Interventional Treatments for Postherpetic Neuralgia

MOHAMMADREZA KAZEMI
PAIN FELLOWSHIP
One of the most resistant chronic pain problems, commonly affecting elderly patients.

It presents as a pain that persists after the resolution of the rash caused by herpes zoster (HZ).
Pain associated with herpes zoster has three phases:

- **An acute herpetic neuralgia:** where the pain that accompanies the rash lasts up to 30 days after the onset of rash.
- **Subacute herpetic neuralgia:** that lasts for 30 – 120 days after the onset of rash
- **Post-herpetic neuralgia,** where the pain persists **beyond 120 days** after the onset of rash.
The duration of PHN is highly variable and about 50% of the patients recover within a year of onset of pain.
The pain of PHN usually follows the typical dermatomal distribution of the rash caused by herpes zoster

- **Unilateral Thoracic** dermatomes
- **Trigeminal** nerve, especially the **ophthalmic** branch, are most frequently affected
PAIN:

- Pain: **Lancinating** or **electric** shock-like sensation.

- Apart from this, patchy **alldynia**, **hyperesthesia**, and **hypoesthesia** can present to varying degrees in the affected region.

- These spontaneous pains, particularly the **alldynia**, can be disabling and debilitating leading to depression, **social isolation**, and increased health care utilization.
Pathophysiology
Varicella zoster virus is a highly contagious double stranded DNA virus of the herpes family.

Primary varicella manifests commonly as chickenpox in a nonimmune or incompletely immune person. During the primary infection, the virus gains entry into the sensory dorsal root ganglia.

Reactivation of the virus occurs following depression of cell-mediated immunity and in advance-aged patients.

The reactivated virus replicates and migrates down the sensory nerve leading to the dermatomal distribution of pain.

The associated inflammation in the peripheral nerves leads to demyelination, wallerian degeneration, and fibrosis.

Thus, as a result, uninhibited and amplified activity in unmyelinated primary afferents leads to pain associated with post-herpetic neuralgia.
Risk Factors

- Delay in treating acute herpes infection
- Older age
- Pain severity
- Greater rash severity
POST HERPETIC NEURALGIA

Pharmacological interventions
- 1st First Line Rx
  - Gabapentin + / - Lidocaine 5%
  - 2nd Second Line Rx
    - Opioid + TCA

Non-pharmacological interventions
- Behavioral therapy, Psychological counseling, TENS, Acupuncture

Refractory PHN pain
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drugs</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral Agents (within 72 hours of symptom onset)</td>
<td>Acyclovir, Famciclovir, Valacyclovir</td>
<td>A</td>
</tr>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>B</td>
</tr>
<tr>
<td>Corticosteroids only in high-risk groups</td>
<td>Prednisolone</td>
<td>I</td>
</tr>
<tr>
<td>Nerve Blocks</td>
<td>Repetitive paravertebral nerve blocks with local anesthetics + / - steroids Sympathetic blocks (e.g, lumbar sympathetic, stellate ganglion block)</td>
<td>I</td>
</tr>
<tr>
<td>Medication</td>
<td>Dosage</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100 to 300 mg orally at bedtime; increase dosage by 100 to 300 mg every three days until dosage is 300 to 900 mg three times daily or response is adequate</td>
<td>Mid peripheral edema, cognitive impairment, somnolence, fatigue, dizziness, ataxia</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>75 mg twice daily, increase to 150 mg bid daily within one week</td>
<td>Sleep disturbance, dizziness</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10 to 25 mg orally at bedtime; increase dosage by 25 mg every two to four weeks until response is adequate, or to a maximum dosage of 150 mg per day.</td>
<td>Sedation, dry mouth, constipation, sweating, xerostomia, confusion, dysrhythmias, weight gain, dizziness</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone ER</td>
<td>10 – 40 mg every 12 hours, as titrated</td>
<td>Nausea, constipation, sedation, cognitive dysfunction, hormonal changes, skin irritation, vertigo</td>
</tr>
<tr>
<td>Morphine SR</td>
<td>5 – 50 mg every 12 hours, titrate as required</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>2.5 mg – 10 mg tds</td>
<td></td>
</tr>
<tr>
<td>Transdermal buprenorphine</td>
<td>5 – 20 mcg / hour, changed every three days</td>
<td></td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>25 mcg / hour – 100 mcg / hour</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg / day, increased to a maximum 400 mg / day</td>
<td></td>
</tr>
<tr>
<td>Topical agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin cream 0.025%</td>
<td>Applied to affected area three to five times daily</td>
<td>Localized erythema and uncomfortable burning, stinging or itching.</td>
</tr>
<tr>
<td>Capsaicin cream 0.075%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin cream 8%</td>
<td>Single-application placed on the skin for 60 minutes after pretreatment with lidocaine cream; Up to four patches may be applied at one time, and repeated as often as every three months</td>
<td></td>
</tr>
<tr>
<td>5% Lidocaine gel</td>
<td>Apply to affected area every four to twelve hours, as needed.</td>
<td>Localized skin irritation</td>
</tr>
<tr>
<td>Transdermal 5% lidocaine</td>
<td>One-to-three patches worn for 12-hour intervals</td>
<td></td>
</tr>
<tr>
<td>Eutectic mixture of local anesthetics (2.5% lignocaine, 2.5% prilocaine)</td>
<td>Apply to affected area every six to twelve hours, as needed.</td>
<td></td>
</tr>
</tbody>
</table>
Refractory PHN pain

Epidural block / Intercostal nerve block / Stellate ganglion block

IV Lidocaine / NMDA antagonist
Capsaicin 0.75%

Severe and Refractory PHN pain

Spinal cord stimulation
Intrathecal steroid injection
Neuroablative surgery
Systemic Therapy

N-methyl-D-aspartate Antagonist
Ketamine
Dextromethorphan
Mementine
Intravenous lidocaine
Interventional Therapies
Postherpetic neuralgia

- Chronic, persistent, debilitating pain
- Dermatomal distribution in patients who have recovered from shingles.
- Aching, itchy, lancinating, or sharp.
- Allodynia, hyperalgesia, areas of anesthesia, and deficits in thermal, tactile, pinprick, or vibration sensations
- Extending beyond the margins of the affected dermatomes.
At 3 months after the onset of shingles:

- Patients aged < 60 years have a 1.8% risk
- Patients aged > 60 years have risks of 3.3% after 12 months
Subcutaneous Botulinum Toxin A Injection

- Botulinum toxin is a neurotoxic protein purified from the bacterium Clostridium botulinum.
- The L-chain, which exhibits Zn2+-dependent protease activity inhibit the release of neurotransmitters (acetylcholine and substance P) from motor and sensory neurons, respectively.
- Additionally, botulinum toxin reduces peripheral nociceptive input by inhibiting the release of glutamate (peripheral neurotransmitter involved in neurogenic inflammation).
Two randomized, double-blind, placebo-controlled trials have evaluated the effectiveness of subcutaneous botulinum toxin A injection for persistent moderate-to-severe post-herpetic neuralgia.

Botulinum toxin was injected subcutaneously within a 1- to 2-cm radius over the painful region.

- Per site 5-10 IU
- The maximum doses did not exceed 200 and 100 IU.
- Benefits in both studies: improved VAS scores and sleep durations and reduced numbers of patients using opioids.
- These effects emerged at 7 days after injection and persisted for 3 months.
Local Triamcinolone Injection

- **Peripheral sensitization**, which involves **neural** damage and **inflammation** with subsequent **edema**.
- The injured tissue releases **inflammatory mediators** that reduce the nociception **threshold**, and thus activate peripheral nociceptors.
- **Corticosteroids** may ameliorate post-**herpetic neuralgia** by modulating this inflammatory process.
- Local (i.e., **intralesional**) injection of triamcinolone plus lidocaine.
- 3 injections at **2-week** intervals and reported pain relief at weeks 6 and 12.
Figure 1 The intracutaneous injections were placed along the axillary line (A), midclavicular line (B), and subscapularis line (C) between T4 and T6.
Transcutaneous Electrical Nerve Stimulation

- Noninvasive and safe application of electrical stimulation to the skin for pain control.
- Segmental inhibition in the dorsal horn as well as descending inhibition and stimulates the release of endogenous opioids to relieve pain at both low and high frequencies.
- Oral Pregabalin
Neuraxial and sympathetic blocks

- Epidural (Paravertebral)
- Sympathetic block
- Intrathecal**
Epidural block.

- 18-gauge Tuohy needle was introduced into the interlaminar space at the second or third level below the target level under fluoroscopic guidance.

- The period of catheterization was limited to within 2 weeks, due to concerns regarding infection.
Paravertebral Block

- Paravertebral block, a common alternative to epidural injection, might provide short-term relief of intractable post-herpetic neuralgia.
- Repetitive paravertebral block comprising bupivacaine and clonidine.
- T3-level catheter for 3 weeks.
Figure 1 Ultrasound-guided thoracic paravertebral block in a sagittal image. Ultrasound image (A) and schematic image (B) are shown.
Fig 1 Radiological spread of radio-opaque dye injected at T2-T3.
Sympathetic Nerves Block

- The sympathetic nervous system is believed to be an important mediator of pain.
- After nerve injury or tissue inflammation, collateral sprouting in the peripheral and dorsal root ganglia and the upregulation of functional adrenoceptors may lead to the formation of anatomic and chemical couplings between sympathetic postganglionic and afferent neurons.
- Sympathetic terminals also contribute to the sensitization of nociceptive afferents.
- However, the mechanisms by which the sympathetic nervous system affects postherpetic neuralgia remain uncertain.
The patients selected for a trial of stellate ganglion block had not yet developed postherpetic neuralgia.

- 150-mg pregabalin twice daily.
The patients selected for a trial of stellate ganglion block had not yet developed postherpetic neuralgia. 150-mg pregabalin twice daily.
Drg prf.
Dorsal Root Ganglion Destruction

- Histopathologic studies have identified the loss of cells, axons, and myelin and concomitant fibrosis in the sensory ganglia of patients with severe post-herpetic neuralgia.

- Accordingly, the pain sensation may be caused by an ectopic discharge in the nociceptors and low-threshold afferents at the dorsal root ganglion.
Pulsed Radiofrequency

- The underlying mechanism is attributed to the effects of a rapidly changing electrical field on neuronal membranes.
- Make electrolyte conduction and subsequent depolarization.
- Satisfactory pain relief that persisted for 6 months.
- Targeted the intercostal nerves.
The needle tip was placed under the pedicle in the anteroposterior view and in the posterocranial portion of the intervertebral foramen in the lateral view for fluoroscopic imaging.

Sensory stimulation was performed using a 50-Hz current. If a tingling sensation was observed in the affected dermatome below 0.5 V, the position of the needle was considered appropriate.

After confirming the needle position, PRF of 42°C (20 milliseconds, 2 Hz, 45 V) was applied for 360 seconds. Impedance was maintained at less than 500 Ω throughout the procedure.
Intercostal Nerve Block
Intrathecal Injection of Methylprednisolone with Local Anesthetics or Midazolam

- **Histopathologic studies**: subacute or chronic inflammatory processes involving the infiltration and accumulation of lymphocytes around the spinal cord and interleukin-8.

- **Intrathecal > epidural**

- **Preservatives** are of considerable concern (potential risks of adhesive arachnoiditis).

- **Midazolam**: improvements in pain, allodynia, sleep quality, and changes in the area of allodynia.
The “gate control theory of pain” suggests that neural signal transmission is regulated by the dorsal horn of the spinal cord. A-beta fibers inhibit the transmission of pain signals carried by C-fibers. Affect the levels of γ-aminobutyric acid and adenosine in the dorsal horn and consequently reduce neuropathic pain.
Initially, the patients received a diagnostic block to identify the segment in which temporary electrodes would be placed, and a permanent pacemaker was implanted subcutaneously after successful trials.
Conclusion
The current evidence is insufficient for determining the single best interventional treatment.
Considering

- Invasiveness
- Price
- Safety
THE END