Pethidine, Fentanyl, and Methadone). Meanwhile, the classifications based on its effect on opioid receptors are agonists, partial agonists, and antagonists. The agonist opioids bind to the receptor, resulting in an analgesic effect. There are three different opioid receptors: μ, δ, and κ opioid peptide receptors (Pathan and Williams, 2012; Trang *et al.*, 2015).

Opioids have multiple routes of administration, including oral, intravenous, and intramuscular. In addition, there are subcutaneous, subdermal, transdermal, transmucosal, rectal, epidural, intrathecal, and nasal sprays. After administration, opioids are rapidly distributed to skeletal muscle, the nervous system, the kidney, the lungs, and the placenta. Most opioids are metabolized in the liver and excreted through the kidney as unchanged substances or metabolites (Nafziger and Barkin, 2018).

Opioids are indicated in limited cases because of severe adverse effects and causing drug tolerance and dependence. The general indications of opioids are postoperative pain, cancer-related pain, chronic pain, or moderate-severe pain (Mikosz *et al.*, 2020). The WHO analgesic ladder is widely acceptable pain management, divided into three strategies based on pain intensity (mild, moderate, and severe). Less potent opioids (Codeine, Tramadol, and Hydrocodone) are recommended for moderate pain, while potent opioids (Morphine, Fentanyl, and Buprenorphine) are for severe pain (Anekar and Cascella, 2022).

OPIOIDS IN PAIN MANAGEMENT FOR ACUTE GOUT ARTHRITIS

No guidelines recommend opioids as an initial analgesic choice in managing acute gout (Richette *et al.*, 2017; Perhimpunan Reumatologi Indonesia, 2018; FitzGerald *et al.*, 2020). Opioid use is limited. However, a recent study showed that about 28.3% of flare cases in the emergency department received opioids at discharge, and 80% were new patients. These prescriptions were twice as common in patients with diabetes mellitus, polyarticular joint flare, and opioids use at hospital admissions. The most commonly used opioid was oxycodone, with a mean dose of 37.9 ± 17.2 mg morphine equivalent (Dalal *et al.*, 2020).

The evidence regarding opioid use for acute gout pain was rare. Both ACR nor EULAR does not mention any opioid use in managing GA. However, IRA says opioid use is for limited cases only. Opioids are indicated in acute GA flare with severe kidney dysfunction if oral and intra-articular corticosteroids are ineffective in reducing pain (Perhimpunan Reumatologi Indonesia, 2018). However, the guideline does not mention any specific types of opioids. Based on the *Formularium Nasional*, the only opioids available in primary healthcare is Codeine 10 and 20 mg (Kementerian Kesehatan RI, 2022).

Despite only limited evidence regarding opioid use in managing gout, evidence regarding opioid use in other inflammatory arthritis (rheumatoid arthritis) showed a contrary result. One Cochrane systematic review that analyzed 11 heterogeneous studies showed weak evidence supporting opioid analgesia in treating rheumatoid arthritis (Whittle *et al.*, 2012). Thus, the adverse effect of opioids that act as analgesics outweighed the benefits.

Another study compared a single dose of oral opioids with a non-opioid analgesic in treating acute extremity pain in the emergency department. The study was a randomized controlled trial at two emergency departments and included 416 patients divided into four groups. The first group received 400 mg of Ibuprofen and 1000 mg of Acetaminophen; the second group received 5 mg of oxycodone and 325 mg of Acetaminophen; the third group received 5 mg of Hydrocodone and 300 mg of Acetaminophen, while the fourth group received 30 mg of Codeine and 300 mg of Acetaminophen. Surprisingly, those groups had no clinical or statistical difference in pain reduction (Chang *et al.*, 2017). Based on this evidence, opioids should be used cautiously in acute gout patients.

CONCLUSION

The evidence of opioids in managing acute gout pain was rare. Opioids should be the last choice in selected cases of acute gout. *Formularium Nasional* (n): a list of drugs compiled based on the latest scientific evidence and stipulated by the Ministry of Health Republic of Indonesia.

REFERENCES

Anekar, A. A. and Cascella, M. (2022) 'WHO Analgesic Ladder', *Journal of the Royal College of Physicians of Edinburgh*, 38(3), p. 284. doi: 10.1007/978-3-642-28753-4_102537.

Chang, A. K. *et al.* (2017) 'Effect of a single dose of oral opioid and non-opioid analgesics on acute extremity pain in the emergency department: A randomized clinical trial', *JAMA - Journal of the American Medical Association*, 318(17), pp. 1661–1667. doi: 10.1001/jama.2017.16190.

Dalal, D. S. *et al.* (2020) 'Prescription Opioid Use Among Patients With Acute Gout Discharged From the Emergency Department', *Arthritis Care and Research*, 72(8), pp. 1163–1168. doi: 10.1002/acr.23928.

Desai, J., Steiger, S. and Anders, H. J. (2017) 'Molecular Pathophysiology of Gout', *Trends in Molecular Medicine*, 23(8), pp. 756–768. doi: 10.1016/j.molmed.2017.06.005.

FitzGerald, J. D. *et al.* (2020) '2020 American College of Rheumatology Guideline for the Management of Gout', *Arthritis care & research*, 72(6), pp. 744–760. doi: 10.1002/ACR.24180.

Jin, M. *et al.* (2012) 'Uric acid, hyperuricemia and vascular diseases', *Frontiers in Bioscience*, 17(2), pp. 656–669. doi: 10.2741/3950.

Kementerian Kesehatan RI (2022) *Daftar Obat FORNAS*. Available at: http://e-fornas.binfar.kemkes.go.id/index.php/front/Daftarobat/obat_fornas (Accessed: 18 June 2022).

Leung, Y. Y., Yao Hui, L. L. and Kraus, V. B. (2015) 'Colchicine-Update on mechanisms of action and therapeutic uses', *Seminars in Arthritis and Rheumatism*, 45(3), pp. 341–350. doi:

10.1016/j.semarthrit.2015.06.013.

Low, Qin Jian *et al.* (2022) 'Management of gout in the primary care practice', *Malaysian Family Physician*, 17(1). doi: 10.1007/s15006-020-9515-x.

Mikosz, C. A. *et al.* (2020) 'Indication-Specific Opioid Prescribing for US Patients With Medicaid or Private Insurance, 2017', *JAMA network open*, 3(5), p. e204514. doi: 10.1001/jamanetworkopen.2020.4514.

Nafziger, A. N. and Barkin, R. L. (2018) 'Opioid Therapy in Acute and Chronic Pain', *Journal of Clinical Pharmacology*, 58(9), pp. 1111–1122. doi: 10.1002/jcph.1276.

Pathan, H. and Williams, J. (2012) 'Basic opioid pharmacology: an update', *British Journal of Pain*, 6(1), pp. 11–16. doi: 10.1177/2049463712438493.

Perhimpunan Reumatologi Indonesia (2018) *Rekomendasi Pedoman Diagnosis dan Pengelolaan Gout*.

Ragab, G., Elshahaly, M. and Bardin, T. (2017) 'Gout : An old disease in new perspective – A review', *Journal of Advanced Research*, 8(5), pp. 495–511. doi: 10.1016/j.jare.2017.04.008.

Richette, P. *et al.* (2017) '2016 updated EULAR evidence-based recommendations for the management of gout', *Annals of the Rheumatic Diseases*, 76(1), pp. 29–42. doi: 10.1136/annrheumdis-2016-209707.

El Ridi, R. and Tallima, H. (2017) 'Physiological functions and pathogenic potential of uric acid: A review', *Journal of Advanced Research*, 8(5), pp. 487–493. doi: 10.1016/j.jare.2017.03.003.

Roddy, E. *et al.* (2020) 'Open-label randomised pragmatic trial (CONTACT) comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care', *Annals of the Rheumatic Diseases*, 79(2), pp. 276–284. doi: 10.1136/ANNRHEUMDIS-2019-216154.

Singh, J. A. and Gaffo, A. (2020) 'Gout epidemiology and comorbidities', *Seminars in Arthritis and Rheumatism*, 50(3), pp. S11–S16. doi: 10.1016/j.semarthrit.2020.04.008.

Skoczyńska, M. *et al.* (2020) 'Pathophysiology of hyperuricemia and its clinical significance – a narrative review', *Reumatologia*, 58(5), pp. 312–323.

Stewart, S. *et al.* (2016) 'The first metatarsophalangeal joint in gout: A systematic review and meta-analysis', *BMC Musculoskeletal Disorders*, 17(1). doi: 10.1186/s12891-016-0919-9.

Stewart, S. *et al.* (2020) 'The experience of a gout flare: a meta-synthesis of qualitative studies', *Seminars in Arthritis and Rheumatism*, 50(4), pp. 805–811. doi: 10.1016/j.semarthrit.2020.06.001.

Trang, T. *et al.* (2015) 'Pain and poppies: The good, the bad, and the ugly of Opioid analgesics', *Journal of Neuroscience*, 35(41), pp. 13879–13888. doi: 10.1523/JNEUROSCI.2711-15.2015.

Whittle, S. L. *et al.* (2012) 'The efficacy and safety of opioids in inflammatory arthritis: A Cochrane systematic review', *Journal of Rheumatology*, 39(SUPPL. 90), pp. 40–46. doi: 10.3899/jrheum.120341.

Zhang, W. Z. (2021) 'Why does hyperuricemia not necessarily induce gout?', *Biomolecules*, 11(2), pp. 1–11. doi: 10.3390/biom11020280.