Ketamine use in Refractory Depression and Neuropathic Pain - A Case Report

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ABSTRACT

Introduction: Depression is a common psychiatric illness in the elderly. It often co-exists with chronic neuropathic pain in old age group.

Case report: We present a case report of an elderly patient who was successfully treated with subanaesthetic intravenous infusion for severe depression with suicidal intention and chronic neuropathic pain.

Conclusion: Ketamine has been reported to be used in depression with suicidal features as well as refractory pain. Depression is a common psychiatric problem across the age groups. It occurs due to neurochemical imbalance in the brain namely dopamine, norepinephrine serotonin.

Keywords: Ketamine, Refractory Depression, Neuropathic Pain

INTRODUCTION

Refractory depression is difficult to treat in the elderly age group. Similarly neuropathic pain also presents difficulty in treatment despite the availability of multimodal analgesia. Traditional antidepressants take at least two weeks to start response. In such a scenario, it is difficult to manage suicidal ideation early in patients with severe depression. Although Electroconvulsive therapy (ECT) has been recommended for faster response in depression but not many people prefer this mode of treatment. Several recent evidences have shown that intravenous ketamine infusions have rapid antidepressant effects.[1,2] Similarly, ketamine infusion has also been used in management of neuropathic pain. We present a case of an elderly gentleman with severe depression, suicidality and neuropathic leg pain, who didn't show any response to multiple antidepressants and analgesic modalities, refused treatment with electroconvulsive therapy and was successfully treated with subanaesthetic intravenous ketamine infusion.

CASE REPORT

A 71 yr old gentleman presented in Psychiatry Outpatient department with severe depression, suicidal ideation and chronic neuropathic leg pain. Onset was insidious, course was progressive, duration of one year for depressive symptoms and eight months for neuropathic leg pain. This was second episode of depression in the patient, his first episode occurred ten years back and during that time he responded to selective serotonin reuptake inhibitor Escitalopram 10 mg at night. He took treatment for six months in that episode and remained asymptomatic till this episode. In this episode, he failed to show any significant improvement to different antidepressants and had developed feelings of hopelessness and multiple suicidal attempts in past 10 days. So he was admitted in psychiatry ward for further evaluation and management.

While being hospitalized, he also complained of worsening of bilateral leg pain which reduced his lower limb movements and further worsening of mood. He was admitted four months back for generalized neuropathic leg pain which decreased his movements. A lumbar magnetic resonance imaging (MRI) was done which didn't reveal any significant abnormality. He consulted different doctors and was prescribed pain relieving medications including pregabalin, tramadol, tapentadol, gabapentin, acetaminophen, Non steroidal antiinflammatiry agents, tricyclic antidepressants as well as antiepileptics. Additional intervention included epidural steroid injection, physiotherapy, acupressure, acupuncture, occupational therapy as well as psychotherapy for chronic pain management.

During this hospitalization, neurologist and pain management team was consulted for their expert opinion. On mental status examination patient's affect was predominantly sad, thinking revealed ideas of hopelessness, worthlessness, suicidal intentions. Patient revealed distress regarding the persistent pain in his both legs which restricted his mobility and he thought his life to be worthless as he was a burden on his family members. He also reported several instances of self harming behaviors, including cutting, strangulating himself with a rope. He also thought of ingesting pesticides. His depression symptoms were rated on Hamilton rating scale for depression (HAM-D) which was 38 (>24 score indicates very severe level of depression). He was placed under strict supervision of family members around the clock. Patient's chronic opd medications included Escitalopram 10 mg at night, lithium carbonate 450 mg twice a day, Pregabalin; sustained release preparation 150 mg at night, Clonazepam 0.25 mg at night. After being hospitalized he was also put on

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Bupropion, but was discontinued due to increased agitation and irritability. He also complained of severe burning bilateral leg pain. In addition, he described his pain in terms of shooting, reporting painful paresthesias, dysthesias and hyperalgesia as well as a numbness characterization to his bilateral leg pain, which followed a neuropathic pattern. His lumbar spine was mildly tender to palpation, but his neurological examination did not reveal any abnormality. While his characterization of pain was neuropathic in nature, he did not meet the criteria for complex regional pain syndrome. There were no features suggestive of allodynia, vasomotor or tropic changes on examination. Even after being prescribed, regimen of pregabalin, lidocaine 5% patch, acetaminophen, tizanidine and subsequently intravenous tramadol thrice a day, his pain continued. He also had been put on morphine, but without much improvement in his pain. Patient was also given a trial of Desvenlafaxine 100 mg at night for ten days with minimal improvement and reported worsening of depressive symptoms, suicidal intentions and neuropathic pain. Patient and family members were given the option of treatment with modified electroconvulsive therapy (ECT),but they did not give consent for the same despite being counseled. It was then decided to start an intravenous ketamine infusion after discussion with patient and family members and receiving consent for the same as ketamine was theorized to have a more rapid clinical onset and effect. Patient was transferred to the Medical intensive care unit for intravenous ketamine infusion and monitoring. Prior to starting intravenous ketamine infusion, his depression score on Hamilton depression rating scale was 36 (>24 indicating very severe level of depression), his leg pain was rated 7/10 on the numerical rating scale (NRS, 0-10 with 10 being the worst pain) of burning quality. There was no weakness or changes in sensation, though the mobility was compromised secondary to pain. Intravenous ketamine infusion was started at 7 micrograms/kilogram/minute (mcg/kg/min). Dose was calculated taking patient's weight (72 kg). Infusion of ketamine was done for 24hrs per day for the entire duration of treatment for ketamine infusion.

Patient didn't report any hallucinatory experiences or dysphoria and remained haemodynamically stable. Patient showed significant improvement in his depressive symptoms on day one of intravenous ketamine infusion. His depression rating scale (HAM-D) revealed score of 18(14-18 indicates moderate level of depression) and the maximum NRS throughout the day was 6/10. On day two, his HAM-D score was 16 and also he reported less pain in legs with maximum NRS score of 5/10. On third day, intravenous ketamine infusion was increased to 8 mcg/kg/min, however physical examination revealed changes in vision and nystagmus, so dose was decreased to 7mcg/kg/min. Patient's maximum NRS score remained at 5/10. On fourth day, his HAM-D score was 13 (8-13 indicates mild level of depression). His maximum NRS score reduced to 4/10. He was able to walk comfortably. On fifth day doses were titrated to 5mcg/kg/min, with HAM-D score of 7(<8 indicates normal mood) and maximum NRS score of 0-10. Intravenous ketamine infusion was further decreased to 2 mcg/kg/min and discontinued the same day. He was able to tolerate physical therapy and maintained analgesia. On mental status examination his mood was normal, thinking revealed normal flow. There was no formal thought disorder and no suicidal ideation, so he was discharged and put on Lithium 300mg twice a day, Escitalopram 10mg at night and was asked to follow up after 10 days. During the follow up period he remained asymptomatic till date (eight months after discharge).

DISCUSSION

Depression often coexists with neuropathic pain in the elderly. This was the first time, a patient was treated with subanaesthetic doses of intravenous ketamine infusion in our hospital. There is one recent report on use of ketamine for depression and chronic pain.[1] In this case neuropathic pain was diagnosed based on clinical description and history. Neuropathic pain is nerve pain, which occurs secondary to peripheral or central nervous injury or dysfunction. It often presents as shooting or burning pain, tingling and numbness. Other symptoms include hyperalgesia,hyperaesthesia, allodynia. Treatment options in management of neuropathic pain are limited due to minimal evidence of efficacy. Traditional first line agents include tricyclic antidepressants, gabapentinoid or serotonin norepinephrine reuptake inhibitors (SNRIs).[4] Opioids have shown mixed efficacy for neuropathic pain. They are considered seond/third line treatment option because of their questionable long term efficacy as well as side effects which includes sedation, constipation, nausea/vomiting, respiratory depression and dependence. Addiction potential of opioid therapy poses risk.[3] Due to nonefficacy of monotherapy, combination therapies are often required. Additional nonpharmacological management include cognitive behaviour therapy (CBT), biofeedback, transcutaneous electrical nerve stimulation (TENS) and physiotherapy.[5] Despite combination therapy, neuropathic pain can be refractory to treatment and multiple novel targets for neuropathic pain are being studied.[6]

Ketamine is a cyclohexanone derivative with analgesic and anaesthetic properties. It has complex mechanism of action with multiple effects throughout central nervous system, inhibiting polysynaptic reflexes in spinal cord as well as excitatory neurotransmitter effects in selected areas of brain. It inhibits N-methyl-D-aspartate (NMDA) receptor activation by glutamate. The NMDA receptors are involved in central sensitization. Ketamine's inhibition of NMDA receptors helps decrease peripheral and central sensitization, thus promoting analgesia. Additional mechanism of action include, descending inhibitory monoaminergic pain pathways and substance P. It's mechanism of action as antidepressant is not well understood and is still under evaluation.

First line of treatment for depression are selective serotonin reuptake inhibitors(SSRIs) group of drugs due to their efficacy and low side effect profile,apart from that for the patients who don't respond adequately to SSRIs second line of drugs include serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine

oxidase inhibitors (MAOIs). ECT is another treatment modality for severe depression refractory to pharmacological agents. While ECT produces rapid response, it requires general anaesthesia and has complications including somatic injuries, dental trauma, confusion and amnesia.[7]

Ketamine has emerged as an alternative treatment of major depressive disorder with or without suicidality. A 24 hr intravenous ketamine infusion has shown large reduction in severity of depression with lasting antidepressant efficacy.[2] Also, the antidepressant effect of ketamine is rapid when compared to other antidepressant medications as shown in our case report.

CONCLUSION

Subanaesthetic intravenous ketamine infusion has the potential for use in refractory depression and neuropathic pain.

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