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Analgesic and Curative Effects of 35kDa Hyaluronan Fragment on Zoster-Associated Pain: A Case Report of Two Patients

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Background: Herpes zoster-associated pain (ZAP) is a challenging neuropathic condition. Clinical reports suggest that a 35kDa hyaluronan fragment (HA35) may effectively relieve this pain with a single local injection. However, evidence of a complete cure is limited.

Case Report: Two patients were treated—one with acute shingles pain diagnosed 10 days prior, and one with postherpetic neuralgia (PHN) diagnosed a year ago. Pain scores before treatment were 7 for Patient 1, and 4 (average) and 8 (most severe) for Patient 2. Clinicians administered varying doses of HA35 based on pain level and disease duration. Both patients reported significantly reduced Visual Analog Scale pain scores and notable improvements in mental state, appetite, and sleep quality.

Conclusions: HA35 not only safely and effectively alleviates and cures ZAP, including acute pain and PHN, without causing side effects, but also improves related issues, such as appetite, sleep, and daily interactions affected by pain.

Key words: Herpes zoster-associated pain, acute pain, postherpetic neuralgia, low-molecular-weight hyaluronan HA35, pain treatment

BACKGROUND

Herpes zoster (shingles) is an infectious skin disease caused by the reactivation of the varicella-zoster virus (VZV), which remains dormant in the dorsal root or cranial nerve ganglia (1). Pain is a primary symptom of herpes zoster, also known as zoster-associated pain (ZAP), and can be categorized into prodromal, acute, subacute, and chronic phases. While pain typically occurs during the rash phase, 9% to 34% of patients continue to experience neuralgia within one month after the rash subsides, and 30% to 50% of patients with postherpetic neuralgia (PHN) suffer from persistent chronic pain one year later (2). This pain is often severe and debilitating, described as burning, stabbing, or throbbing, and can significantly impact quality of life. Effective management of PHN typically involves a combination of pharmacological treatments, such as anticonvulsants, antidepressants, and topical agents, along with nonpharmacological approaches like physical therapy and psychological support (3). Despite the range of treatment options, achieving a definitive cure and long-term effective control of neuropathic pain remains challenging. The 35kDa low-molecular-weight hyaluronan (HA35) is a medication used for treating inflammatory and neuropathic pain (4). While HA35 has demonstrated efficacy in alleviating PHN pain over a short period, research on its effectiveness in curing ZAP pain is limited. This case report aims to evaluate the efficacy of HA35 in treating ZAP pain using the Visual Analog Scale (VAS).

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CASES

Patient 1

A 47-year-old Chinese man with no history of anxiety, depression, or herpes simplex virus (HSV) infection presented to the dermatology clinic with clusters of vesicles and pain in his left chest and back for 10 days. Approximately 10 days prior, he had experienced spontaneous, intermittent, stabbing pain in the left abdomen and back, occurring about 10 times per day, with each episode lasting around 2 minutes. This pain severely impacted his daily life and sleep. Two days later, the pain intensified and was accompanied by itching. He then developed soybean-sized vesicles in a band-like distribution from the left chest to the abdomen and the left side of the back. These vesicles did not rupture or suppurate. He was diagnosed with acute herpes zoster and received antiviral treatment, which led to the resolution and crusting of the vesicles. However, the pain persisted, prompting him to seek further treatment at our hospital. Upon examination at our facility, the patient had patchy erythema and crusts on the left chest, abdomen, and back, without swelling, ulceration, or suppuration. His temperature was normal, but he exhibited hypersensitivity to pain. The patient's medical history was unremarkable, with no past surgeries or blood transfusions. Using the VAS, his pain was rated at 7 before treatment, significantly affecting his daily work, communication, and mood (Table 1).

The clinical team administered HA35, a mixture of hyaluronidase (1,500 units, SPH No. 1 Biochemical & Pharmaceutical Co., Ltd., China) and hyaluronan (10mg/mL, Shanghai Haohai Biotechnology Co., Ltd., China). The injection was given subcutaneously into the abdominal fat layer for pain relief, twice daily, with each dose comprising 2 injections of 100mg/5mL each. As shown in Table 1, after one day, the patient's pain was significantly alleviated, with the VAS score dropping from 7 to 3, reflecting a 57.1% improvement. His mood improved, and his eating and sleeping patterns normalized. By the second day, the pain score decreased from 3 to 0, indicating complete pain relief, with a 100% improvement rate. During the treatment of PHN, the patient remained hospitalized and received antiviral medication acyclovir (5 mg/kg/d) for managing the rash. Throughout the 7-day treatment period, there was no recurrence of severe pain. Follow-up over 6 months postdischarge showed no recurrence of pain. Throughout the treatment, the patient reported no side effects (Table 1).

Patient 2

A 52-year-old Caucasian American man with no history of neurological diseases, chickenpox, or HSV infection presented to our hospital with neuropathic pain resulting from clusters of herpes zoster extending from his right armpit to his waist. The patient had been diagnosed with herpes zoster a year prior. Initially, he received antiviral medication, which resolved the herpes lesions but left behind crusted areas and erythema. The pain was described as sharp, burning, or electric shock-like, occurring intermittently and lasting over 30 minutes each time, often causing visible distress during episodes. The patient had been treated with oral pregabalin (50 mg 3 times daily, increased to 150 mg twice daily after 2 weeks) and oxycodone-acetaminophen tablets (1 tablet every 6 hours during the day), as well as anxiolytics, such as tartaric acid pizotifen tablets. Despite these treatments, he experienced significant gastrointestinal discomfort, and the pain persisted. Pain assessment using the VAS revealed an average pain score of 4 and a most severe pain score of 8, which severely impacted his ability to work, eat, and sleep, leading to poor mental health (Table 2).

Upon examination, the patient had no history of major surgeries, hypertension, hyperglycemia, or cardiovascular diseases, and routine blood tests were normal. Given the severity of his pain, it was decided to administer HA35 injections. The patient received subcutaneous injections into the abdominal fat layer once daily for 15 days, targeting severe or worsening pain. Results in Table 2 showed a significant reduction in pain within one hour of the first injection, with the VAS score for the most severe pain dropping to 4 (a 50% improvement) and average pain decreasing to 2 (a 50% improvement). On the second day, pain scores further decreased, with the most severe pain reducing to 2, indicating a 75% improvement. By the end of the 15-day treatment, the patient reported complete relief from PHN, with improvements in mental state and appetite. A 6-month follow-up via telephone revealed no recurrence of pain and no side effects (Table 2).

DISCUSSION

Pain that occurs during the period from the onset of herpes zoster to lesion healing, as well as pain persisting for > 90 days after lesion appearance, is classified as ZAP. Mild-to-moderate pain can be managed with acetaminophen, nonsteroidal anti-inflammatory drugs, or tramadol, while moderate-to-severe pain may require

Table 1. The pain scores and observation indicators of Patient 1.

	Time	Pain Score	Remission Rate	Observation Record
Before Treatment	0-day	7	-	The patient experienced intermittent, stabbing pain in the left abdomen and back, occurring around 10 times a day, with each episode lasting about 2 minutes and accompanied by itching at the herpes lesion site. Additionally, the patient had a poor appetite, difficulty sleeping, felt depressed, and lacked motivation to work.
Treatment	1-day	3	57.1%	Within one hour of the injection, the severity of the stabbing pain significantly decreased, reducing to a mild pricking sensation with a duration of about one minute. The number of pain episodes decreased to 3-4 times per day. The patient's appetite improved, and he slept well through the night.
	2-day	0	100%	After the second injection, the patient experienced almost complete pain relief and was able to move and stretch freely. Appetite and sleep returned to normal, and the patient resumed work.
Observation After Treatment	7-day	0	100%	During the 7-day hospital observation period, the patient occasionally experienced pain, but it quickly subsided and did not interfere with normal work or social activities.
Follow-up	1-month to 6-month	0	100%	The herpes zoster lesions had scabbed over, leaving only faint scars, with no signs of recurrent zoster-associated pain. Posttreatment observations revealed no adverse effects.

Table 2. The pain scores and observation indicators of Patient 2.

	Time	Pain Score		Remission Rate		Observation Record
		Most Severe	Average	Most Severe	Average	
Before Treatment	0-day	8	4	-	-	The pain was characterized by sharp, burning, or electric shock-like sensations, occurring intermittently, lasting for about 30 minutes at each time. Prolonged pain led to mental stress, poor appetite, and reliance on sedatives for sleep, significantly affecting work efficiency and daily activities.
Treatment	1-day	4	2	50%	50%	Within one hour of the first injection, the patient experienced noticeable relaxation and significant pain relief. The sharp, burning, or electric shock-like pain was reduced by 50%, with the duration of pain decreasing to about 10 minutes. Additionally, the patient's diet and sleep showed improvement.
	2-day	2	1	75%	75%	Within one hour, the patient experienced almost complete pain relief. Throughout the day, the severity of pain during episodes significantly decreased, and the frequency of pain episodes was reduced. The patient's diet and sleep showed continued improvement.
	3-day	1	0	87.5%	100%	The patient experienced almost no pain, with pain episodes occurring only 1-2 times and lasting 1-2 minutes each.
	7-day to 15-day	0	0	100%	100%	The patient's pain was well-controlled, diet and sleep had returned to normal, and there were no obstacles in daily communication or work. The patient reported unprecedented relief.
Follow-up	1-month to 6-month	0	0	100%	100%	The patient's herpes zoster had resolved, with no signs of recurrence of PHN.

calcium channel modulators, such as gabapentin and pregabalin for neuropathic pain, tricyclic antidepressants like amitriptyline, or opioids such as morphine or oxycodone (5). Data indicate that over 90% of adults harbor the VZV, with approximately one-third developing herpes zoster at some point in their lifetime (6). Severe acute pain during herpes zoster is a risk factor for PHN, and the transition from ZAP to PHN may necessitate years of treatment. Therefore, it is crucial to address both acute ZAP and PHN. However, no ideal

treatment method currently exists, considering the safety and tolerability of available medications.

ZAP is a common form of neuropathic pain, and HA35 has been reported to have analgesic clinical efficacy in treating PHN (4). In 10 cases of PHN, a single injection of HA35 effectively relieved pain within 30 to 180 minutes, with no recurrence for 24 hours (4). HA35 is a specific molecular-weight hyaluronan generated by the enzymatic cleavage of high-molecular-weight hyaluronan (7). An imaging study (8) with an intensified quantum imaging detector has shown that HA35 labeled with 125I and 99mTc reaches lymph nodes and the spleen within 5 minutes of injection into the hind limbs of mice, indicating good tissue permeability. Hyaluronan commonly serves physical roles in filling and cosmetic applications, as well as in intraarticular injections for treating joint inflammation. Although studies directly related to herpes zoster pain are limited, research on hyaluronan for pain relief exists. Caires et al (9), as well as de la Pena et al (10), demonstrated that hyaluronan inhibits Ca2+ influx through the transient receptor potential vanilloid 1 channel, blocking pain activation. The long-lived naked mole rat, known for its resistance to cancer, lack of pain sensation, and longevity, attributes these traits to hyaluronan (11). The HA35 used in this study is a clinically validated drug with no reported side effects (12). Two patients, one with acute ZAP and the other with PHN, experienced significant pain relief following HA35 injection treatment. Patient 1, with early-stage mild-to-moderate pain, achieved pain suppression with short-term treatment. Patient 2, who had been suffering from long-term PHN, required a longer treatment period but still experienced significant pain relief after 15 days. During the 6-month follow-up after treatment, neither patient reported a recurrence of pain (Tables 1 and 2). These findings suggest that HA35 injections may not alleviate pain merely by numbing the nerves, but instead by repairing and restoring nerve tissue. However, this case report has certain limitations, including a short follow-up duration, limited data collection, and the inclusion of only 2 relatively young patients, which may not fully represent the broader zoster-associated pain population, particularly the elderly who are commonly affected. Therefore, rigorous and larger-scale clinical studies are necessary to quantitatively evaluate the appropriate dosage, administration, and long-term effectiveness of HA35, especially in geriatric patients with ZAP and PHN. Despite these limitations, the treatment outcomes presented in our study contribute to existing pain management strategies, suggesting that HA35 is a promising, safe, and effective option for neuropathic pain. Future studies should focus on diverse patient populations to validate these preliminary findings.

CONCLUSIONS

This case report enhances existing management strategies for zoster-associated pain. HA35 not only safely and effectively alleviates and cures zoster-associated pain, including acute pain and PHN, without causing side effects, but also improves related issues, such as appetite, sleep, and daily interactions affected by pain.

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