Received: 4 August 2023 | Accepted: 20 September 2023

DOI: 10.1002/ams2.898

ACUTE MEDICINE & SURGERY WILEY

CASE REPORT

Anaphylactic shock due to intra-articular injection of diclofenac etalhyaluronate sodium: A case report

Tomoaki Yatabe[1] | **Akihito Mizutani**[2] | **Takashi Ito**[2] | **Yukika Ono Ricart**[2] | **Maasa Watanabe**[2] | **Sohta Uchiyama**[2]

[1]Emergency Department, Nishichita General Hospital, Tokai, Japan

[2]Department of Anesthesiology and Intensive Care Medicine, Nishichita General Hospital, Tokai, Japan

Correspondence
Tomoaki Yatabe, Emergency Department, Nishichita General Hospital, 3-1-1, Nakanoike, Tokai, Aichi 477-8522, Japan.
Email: yatabe.tomoaki@katch.ne.jp

Abstract

Background: Anaphylactic shock of diclofenac etalhyaluronate agent can be prolonged and recurrent. However, its reports are rare, and consequently, its method of management remains to be established.

Case Presentation: A 65-year-old woman received an intra-articular injection of diclofenac and hyaluronate. After 20 min, systemic urticaria and severe hypotension developed after walking. After an intramuscular adrenaline injection, she was transferred to our hospital. Despite administration of continuous noradrenaline and adrenaline, hypotension persisted. Seven hours after the joint injection, 25 mL of knee joint fluid was aspirated under ultrasound guidance. Mobilization was performed 24 h after joint injection. However, urticaria rapidly spread after standing. At 45 and 46 h after joint injection, we confirmed that no symptoms, including urticaria, recurred after walking.

Conclusion: Anaphylactic shock due to intra-articular injection of diclofenac etalhyaluronate is prolonged and requires extended observation. Aspiration of joint fluid may be one of the treatment options.

KEYWORDS
anaphylactic shock, diclofenac, etalhyaluronate sodium, intra-articular injection

INTRODUCTION

Anaphylactic shock is a serious and life-threatening adverse effect.[1] Diclofenac etalhyaluronate is a novel intra-articular injection agent for knee osteoarthritis.[2] Although reports of anaphylactic shock of this new agent are rare, it can be recurrent when it occurs.[3] However, the optimal method of managing it has not yet been established. Here, we describe a case of anaphylactic shock following intra-articular administration of diclofenac and hyaluronate sodium, wherein aspiration of joint fluid was performed as treatment.

CASE REPORT

A 65-year-old woman (height, 163 cm; weight, 61 kg) received joint injections of sodium hyaluronate and flurbiprofen patches for right knee osteoarthritis. She had been receiving vildagliptin (100 mg) and metformin (1000 mg) for diabetes and nifedipine (20 mg) for hypertension. The patient had no history of asthma or any known allergies. At the orthopedic clinic, she received an intra-articular injection of diclofenac and hyaluronate sodium for the first time. After ~20 min, severe right knee swelling and systemic urticaria developed after walking. Subsequently, her systolic blood pressure decreased to 60 mm Hg, and throat discomfort developed. An orthopedic surgeon immediately injected intramuscular adrenaline (0.5 mg), and the patient was transferred to our emergency department by ambulance. On arrival, blood pressure was 112/76 mm Hg, heart rate was 110/min, and SpO_2 was 91% (nasal oxygen, 2 L/min). Although 1500 mL of crystalloid solution and 100 mg of hydrocortisone were administered, her blood pressure decreased to 76/53 mm Hg, 3 h after the intra-articular injection. The patient was

transferred to the intensive care unit (ICU) after initiation of continuous noradrenaline infusion with arterial blood pressure monitoring. On ICU admission, arterial blood gas analysis revealed pH, 7.478; PaO_2, 66.3 Torr (nasal oxygen 3 L/min); HCO_3^- concentration, 26.7 mmoL/L; base excess, 3.3 mmoL/L; and lactate concentration, 5.2 mmoL/L. Despite administering continuous noradrenaline at 0.03 mcg/kg/min and adrenaline at 0.01 mcg/kg/min, hypotension persisted at 70–90/50–55 mm Hg, and the urticaria worsened (Figure 1). Seven hours after the joint injection, 25 mL of knee joint fluid was aspirated under ultrasound guidance. The joint fluid was yellow and viscous, and its bacterial culture showed no growth. The urticaria appeared to improve 10 h after the joint injection. Lactate concentration remained at 5.2 mmoL/L. Continuous adrenaline and noradrenaline infusions were discontinued 11 and 13 h after joint injection, respectively, because the blood pressure improved at 130–145/73–76 mm Hg. The patient's blood pressure, heart rate, and respiratory rate were stable; therefore, mobilization was performed 24 h after joint injection. However, urticaria rapidly spread after standing without any other symptoms. After further improvement to the urticaria, mobilization was again performed 29 h after the joint injection, and exacerbation of urticaria was not observed. At 45 h and 46 h after joint injection, we confirmed that no symptoms, including urticaria, recurred after walking. The patient was discharged from the ICU and hospital 48 h and 72 h after the joint injection, respectively.

DISCUSSION

A novel intra-articular injection agent for knee osteoarthritis, diclofenac etalhyaluronate (diclofenac), which is covalently linked to hyaluronic acid, has been available in Japan since 2021.[2] The main feature of this agent is that the sustained release of diclofenac from diclofenac etalhyaluronate after one injection into the joint tissue has potential analgesic effects that last up to 28 days.[2] However, physicians should pay adequate attention to any anaphylactic reactions. Anaphylactic reactions may be prolonged because of the long half-life of diclofenac (61.25 h, according to the medical package insert). Yanagawa et al.[3] reported repeated anaphylactic reactions after walking following intra-articular injection of diclofenac etalhyaluronate sodium over a 3-day period. Although the patient immediately received intramuscular adrenaline and her symptoms subsided, she received intermittent adrenaline injections three times for repeated anaphylactic reactions after walking over a 3-day period.[3] Similar to this case, our patient required continuous adrenaline and noradrenaline administration for 12 h to maintain her blood pressure. A recent systematic review reported that 4 h was the most commonly suggested period for post-anaphylactic observation.[4] This case and that of Yanagawa[3] indicate that a long-term observation period may be warranted in such cases. As a previous report pointed out,[3] we think joint movement, such as by walking, might disseminate the allergen from the injected joints into the blood. Therefore, observation should be performed at least until it is confirmed that walking does not cause breathing or circulatory symptoms in patients with anaphylactic shock following intra-articular injection of diclofenac etalhyaluronate sodium.

The European Academy of Allergy and Clinical Immunology Guidelines for Anaphylaxis state that the trigger should be removed where possible, in addition to early introduction of adrenaline.[1] In a previous report, joint fluid was aspirated the day after diclofenac etalhyaluronate sodium injection.[3] The authors reported that if the intra-articular diclofenac etalhyaluronate sodium had been removed soon

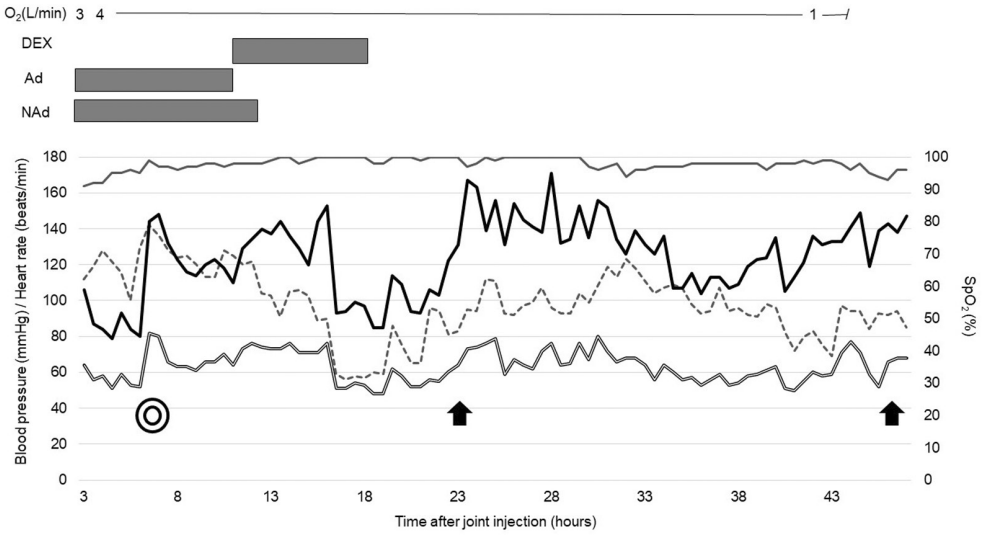

FIGURE 1 Clinical course. Gray line indicates SpO_2, and the gray dashed line indicates alternations in heart rate. Black line and black double line indicate alternations in systolic and diastolic blood pressure, respectively. Double circle indicates aspiration of the knee joint fluid. Black arrow indicates mobilization. Ad, adrenaline; DEX, dexmedetomidine; NAd, noradrenaline.

after the first anaphylactic reaction, repeated anaphylactic reactions may have been avoided.[3] In our case, the joint fluid was aspirated 7 h after the injection of diclofenac and hyaluronate sodium. Although the erythema worsened with standing 14 h after aspiration of the joint fluid, no respiratory or circulatory symptoms occurred. In another case report of intra-articular chitosan-induced anaphylaxis, the patient completely recovered 1 h after the injection.[5] Therefore, although joint fluid aspiration might not be necessary for all cases of anaphylaxis due to joint injection, the agent injected into the joint is important to our decision. These two cases indicate that aspiration of joint fluid might be one of the treatment options for anaphylactic shock following an intra-articular injection of diclofenac etalhyaluronate sodium because the trigger might remain in the joint cavity for a longer time because of the drug's long half-life. However, aspiration cannot entirely remove diclofenac etalhyaluronate from the joint. Therefore, as mentioned above, the observation period should be extended until it is confirmed that walking does not cause any further symptoms of anaphylactic shock.

There are some limitations in this case report. First, we could not demonstrate the effectiveness of joint fluid suctioning given that this is a case report. In this case, aspiration of the joint fluid was performed under ultrasound guidance after adequate disinfection. Therefore, other adverse events did not occur, and we think that this treatment option might be safe. Second, the benefits and harm of lavage and drainage of joint fluid were unclear. We did not perform lavage and drainage for the following reasons: (1) lavage might inject diclofenac etalhyaluronate from the joint into the bloodstream, and (2) there might be a risk of retrograde infection in drainage[6] despite uncertain effectiveness. Therefore, further case reports are necessary to clarify the balance of risk or benefit of lavage and drainage. Finally, the dose of continuous noradrenaline and adrenaline were 0.03 mcg/kg/min and 0.01 mcg/kg/min, respectively, in our case. The dose of catecholamines should have been increased.

In conclusion, anaphylactic shock due to intra-articular injection of diclofenac etalhyaluronate sodium is prolonged and requires extended observation. Furthermore, aspiration of the joint fluid may be one of the treatment options.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article because it is a case report.

ETHICS STATEMENT

Approval of the research protocol: Not applicable.
Informed Consent: Written informed consent was obtained from the patient and patient's family for publication of this case report.
Registry and the Registration No. of the Study/Trial: Not applicable.
Animal Studies: Not applicable.

ORCID

Tomoaki Yatabe https://orcid.org/0000-0002-3522-6857

REFERENCES

1. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022;77:357–77.
2. Nishida Y, Kano K, Nobuoka Y, Seo T. Efficacy and safety of diclofenac-hyaluronate conjugate (diclofenac Etalhyaluronate) for knee osteoarthritis: a randomized phase III trial in Japan. Arthritis Rheumatol. 2021;73:1646–55.
3. Yanagawa Y, Jitsuiki K, Kushida Y, Morohashi I. Repeated anaphylactic reaction after walking following an intraarticular injection of diclofenac etalhyaluronate sodium during a 3-day period. Acute Med Surg. 2022;9:e729.
4. Simard D, Bouchard V, Plourde A, Lefebvre S, Herman-Lemelin A, Lapointe S, et al. Factors influencing emergency department observation time following anaphylaxis: a systematic review. CJEM. 2021;23:480–93.
5. Peng S, Liang Y, Xiao W, Liu Y, Yu M, Liu L. Anaphylaxis induced by intra-articular injection of chitosan: a case report and literature review. Clin Case Rep. 2022;10:e6596.
6. Zhang Q, Liu L, Sun W, Gao F, Zhang Q, Cheng L, et al. Are closed suction drains necessary for primary total knee arthroplasty?: a systematic review and meta-analysis. Medicine. 2018;97:e11290.

How to cite this article: Yatabe T, Mizutani A, Ito T, Ono Ricart Y, Watanabe M, Uchiyama S. Anaphylactic shock due to intra-articular injection of diclofenac etalhyaluronate sodium: A case report. Acute Med Surg. 2023;10:e898. https://doi.org/10.1002/ams2.898