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CASE REPORT

Ketamine in Acute Paclitaxel Pain Syndrome: A Promising New Ally

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Abstract

Paclitaxel, a commonly used potent antineoplastic drug, induces two types of pain syndromes - acute and chronic. Paclitaxel associated acute pain syndrome (P-APS) is a transient widespread myalgia, arthralgia and polyneuropathy like pain following the first dose of Paclitaxel. Although typically mild to moderate, the pain can occasionally be severe and debilitating. We report the successful management of severe paclitaxel acute pain syndrome with intravenous ketamine, in a 22-year-old male with metastatic carcinoma stomach. To our knowledge, this is the first documented case of ketamine being used to treat P-APS.

Keywords: Paclitaxel; Acute paclitaxel pain syndrome; Ketamine; Chemotherapy; Pain management; Neuropathic pain.

Introduction

Paclitaxel is a chemotherapeutic agent derived from the bark of western yew tree (Taxus brevifolia). The drug exerts its antineoplastic effects by binding to intracellular tubulin, inhibiting mitosis, and inducing apoptosis.[1] It is widely used for the treatment of solid tumors like breast, lung, bladder, prostate and oesophagus. Use of paclitaxel is associated with a wide variety of side effects like nausea, vomiting, alopecia, bleeding, fever with chills, dizziness, pruritis, difficulty in breathing, myalgia, arthralgia, tingling numbness and polyneuropathy.

The pain syndromes associated with paclitaxel are of two types - an initial acute pain (P-APS), which is a transient, myalgia-dominant condition occurring shortly after the first dose and a chronic sensory neuropathy, which is a dose-dependent, long-term complication.[2] It has an incidence of around 70%.[3] P-APS typically resolves spontaneously but can be severe enough to warrant intervention. In this case report, we explore the use of ketamine as an effective treatment for severe P-APS after consent by the patient's relatives.

Case Report

A 22-year-old male, weighing 42 kg, with metastatic carcinoma stomach was referred to our Pain Unit for the management of acute severe intractable pain of two days following the first dose of chemotherapy. He was apparently asymptomatic six months back, then developed severe pain abdomen. His medical history revealed an initial misdiagnosis of abdominal tuberculosis for which he was started on ATT (Anti-tubercular treatment) without relief for 2 months. Subsequent upper gastrointestinal endoscopy revealed a growth along the lesser curvature of stomach. Following which, laparotomy was performed in the fourth month. Intraoperatively, a 'cocoon abdomen', suggestive of a desmoplastic reaction, was observed and the definitive surgery was aborted. The biopsy revealed gastric adenocarcinoma. In the post-operative period, his recovery was prolonged for more than one month with severe pain that was poorly controlled with intravenous fentanyl patient-controlled analgesia and NSAIDS as well as adjuvants like gabapentin. An ensuing PET (positron emission tomography) scan confirmed the metastatic adenocarcinoma with severe osteopenia, after which chemotherapy was initiated with palliative intent. The patient was cachexic and mostly bed ridden by the 6th month of diagnosis and was on NSAIDS and paracetamol on as and when required basis, having an NRS of 3-4/10. The patient had also received intravenous Zolendronic acid for severe osteopenia causing generalized body pains and aches. Opioids were avoided as on a suspicion of opioid induced hyperalgesia.

First dose of Paclitaxel 276mg, Carboplatin 407 mg and Bevacizumab 375mg was given. Within six to eight hours of the first dose of chemotherapy, he started complaining of severe excruciating pain and distress (NRS 10/10), that had escalated progressively. The pain initiated as a vague discomfort, continuous, non-radicular dull aching, crushing, muscular in nature, gradually increasing that progressed from calf to both lower limbs up to the knees and both upper limbs and shoulders. It was associated with sleep interference, occasionally with pricking sensation but not burning or sharp shooting in character. Examination revealed allodynia and hyperalgesia over the legs and arms. There was no sensory, motor or focal neurological deficits noted on examination. Neuropathic pain was ruled out (DN4 score- < 4) and bony pain as the distribution was distal to proximal. A normal nerve conduction velocity test ruled out peripheral neuropathy and the absence of accompanying heliotropic rashes and papules ruled out polymyositis.

Despite multimodal analgesia - including a buprenorphine patch (10 mcg/hr), amitriptyline (25 mg), gabapentin (600 mg), and tapentadol (100 mg twice daily) - his pain remained uncontrolled (NRS 9/10). As the pain started hours after the paclitaxel infusion, peaked on the second day and had characteristics of a muscular pain, a provisional diagnosis of Acute Paclitaxel induced pain was suspected. There was a history of difficult to treat pain in the past so opioids were avoided and ketamine infusion was opted to tide over the acute pain crisis (NRS 9/10).

After evaluation, ketamine infusion was initiated at the rate of 0.3 mg/kg in 100ml normal saline slow bolus for 15 minutes followed by continuous infusion at 0.1 mg/kg/hour for four hours with vigilant monitoring of vitals for complications like drowsiness, nausea, hallucinations, tachycardia and hypertension, etc. His NRS reduced to 6/10 within 30 minutes of starting and further decreased to 4/10 when the infusion was stopped. It stabilised at NRS of 3/10 on the second and third post-infusion day. Buprenorphine patch was removed. The doses of ongoing pain medications were reduced - gabapentin to 300mg, amitriptyline to 10 mg and tapentadol to 50 mg once daily. The patient was discharged on the day 3 of chemotherapy with the instructions to continue medications for another 3 days. Follow up was done in pain clinic after a week. Notably, on subsequent visits and chemotherapy admissions, he did not complain about similar severe pain and did not require ketamine. His pain was managed with NSAIDS and tapentadol 50 mg only.

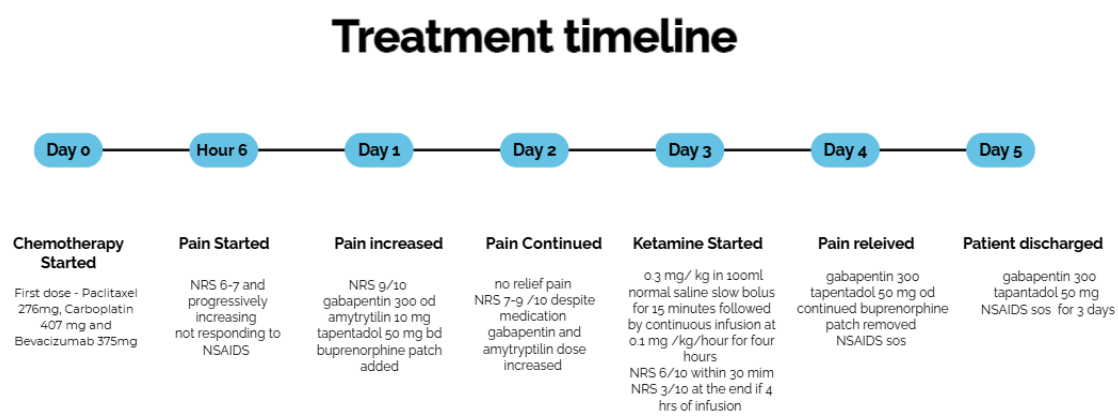


Fig. 1: Clinical course showing NRS scores relative to chemotherapy infusion, ketamine administration, and discharge.

Discussion

Paclitaxel induced acute pain syndrome is common amongst patients receiving the first dose Taxane chemotherapy regimen. It typically occurs a few hours after the first dose and peaks at around the second day and subsides in the subsequent week. The pain is usually mild to moderate but sometimes severe as in our reported case. Paraneoplastic syndromes like polymyositis, dermatomyositis, peripheral neuropathies and osteoporosis as well as generalized pains due to chronic disease may also present in such patients. So the timing of pain is very important to make a diagnosis of P-APS.

Chemotherapeutic agents bind to cancer cell microtubules leading to microtubule polymerization which arrests somatic cell mitosis and causes apoptosis or cell death.[2,4] This stabilization caused by microtubule polymerization also affects the cells of the central and peripheral nervous systems accounting for sensory neuropathy seen commonly in patients treated with such chemotherapeutic agents. There is impaired axonal transport and mitochondrial dysfunction along with generation of reactive oxygen species.[5] These phenomena activate microglial cells that release substance P, calcitonin gene-related peptide (CGRP) and other pro inflammatory mediators which activate mitogen-activated protein kinase (MAP-K) pathway leading to upregulation of NMDA receptors, Na+ channels, TRPs channels and protein kinase C. All are key mediators in the pain processing pathway and cause peripheral neuropathy.[6]

Carboplatin and Paclitaxel cause dose dependent sensory neuropathy. Bevacizumab may also cause generalized aches and pains as a side effect. Acute transient pain that starts one to 3 days after chemotherapy and lasts for three to seven days has been reported only with Paclitaxel and is known as acute paclitaxel pain syndrome (P-APS).[4]

The mechanism of the acute pain, a mix of myalgia, arthralgia and neuropathic pain,[7] has been shown to be induced by direct activity of Toll-like receptors 4 (TLR4) receptors in the dorsal horn of the spinal cord.[8] It has been observed that Interleukin-1β (IL-1β) is a crucial molecule used by microglia, to bring about change in functions of neurons after activation of TLR4.[9] This is the way paclitaxel induces acute inflammation in the spinal cord and dorsal root ganglia. The N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are positively modulated by IL-1β.[10] This gives a rationale for the use of ketamine, an NMDA receptor antagonist, for interrupting the acute pain caused after administration of Paclitaxel.

Ketamine can also activate the monoaminergic descending inhibitory pain pathways via NMDA receptors in anterior cingulate cortex, orbital frontal cortex, insula, and brainstem.[2] Ketamine infusions have been used to treat refractory pain specially to break the pain cycle in complex regional pain syndrome (CRPS), spinal cord injury, phantom limb pain, fibromyalgia and cancer related neuropathic pain.

There is some evidence that Memantine, an oral NMDA receptor antagonist, could reduce the mechanical hypersensitivity of P-APS.[11] Ketamine infusion is a promising treatment for the management of P-APS. Not only via NMDA receptor antagonism, ketamine exerts its analgesic effects via several non-NMDA binding sites also including nicotinic and muscarinic receptors, D2 dopamine receptors, Gamma-aminobutyric acid (GABA) receptors and voltage gated calcium channels which may also contribute to antagonism of neuropathic and myopathic pain in patients of P-APS.

Conclusion

Paclitaxel-associated acute pain syndrome (P-APS) is a debilitating but transient condition that often resists conventional analgesics. In this case, low-dose ketamine infusion provided significant relief, suggesting its utility as a rescue therapy for severe P-APS. Further studies are warranted to establish ketamine's efficacy and optimal dosing in this context.

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Declarations

Declaration by the authors

The manuscript has been read and approved by all the authors and the requirements for authorship have been met. Each author believes that the manuscript represents honest work.

Ethics Approval

Formal institutional ethics committee approval was not required for this single-patient case report, in accordance with standard journal policy for case reports.

Patient Consent

Written informed consent for publication of this case report and accompanying clinical details was obtained from the patient's next of kin/relatives.

Conflict of Interest

The authors declare no competing interests.

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Nimisha Verma: Concept and design of study, drafting the article and revising it critically for important intellectual content. Sonu Kashyap: Acquisition of data and drafting the article. Santhosh Arulprakasam: Drafting the article. Neville J F: Drafting the article.