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Resolution of Chemotherapy-Induced Peripheral Neuropathy with Subanesthetic Ketamine

Khan M¹, Nguyen M¹, Prabhneet P²*, Kerulis M³, Bal N⁴ and Irv W⁴

¹Chicago College of Osteopathic Medicine, Midwestern University, Downers Grove, IL, USA
²Aureus University School of Medicine, Oranjestad, Aruba
³The Family Institute at Northwestern University, Evanston, IL, USA
⁴Ketamine Centers of Chicago, Chicago, IL, USA

*Correspondence: Prabhneet Pannu, Aureus University School of Medicine, Oranjestad, Aruba, E-mail: ppannu.vpp@gmail.com

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Abstract

Chemotherapeutic drugs have been shown to induce peripheral neuropathy which can become very painful, diminish functional ability, and decrease quality of life. Although Chemotherapy-Induced Peripheral Neuropathy (CIPN) may resolve completely in some individuals, others demonstrate partial or no resolution of symptoms. Presented is a case in which a female patient with a 2-year history of severe CIPN following the diagnosis and treatment of stage 3 triple negative BRCA 1 breast cancer was able to attain complete resolution of her symptoms after the use of subanesthetic ketamine.

Keywords: Chemotherapy, Neuropathy, Ketamine

Abbreviations: CIPN: Chemotherapy-Induced Peripheral Neuropathy; NMDA: N-methyl-D-aspartate; NMDAR: N-methyl-D-aspartate receptor; CRPS: Complex Regional Pain Syndrome; VAS: Visual Analogue Scale

Introduction

Peripheral neuropathy is a condition where the nerves outside the brain and spinal cord become damaged, which often causes a variety of symptoms such as weakness, sensory loss, allodynia, hyperalgesia, and pain. While Peripheral neuropathy can be caused by several conditions including but not limited to, autoimmune diseases, diabetes, infections, inherited disorder, kidney disease, liver disease, trauma, tumors, and medications [1]. Cancer-related neuropathic pain can arise from several different mechanisms, the tumor itself impinging on a nerve, increase in cytokines and chemokines (IL-8, IL-10, IL-6), or from chemotherapy and radiation. Drugs such as paclitaxel, vincristine, cisplatin, and bortezomib have been widely reported to produce neuropathies [2].

Neuropathic pain arises from changes in damaged nerves which alter function in the spinal cord and brain. The damage increases the excitability in both affected and unaffected nerve fibers. In the spinal cord, the activity of calcium channels on peripheral nerves and receptors for glutamate, especially N-methyl-D-aspartate (NMDA) receptors, are increased [2]. These changes overall increase the baseline excitability of nerve cells.

Common treatments for peripheral neuropathy include analgesics, anti-seizure medications such as gabapentin, antidepressants, and physical therapy. Ketamine is a dissociative anesthetic which primarily binds noncompetitively to N-methyl-D-aspartate glutamate receptors (NMDAR). It has been known that ketamine has been used to treat Complex Regional Pain
Syndrome (CRPS). In this condition, NMDA is activated and upregulated in the spinal cord, similar to patients with neuropathic pain [3]. However, current literature on the use of topical ketamine for treating CIPN is inconclusive [4].

In the following case, a patient with CIPN observed complete resolution of her symptoms with subanesthetic intravenous ketamine treatments.

**Case Presentation**

A 37-year-old right-handed woman presented to our clinic with CIPN. Patient was previously diagnosed with stage 3 triple negative BRCA 1 breast cancer in February 2016. In April of 2016, the patient enrolled in the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY 2 Trial), which aims to determine how women with breast cancer respond to standard chemotherapy and standard chemotherapy combined with experimental drugs. As part of this trial, the patient received paclitaxel 126.4 mg in sodium chloride 0.9% 250 mL once a week along with pembrolizumab 200 mg in sodium chloride 0.9% 100 mL once every two weeks for 12 weeks as an IV infusion followed by 8 weeks of doxorubicin injection 94.8 mg and cyclophosphamide injection 948 mg. In August of 2016, the patient had bilateral prophylactic mastectomy with immediate reconstruction. From October to November of 2016, the patient received 28 rounds of radiation. Patient developed paresthesia with sensations of pins and needles and numbness in the entire left arm. Additionally, the patient experienced weakness and pain of her left arm. She also had limited range of motion of her bilateral arms. Limited range of motion included decreased flexion, extension, abduction, and adduction presumably due to scarring from bilateral mastectomy. The patient used gabapentin 300 mg for the neuropathy but had no relief of her neuropathic symptoms and discontinued the medication due to experiencing the adverse effect of severe fatigue leading to decreased daily function.

Informed consent was obtained from the patient, and she completed a protocol of four ketamine infusions over two weeks followed by maintenance infusions. The patient was initially started on an intravenous ketamine dose of 0.5 mg/kg (35 mg), which was incrementally increased as tolerated to reach a desired target pain inventory rating (i.e., a 50% change from initial rating). Each infusion was approximately 45 minutes long after which the patient rested for another 30 minutes. Vitals were monitored at 15-minute intervals. The patient experienced dissociation which was tolerated well and reported no adverse or lingering side effects.

Patient progress was tracked with a self-reported pain score on the Visual Analogue Scale (VAS). The staff administered the VAS prior to each treatment with interpretation as follows: Scale 1-10. 1-3 = mild pain, 4-6 = moderate pain, 7-10 = severe pain.

Prior to the first treatment, the patient was categorized as having severe pain according to VAS with a score of 10. The following table 1 was recorded throughout the patient’s course of treatment:

<table>
<thead>
<tr>
<th>Date</th>
<th>VAS</th>
<th>Interpretation</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/20/18</td>
<td>10</td>
<td>Severe pain</td>
<td>35 mg</td>
</tr>
<tr>
<td>12/26/18</td>
<td>7</td>
<td>Severe pain</td>
<td>50 mg</td>
</tr>
<tr>
<td>12/28/18</td>
<td>0</td>
<td>No pain</td>
<td>60 mg</td>
</tr>
<tr>
<td>1/2/19</td>
<td>0</td>
<td>No pain</td>
<td>60 mg</td>
</tr>
<tr>
<td>4/19/19*</td>
<td>0</td>
<td>No pain</td>
<td>60 mg</td>
</tr>
<tr>
<td>5/13/19*</td>
<td>0</td>
<td>No pain</td>
<td>60 mg</td>
</tr>
<tr>
<td>8/13/19*</td>
<td>0</td>
<td>No pain</td>
<td>60 mg</td>
</tr>
<tr>
<td>8/15/19*</td>
<td>0</td>
<td>No pain</td>
<td>60 mg</td>
</tr>
</tbody>
</table>

*maintenance infusions

The patient also reported full dissipation of paresthesia with pins and needles sensation after the initial infusion. The patient continued to have limited range of motion of her bilateral arms for which she started occupational therapy.

Last follow up with this patient was done on July 7th, 2020 during which she reported a VAS score of 0 and continued absence of paresthesia. This marked 18 consecutive months of complete relief of pain and paresthesia of CIPN.

**Discussion**

We describe a patient with a 2-year history of severe, refractory CIPN. The patient experienced paresthesia, paresis, allodynia, and limited range of motion. She experienced no relief of her symptoms with the use of pharmaceuticals, such as gabapentin, physical therapy, and traditional medicine, such as acupuncture. After 2 ketamine infusions, she experienced a complete resolution of her pain and paresthesia, and to this day, that relief has been sustained.
Currently, there is no specific treatment option available for CIPN. Common agents used to treat neuropathic pain include tricyclic antidepressants and anticonvulsants; however, these drugs are not recommended due to limited benefits and having adverse effects [5-8]. The only drug recommended for the treatment for CIPN by the American Society of Clinical Oncology is duloxetine [9]. Additionally, research shows that photobiomodulation therapy may also offer a modest benefit for patients with CIPN [10].

We decided to use subanesthetic ketamine infusions as opposed to other treatments due to the cursory response time from induction and to minimize potential adverse effects associated with other options. Although the pathophysiology of CIPN is complex and mostly unknown, recent research suggests that sensitization of the central nervous system may play a role in CIPN. Additionally, research demonstrates that afferent neurons in the spinal cord may have increased rates of glutamate release, thus leading to increased activation of the NMDA receptors [11]. Ketamine infusions are a potential treatment modality for patients with CIPN due to its actions of being a NMDA receptor antagonist and desensitizing the central nervous system [12]. Although limited to a single patient, our report shows that complete resolution of CIPN with subanesthetic ketamine infusions can be obtained. Further research to find the exact mechanism behind this action may lead to a better understanding of how CIPN is developed and ultimately lead to disease prevention and treatment.

Declarations

A signed consent from the patient was obtained prior to treatment to participate in this study and to have deidentified data published. De-identified data is available for review upon written request of the Journal's Editor. Drs. Nandra and Weisman have a financial interest in the Ketamine Centers of Chicago as owners/operators. The study has received no internal or external funding. Each author has contributed substantively to the study by data analysis, background research, delivery of care, and manuscript preparation.

References


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