Title: Prevention of Post Herpetic Neuralgia by Ultrasound Guided Single Nerve Block in the Emergency Department

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I. Introduction

Herpes zoster causes significant morbidity on over 1 million Americans every year.[1] Although the majority of herpes zoster pain will self-resolve within one week, a significant proportion of patients will develop postherpetic neuralgia (PHN), which is characterized by debilitating pain that persists more than three months after the initial symptoms.[2,3] Nerve blocks have been previously studied as a method to control herpes zoster pain in outpatient pain clinics and inpatient settings. This study aims to investigate whether emergency department ultrasound guided nerve blocks can prevent PHN and effectively treat acute herpes zoster pain.

II. Background and Significance

Varicella-zoster virus causes acute herpes zoster, which causes characteristic burning dermatomal pain that self resolves within two to three days for most patients. Unfortunately for some, the pain can persist for months after initial symptoms.[4] Pain that persists between one to three months is commonly classified as subacute herpetic neuralgia. Pain that persists three or more months after initial symptoms is classified as postherpetic neuralgia (PHN).[5] The pain associated with acute herpes zoster is due to hemorrhagic inflammation and fibrosis of the peripheral nerve, dorsal root, and dorsal root ganglion, but the mechanism of PHN is not well understood. It is hypothesized that the afferent neuron activity triggered by tissue damage causes changes in dorsal nerve roots leading to hypersensitivity and eventually spontaneous activity and ectopic discharges from the inured nerves and dorsal roots regardless of tissue insult.[6,7,8]

Over 200,000 cases of herpes zoster are managed in the emergency room every year in the United States and up to 43% of these patients may develop PHN.[2,3, 14] Of all patients with acute herpes zoster, 10% will require 3 or more follow-up visits for pain management causing significant burden on the medical system.[9] Herpes zoster pain can be chronic and intractable, and can significantly decrease a patient's perceived quality of life which in some cases can lead to depression and even suicide.[10] Commonly, the initial presentation occurs in the emergency department; thus, it is paramount for an emergency room physician to adequately manage the acute pain of herpes zoster. However, herpes zoster pain can be difficult to control. In addition, it is unknown if any treatment modality can minimize the risk of PHN. Current treatment modalities including antivirals, anticonvulsants, oral corticosteroids, and opioids have not shown to be prevent postherpetic neuralgia.[11]

In outpatient pain clinics and inpatient settings, ultrasound guided nerve blocks using local anesthetics and corticosteroids have been shown to effectively treat acute herpes zoster pain. Several studies have found that patients who received nerve blocks for acute herpes zoster had a reduced incidence of PHN at 3 months.[12-16] Local anesthetics reduce afferent neuron activity preventing dorsal root automaticity while steroids decrease vasogenic edema reducing tissue damage.[14] Ultrasound guided nerve blocks have become a widespread method of pain management in the emergency department for various clinical scenarios. The purpose of this study is to investigate the efficacy of utilizing ultrasound guided nerve blocks in preventing PHN in the emergency department and managing acute herpes zoster pain.

III. Study Objectives

The goal of this study is to evaluate the rate of PHN development in emergency department patients who receive ultrasound guided nerve blocks using bupivacaine and dexamethasone for acute herpes zoster. We will also study the effectiveness of the block in managing acute herpes zoster pain. The primary outcome is the percentage of patients who have significant herpetic pain at 1 month and 3 months after receiving the nerve block. Secondary outcomes measured are pain scores at 1 hour, 1 month, and 3 months post-nerve block. The amount of opioids used after discharge as well as the number of return visits for herpetic pain will also be recorded.

IV. Hypothesis

Our hypothesis is that patients who receive nerve blocks will decrease the occurrence of PHN development at 1 month and 3 months post-treatment. Our secondary hypothesis is that nerve blocks will decrease pain scores at 1 hour, 1 month, 3 months, as well as reduce the amount of opioids used and number of return visits for herpetic pain.

V. Study Design

This study will be a single center prospective observational study that will be conducted in the emergency department of an urban hospital center. A trained emergency medicine physician will screen and assess the patient for eligibility. Once the patient is determined to be eligible, informed consent will be obtained. A trained EM physician will then administer a nerve block using bupivacaine and dexamethasone to a patient with acute herpes zoster. The patient will be started on Acyclovir 800 mg five times daily for seven days. For mild to moderate breakthrough pain, the patient will be prescribed a 5-day course of Tylenol 650 mg and Ibuprofen 400 mg taken up to every 8 hours together. For severe breakthrough pain, the patients will be prescribed a two-day course of 7.5 mg morphine sulfate immediate release to be taken up to every 6 hours. The location of the nerve block and dosage of injected medications will depend on the distribution of the affected dermatome. The dermatomal distributions with their associated nerve blocks and medication dosages are shown the table below.

Herpes Zoster Distribution	Nerve Block Type	Medication
T2-T9	Serratus Plane	30 mL 0.25% bupivacaine and 8 mg Dexamethasone
C2-C3	Greater Occipital Nerve	2 mL 0.25% bupivacaine and 4 mg dexamethasone
C3-C4	Superficial Cervical Plexus	10 mL 0.25% bupivacaine and 4 mg dexamethasone
Anterior Abdominal Wall T6 – L1	Transversus Abdominis Plane	30 mL 0.25% bupivacaine and 8 mg dexamethasone

A numerical verbal rating scale will be used to assess the patient's pain pre-injection and at 1-hour post nerve block. We will then call the patient at the 1 week, 1 month, and 3-month

post-nerve block time intervals to assess the patients' pain. We will also record the number of follow-up visits for herpetic pain and the amount of additional pain medications used.

When called the patient will be asked a series of questions:

1. Do you continue to have pain associated with your herpes zoster infection?
2. If so, how would you rate your pain from a scale of 0-10? 10 being the worst pain you have ever had in your life.
3. About how much pain medication have you been using since the initial nerve block? How many doses of Ibuprofen or Tylenol per day for how many days? How many doses of morphine sulfate immediate release or other opioids were taken per day for how many days?
4. If you used other forms of pain controllers, what were they and how often and for how long did you use them?
5. Have you seen your primary care doctor, pain clinic, emergency department, or other pain management follow-up visits for management of your herpes pain? If so, how many visits have you made?
6. What side effects have you had since the nerve block?

1. Subjects:

The study population is Maimonides Medical Center emergency department patients older than 18 years of age presenting with acute herpes zoster patient with characteristic dermatomal vesicular skin lesions within 30 days of initial symptoms.

2. Eligibility Criteria:

The inclusion criteria are patient age over 18 with herpes zoster pain onset within 30 days of characteristic dermatomal herpes zoster rash. The exclusion criteria are allergy to bupivacaine, signs of infection over herpes zoster site, greater than 30 days duration of pain, pain across more than one dermatome and pregnant and/or breastfeeding women.

3. Design:

The primary outcome is the percentage of patients who have significant herpetic pain at 1 month and 3 months after receiving the nerve block. Secondary outcomes measured are pain scores pre-injection, and 1 hour, 1 month, and 3 months post-nerve block. The number of tablets of opioids and other analgesics used after discharge as well as the number of return visits for herpetic pain will also be recorded.

4. Data Collection Procedures:

The numerical verbal rating scale pain score will be recorded by a research staff member at 1 hour after administration of nerve block. The patients will then be called at 1 week, 1 month, and 3 months post nerve block for assessment of NRS as well as number of follow-up visits and amount of analgesics used. A medication track form/log will be given to the patients to help record the amount of medications taken in the first week. The patients will be stratified by age: those under 50, 50-59, 60-69, and 70 and older as well as herpes zoster vaccination status.

5. Sample Size:
Earlier studies show the incidence of post herpetic neuralgia to be up to 43% in patients who are diagnosed with acute herpes zoster.[14] We will calculate a sample size required to achieve an α of 5 and power of 80% to detect a clinically relevant reduction in the incidence of PHN from 43% to 10%. We will allow for 10% loss of follow-up.

6. Expected Outcomes:
We expect that patients undergoing ultrasound guided nerve block will have decreased incidence of subacute herpetic neuralgia and PHN. We also expect pain to be well controlled at 1 hour, 1 week, 1 month, and 3 months post nerve block.

7. Adverse Event Reporting:
Side effects of local anesthetics are rare but usually target the central nervous system (numbness, metallic taste, anxiety, visual changes, muscle twitching, seizure, somnolence, coma, respiratory depression) and the cardiovascular system (hypertension or hypotension, tachycardia or bradycardia, ventricular arrhythmias and/or asystole). All adverse and unexpected events will be recorded during the calls in the 3-month follow-up period and reported to the IRB as per hospital policy. Adverse events will also be included in the final publication.

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