Medical Science Journal for Advance Research

Vol. 6, No. 4, December 2025
e-ISSN: 2774-4892

The effect of Chitosan IFNα-pDNA Nanoparticle on the Pain induced by Varicella-zoster Virus in a Rat Model of Post-Herpetic Neuralgia

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ABSTRACT

Background *and* ***Aim:*** *Acute and chronic pain (post-herpetic neuralgia or PHN) are encountered in patients with herpes zoster that is caused by reactivation of varicella-zoster virus (VZV) from a state of neuronal latency. PHN is often refractory to current treatments, and additional strategies for pain relief are needed. The present study aims to assess the effects of Chitosan IFNα-pDNA Nanoparticle(CIN) on the pain induced by varicella-zoster virus in Sprague–Dawley rat model of post-herpetic neuralgia.* ***Methods:*** *: Rats were injected with 0.2mL of PBS, Chitosan IFNα-pDNA Nanoparticle(dose corresponding to 50μg pDNA in 1mL) and IFNα-pDNA(50μg/mL) 3 days before VZV infection. MA and TH ipsilateral/contralateral responses were measured according to days after VZV infection. And also rats inoculated with VZV and showing significant mechanical and thermal hypersensitivity by 19 days post infection were then inoculated at the same footpad with 0.2mL of PBS, Chitosan IFNα-pDNA Nanoparticle(dose corresponding to 50μg pDNA in 1mL) and IFNα-pDNA(50μg/mL). Animals receiving PBS, Chitosan IFNα-pDNA Nanoparticle(CIN) and IFNα-pDNA continued to measure MA and TH ipsilateral/contralateral responses according to days after vector administration.* ***Results:*** *Chitosan IFNα-pDNA Nanoparticle(CIN) effectively reduced chronic VZV-induced nocifensive indicators of pain such as mechanical allodynia(MA), thermal hyperalgesia (TH).* ***Conclusion:*** *These results indicate that administration of Chitosan IFNα-pDNA Nanoparticle(CIN) relieved VZV-induced pain and prophylactic CIN administration prevented VZV-induced pain from developing.*

Keywords: Chitosan IFNα-pDNA Nanoparticle, Varicella-zoster virus, Post-herpetic neuralgia.

Article Information
Received: November 21, 2025; Revised: December 14, 2025; Online: December, 2025

INTRODUCTION

Herpes zoster (HZ), a painful and debilitating disease seen most often in the elderly and immune compromised, is the clinical manifestation of reactivation of the human alphaherpesvirus Varicella Zoster Virus (VZV) from a neuronal latent state that was established during the primary infection, chickenpox (varicella). HZ affects about a

https://doi.org/10.46966/msjar.v6i4.338

quarter of the population in their lifetimes, with incidence rising with age and/or cellular immune decline. [1] Of numerous neurological complications associated with HZ, the most common by far is pain, which is the major contributor to HZ morbidity.

Pain may occur before, during and/or after the skin disease of zoster and even occurs in its absence.[2] Up to 90% of zoster patients experience acute pain,[3] which may be alleviated by timely antiviral administration to limit viral replication. However, one-third of patients develop chronic, more difficult to treat pain states known as post-herpetic neuralgia (PHN) that usually fail to respond to antiviral treatments. These may become so severe that they lead to disparate secondary consequences that affect quality of life, causing depression, withdrawal from society and even suicide.[4]

It is acknowledged that the currently available options for the treatment and management of chronic pain are limited due to significant adverse side effects, particularly of our most effective and most commonly used analgesics; NSAIDS and opioids.[5]

PHN remains a significant public health concern in urgent need for improved treatment strategies.[6] Interferon alpha (IFNα) is a cytokine that exhibits a broad spectrum of antiviral, immunomodulatory, antiproliferative and antitumoral activities.[7] The half-life of IFNα is 2-3 h after intravenous injection, and 3-8 h following intramuscular or subcutaneous administration.[8] Consequently, frequent injections and/or increased dosing are required to reach pharmacologically efficient IFNα levels; this often ties in with high peak concentrations and undesired effects. Systemic application of IFNα causes flu-like, neuro-psychiatric, hematologic, and hepatic symptoms.[9]

To overcome these limitations to their therapeutic use, several investigators have used expression vectors containing the cloned cytokine complementary deoxyribonucleic acid (cDNA) under the regulation of a constitutive promoter as a means of boosting in vivo production of specific cytokines.[10] One important development in gene transfer was the discovery that chitosan (a biocompatible cationic polysaccharide derived from crustacean shell chitin) in the form of nanoparticles (100–200 nm) could be used to deliver plasmids.[11]

Chitosan(CS), a hydrophilic polysaccharide, is characterized for its biodegradable, nontoxic, and biocompatible properties, providing several pharmaceutical applications.[12] Chitosan(CS) nanoparticulate systems have shown potential to be successful carriers for proteins, peptides, DNA and small drug molecules.[13]

So we investigated the inhibitory effect of Chitosan IFNα-pDNA Nanoparticle on the pain induced by varicella-zoster virus in Sprague–Dawley rat model of post-herpetic neuralgia.

MATERIAL AND METHODS

Animals

Male 200–250 g Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA, USA) were acclimatized to housing for 1 week, and then assessed for baseline MA and TH responses, as detailed below, to identify and exclude pre-existing atypical responses. So 14 rats are randomly chosen and during the experiment, feed and water were available to rats at any time.

Rat model of post-herpetic neuralgia

Following isoflurane-induced anesthesia, VZV inoculates were washed in ice-cold PBS, resuspended at 2×106 PFU/mL (or cell equivalents) in PBS and inoculated into the glabrous region of the right rear footpad of male Sprague-Dawley rats.

Rats were monitored for recovery and return to normal activity.

Chitosan IFNα-pDNA Nanoparticle(CIN)

Chitosan/TPP nanoparticles were prepared according to the ionotropic gelation technique

previously developed.(16). Nanoparticles were formed instantaneously upon the dropwise addition of a fixed volume of TPP (e.g. 1.2 ml) solution to a fixed volume of chitosan solution (e.g. 3 ml) under magnetic stirring. For their encapsulation, pvax-IFNα were incorporated into the TPP solution prior to nanoparticle formation. The theoretical DNA loadings were 10% with respect to the total amount of Chitosan used for particle preparation. Nanoparticles were produced at a constant pvax-IFNα concentration of 50μg/mL for use in the *in vivo* studies. Rats were injected with 0.2mL of PBS, Chitosan IFNα-pDNA Nanoparticle(CIN) and IFNα-pDNA 3 days before VZV infection.

And other rats inoculated with VZV and showing significant mechanical and thermal hypersensitivity by 19 days post infection were then inoculated at the same footpad with 0.2mL of PBS, Chitosan IFNα-pDNA Nanoparticle(CIN) and IFNα-pDNA(50μg/mL).

Mechanical allodynia(MA)

MA was determined using one set of calibrated von Frey filaments (Stoetling, Wood Dale, IL, USA) and the 'up down' method established previously.

In brief, animals were allowed to equilibrate on a wire gridbased platform apparatus (IITC Life Sciences, Woodland Hills, CA, USA) for 15 min. Starting with a von Frey filament of 10 g weight of force, each filament was applied for 6 s with sufficient force to cause bending against the paw when applied to one foot at a time. A positive response was defined as rapid withdrawal and/or licking of the paw upon application of the stimulus, and was followed by application of the next finer von Frey filament. A negative response was followed by testing with the next higher weight von Frey filament. A total of six measurements were recorded for both left contralateral (uninoculated) and right ipsilateral (inoculated) footpads.

As some animal to animal variation of sensitivity was occasionally found, MA sensitivity variations from animal to animal were minimized by representing responses as a ratio of the calculated mean ipsilateral/contralateral response for each animal.

Thermal hyperalgesia (TH)

TH was determined using a Hargreaves apparatus (IITC) according to established methodology. In brief, rats were allowed to equilibrate on a glass stage heated to 34 °C for at least 15 min, and then a calibrated focused radiant heat source was placed at a set distance under each rear paw, starting with the contralateral paw. The time recorded for animals to remove their paw from the heat source (latency withdrawal period) was determined from three measurements per paw, with a cut-off of 25 s and a minimum a 1–2 min rest period between measurements. Responses were also calculated as a ratio of ipsilateral to contralateral per animal.

Statistical analysis

Quantitative data are reported as mean ± standard error of the mean. Statistical differences in basal characteristics between the groups were calculated by one-way analysis of variance and t-test for continuous variables. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS 16.0 software.

RESULTS

Rats were injected with 0.2mL of PBS, Chitosan IFNα-pDNA Nanoparticle(CIN) and IFNα-pDNA 3 days before VZV infection. MA and TH ipsilateral/contralateral responses were measured according to days after VZV infection.

As shown in figure 1, 2 the MA and TH score(ipsilateral/contralateral) in Chitosan IFNα-pDNA Nanoparticle(CIN) group was significantly increased compared with other groups($p<0.05$).

Rats inoculated with VZV and showing significant mechanical and thermal hypersensitivity by 19 days post infection were then inoculated at the same footpad with 0.2mL of PBS, Chitosan IFNα-pDNA Nanoparticle(CIN) and IFNα-pDNA.

As shown in figure 3, 4 the MA and TH score(ipsilateral/contralateral) in Chitosan IFNα-pDNA Nanoparticle(CIN) group was significantly increased compared with other model groups($p < 0.05$).

DISCUSSION

Acute and chronic pain (post-herpetic neuralgia or PHN) are encountered in patients with herpes zoster that is caused by reactivation of varicella-zoster virus (VZV) from a state of neuronal latency. PHN is often refractory to current treatments, and additional strategies for pain relief are needed.[6] Interferon alpha (IFNα) is a drug used to treat viral infections and cancer diseases.

Due to its poor stability in the gastrointestinal tract, only parenteral administration ensures bioavailability, which is associated with severe side effects.[9] The half-life of IFNα is 2-3 h after intravenous injection, and 3-8 h following intramuscular or subcutaneous administration.[8]

Chitosan(CS) nanoparticulate systems have shown potential to be successful carriers for proteins, peptides, DNA and small drug molecules.[13] In this work, we produced pvaxIFNα-loaded chitosan nanoparticles by the ionotropic gelation method and investigated the inhibitory effect of Chitosan p^{vax}IFNα Nanoparticle on the pain induced by varicella-zoster virus in Sprague–Dawley rat model of post-herpetic neuralgia. First, rats were injected with 0.2mL of PBS, Chitosan IFNα-pDNA Nanoparticle (CIN) and IFNα-pDNA 3 days before VZV infection. As shown in figure 1, 2 the MA and TH score(ipsilateral/contralateral) in Chitosan IFNα-pDNA Nanoparticle(CIN) group was significantly increased compared with other groups.

As a result, we conclude that prophylactic administration of CIN can block the development of VZV-induced pain. Then rats inoculated with VZV and showing significant mechanical and thermal hypersensitivity by 19 days post infection were then inoculated at the same footpad with 0.2mL of PBS, Chitosan IFNα-pDNA Nanoparticle(CIN) and IFNα-pDNA. Figure 3 ,4 showed that Animals receiving PBS or IFNα-pDNA continued to show significantly biased MA and TH ipsilateral/contralateral responses after vector administration. Remarkably VZV-induced MA and TH nocifensive responses showed prolonged relief following a single inoculation of Chitosan IFNα-pDNA Nanoparticle(CIN).

CONCLUSION

Our study showed that Chitosan IFNα-pDNA Nanoparticle(CIN) can inhibit the pain induced by varicella-zoster virus in Sprague–Dawley rat model of post-herpetic neuralgia.

ACKNOWLEDGMENT

None.

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