

Acute allergic reaction caused by hyaluronidase used in the pain management: a case report and literature review –A case report–

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Hyaluronidase is a protein enzyme extracted from goat or ovine testis. It breaks down hyaluronic acid in connective tissues, thereby reducing swelling and edema and increasing drug penetration into tissues after injection. Because of these properties, it is being increasingly used in the field of pain management. The most frequently reported hyaluronidase-induced complications are allergic reactions, and are usually reported in cases involving eye surgery. However, there are only a few cases of allergic reactions reported in the field of pain management. Here, we report a case involving a 52-year-old patient diagnosed with an allergic reaction after receiving epidural administration of hyaluronidase. A literature review and comparison of our case with similar cases suggested the potential mechanisms underlying these allergic reactions and emphasized the importance of considering the possibility of these reactions in patients receiving hyaluronidase during the course of pain management procedures. (*Anesth Pain Med* 2014; 9: 174-178)

Key Words: Allergic reaction, Epidural injection, Hyaluronidase.

Hyaluronidase is an enzyme with the ability to degrade hyaluronic acid (HA), one of the main components of interstitial gel, which controls the flow of substances through the tissue. It is widely used as a spreading factor to improve the diffusion of drugs and reduce edema or swelling in plastic surgery, ophthalmic surgery, and anesthesiology. With recent evidence showing hyaluronidase can improve the diffusion of drugs mixed with local anesthetics, thereby enhancing the anti-inflammatory activity of the drugs and prolonging the analgesic effect, the use of this enzyme in pain management procedures has increased [1]. Although there are very few

reports on hyaluronidase-induced adverse reactions in pain management, the enzyme has been known to have the ability to cause allergic reactions. Here, we report a case of hyaluronidase-induced allergic reaction in a patient who received the enzyme during a pain management procedure. The authors received written permission from the patient to report this case and provide details regarding it.

CASE REPORT

A 52-year-old woman visited our clinic with the primary complaint of bilateral medial elbow pain that had begun 6 months earlier. About 2 years before this episode, she had received injections of a local anesthetic and steroid (triamcinolone acetate) on 2 occasions, and experienced pain relief after the injections. She had been taking hypertension medication for 5 years, had been diagnosed with Behcet's disease, and had been receiving medications for 4 years. On physical examination, severe tenderness over the medial epicondyle of the humerus was noted. The patient had no history of surgery or allergic reaction to any foods, drugs, or pollen. Radiography of the elbow showed no specific findings such as bony erosion or calcification. However, ultrasonography findings around the lateral epicondyle showed a focal hypoechoic lesion and increased vascularity, indicating lateral epicondylitis. A mixture of triamcinolone acetate 10 mg, hyaluronidase 1,500 IU (H-lase[®]; Kuhnill pharm, Seoul, Korea), and 0.5% mepivacaine 2 ml (up to a total volume of 3 ml) was injected to the elbow. Injection was performed without significant problems, and the pain disappeared after the injection.

Four months later, the patient returned to our clinic with the chief complaint of back pain and radicular pain to the left

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lower leg. A transfer note from another clinic confirmed that before the current visit, she had received an epidural steroid injection without hyaluronidase in that clinic. A plain radiograph of the lumbar spine was obtained. With a suspected diagnosis of a herniated lumbar disc at L4/5, a caudal epidural steroid injection was administered with 0.5% mepivacaine 8 ml, triamcinolone acetate 20 mg, and hyaluronidase 1,500 IU. The procedure was performed under ultrasonographic guidance, and the drugs were injected after aspiration of blood, ensuring that there was no vascular uptake. Ten minutes after the injection, nausea, urticaria, hypotension (80/40 mmHg), and skin flares occurred. A skin rash was observed on the face, both hands, knees, lower legs, and abdomen (Fig. 1). Ringer's lactate solution was administered along with 100% oxygen via nasal prongs. This was immediately followed by an intravenous injection of ephedrine 10 mg and dexamethasone 5 mg. The symptoms spontaneously subsided after 1 hour, and the

patient's vital signs became stable. Additional blood tests showed that the total IgE level was 18.06 IU/ml (0–183 IU/ml), which was normal. Skin prick test showed positive findings with a wheal and flare of 8 mm and 4 mm diameter in response to hyaluronidase 1,500 IU/ml (1 : 1) and 150 IU/ml (1 : 10), respectively, and negative findings in response to mepivacaine. An intradermal test also showed positive findings for both 1,500 IU/ml (1 : 1) and 150 IU/ml (1 : 10) hyaluronidase, but not to mepivacaine.

DISCUSSION

In 1929, Duran-Reynals was the first to identify hyaluronidase as a spreading factor found in certain strains of streptococcal bacteria that had the ability to facilitate the uptake of subcutaneously applied vaccines and toxins [2]. Hyaluronidase is derived from crude extracts of ovine or

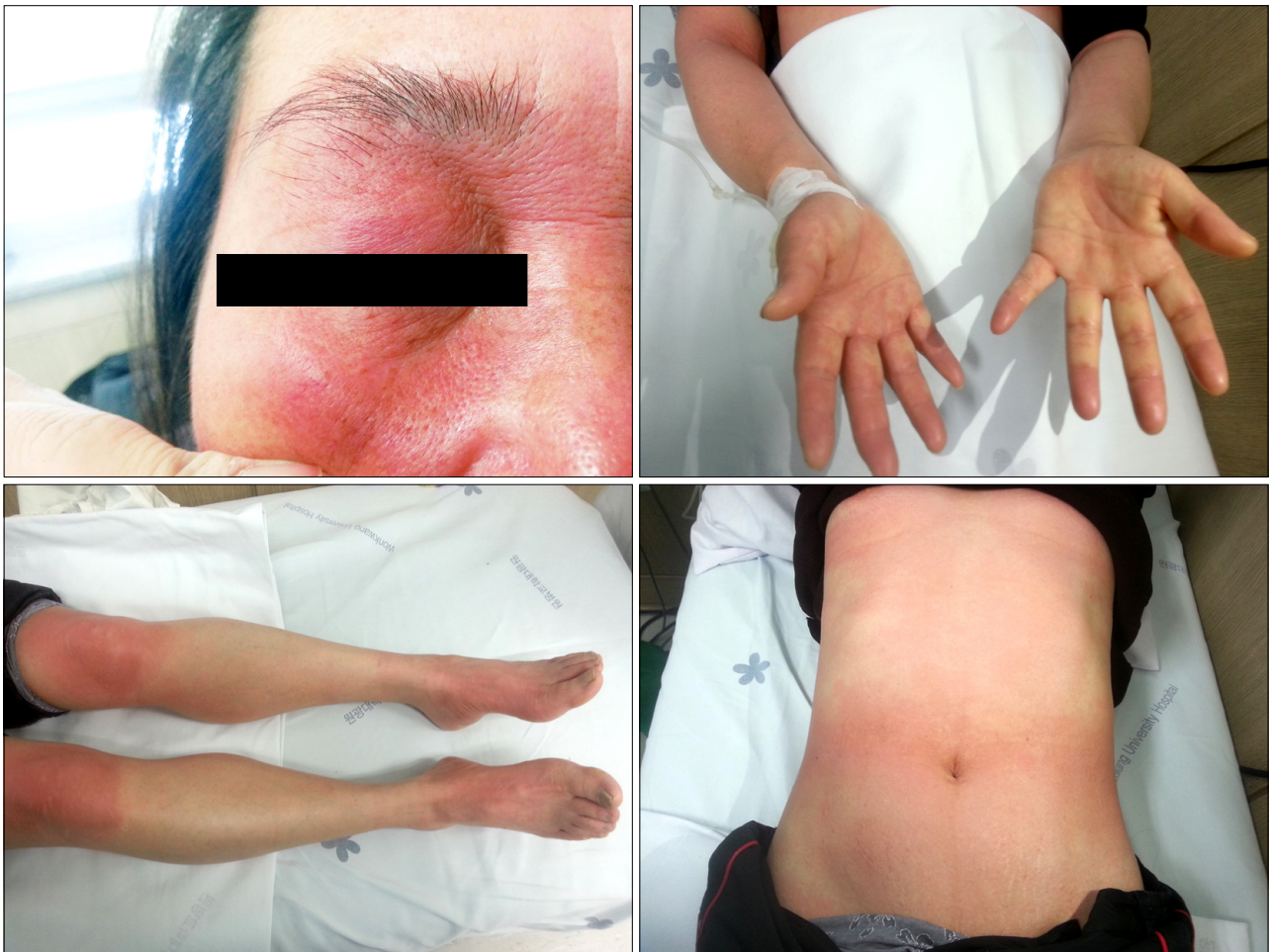


Fig. 1. Skin rash observed on the face, both hands, knees, lower legs and abdomen.

bovine testicular tissue [1]. It degrades HA, a glycosaminoglycan found extensively in the interstitial matrix and basement membrane of the connective tissue. Hyaluronic acid, one of the main components of interstitial gel, inhibits the flow of substances through tissue. The "spreading ability" of hyaluronidase in combination with local anesthetics has been proven by many clinical reports. The addition of hyaluronidase to local anesthetics improves the diffusion of local anesthetics, resulting in an adequate retrobulbar/peribulbar block for eye surgery [3]. It also increases the duration of local anesthetic effects in peripheral nerve blocks [4]. Because of these effects, hyaluronidase has been used in the management of various medical conditions, e.g., in the management of nasal bone fracture to reduce edema and swelling of the tissue [5], and the treatment of contrast-induced extravasation or compartment syndrome for the purpose of decompressing the elevated pressure in the compartments by absorbing the extravasated fluid [6]. With regard to the spinal region, Benoist et al. [7] found that HA is also found in keloids (dense scar tissue) and epidural adhesion tissue, which is considered to be responsible for failed back surgery syndrome (FBSS). When used with local anesthetics and steroids, hyaluronidase is believed to render tissues more permeable to injected fluids. It also reduces fibrosis, which is important because defects in fibrinolytic activity may lead to fibrin deposits and chronic inflammation [8]. Similarly, the supposed ability of hyaluronidase to disrupt epidural adhesions underlies the rationale for its use in patients with FBSS. Its primary action is to depolymerize hyaluronic acid and, to some extent, chondroitin-4 and chondroitin-6 sulfate. Hyaluronidase disrupts the proteoglycan ground substance, thus accelerating the diffusion of injected substances. Epidurally administered hyaluronidase presumably disrupts the ground substance found in the epidural adhesions. However, the dura, which is composed of collagen, elastin, and surface fibroblasts, is preserved [9]. Recently, hyaluronidase has been used with local anesthetics and found to show clinical effectiveness in various pain management procedures.

Allergic reactions are the main concern following hyaluronidase administration. The prevalence of these reactions is known to be around 1/2,000, which indicates a relatively low incidence [10]. Kempeneers et al. [10] was the first author to describe allergic reactions in 5 patients and to prove the immunoallergic etiology of such reactions to hyaluronidase. However, this quoted incidence was only in relation to eye surgery. There are limited reports of allergic reactions in pain

management studies; therefore, the actual incidence of these reactions in pain management procedures is not yet known. This is the first article that reviews cases of hyaluronidase-induced allergic reactions in pain management procedures. In Table 1, we have summarized a review of previously described cases of allergic reactions in pain management procedures [11-13]. The symptoms in these cases varied from a weak reaction (urticaria, skin rash) to shock (hypotension, dyspnea, and nausea). The most common injection sites were the epidural space, knee, and elbow. In most cases (5 of 7), the patient had a history of more than 1 prior uneventful injection of hyaluronidase. However, 2 cases had no history of prior injection, suggesting that there might be different mechanisms causing these hypersensitivity reactions. The onset time of allergic reactions is also variable and ranges from immediate to delayed onset. Two suggested mechanisms can be proposed on the basis of these findings: type I and type IV hypersensitivity. An immediate reaction with edema, skin flare, and urticaria without prior exposure to hyaluronidase represents type I hypersensitivity with an immediate immunoglobulin IgE-mediated response [14]. However, in some cases, as shown in the table, the onset of symptoms was delayed from 1 hour to 24 hours, suggestive of a type IV delayed hypersensitivity reaction, which is a T-cell mediated allergic reaction [15]. As is especially true of the animal-derived formulations for reasons previously mentioned [1], hyaluronidase may be frequently contaminated with proteases or immunoglobulins and can induce IgE-mediated allergic reactions. Although there are no previously reported cases, there is a possibility of a prion-like illness related to the use of crude animal products. The dosage used in all cases was 1,500 IU. This was a relatively higher dose than the doses reportedly used in ophthalmic surgery (100-150 IU) [10,14]. However, theoretically, although the risk of allergic reaction is increased by repeat injections, none of the reports documented whether the risk was a clinical problem associated with specific types of hyaluronidase formulations. One report has also stated that the cumulative dose does not seem to be related to the clinical manifestations [15]. Therefore, clinically useful dosages in pain management also need to be investigated in more detail. Most of the cases showed positive results in skin prick tests or intradermal tests. Blood tests, including white blood cell count, erythrocyte sedimentation rate determination, and C-reactive protein level measurement are also useful in order to rule out infections related to drug injection. In cases involving delayed hypersensitivity reactions, differential diagnosis may suggest

Table 1. Summarization of Reports Related to Hyaluronidase-Induced Allergic Reaction Used in the Pain Management

Report	Patient	Symptoms	Used drugs	Injected site	Time to onset of symptoms	Allergy related test results	History of drug used	Clinical results
Lee et al. [11]	46/F	Nausea, skin flare, urticaria, respiratory distress, hypotension	Levobupivacaine triamcinolone hyaluronidase 1,500 IU	Epidural	Immediately	Skin prick test: (-) Intradermal test: (+) Blood test: (-)	Epidural (+)	Cured with fluid, antihistamine
	35/M	Nausea, vomiting skin flare, urticaria hypotension	Levobupivacaine triamcinolone hyaluronidase 1,500 IU	Epidural	Immediately	Skin prick test: (+) Intradermal test: (+) Blood test: (+)	None	Cured with fluid, antihistamine
Kim et al. [12]	55/F	Urticaria	Mepivacaine triamcinolone morphine hyaluronidase 1,500 IU	Epidural	1 hour later	Skin prick test: (+) ELISA hyaluronidase with IgE Ab: (+)	Epidural (+)	Cured with oral steroid, antihistamine
Kim et al. [13]	68/F	Itching, skin rash	Lidocaine hyaluronidase 1,500 IU	Epidural	Immediately	Intradermal test: (+)	Epidural (+)	Cured
	35/F	Swelling on injection site	Lidocaine hyaluronidase 1,500 IU	Extensor tendon (elbow)	12 hours later	Intradermal test: (+) Blood test: (-)	None	Cured without treatment
	55/F	Swelling on injection site	Lidocaine hyaluronidase 1,500 IU	Anserinus bursa (knee)	24 hours later	Intradermal test: (+) Blood test: (-)	Anserinus bursa (+) (knee)	Cured without treatment
Our case	52/F	Nausea, skin flare, urticaria, hypotension	Mepivacaine triamcinolone hyaluronidase 1,500 IU	Epidural	10 minutes later	Skin prick test: (+) Intradermal test: (+) Blood test: (-)	Extensor Tendon (+) O (elbow)	Cured with fluid, antihistamine

F: Female, M: Male.

infection with normal laboratory findings, as mentioned above. In such cases, skin allergy tests are useful diagnostic tools to confirm an allergic reaction to hyaluronidase. The skin prick test and intradermal test are the recommended skin tests for this purpose. A skin prick test is positive when any injection induces a skin wheal greater than 4 mm in diameter. An intradermal test is positive when the wheal is greater than 8 mm in diameter [11]. In all cases, the outcomes were uneventful after the patients received immediate treatments such as antihistamine injection and fluid treatment or even with no treatment.

In conclusion, this review of cases shows that allergic reactions to hyaluronidase are rare, but possible. These reactions can occur irrespective of an allergic history in patients who receive this enzyme. In patients who show an anaphylactic shock, a fatal outcome is possible if careful rapid treatment is not administered. Therefore, physicians should consider the possibility of allergic reactions to hyaluronidase whenever it is used in pain management. The clinically useful dosage of the drug needs to be more thoroughly investigated.

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