

CANCER PAIN & PALLIATIVE CARE SECTION

Intravenous Ketamine for Cancer Pain Management, Including Flares During the COVID-19 Pandemic: A Retrospective Study

Daniel Oh , MD, MS,* Paul Haffey, DO,* Ankur Patel, DO,* and Amitabh Gulati, MD[†]

*Department of Rehabilitation and Regenerative Medicine, NewYork-Presbyterian Hospital—University Hospital of Columbia and Cornell, New York, New York; [†]Department of Anesthesiology and Critical Care, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Correspondence to: Amitabh Gulati, MD, Department of Anesthesiology and Critical Care, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA. Tel: 212-639-6851; Fax: 212-717-3206; E-mail: gulatia@mskcc.org.

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Abstract

Objectives. Cancer-related neuropathic pain (CNP) affects an increasing proportion of cancer patients, given improved survival, but it remains difficult to treat. There are no studies on an extended intravenous ketamine protocol and its synergies with common neuropathy treatments to treat CNP. This study aims to 1) evaluate the safety and effectiveness of an intravenous ketamine protocol to treat refractory CNP and 2) uncover synergies between ketamine and common neuropathy treatments. **Methods.** This is a single-center, retrospective review of 57 patients and 192 infusions, with prospective follow-up on 14 enrolled patients during the coronavirus disease 2019 (COVID-19) pandemic. **Results.** The etiologies of CNP were as follows: 13 from tumor compression, 25 with chemotherapy-induced peripheral neuropathy, 13 from surgery, and 6 from radiation therapy. Overall, 42 of 57 patients (73.7%) were responders, and 71.8% of responders received >3 weeks of pain relief on their last infusion. Analysis of adjuvant treatments revealed that the combination of serotonin-norepinephrine reuptake inhibitors and ketamine resulted in an increase in responders compared with nonresponders ($P < 0.01$). Adverse events occurred in 32 of 192 infusions (16.7%). All side effects self-resolved or resolved with intervention per the adverse events protocol. During the pandemic, all 14 currently enrolled patients did not receive ketamine infusions. Thirteen of the 14 patients returned to baseline pain, with 61.5% increasing medications. All experienced worsened function, mobility, mood, or anorexia. **Conclusion.** Intravenous ketamine may be a safe and effective adjuvant treatment for CNP, especially with serotonin-norepinephrine reuptake inhibitors. Larger, prospective studies are warranted and should explore parameters to help prognosticate response to ketamine infusions.

Key Words: Ketamine; Cancer Pain; Neuropathic Pain; Analgesic; Synergy

Introduction

Advances in cancer treatments, including chemotherapy, surgery, and radiation therapy, have improved the survival of cancer patients. Unfortunately, these treatments may have serious painful side effects. Cancer-related neuropathic pain (CNP) affects up to 70% of all cancer patients [1]. CNP significantly contributes to loss of

function and mobility, as well as worsened quality of life (QOL) [2–4]. Additionally, patients with neuropathic pain are reported to have worse sleep, mood, cognition, and physical and social functioning [5].

The etiology of CNP is diverse and can be divided into tumor-related (i.e., direct tumor compression of a peripheral nerve) and treatment-related pain syndromes [6].

Treatment-related pain can be further categorized into chemotherapy-induced peripheral neuropathy (CIPN), postsurgical pain syndromes, and postradiation pain and related neuritis [1]. It is estimated that 64% of CNP is due to direct tumor compression, while 20% is from an adverse event after treatment [1]. The most common treatment-related pain is CIPN, which occurs in 90% of patients receiving neurotoxic chemotherapy [7]. After initial insult to the nerve, pain fibers become hypersensitive and eventually transmit spontaneous pain signals to the brain [1]. CNP is characterized by acute flares on a chronic background, associated with paresthesia, dysesthesia, allodynia, hyperalgesia, or numbness [7,8].

Treating CNP is challenging because of its chronicity, which results from abnormally excitable neurons [9]. Traditional treatment modalities are limited to medications such as opioids, tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentinoids (gabapentin, pregabalin), other anticonvulsants, and topical analgesics, as well as desensitization techniques, offering modest relief [7]. Furthermore, N-methyl D-aspartate (NMDA) antagonists in the form of oral, topical, intranasal, or parenteral ketamine are used to supplement existing treatments for refractory CNP. The NMDA channel is the principal receptor involved in central sensitization and windup phenomena that may lead to chronic pain. Ketamine's antagonistic effect on NMDA receptors is thought to confer benefit by reversing central sensitization and windup [10].

Ketamine has a unique combination of hypnotic, analgesic, and amnestic effects and is used for post-traumatic and perioperative pain treatments [10]. However, these effects occur at anesthetic doses that are higher than the sub-anesthetic doses used to treat chronic neuropathic pain or complex regional pain syndromes. At sub-anesthetic doses, the main analgesic mechanism of action for ketamine is through noncompetitive NMDA receptor antagonism [11]. Given that chronic pain and depression often occur together, there has been an increased interest in ketamine as an agent to treat chronic pain syndromes [10]. Specifically, several randomized controlled trials (RCTs) support the effectiveness of ketamine in CNP with positive results, but they lack robust statistical measures demonstrating significance [10].

Previous studies have assessed the effectiveness of intranasal, topical, and oral ketamine, but intravenous (IV) ketamine infusions appear to be the most promising route of administration [10]. IV ketamine has been successfully used to treat non-oncologic neuropathic pain [12]. In the oncologic population, IV ketamine with morphine was shown to improve CNP [13]. However, another RCT could not confirm the effectiveness of a combination of IV ketamine and morphine to treat refractory cancer pain, including CNP [14]. These studies are limited by few contiguous infusions and short-term follow-up, with each patient receiving one to three infusions, with follow-up of pain reduction within hours to 2

days after infusion. A Cochrane Review by Bell et al. concluded that there is insufficient evidence for the role of ketamine by any route to treat cancer pain, including CNP [15].

Although IV ketamine is used to treat non-oncologic neuropathic pain, it has not been well studied in the setting of CNP. The present study explores the effectiveness and safety profile of an IV ketamine protocol for the treatment of CNP in patients with refractory pain control. This is the first long-term data set in the literature for cancer patients and will help establish an RCT in this population.

Methods

Study Design

This is a single-centered, retrospective analysis of 57 consecutive patients who, between April 2018 and May 2020, were diagnosed with neuropathic pain secondary to various malignancies and associated treatments and underwent an IV ketamine infusion protocol. Patients' demographics, medical history, primary oncologic disease, presence of metastases, cancer treatments, etiology of neuropathic pain, symptomatology, pre- and post-infusion pain and function levels, patient satisfaction, adjuvant analgesics, adverse events, and interventions for adverse events were obtained via retrospective chart review.

This study was approved via a waiver for informed consent by Memorial Sloan Kettering Cancer Center's Internal Review Board and was supported by the Department of Anesthesiology and Critical Care (NIH Core Grant P30). Etiologies of neuropathic pain in this population included direct tumor compression, CIPN, postsurgical pain such as postmastectomy and post-thoracotomy syndromes, and postradiation pain and neuritis. Exclusion criteria included a concurrent diagnosis of diabetes mellitus or underlying peripheral neuropathy before the onset of CNP.

IV Ketamine Infusion Protocol

The IV ketamine protocol consists of a series of 4-hour infusion sessions. Before the start of each infusion, the patient's baseline parameters, including pain via the numeric pain rating scale (NPRS), function, satisfaction, and use of analgesics, were obtained by a registered nurse. All premenopausal women had negative pregnancy tests before infusion. All patients were premedicated with oral ondansetron 4 mg and oral lorazepam 0.5 mg.

The first ketamine infusion started at 10 mg/h and was titrated by 5 mg/h to a maximum of 25 mg/h, as tolerated. All patients were eligible for a second and third infusion 1 week after the previous one, starting at 25 mg/h and titrated by 5 mg/h to a maximum of 40 mg/h. Responders continued with infusions roughly every

4 weeks and were titrated to a maximum dose of 70 mg/h, as tolerated. Patients continued the infusions until they discharged because of undesirable side effects or unsatisfactory pain relief or until death.

IV Ketamine Adverse Events Protocol and Monitoring

Patients' body temperatures, blood pressures, pulse rates, and oxygen saturations were continuously monitored during each infusion session. If patients developed restlessness, they were given oral lorazepam 0.5 mg every 4 hours up to 2 mg as needed, or if they were unable to tolerate oral medications, they were given IV lorazepam 0.5 mg once. If they developed nausea, they were given oral ondansetron 4 mg every 6 hours as needed. If they developed other side effects, such as tachycardia, hypertension, somnolence, headache, or hallucinations, a physician evaluation was performed, which led to administration of as-needed medications, continuing with the infusion, or decreasing/discontinuing the infusion. If adverse events quickly self-resolved, no intervention was performed. Twenty-four hours after infusion, patients were contacted by the patient care team to assess pain parameters and adverse events. All patients followed up in clinic with our service as per standard care (on average 4 weeks after infusion), at which time pain improvement, adverse events, functional improvement, satisfaction with relief, current analgesics, and adverse events due to ketamine therapy were discussed, and a decision was made to continue or cease the treatment.

Definition of a Responder

In this study, responders were defined as patients who reported $\geq 30\%$ reduction in pain based on NPRS or positive subjective qualifiers, including but not limited to "good," "excellent," or "significant" pain relief, as well as functional improvements and/or a reduction in adjuvant analgesics. Responders must have had ≥ 24 hours of pain relief after their first infusion or ≥ 2 weeks of pain relief after their subsequent infusions to continue on the protocol.

Follow-Up of Enrolled Patients During the COVID-19 Pandemic

Because of unforeseen and unfortunate circumstances surrounding the coronavirus disease 2019 (COVID-19) pandemic, 14 patients on the IV ketamine protocol could not proceed with monthly infusions. These patients were contacted in a prospective manner to assess return to baseline pain, impact of pain, change in pain management, adverse events from the last infusion, and length of response. Furthermore, all patients who have since received an infusion were tested for SARS-CoV-2 before infusion. If the test was positive or the patient had symptoms of the virus, the infusion was not offered.

Statistical Analysis

The response rate to IV ketamine therapy was calculated for the total population and was also stratified by the etiology of pain and use of analgesics. Differences between the responder and nonresponder groups were compared with the chi-squared test, with significance defined as $P < 0.05$. If subgroups had fewer than six patients, Fisher's exact test was applied, with significance defined as $P < 0.05$.

Results

Demographics

A total of 57 patients with CNP were treated with the IV ketamine protocol (Table 1). Patients who had underlying neuropathy or peripheral neuropathy before the onset of their CNP were excluded from the analysis. Each patient's pain was identified as being secondary to direct tumor compression ($n = 13$), CIPN ($n = 25$), surgery ($n = 13$), or radiation ($n = 6$). The mean age was 52.23 years (standard deviation 13.33). The most common primary cancer diagnosis was breast cancer (13 patients, 22.8%), followed by nerve sheath tumors (seven patients, 12.3%). Eight of 57 patients (14.0%) had metastases.

Within the tumor compression group, most patients had pain secondary to nerve root compression (eight patients, 61.5%). Within the CIPN group, patients had peripheral neuropathy resultant from vinca alkaloids, taxanes, platinum compounds, bortezomib, lenalidomide, cyclophosphamide, or cytarabine. One patient had peripheral neuropathy from chronic treatment for a pituitary tumor with a somatostatin analog, resulting in small-fiber neuropathy. Within the postsurgical group, six patients (46.2%) had post-thoracotomy or postmastectomy syndromes. Within the postradiation group, most patients had undergone head and neck radiation (four patients, 66.7%), followed by spine radiation (two patients, 33.3%).

IV Ketamine Protocol Response Rate

In total, 42 of 57 patients were responders (73.7%), with 12 of the 42 patients (26.7%, $P = 0.0003$) choosing to discontinue treatment because of unsatisfactory pain relief or undesirable adverse effects (Table 2). Importantly, all responders had improvement in function or mobility while on the IV ketamine protocol. Among the responders who received subsequent infusions, seven of 39 patients (17.9%) had pain relief for less than 2 weeks with their last infusion, four of 39 patients (10.3%) had pain relief for 2 to 3 weeks, and 28 of 39 patients (71.8%) had pain relief for more than 3 weeks ($P < 0.01$, Table 3). Nine of 13 patients (69.2%) with neuropathic pain from tumor compression were responders, with three of the nine patients (33.3%) deciding to forgo future infusions because of unsatisfactory pain

Table 1. Patient demographics

	Tumor Compression	CIPN	Postsurgical	Postradiation	Total
Total	n = 13	n = 25	n = 13	n = 6	N = 57
Age, y, mean ± standard deviation	50.92 ± 18.14	53.48 ± 11.22	46.23 ± 11.26	62.83 ± 7.22	52.23 ± 13.33
Gender, n (%)					
Male	9 (69.2)	9 (36.0)	2 (15.4)	3 (50.0)	23 (40.4)
Female	4 (30.8)	16 (64.0)	11 (84.6)	3 (50.0)	34 (59.6)
Primary cancer, n (%)					
Germ cell tumors	2 (15.4)	1 (4.0)	–	–	3 (5.3)
Gynecological	–	2 (8.0)	–	–	2 (3.5)
Skin	2 (15.4)	1 (4.0)	2 (15.4)	–	5 (8.8)
Breast	1 (7.7)	9 (36.0)	3 (23.1)	–	13 (22.8)
Colorectal	–	1 (4.0)	–	–	1 (1.8)
Lymphoma/leukemia	–	5 (20.0)	–	1 (16.7)	6 (10.5)
Prostate	–	1 (4.0)	–	–	1 (1.8)
Lung	–	–	2 (15.4)	–	2 (3.5)
Esophageal	–	1 (4.0)	2 (15.4)	4 (66.7)	7 (12.3)
Multiple myeloma	–	2 (8.0)	–	–	2 (3.5)
Kidney	–	–	1 (7.7)	–	1 (1.8)
Pituitary	–	1 (4.0)	–	–	1 (1.8)
Pancreas	–	1 (4.0)	–	–	1 (1.8)
Nerve sheath	5 (38.5)	–	1 (7.7)	1 (16.7)	7 (12.3)
Bone/soft tissue	2 (15.4)	–	2 (15.4)	–	4 (7.0)
Head and neck	1 (7.7)	–	–	–	1 (1.8)
Metastases, n (%)					
Yes	4 (30.8)	2 (8.0)	1 (7.7)	1 (16.7)	8 (14.0)
No	9 (69.2)	23 (92.0)	12 (92.3)	5 (83.3)	49 (86.0)
Location of tumor compression, n (%)					
Cranial nerve	3 (23.1)	–	–	–	–
Nerve roots	8 (61.5)	–	–	–	–
Plexus	2 (15.4)	–	–	–	–
CIPN: causative regimen, n (%)					
Oxaliplatin	–	1 (4.0)	–	–	–
Octreotide	–	1 (4.0)	–	–	–
Docetaxel	–	1 (4.0)	–	–	–
Exemestane	–	1 (4.0)	–	–	–
Paclitaxel	–	2 (8.0)	–	–	–
Cetuximab	–	1 (4.0)	–	–	–
Paclitaxel/herceptin	–	1 (4.0)	–	–	–
Paclitaxel/carboplatin	–	2 (8.0)	–	–	–
Cisplatin/etoposide	–	1 (4.0)	–	–	–
THP	–	1 (4.0)	–	–	–
FOLFOX	–	2 (8.0)	–	–	–
R-GEMOX	–	1 (4.0)	–	–	–
ddAC	–	2 (8.0)	–	–	–
RVd	–	1 (4.0)	–	–	–
CyBorD	–	1 (4.0)	–	–	–
AC-T	–	2 (8.0)	–	–	–
FLAG-IDA	–	1 (4.0)	–	–	–
Hyper-CVAD	–	1 (4.0)	–	–	–
EPOCH	–	1 (4.0)	–	–	–
HiDAC	–	1 (4.0)	–	–	–
Type of chronic postsurgical pain after resection, n (%)					
Post-thoracotomy syndrome	–	–	3 (23.1)	–	–
Postmastectomy syndrome	–	–	3 (23.1)	–	–
Postsurgical pain after nephrectomy	–	–	1 (7.7)	–	–
Other	–	–	6 (46.2)	–	–
Location of radiation therapy, n (%)					
Head and neck	–	–	–	4 (66.7)	–
Spine	–	–	–	2 (33.3)	–

THP=docetaxel, trastuzumab, pertuzumab; FOLFOX=folinic acid, fluorouracil, oxaliplatin; R-GEMOX=rituximab, gemcitabine, oxaliplatin; ddAC=dose dense doxorubicin, cyclophosphamide; RVd=lenalidomide, bortezomib, dexamethasone; CyBorD=cyclophosphamide, bortezomib, dexamethasone; AC-T=doxorubicin, cyclophosphamide, paclitaxel; FLAG-IDA=fludarabine, high-dose cytarabine, idarubicin, granulocyte-colony stimulating factor; hyper-CVAD=hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; EPOCH=etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; HiDAC=high-dose cytarabine.

Table 2. Response to IV ketamine

	Tumor Compression	CIPN	Postsurgical	Postradiation	Total
Total number	n = 13	n = 25	n = 13	n = 6	N = 57
Responders, n (%)	9 (69.2)	21 (84.0)	9 (69.2)	3 (50.0)	42 (73.7)
Pain/adverse event–limited (% of total responders)	3 (33.3)	4 (19.0)	4 (44.4)	1 (33.3)	12 (26.7)
Nonresponders, n (%)	4 (30.8)	4 (16.0)	4 (30.8)	3 (50.0)	15 (26.3)
P value	0.17	<0.01	0.17	1.00	<0.01

Pain/adverse event–limited refers to patients who came off the IV ketamine program, despite pain relief, because of an infusion-related adverse event or because subsequent infusions resulted in reduced efficacy.

Table 3. Duration of response (of last infusion)

	Tumor Compression	CIPN	Postsurgical	Radiation Therapy	Total
<2 weeks, n (%)	3 (33.3)	1 (4.8)	2 (28.6)	1 (50.0)	7 (17.9)
2–3 weeks, n (%)	1 (11.1)	3 (14.3)	0	0	4 (10.3)
≥3 weeks, n (%)	5 (55.6)	17 (81.0)	5 (71.4)	1 (50.0)	28 (71.8)
No. responders receiving ≥2 infu- sions, n (%)	9 (100.0)	21 (100.0)	7 (77.8)	2 (66.7)	39 (92.9)
P value	0.26	<0.01	0.07	0.61	<0.01

improvement or undesirable adverse events with subsequent infusions (Table 2).

Twenty-one of 25 patients with CIPN (84.0%, $P = 0.0007$) responded, with four of 25 patients (19.0%) deciding to forgo more infusions because of the return of pain or adverse events, as outlined above. Nine of 13 patients (69.2%) with postsurgical neuropathic pain responded, with four of nine patients (44.4%) forgoing future infusions because of the return of pain or adverse events. Three of six patients (50.0%) with postradiation neuropathic pain responded, and one of the three responders (33.3%) decided to forgo further treatments because of pain or adverse events.

Duration of Response to Last Infusion

Thirty-nine of 42 responders (92.9%) received two or more infusions. Twenty-eight of 39 responders (71.8%) had pain relief for 3 or more weeks (Table 3). Four of 39 responders (10.3%) had pain relief for 2 to 3 weeks. Seven of 39 responders (17.9%) had pain relief for under 2 weeks ($P < 0.01$). This association was statistically significant in the CIPN group ($P < 0.01$), with 17 of 21 responders (81.0%) having more than 3 weeks of pain relief.

Adjuvant Pain Treatments and Rate of Response

All patients were stratified by whether they were on concurrent opioids, SNRIs, TCAs, or gabapentinoids in relation to response rates to IV ketamine (Table 4). There was no association with improved response rate when opioids ($P = 0.9299$), TCAs ($P = 0.5681$), or gabapentinoids ($P = 0.7985$) were used in conjunction with IV ketamine. Specifically, no patients were on an anticonvulsant (other than gabapentinoids); thus, this

association was not explored. However, the use of SNRIs such as duloxetine with IV ketamine resulted in a statistically significant improvement in response rate, from 35.6% in patients who did not use SNRIs while on IV ketamine to 91.7% in those who did use SNRIs while on IV ketamine ($P = 0.0017$).

Adverse Events

There were 57 patients in this study, who underwent 192 infusions (Table 5). In total, 25 of 57 patients (43.9%) had an adverse event at some point during the duration of their IV ketamine protocol. However, 34 of 192 infusions (17.7%) resulted in an adverse event. The most common adverse events were neurological (7.8%), including headache, dizziness, and somnolence. These were followed by gastrointestinal adverse events (3.6%), consisting of nausea and vomiting. Cardiovascular events occurred in 2.1% of infusions, consisting of hypertension and tachycardia. Of the adverse events, 64.7% self-resolved without intervention or a change in the infusion rate, and 35.3% resolved after the patient received as-needed medications or the infusion rate was reduced or stopped. Importantly, no patients had life-threatening or serious adverse events requiring hospitalization. All adverse events resolved before discharge.

Follow-Up of Enrolled Patients During the COVID-19 Pandemic

Fourteen patients were on the IV ketamine protocol when the decision was made to postpone all infusions during the COVID-19 pandemic (Table 6). All patients were responders to multiple infusions before the pandemic, with improvement of function, mobility, and mood with ketamine infusions. With the last infusion

Table 4. Adjuvant pain treatments

	Tumor Compression	CIPN	Postsurgical	Postradiation	Total
Total number of patients	n = 13	n = 25	n = 13	n = 6	N = 57
Opioids					
Total users (opioid/non-opioid), n (%)	8 (61.5) / 5 (38.5)	12 (48.0) / 13 (52.0)	10 (76.9) / 3 (23.1)	3 (50.0) / 3 (50.0)	33 (57.9) / 24 (42.1)
Opioid responders, n (%)	6 (75.0)	9 (75.0)	6 (60.0)	2 (66.7)	22 (66.7)
Non-opioid responders, n (%)	3 (60.0)	12 (92.3)	3 (100.0)	1 (33.3)	19 (79.2)
<i>P</i> value	0.57	0.53	0.29	0.50	0.93
SNRIs					
Total users (SNRI/non-SNRI), n (%)	2 (15.4) / 11 (84.6)	6 (24.0) / 19 (76.0)	3 (23.1) / 10 (77.0)	1 (16.7) / 5 (83.3)	12 (21.1) / 45 (78.9)
SNRI responders, n (%)	1 (50.0)	6 (100.0)	3 (100.0)	1 (100.0)	11 (91.7)
Non-SNRI responders, n (%)	8 (72.7)	0	6 (60.0)	2 (40.0)	16 (35.6)
<i>P</i> value	0.54	< 0.01	0.29	0.50	< 0.01
TCA s					
Total users (TCA/non-TCA), n (%)	2 (15.4) / 11 (84.6)	–	1 (7.7) / 12 (92.3)	–	3 (5.3) / 54 (94.7)
TCA responders, n (%)	0	–	0	–	0
Non-TCA responders, n (%)	9 (81.8)	–	9 (90.0)	–	18 (33.3)
<i>P</i> value	0.08	–	0.31	–	0.31
Gabapentinoids					
Total users (gabapentinoids/non-gabapentinoids), n (%)	7 (53.8) / 6 (46.2)	14 (56.0) / 11 (44.0)	8 (61.5) / 5 (38.5)	4 (66.7) / 2 (33.3)	32 (56.1) / 25 (43.9)
Gabapentinoid responders, n (%)	4 (57.1)	13 (92.9)	4 (50.0)	3 (75.0)	24 (75.0)
Non-gabapentinoid responders, n (%)	5 (83.3)	8 (72.3)	5 (100.0)	0	18 (72.0)
<i>P</i> value	0.34	0.42	0.20	0.20	0.80

before the pandemic, 11 of 14 patients (78.6%) continued to be responders, with nine of 14 patients (64.3%) having more than 3 weeks of pain relief. Notably, one patient in the postsurgical group had sustained relief for more than 3 months without a return to baseline pain. The other 13 patients had a return of baseline pain. All patients subsequently reported decreased mobility, reduced ability to perform activities of daily living, worsened mood, or anorexia. Eight of 14 infusions (57.1%) did not result in an adverse event, with neurological adverse events being the most common (21.4% of cases). Given the resumption of baseline pain, four of 13 patients (30.8%) increased their opioids, two patients (15.4%) increased their gabapentinoids, and two patients (15.4%) started cannabis. Five of 13 patients (38.5%) did not change their pain medications.

Discussion

In this retrospective study of 57 patients, 42 patients (73.7%) were responders to the IV ketamine protocol, regardless of the etiology of CNP (Table 2). The highest response rate was in patients suffering from CIPN, with 21 of 25 patients (84.0%) responding. Patients with neuropathic pain from direct tumor compression or with postsurgical pain had 69.2% response rates. Patients with postradiation pain had a 50.0% response rate, with a sample size of six patients. This suggests that the extended IV ketamine protocol is effective to treat CNP of varying etiologies.

The IV ketamine protocol and follow-up encounters in the present study were administered over a longer time

frame than the IV ketamine programs that are currently reported [3,13]. Patients were followed up via phone within 24 hours of infusion and at routine outpatient follow-up at the pain medicine clinic, averaging about 4 weeks after infusion. A significant portion of the population underwent multiple infusions over the course of several months. Thirty-nine of 42 responders underwent two or more infusions, of whom 28 of 39 responders (71.8%) had substantial pain relief for more than 3 weeks after their last infusion ($P < 0.01$).

A RCT of ketamine to treat complex regional pain syndromes found that patients received up to 11 weeks of statistically significant pain relief as compared with placebo [16]. Most patients in the present study did not have recorded long-term follow-up data beyond 3 weeks after the last ketamine infusion. However, 71.8% of responders had more than 3 weeks of pain relief after their last infusion. Although this difference in IV ketamine duration in the population with complex regional pain syndromes vs the population with CNP may be attributable to a lack of long-term data, it is possible that increased mechanical compression from tumor growth or continued cancer treatments have a cumulative effect on pain symptoms. Nevertheless, although the duration of relief from ketamine infusions may be short, cancer patients may still benefit from ketamine infusions—for example, as inpatients suffering from uncontrolled pain.

It is notable that of the 42 responders, 12 patients (26.7%) self-discontinued the IV ketamine protocol given that subsequent infusions did not confer satisfactory pain relief or resulted in undesirable adverse events. In the CIPN group, this occurred in only four of 25 patients

Table 5. Adverse events

	Tumor Compression	CIPN	Postsurgical	Postradiation	Total
Total number of patients	n = 13	n = 25	n = 13	n = 6	N = 57
Total number of infusions	n = 34	n = 113	n = 32	n = 13	N = 192
Any adverse event during ketamine course (% based on total number of patients)					
Yes	5 (38.5)	14 (56.0)	6 (46.2)	0 (0.0)	25 (43.9)
No	8 (61.5)	11 (44.0)	7 (53.8)	6 (100.0)	32 (56.1)
<i>P</i> value	0.41	0.55	0.78	0.01	0.35
Type of adverse events (% based on total number of infusions)					
Anaphylaxis	0	0	0	0	0
Cardiovascular (hypertension, tachycardia)	1 (2.9)	2 (1.8)	1 (3.1)	0	4 (2.1)
Gastrointestinal (nausea, vomiting)	3 (8.8)	2 (1.8)	2 (6.3)	0	7 (3.6)
Muscular (stiffness, spasms)	1 (2.9)	1 (0.9)	1 (3.1)	0	3 (1.6)
Neurological (headache, dizziness, somnolence)	3 (8.8)	11 (9.7)	1 (3.1)	0	15 (7.8)
Ophthalmologic (diplopia)	0	0	0	0	0
Psychiatric (anxiety/depression, dissocia- tion, hallucinations)	0	3 (2.7)	1 (3.1)	0	4 (2.1)
Respiratory (laryngospasms, respiratory de- pression, etc.)	0	0	0	0	0
Skin (rash)	0	1 (0.9)	0	0	1 (0.5)
Total number of any adverse event	8 (23.5)	20 (17.7)	6 (18.8)	0	34 (17.7)
Resolved with intervention (% based on to- tal number of any type of adverse event)					
Self-resolved (resolved without intervention, and infusion not adjusted because of ad- verse event)	4 (50.0)	15 (75.0)	3 (50.0)	–	22 (64.7)
Yes (stopping/reducing infusion, as-needed medications)	4 (50.0)	5 (25.0)	3 (50.0)	–	12 (35.3)
No	0	0	0	–	0

Several patients had multiple adverse events. “Any adverse event” is a binary measure that is positive if the patient had an adverse event during any of his or her infusions within the full duration of the IV ketamine program. Type of adverse event was calculated based on infusions.

(19.0%). Many of the patients in this subset received adequate pain relief at a higher dose of IV ketamine but had undesirable or intolerable adverse events that precluded them from continuing in the program. One patient did not continue with the infusion protocol because of social circumstances and difficulty with arranging transportation for infusions and follow-up appointments. This highlights the social complexities faced by many cancer patients. Additional studies evaluating the socioeconomic and social challenges faced by cancer patients with chronic painful conditions may be warranted. Furthermore, future infusion protocols may consider exploration of the possibility of home infusions.

The definition of a responder was a participant with $\geq 30\%$ reduction in pain based on NPRS or positive subjective qualifiers, as well as functional improvements and/or reduction in adjuvant analgesics. Although no specific outcome measures directly described QOL, improvements in functional status and reduction of analgesics suggest that IV ketamine may improve QOL in patients suffering from CNP. Improvements in functional status may lead to decreased morbidity from falls and decreased utilization of the health care system. This has profound implications, as sensory loss from CIPN already increases the risk of falls three-fold [17].

Additionally, decreasing opioid use and overall medication burden would confer numerous benefits on patient health and health care utilization. Interestingly, as ketamine may improve depressive symptoms in the population with cancer, it is conceivable that ketamine may improve pain by improving depression.

Prior studies have attempted to evaluate the utility of ketamine as a synergistic agent with opioids and other medications to treat CNP [14,18]. In this investigation, 11 of 12 patients (91.7%) using adjuvant SNRIs were responders, compared with 16 of 45 patients (78.9%) not on adjuvant SNRIs who were deemed nonresponders ($P < 0.01$, Table 3). This difference was statistically significant in only the CIPN population ($P < 0.01$), whereas in the tumor compression, postsurgical, and postradiation CNP populations, statistical significance was not achieved. Importantly, there were no significant differences when opioids were compared with non-opioids, TCAs with non-TCAs, and gabapentinoids with non-gabapentinoids. SNRIs such as duloxetine are commonly used to treat various neuropathic pain syndromes and may secondarily treat anxiety and depression. Duloxetine inhibits a P450 liver enzyme, CYP2B6, which metabolizes ketamine [19]. Thus, by inhibiting CYP2B6, SNRIs could theoretically augment the effects of ketamine [20,21]. In animal models, NMDA receptor blockade is

Table 6. Follow-up on enrolled patients during the COVID-19 pandemic

	Tumor Compression	CIPN	Postsurgical	Postradiation	Total
Total number of patients	n = 2	n = 9	n = 3	n = 0	N = 14
Responders, n (%)	2 (100.0)	7 (77.8)	2 (66.7)	0	11 (78.6)
Duration of relief, n (%)					
<2 weeks	0	2 (22.2)	1 (33.3)	0	3 (21.4)
2–3 weeks	1 (50.0)	1 (11.1)	0	0	2 (14.3)
≥3 weeks	1 (50.0)	6 (66.7)	2 (66.7)	0	9 (64.3)
Adverse events, n (%)					
Gastrointestinal (nausea, vomiting)	1 (50.0)	1 (11.1)	0	0	2 (14.3)
Neurological (headache, somnolence)	1 (50.0)	1 (11.1)	1 (33.3)	0	3 (21.4)
Psychiatric (hallucinations)	0	1 (11.1)	0	0	1 (7.1)
None	0	6 (66.7)	2 (66.7)	0	8 (57.1)
Pain medication changes, n (%)					
Opioids	1 (50.0)	3 (33.3)	0	0	4 (30.8)
Gabapentinoids	0	2 (22.2)	0	0	2 (15.4)
Cannabis	0	1 (11.1)	1 (50.0)	0	2 (15.4)
No change	1 (50.0)	3 (33.3)	1 (50.0)	0	5 (38.5)

“Pain medication changes” refers to medication changes in the 13 patients whose pain returned to baseline.

thought to enhance the effect of duloxetine [19]. Interestingly, a Cochrane Review concludes that there is moderate-quality evidence that duloxetine at higher doses (60 mg to 120 mg daily) is effective for treating peripheral neuropathy [22]. Additionally, an RCT by Smith et al. demonstrated a benefit of duloxetine in treating CIPN [23]. An enhanced effect of duloxetine may mimic higher doses. The present study suggests the need for further investigation to evaluate the potential synergistic properties of SNRI medications and ketamine in treating CNP.

Notably, adjuvant opioids did not confer a statistically significant difference in response to IV ketamine. Some studies have demonstrated that clinically, ketamine enhances the effect of opioids [17]. Mouse models have suggested ketamine-mediated NMDA antagonism to potentiate the antinociceptive effects of mu-opioid agonists [24]. However, a Cochrane Review found low evidence for ketamine as an adjuvant to opioids for cancer pain treatment [15]. The present study was consistent with this finding, given that there was no difference in response rate between patients with adjuvant opioids and those with no opioids (66.7% vs 79.2%, respectively).

Of note, there were three patients who were not on any adjuvant medications after choosing to forgo any other medications, given lack of effectiveness, and who responded to the IV ketamine protocol. The different effects of adjuvant pain treatments or the absence of adjuvants with IV ketamine is particularly interesting, given that ketamine antagonizes NMDA receptors and interacts with many other receptors [25]. By uncovering synergistic effects with certain adjuvants, IV ketamine has the potential to decrease medication burden and, most significantly, opioid burden. More studies are warranted to confirm the utility of IV ketamine in decreasing pain and opioid burden, as well as increasing function, mobility, sleep, pain relief satisfaction, and ultimately QOL.

Several studies with a limited number of infusions concluded that IV ketamine is a relatively safe

medication [13,14]. Our study is congruent with the current literature, with 17.7% of infusions resulting in an adverse event (Table 4). The most common adverse events were neurological complaints, followed by gastrointestinal complaints. Cardiovascular and psychiatric side effects were the third most common. Importantly, none of the adverse events were life-threatening, with 64.7% that were brief and self-resolving and 35.3% that resolved after our adverse events protocol was followed, as outlined previously.

Given the unprecedented COVID-19 pandemic, 14 patients who were enrolled in the IV ketamine protocol could not proceed with infusions. One of these patients had relief and functional improvement from her last infusion for more than 3 months. The remaining 13 patients reported reduced mobility, reduced function, worsened mood, or anorexia. Although 78.6% of patients had met the definition of response to their last IV ketamine infusion, it is notable that some nonresponders had had a good response when pairing ketamine with acupuncture or deep tissue massages, with which they could not proceed during the pandemic. Because of the return of baseline pain, 61.5% of patients increased their other analgesics, such as opioids, gabapentinoids, or cannabis, to cope. Although not a true crossover analysis, these insights propose that IV ketamine may be an integral part of CNP treatment that patients rely on to maintain their function and mobility and decrease their adjuvant analgesics. However, further prospective crossover studies may further investigate the use of IV ketamine in CNP treatment.

This study has several limitations. Objective outcome measures were inconsistently used, particularly those pertaining to specific neuropathic pain scales (i.e., Short-Form McGill Pain Questionnaire), QOL, functional measures, patient satisfaction, and NPRS scores. Additionally, the sample size is small, though it is the largest study to date. A larger, prospective study that is

well designed with consistent and validated outcome measures is warranted. Ultimately, this would be important and useful, as CNP can be debilitating and strenuous in patients' day-to-day function and QOL. Adequate pain control may also be important to minimize caregiver burnout.

This investigation suggests that IV ketamine at sub-anesthetic doses may be a viable adjuvant to existing treatments, particularly SNRIs, to treat CNP. IV ketamine was especially effective in treating CIPN. Additionally, these data demonstrate that an extended IV ketamine protocol is safe and well tolerated, with minimal adverse events and several patients who had long-term pain relief. Neurological adverse events were the most common but were rare. Larger, prospective studies must be conducted to further illustrate the effects of IV ketamine on CNP and to explore the different parameters that may help prognosticate a good response to IV ketamine.

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