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Acute Management of Crystal-Induced Arthropathies: an Overview

Felipe Velasquez Botero[1]*, Tabata Elizabeth Hernandez Henriquez[2], Johanna Stefany Canenguez Benitez[3]*, Guadalupe Abigail Benítez López[4], Tania Siu Xiao[5], Andreina del Valle Rojas Marron[6], Miguel Eduardo Rodriguez Rodriguez[7], Maria Soledad Ostorga Menjivar[8], Jose Luis Hernandez Aparicio[9], Giuliana Colombari Arce[10] and Mehwish Alam[11]

[1]*Felipe Velasquez Botero, CES University, Larkin Community Hospital, USA*

[2]*Tabata Elizabeth Hernandez Henriquez, University of El Salvador, Larkin Community Hospital, USA*

[3]*Johanna Stefany Canenguez Benitez, University of El Salvador, Larkin Community Hospital, USA*

[4]*Guadalupe Abigail Benítez López, University of El Salvador, Larkin Community Hospital, USA*

[5]*Tania Siu Xiao, Catholic University of Honduras, Larkin Community Hospital, USA*

[6]*Andreina del Valle Rojas Marron, Universidad de Oriente, Larkin Community Hospital, USA*

[7]*Miguel Eduardo Rodriguez Rodriguez, Universidad de Oriente, Larkin Community Hospital, USA*

[8]*Maria Soledad Ostorga Menjivar, Universidad Evangélica de El Salvador, Larkin Community Hospital, USA*

[9]*Jose Luis Hernandez Aparicio, University of El Salvador, Larkin Community Hospital, Miami, Florida, USA*

[10]*Giuliana Colombari Arce, Universidad de Ciencias Medicas, Costa Rica*

[11]*Mehwish Alam, Avalon University School of Medicine, Larkin Community Hospital, USA*

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***Corresponding author:** Felipe Velasquez Botero, Johanna Stefany Canenguez Benitez, CES University, University of El Salvador, Larkin Community Hospital, Miami, Florida, USA

Abstract

Gout and pseudogout are the two major Crystal-induced Arthropathies. Patients with these conditions can experience symptoms such as asymmetric joint pain, swelling, and functional limitation. Acute presentation is due to intra-articular deposition of monosodium urate (Gout) or calcium pyrophosphate (Pseudogout). Risk factors include male gender, binge drinking, obesity, and postmenopausal status. The acute management for crystal-induced arthropathies includes Non-Steroidal Anti Inflammatory Drugs such as indomethacin, the most commonly used medication. NSAID should not be used in patients with renal insufficiency, gastrointestinal disorders (e.g., peptic ulcer, GI bleeding), patients in the Intensive Care Unit. Colchicine is a medication that has a more significant benefit when used within the first 24 hours of the condition's onset, but it needs to be used with caution in patients with renal and hepatic dysfunction. Glucocorticoids have a very effective anti-inflammatory effect in acute flares of the disease, and therefore, can significantly reduce the symptoms, but it may cause severe adverse effects if the patient uses them for a long time. The most appropriate approach of crystal-induced arthropathies should be based on the comorbidities of the patient.

Keywords: Gout; Pseudogout; Indomethacin; Colchicine; Glucocorticoid

Abbreviations: NSAID: Non-Steroidal Anti Inflammatory Drug, GI: Gastrointestinal

Introduction

Crystal-induced arthropathies include two major pathologies: gout and pseudogout. The formation and deposition of monosodium urate are characteristic of gout, and pseudogout is composed of calcium pyrophosphate. Common risk factors include advanced age, inherited genetic disorders, history of joint surgery, or trauma. Some of the symptoms of these pathologies include joint pain, inflammation, and reduced range of motion. Cartilage and bone may also be involved, and crystals might be present in the synovial fluid as well. In addition, different crystals may exist spontaneously in synovial fluid, synovium, and adjacent bone and cartilage. In order to confirm the diagnosis, it is recommended to perform a physical examination and specific tests, such as blood tests, arthrocentesis, and imaging (X-ray), to rule out other pathologies. Crystal-induced arthropathy is more common in people older than 65 years old. According to an article published in 2016, between 3 and 8 million American adults

(3% of the population) have gout, and 1 per 1000 individuals have pseudogout [1]. There are several pharmacological options to treat these arthropathies, but the three most effective are: non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids. NSAIDs are drugs used to alleviate pain and decrease inflammation and fever by reversible inhibiting the cyclooxygenase (COX) pathway (both COX-1 and COX-2), blocking prostaglandin synthesis. Colchicine prevents microtubule polymerization, interfering with neutrophil's chemotaxis and degranulation. Finally, corticosteroids impair B and T cell function by decreasing the transcription of cytokines. This article aims to identify when to use these drugs, considering the adverse effects of the drugs and the symptoms and comorbidities of the patient (renal disease, gastric ulcer, cytopenias), which could worsen it.

The most common treatment options for managing acute inflammation in crystal-induced arthropathies are non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroid. In order to choose the best treatment, we must take into consideration the side effects of the drug and the patient's comorbidities. NSAIDs are the drugs of choice in the majority of patients with acute gout without underlying health problems. Even though indomethacin has been traditionally chosen for acute gout, most of the other NSAIDs can be used as well [2]. These drugs are a class of analgesics that includes selective and nonselective cyclooxygenase inhibitors, which work by blocking the biosynthesis of prostaglandins and thromboxane. We should avoid this class of medications in patients with renal insufficiency, gastrointestinal bleeding, history of peptic ulcer disease, and hepatic disease. NSAIDs also should be avoided in patients taking warfarin and those in the intensive care unit. Almost every type of NSAID has shown effectiveness in treating acute gout, but indomethacin is one of the most common treatment choices. Even though there is no recent information indicating that indomethacin is more effective than other NSAIDs, it is still used as a first treatment option in patients without contraindications for its use. Even studies have shown equal efficacy to other NSAIDs to treat crystal arthropathies such as gout. This can be illustrated by a study conducted in 2007 found similarities between the use of indomethacin and lumiracoxib. The study has demonstrated that lumiracoxib 400 mg o.d. has comparable efficacy to indomethacin 50 mg t.i.d., the current 'gold standard' NSAID for managing acute gout. In addition, lumiracoxib was well tolerated and had numerically fewer AEs and a better blood pressure profile than indomethacin. This and previous studies would suggest that lumiracoxib represents an alternative option for the management of gout that also minimizes the potential for GI ulcer complications [3]. Therefore, when choosing the treatment for a patient with crystal arthropathy, the adverse effects mentioned above should be considered since no literature shows differences in effectiveness between the NSAIDs.

The classical treatment for acute crystal-induced arthropathies is colchicine therapy. Colchicine prevents microtubule assembly and the disruption of inflammasome activation, microtubule-based inflammatory cell chemotaxis, generation of leukotrienes and cytokines, and phagocytosis [4]. Therefore, by modulating the inflammatory process, colchicine has been a valuable agent for managing acute inflammation associated with acute crystal-induced arthropathies; it can also be used for gout prophylaxis. The use of low-dose oral colchicine is recommended in some patients with contraindication to glucocorticoids (e.g., systemic fungal infection, diabetes mellitus, glaucoma, joint infection) and NSAID (e.g., bleeding disorder, congestive heart failure, peptic ulcer disease, allergy to NSAID) use. Additionally, a more significant benefit has been seen when colchicine is used within 24 hours of flare onset. Since NSAID is the first-line agent in managing acute crystal-induced arthropathies, colchicine is recommended rather than oral glucocorticoids as the second-line agent when NSAIDs are contraindicated or when the use of NSAID has not reduced pain, and only if flare onset is within 36 hours. Treatment of acute gout flare: 1.2 mg at the first sign of gout flare followed by 0.6 mg one hour later [5]. The most common adverse effects are related to the gastrointestinal tract (e.g., diarrhea, vomiting, nausea); less common (e.g., sensorimotor neuropathy, pancytopenia, elevated AST and ALT, myopathy, rhabdomyolysis, azoospermia/oligospermia) are reversible with discontinuation or lowering the dose of colchicine. Colchicine should be avoided in older adults and patients with renal or hepatic impairment or known gastrointestinal tract symptoms. Drug-drug interactions should be considered when using colchicine, primarily with drugs known to inhibit CYP3A4 (e.g., erythromycin, clarithromycin, ketoconazole, grapefruit juice, verapamil, ritonavir) and/or P-glycoprotein (e.g., cyclosporine, ranolazine), which increased concentrations of colchicine.

On the other hand, glucocorticoids are very effective as rapidly acting anti-inflammatory drugs. The most notable anti-inflammatory action of glucocorticoids in acute gout is based on the ability for the prevention of the activation of pro-inflammatory transcription factors such as NFκB and activating protein-1 (AP-1) [6]. In particular, glucocorticoids increase the expression of the inhibitor of κB (IκB), the cytoplasmic chaperone that prevents translocation of NFκB to the nucleus, inhibiting IL-1beta production [6]. In addition to NFκB and AP-1, other transcription factors are negatively regulated by the glucocorticoid receptors, and target genes include those encoding for a broad range of inflammatory cytokines, enzymes, receptors, and adhesion molecules such as IL-1beta, COX-2, E-selectin, and TNF-alpha [6]. Comparing glucocorticoids with NSAIDs, some studies revealed that corticosteroids are significantly better in reducing swelling and tenderness, and they are equally effective as NSAIDs in reducing erythema and improving activity limitation. Therefore, treatment with glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH is strongly recommended for patients who cannot take oral medications [7]. According to American College of Rheumatology Guidelines of 2020 for the Management of Gout, selecting the appropriate treatment should be determined by patient features, such as

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comorbidities, access to the drug, preferences, and experience. Additionally, the long-term use of corticosteroids may cause many adverse effects, for example, Cushing syndrome, diabetes mellitus, hypertension, and osteoporosis. However, corticosteroids can only cause severe adverse effects when used long-term at high doses, and few adverse effects occur if they are taken in low to moderate doses for short periods. The GI tract adverse effects of prednisone also appear to be less severe than those of NSAIDs.

Conclusion

Crystal-induced arthropathies are joint inflammatory disorders characterized by the deposition of crystals in joints and surrounding tissues that can lead to joint damage. Therefore, the treatment should be started as soon as possible. As a common therapeutic rule, NSAIDs are the first choice to treat crystal-induced arthropathies. Indomethacin is the most common choice of NSAIDs, even though no studies indicate effectiveness than other NSAIDs. Colchicine is the second choice to treat crystal-induced arthropathies when the use of NSAIDs and glucocorticoids is contraindicated. Colchicine is the first choice to treat acute gout flare during the first 36 hours. Comparing glucocorticoids with NSAIDs, some studies revealed that corticosteroids are significantly better in reducing swelling and tenderness, and they are equally effective as NSAIDs in reducing erythema and improving activity limitation. The use of corticosteroids for the long-term may cause many adverse effects used at high doses, but fewer adverse effects are used in low to moderate doses and for a short time. The use of NSAIDs, colchicine, or glucocorticoids is not superior to each other. Each treatment has a purpose and indication in specific. The selection of treatment of crystal-induced arthropathies should be based on the comorbidities of the patient, access to the drug, preferences, and experience. We encourage our colleagues to be informed and keep updated in regards to the treatment of crystal-induced arthropathies.

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