

Acute Pseudogout Attack Precipitated by Intra-Articular Injection of a Cross-Linked Hyaluronate Combined with Triamcinolone Hexacetonide

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Abstract

Intra-articular hyaluronic acid (IAHA) injection is widely used in the day-to-day management of symptomatic osteoarthritis (OA) of the knees with good efficacy and minimal side effects. Occasionally OA and chondrocalcinosis can co-exist in some patients. IAHA injection is widely used in the day-to-day management of symptomatic OA knees with good efficacy and minimal side effects in my clinic. Induction of an acute attack of calcium pyrophosphate dihydrate (CPPD) arthritis by IAHA has been rarely reported. We report a patient who developed acute pseudogout after IA Cingal injection, despite the triamcinolone hexacetonide given in the IA, and also reviewed previous reports and discussed preventive and management approaches to avoid such an unpleasant but, thankfully, a rare occurrence.

Keywords: *Pseudogout Trigger; Intra-articular Hyaluronic Acid; Injection*

Abbreviations

OA: Osteoarthritis; IAHA: Intra-Articular Hyaluronic Acid; CPPD: Calcium Pyrophosphate Dihydrate; HMW: High Molecular Weight; LMW: Low Molecular Weight

Introduction

Osteoarthritis (OA) of the knees is increasing in prevalence in Asia with an aging population. While gout is relatively common among our Asian patients, pseudogout is less commonly seen in clinical practice, but on the other hand, OA and chondrocalcinosis do co-exist in some patients. Intra-articular hyaluronic acid (IAHA) injection is widely used in the day-to-day management of symptomatic OA knees with good efficacy and minimal side effects in my clinic for the last 22 years. Induction of an acute attack of calcium pyrophosphate dihydrate (CPPD) arthritis by IAHA has been rarely reported [1]. We report a patient who developed acute pseudogout after IA Cingal injection.

Case Report

TTH, a 70-year-old. Chinese businessman with a history of gout, lumbar spondylosis, cervical spondylosis, has grade 2 OA knees for 10 years. He has been given previous IAHA including Orthovisc, Arthrum H, ArthroMac (sodium hyaluronate with chondroitin sulphate), Happy-Cross (cross-linked sodium hyaluronate with mannitol), Hylan GF-20, and KD intra-articular Gel over the last 10 years without any reactions, and with good alleviation of his knee pain. Previous x-rays and ultrasound of the knees done did not show any chondrocalcinosis or CPPD deposits.

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He presented with right knee pain and swelling for 2 weeks on 05.04.21 due to excessive walking. Clinically there was mild to moderate knee effusion. Ultrasound of the knee done showed synovitis 2+ and effusion 2+ (Figure 1 and 2). No hyperechoic deposits were seen in the cartilage or meniscus, nor were there hyperechoic spots in the synovial fluid. Right knee aspiration was done via the lateral mid-patellar approach and 10 mls of yellow fluid was redrawn and sent for fluid analysis. This was immediately followed by administration of 1ml of 1% ropivacaine and IA Cingal. The injection was uneventful and he went home.

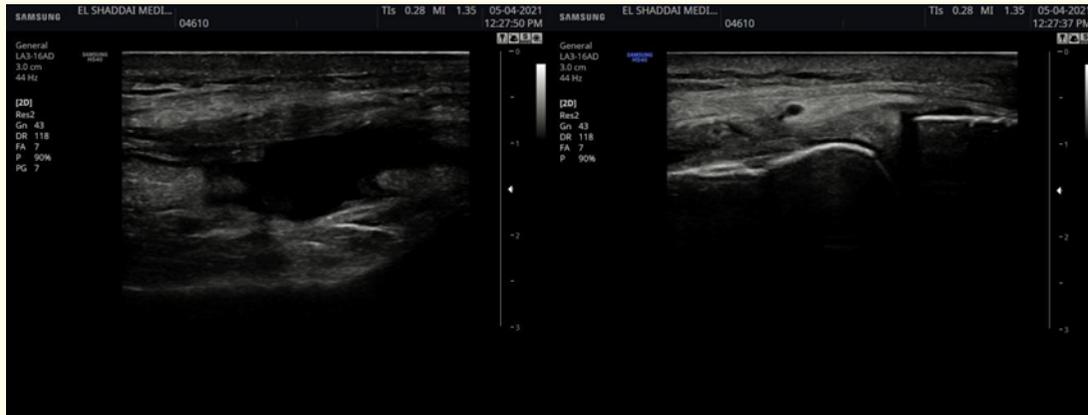


Figure 1 and 2: Showing synovitis and effusion in the right knee before the IA cingal injection.

Two hours later, while he was resting at home, he developed progressive knee pain and swelling until he could not walk or stand. He returned to the clinic 4 hours post injection with a severe right knee effusion. 30 mls of turbid yellow fluid was aspirated from the inflamed right knee and sent for analysis (See table 1 for the comparative knee fluid analysis) IA tramadol 50 mg was injected together with 1ml of betamethasone 7 mg and 2 mls of SynolisVA. No oral medications were given. The patient returned home.

	Before IA Cingal	After IA Cingal
Fluid volume	10 mls	30 mls
Appearance	Yellowish, Slightly Turbid	Yellowish and Turbid
Protein	4.0 G/DL	2.3G/DL
Glucose	137 MG/DL	0
White blood cells	0.09 X 10 ⁹ /L	48.32 X 10 ⁹ /L
Neutrophils	26%	95%
Lymphocytes	74%	5%
Crystals	Nil	Calcium Pyrophosphate Dihydrate (CPPD) seen

Table 1: Synovial fluid analysis before and after IA cingal injection.

By the following morning, the patient was much better and able to walk. He was reviewed on the 3rd day in the clinic and the right knee effusion had mostly resolved. He could walk normally and had no more pain. A repeat knee ultrasound showed remnant effusion and moderate synovitis (Figure 3 and 4). The knee fluid analysis post IA Cingal injection showed the presence of CPPD crystals, which were not present before the injection. There was also acute leukocytosis of 48.32 X 10⁹/L with 95% neutrophilia. The synovial fluid level also

dropped from 137 mg/dl to 0 mg/dl, clearly indicative of severe acute inflammation. The patient was very relieved that the acute pseudogout attack was quickly aborted with the second treatment rendered. And this was the first time that he had ever experienced such an acute and disabling knee inflammation from a pseudogout attack.

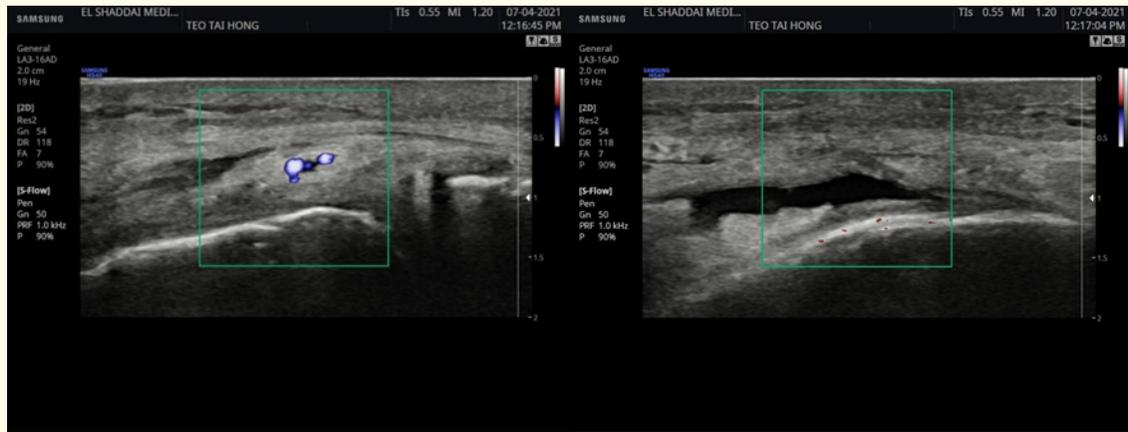


Figure 3 and 4: Showing residue effusion and synovitis a with positive doppler signal after resolution of the acute pseudogout attack induced by the IA cingal.

Discussion

Cingal (Anika Therapeutics, Inc, Bedford, MA) is an established IAHA for the treatment of OA knee [2]. Cingal is a cross-linked sodium hyaluronate 4 ml of 88 mg HA plus 18 mg triamcinolone hexacetonide. So far there has not been any previous report of acute pseudogout following IA Cingal. This is different from acute pseudoseptic arthritis following IAHA, which can be similar in presentation, occurring within hours after IAHA with severe joint pain and effusion but have negative cell cultures and lack of crystallization [3]. Ours is the first case report of such a rare occurrence with IA Cingal.

Pseudogout is the term to describe acute attacks of CPPD-induced synovitis, which clinically resemble acute attacks of (monosodium urate) gout [4]. However, the majority of individuals with CPPD never experience such episodes. Deposits of CPPD in articular tissues like the knees and wrist occurs in the elderly up to 10 - 15% in those aged 65 - 75 years old. Chondrocalcinosis refers to radiographic calcification in hyaline and/or fibrocartilage. It is commonly present in patients with CPPD crystal deposition disease. Ultrasound is useful in CPPD disease. Typically, crystal deposition is seen embedded within the substance of the hyaline cartilage in 'rose bead' appearance. Calcific deposits can also be seen in the triangular fibrocartilage of the wrist, menisci of the knee and tendons. The gold standard for diagnosis is synovial fluid analysis. This demonstrates characteristic positively birefringent CPP crystals (seen by polarized light microscopy).

Release of CPPD crystals into the joint space leads to phagocytosis of the crystals by the monocytes-macrophages and neutrophils, activation of the inflammasome, with the release of chemotactic and inflammatory substances, much like MSU crystals.

A literature review conducted showed that there has only been 7 cases of acute CPPD arthritis induced by IAHA, of which 4 involved hylan GF-20(Synvisc), a high molecular weight HA (HMW HA) [5-9]. The one reported by Disla, *et al.* was one of recurrent CPPD arthritis on hylan GF-20 [10]. HMW HA could be a rare trigger in subclinical CPPD arthritis, as low molecular weight HA (LMW HA) on the other

hand have been used successfully to treat pseudogout that did not respond to NSAIDs [11]. It is of interest to note that the presence of triamcinolone hexacetonide in the Cingal HA did not prevent the attack of pseudogout and did not ameliorate the severity of the inflammatory response.

The learning point in this case is to do pre-injection ultrasound or x-ray for all cases of OA knee prior to IAHA. And for those patients who have CPPD deposits on ultrasound or chondrocalcinosis on X-ray should avoid HMW HA and use LMW HA like Orthovisc or SynolisVA instead to avoid the rare but disabling event of an acute pseudogout attack post IAHA.

And the treatment for such a rare IAHA-induced complication includes the following:

1. Aspiration of the inflamed joint with the fluid sent for crystal analysis.
2. IA tramadol 25 - 50 mg for rapid analgesic effect [12].
3. IA betamethasone 7 mg for rapid anti-inflammatory effect [13,14].
4. IA NSAIDs can also be used [15].
5. IA low-to-medium HA 2 ml with or without sorbitol for additional anti-inflammatory effects [16-18].

As shown in my patient, he had a rapid alleviation of the acute IAHA-triggered pseudogout attack the following morning and made full clinical recovery on the 3rd day.

Conclusion

Acute pseudogout attack following IAHA is a rare occurrence but nevertheless the clinician administering the IAHA should be aware of such a possible event and be adapt to manage and reverse the complication to ensure a good patient outcome.

Conflict of Interest

There is no financial interest, or any conflict of interest exists.

Bibliography

1. Hamburger MI, *et al.* "Intra-articular hyaluronans: a review of product-specific safety profiles". *Seminars in Arthritis and Rheumatism* 32.5 (2003): 296-309.
2. Hangody L, *et al.* "Intraarticular Injection of a Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide (Cingal) to Provide Symptomatic Relief of Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Multicenter Clinical Trial". *Cartilage* 9.3 (2018): 276-283.
3. Sedrak P, *et al.* "Differential characteristics and management of pseudoseptic arthritis following hyaluronic acid injection is a rare complication: a systematic review". *Journal of ISAKOS* 6.2 (2021): 94-101.
4. Parperis K, *et al.* "Management of calcium pyrophosphate crystal deposition disease: A systematic review". *Seminars in Arthritis and Rheumatism* 51.1 (2021): 84-94.

5. Maillefert JF, *et al.* "Acute attack of chondrocalcinosis after an intraarticular injection of hyaluronan". *Revue du Rhumatisme (English Edition)* 64.10 (1997): 593-594.
6. Luzar MJ and Altawil B. "Pseudogout following intraarticular injection of sodium hyaluronate". *Arthritis and Rheumatology* 41.5 (1998): 939-940.
7. Pullman-Mooar S, *et al.* "Are there distinctive inflammatory flares of synovitis after hylan GF intraarticular injections?" *Journal of Rheumatology* 29.12 (2002): 2611-2614.
8. Ali Y, *et al.* "Acute pseudogout following intra-articular injection of high molecular weight hyaluronic acid". *American Journal of Medicine* 107.6 (1999): 641-642.
9. Kroesen S., *et al.* "Induction of an acute attack of calcium pyrophosphate dihydrate arthritis by intra-articular injection of hylan G-F 20 (Synvisc)". *Clinical Rheumatology* 19.2 (2000): 147-149.
10. Disla E., *et al.* "Recurrent acute calcium pyrophosphate dihydrate arthritis following intraarticular hyaluronate injection". *Arthritis and Rheumatology* 42.6 (1999): 1302-1303.
11. Punzi L, *et al.* "Pseudogout and intraarticular hyaluronate injections: comment on the article by Disla *et al.*". *Arthritis and Rheumatology* 43.7 (2000): 1660-1661.
12. Ryan T, *et al.* "Tramadol as an adjunct to intra-articular local anaesthetic infiltration in knee arthroscopy: a systematic review and meta-analysis". *ANZ Journal of Surgery* 89.7-8 (2019): 827-832.
13. Siró B. "The intraarticular and local administration of glucocorticosteroid preparations". *Orvosi Hetilap* 150.6 (2009): 251-260.
14. M Rull, *et al.* "Intra-articular corticosteroid preparations: different characteristics and their effect during inflammation induced by monosodium urate crystals in the rat subcutaneous air pouch". *Rheumatology (Oxford)* 42.9 (2003): 1093-100.
15. Yoon KH. "Intraarticular Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in the Treatment of Inflammatory Arthritis: Establishing a Role in Arthritis Patient Care Today". *EC Orthopaedics* 10.11 (2019): 52-63.
16. Romera M. "Effect of intraarticular hyaluronate injections in chondrocalcinosis: comment on the article by Martens". *Arthritis and Rheumatology* 46.3 (2002): 847.
17. Mongkhon JM, *et al.* "Sorbitol-modified hyaluronic acid reduces oxidative stress, apoptosis and mediators of inflammation and catabolism in human osteoarthritic chondrocytes". *Inflammation Research* 63.8 (2014): 691-701.
18. Conrozier T. "Is the Addition of a Polyol to Hyaluronic Acid a Significant Advance in the Treatment of Osteoarthritis?" *Current Rheumatology Reviews* 14.3 (2018): 226-230.

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