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Analgesic Effect of High-Concentration 35 kDa Hyaluronic Acid Fragment Gel in Herpes Zoster–Related Pain: A Case Series

Fenghe Xu[1],Xiaoxiao Jia[2], Jessica H Hui[2],Vera Gorbunova[3*], Mizhou Hui[2*]

[1]Department of Pain Diagnosis and Treatment, Affiliated Hospital of Qingdao University，Qingdao, China；
xufenghe126@126.com
[2]Hynaut Laboratories, Qingdao, China；
[3]Departments of Biology and Medicine, University of Rochester, Rochester, New York, USA；
Xiaoxiao Jia, 15621486915@163.com; ORCID: https://orcid.org/0009-0007-2139-1898
Jessica H Hui, Jhhui@alumni.stanford.edu
Vera Gorbunova, vgorbuno@UR.Rochester.edu; https://orcid.org/0000-0001-8979-0333
Mizhou Hui, mizhou.hui@alumni.utoronto.ca; ORCID: https://orcid.org/0009-0003-4283-189X

Corresponding author: Vera Gorbunova, Mizhou Hui

Corresponding Author

Vera Gorbunova,Departments of Biology and Medicine, University of Rochester, Rochester, New York, USA；
Email: 15621486915@163.com

Mizhou Hui
Hynaut Laboratories, Qingdao, China
Email:*mizhou.hui@alumni.utoronto.ca*

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Abstract:

Background: Herpes zoster (HZ) is often accompanied by severe neuropathic pain, known as herpes zoster–related pain (ZAP), which greatly impairs patients' quality of life. Hyaluronic acid (HA) possesses anti-inflammatory and neuroprotective properties. Previous studies have shown that subcutaneous injection of 35 kDa HA fragments can rapidly relieve various types of pain, including ZAP. This study aimed to evaluate the analgesic efficacy of a 10% high-concentration 35 kDa HA fragment (HA35) gel applied topically in patients with ZAP. Methods: Four patients with ZAP (aged 57–77 years) were included. All received topical application of 10% HA35 gel; one patient additionally used a skin protective film to prevent gel drying. Pain intensity was assessed using the Numeric Rating Scale (NRS, 0–10) before and after treatment. Results: In three patients with acute ZAP, the mean NRS score decreased by approximately 55% within 2 minutes after application and dropped to 1–2 after 20 minutes, with analgesic effects lasting about 4 hours. In one patient with postherpetic neuralgia (PHN), the combination of HA35 gel and skin protective film extended the analgesic duration beyond 8 hours and significantly reduced erythema and swelling. Conclusions: The 10% high-concentration HA35 gel provided rapid and safe analgesia in ZAP, and the addition of a skin protective film further prolonged the duration of pain relief. This non-invasive, simple, and well-tolerated method offers a promising new topical approach for managing ZAP.

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Introduction

Herpes zoster (HZ) is a common neurocutaneous disorder caused by reactivation of the varicella-zoster virus (VZV) latent in the dorsal root or cranial nerve ganglia. It is characterized by clusters

of vesicular eruptions distributed along a dermatome, often accompanied by persistent or paroxysmal neuropathic pain (1). Epidemiological studies indicate a lifetime incidence of approximately 20–30% (2), with a significantly higher rate in individuals over 50 years of age. With the aging population, the societal burden of HZ and its associated pain continues to increase.

Herpes zoster–related pain (ZAP) encompasses both acute pain during the active phase and postherpetic neuralgia (PHN) [3]. Clinically, ZAP manifests as continuous or intermittent burning, stabbing, or electric shock–like pain, often accompanied by allodynia and hyperalgesia. Some patients experience chronic neuropathic pain for months or even years after rash resolution [4]. ZAP severely impairs quality of life, leading to anxiety, depression, and sleep disturbances. The underlying mechanisms are complex, involving neuroinflammation, peripheral and central sensitization, and altered sodium channel expression [5].

Current HZ management includes antiviral therapy, analgesics, and vaccination. Live attenuated (e.g., Ganwei, Changchun Baike Biological Co., China) and recombinant zoster vaccines [6] have been shown to reduce the incidence of HZ and PHN but cannot completely prevent them. For patients who develop the disease, topical agents (e.g., 5% lidocaine patch “Debaining”, Beijing Tide Pharmaceutical Co.; capsaicin preparations), oral neuropathic pain medications (gabapentin, pregabalin), and interventional approaches such as nerve blocks or spinal cord stimulation (SCS, efficacy ≥80%) are used. However, complete and sustained pain relief remains challenging.

In recent years, hyaluronic acid (HA) has attracted attention for its moisturizing, anti-inflammatory, tissue-repairing, and neuroprotective effects. Studies have demonstrated that high-molecular-weight HA injections can attenuate local inflammation, reduce pain hypersensitivity, and promote nerve regeneration [7]. Our previous studies found that local injection of 2% 35 kDa HA fragments (HA35) significantly alleviated superficial ZAP within a short period [8,9]. Furthermore, recent results (Chinese Patent Application No. 202501344377) revealed that a 10% high-concentration HA35 gel (Production lot number : Q / 0285HND 045) markedly improved refractory pruritus. Based on these findings, we further investigated the analgesic effects of topical 10% HA35 gel in ZAP, particularly comparing the outcomes of gel alone versus combination with a skin protective film. This case series evaluated its immediate analgesic efficacy, safety, and duration to provide reference data for future clinical applications and mechanistic studies.

2. Case Reports

2.1 Patient Overview (Patients 1–3)

Patient 1 was a 77-year-old female, Patient 2 a 68-year-old male, and Patient 3 a 57-year-old female. All were of Chinese ethnicity, generally healthy, with no history of surgery, blood transfusion, anxiety, depression, or prior herpes simplex virus (HSV) or HZ infection. Patient 1 presented with right upper limb pain for 4 days and new vesicular eruptions for 1 day (Figure 1A). Patient 2 had right upper limb pain for 14 days and rashes for 3 days (Figure 1B). Patient 3 reported right foot herpes and pain for 3 weeks (Figure 1C).
All were clinically diagnosed with acute HZ-related pain. Each patient provided written informed consent, and pain intensity was self-rated using the standard Numeric Rating Scale (NRS; 0 = no pain, 10 = worst pain) [10,11].

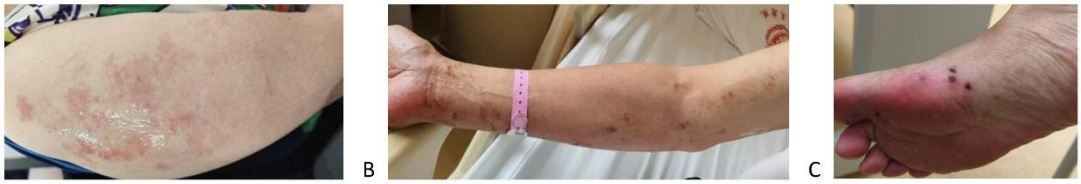

Figure 1. Lesion locations and distribution patterns in Patients 1–3. (A–C: Lesion sites of Patients 1, 2, and 3, respectively)

2.1.1 Patient 1

The patient reported continuous burning and stabbing pain in the right upper limb for 4 days, severely disrupting sleep and daily activities. On

day 3, clustered vesicles and erythema appeared in a dermatomal distribution with mild swelling but no ulceration or purulence. Baseline NRS was 9 (Table 1).
Topical application of 10% HA35 gel (Product code:Q/0285HND045)(without protective film) was performed. After 2 minutes, NRS decreased to 4 (55.6% reduction), further decreasing to 1 after 20 minutes. Pain relief lasted approximately 4 hours, after which NRS returned to 3. No local irritation or discomfort was reported.

2.1.2 Patient 2

The patient reported burning and stabbing pain in the left upper limb for 14 days, exacerbated at night and interfering with sleep. Rashes appeared 3 days prior, presenting as clustered papulovesicles with erythema but no ulceration. No systemic antiviral therapy had been initiated. Baseline NRS was 9 (Table 1).
Following application of 10% HA35 gel (without protective film), NRS decreased to 4 after 2 minutes and to 1 after 20 minutes. Analgesia lasted approximately 4 hours before pain recurred (NRS=3). The treatment was well tolerated without allergic reactions.

2.1.3 Patient 3

The patient presented with right dorsal foot herpes and persistent dull pain with intermittent stabbing sensations for 3 weeks, affecting ambulation. Examination showed crusted erythematous plaques without exudation; local skin appeared indurated and tender. Baseline NRS was 5 (Table 1).
Initial treatment with 10% HA35 gel alone yielded minimal pain relief (NRS remained at 4 after 20 minutes). Considering the dense structure and reduced permeability of foot tissue, treatment was modified to combine 10% HA35 gel with a 5% lidocaine patch. After 2 minutes, NRS decreased to 3; after 20 minutes, to 2. Pain relief lasted for about 4 hours. The treatment was well tolerated with no adverse reactions.

Table 1. Pain score changes in patients with acute ZAP after topical 10% HA35 gel application

Patient	Before treatment	2 min after treatment	20 min after treatment	4 h after treatment
1	9	4	1	3
2	9	4	1	3
3	5	3	2	2

2. 4 Patient Overview (Patients 4)

A 72-year-old female with no prior HSV infection or psychiatric history reported clustered chest vesicles 3 months prior (Figure 2A). Despite rash healing, she developed persistent stabbing and burning pain recurring several times daily, consistent with PHN. Physical examination revealed scattered erythema and crusts over the anterior chest and left back, without exudation or infection. Baseline NRS was 9 (Table 2).
Topical 10% HA35 gel combined with a skin protective film was applied. After 8 hours, NRS decreased to 1; after 12 hours, it increased to 3, and after 24 hours, to 6—remaining significantly below baseline. Redness and local warmth were markedly reduced (Figure 2B-C). Areas with thinner gel application (e.g., left index finger, Figure 2D) exhibited earlier recurrence, suggesting that local gel concentration and retention time are associated with analgesic efficacy.

Table 2. Pain score changes after 10% HA35 gel combined with skin protective film

Patient	Before treatment	8 h after treatment	12 h after treatment	24 h after treatment
4	9	1	3	6

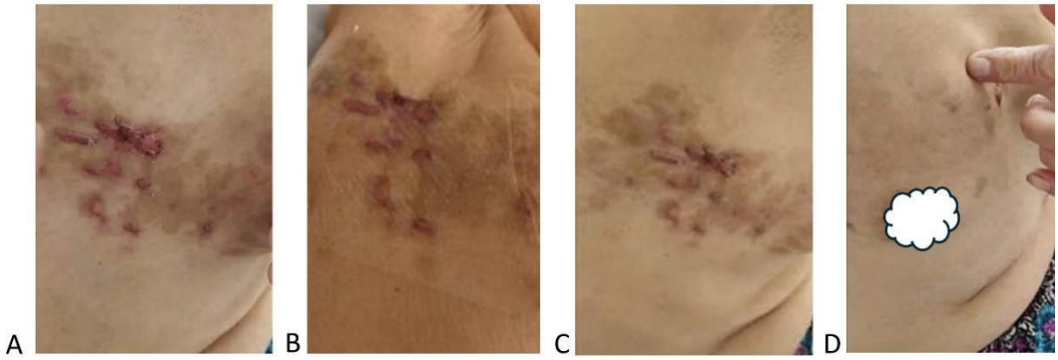

Figure 2. Changes in chest and back lesions in Patient 4 before and after treatment.

3. Discussion

Previous studies have demonstrated that local injection of 2% HA35 can significantly alleviate various types of pain, including inflammatory pain, traumatic pain, cancer-related pain, and neuropathic pain [12–15]. The potential mechanisms are thought to involve modulation of TRPV1/A1 calcium channels and interactions with the lymphatic endothelial hyaluronan receptor LYVE-1 [16–20], thereby reducing peripheral sensory neuron sensitivity and attenuating local inflammatory responses. Clinical evidence has further confirmed that injectable 2% HA35 produces rapid and marked analgesic effects in both acute herpes zoster pain and PHN [8]. However, injectable formulations have inherent limitations in routine home use. Therefore, the present study further explored a more convenient topical formulation of higher-concentration HA35, aiming to expand its potential clinical application scenarios while improving patient compliance.

The results of this case series demonstrate that a single topical application of 10% high-concentration HA35 gel produced significant analgesic effects in patients with ZAP within minutes, with an average duration of analgesia of approximately four hours (Table 1). This gel offers the advantages of rapid onset and ease of use; however, its high viscosity leads to rapid drying, which may limit the duration of its analgesic effect. Notably, when combined with a skin barrier film to maintain local moisture, the duration of analgesia was markedly prolonged to more than eight hours, and visible reductions in erythema and inflammation at lesion sites were observed (Table 2). These findings suggest that prolonging the local residence time of HA35 gel may enhance its anti-inflammatory properties, thereby facilitating the resolution of local swelling and further improving analgesic efficacy [17–20].

On the other hand, Patient 3 exhibited a relatively weaker analgesic response in the foot region, which may be attributable to the dense tissue structure and relatively limited blood supply, resulting in reduced transdermal absorption. When combined with a 5% lidocaine gel patch, the analgesic effect was significantly enhanced and the onset of action was faster. This observation suggests a potential synergistic analgesic interaction between HA35 gel and small-molecule local anesthetics. Such combination strategies may be particularly suitable for ZAP lesions located in areas with dense tissue or limited drug permeability and provide a novel direction for the development of combination topical formulations or adjunctive therapeutic approaches.

The above results indicate that a 10% high-concentration HA35 preparation can significantly eliminate deep tissue pain within 1–2 minutes. This rapid onset strongly suggests that its clinical effects are unlikely to be mediated by direct penetration of HA35 molecules into gingival or deep tissues within such a short time frame. Instead, its analgesic action may involve mechanisms that do not require direct molecular penetration. This mode of action deviates from classical pharmacokinetic and pharmacodynamic models and therefore warrants further mechanistic investigation.

In addition, informal clinical observations indicated that 10% high-concentration HA35 gel may also exert analgesic effects in other pain conditions. Specifically, in four additional cases of neuropathic pain—including persistent brow and temple pain, scalp pain triggered by wind exposure, ocular pain

induced by foreign body stimulation, and joint pain localized at the left palm—as well as in one case of acute gouty arthritis characterized by severe pain and swelling of the toe joint, topical application of the gel resulted in rapid pain relief within approximately one minute, with no adverse reactions observed. These preliminary observations suggest that the analgesic effects of HA35 gel may not be limited to herpes zoster–related pain and that it may hold potential therapeutic value for a broader spectrum of neuropathic and inflammatory pain conditions, warranting dedicated future investigations.

In summary, this study is the first to report the topical analgesic efficacy of a 10% high-concentration HA35 gel for herpes zoster–associated pain. The results demonstrate that this formulation provides rapid onset of action, significant pain relief, and good tolerability. Combination with a skin barrier film or local anesthetic agents further enhances and prolongs its analgesic effects. The primary limitation of this study is that only single-application effects were evaluated, and its potential for disease modification or long-term benefit remains unclear. Future studies with larger sample sizes and randomized controlled clinical trials are needed to validate these findings and to further explore the application value of high-concentration HA35 gel across different disease stages and anatomical sites in patients with ZAP.

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COMPETING INTERESTS

Author have declared that no competing interests exist.

CONSENT AND ETHICS STATEMENT

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

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