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Case Report

Ketamine Use in Opioid-Induced Hyperalgesia Presented in a Patient With History of Chronic Pain Due to Traumatic Brain Injury

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A B S T R A C T

Background: In the literature, there are studies supporting the possible role of ketamine in pain management while further research is needed mainly in long-term settings.

Case: This study highlights the response of a 53 years old male patient diagnosed with chronic central pain, following a brain injury, and opioid-induced hyperalgesia in the administration of oral ketamine, as an add-on treatment, along with drastic reduction of opioids.

Conclusion: A combination of oral ketamine administration along with a reduction in opioids in a patient suffering from chronic central pain as well as opioid tolerance reduced significantly the perception of pain.

Keywords: Ketamine; Pain management; Opioid-induced hyperalgesia; Opioid tolerance

Introduction

Opioid use in chronic pain is common and, in many cases, there is a need for increasing dosage either due to recrudescence of the primary cause of pain or due to opioid tolerance[1-5]. Chronic pain becomes more complex when opioid-induced hyperalgesia appears and, if so, it is suggested to lower the dose of opioids, sometimes until complete abstention[6]. To cope with opioid-induced hyperalgesia in chronic pain patients, a strategy involving blocking activation of NMDA receptors with the use of NMDAR antagonists, such as ketamine, is suggested[7]. We report a case highlighting the effectiveness of ketamine oral administration in a patient with refractory, chronic pain syndrome and opioid-induced hyperalgesia, along with drastic reduction of opioids. Informed written consent was obtained from the subject for publication of the case.

Case Description

A 53 years old male patient diagnosed with chronic pain disorder (according to DSM-V criteria) was admitted to the hospital, in the psychiatric clinic, due to opioid tolerance and opioid-induced hyperalgesia. The patient had been monitored on a regular basis in the outpatient pain clinic of our hospital for the last 3 years due to central pain, which emerged 7 months after a car accident 22 years ago. Among other craniocerebral injuries, lesion in the left thalamus had been illustrated[8]. Hypoesthesia and numbness, which appeared in the right half of the body, were replaced gradually by dysaesthesia and allodynia. Qualities of neuropathic pain presented on the patient include mainly burning and less sense of electric shock so as ‘’pins and needles” sensation. Dysaesthesia was constant, with exacerbations, spontaneous or triggered by stimuli. Allodynia appeared in the

same side of the body as dysaesthesia and was triggered mostly by temperature (hot, cold) and less by scrubbing. Patient's pain had a daily fluctuation and was also affected by mood and psychological factors. It was perceived by the patient as very intense, annoying and torturous, especially when exacerbated, and was unchanged through time. Due to the severity and chronicity of his state the patient became disabled, incapable of working and socially withdrawn. Pain was considered refractory to treatment and, as a result, an increasing dose of opioids had been administered. Pain response to other treatments such as antidepressants, antiepileptics, anti-inflammatory drugs, psychotherapy, physiotherapy and acupuncture was poor and relief was minor. Opioid tolerance was observed for the first time 5 years ago, followed by a three-month detoxification program while hospitalized. Tolerance gradually re-appeared approximately 1 year before present hospital admission. The continuous need for opioids dosage escalation due to poor analgesia was followed by hyperalgesia, first observed 3 months before admission. This complication caused severe malfunction to patient's life, affecting simple daily activities, worsening sleep quantity and quality and constituted aggravating factor for development of depressive symptoms such as hopelessness, depressive feeling, uselessness and suicidal thoughts. Thus, the need for hospitalization became urgent and was mutually agreed.

Hospitalization lasted 2 months. Monthly opioid dosage before admission was as follows: Loz Fentanyl 1200mcg 1 X 6 (daily), TTS Fentanyl 300 mcg/h (per 72h) and 6 amp morphine 10mg/ml (1ml) which were used in exacerbations of pain during the month. Fentanyl was converted to oral morphine and the equi-analgesic dosing was approximately 1400mg/24h. Rest of pharmacological treatment remained stable and included caps Pregabalin 150mg X 3 and caps Duloxetine 60mg X 1. Beck's Depression Inventory (BDI) was administered upon admission with a score of 30. Pain was assessed with the use of Numeric Rating Scale (NRS) and found to be 7 upon admission with a fluctuation 5-8 during the last month. Hydroxyzine hydrochloride was added orally (100mg), at night, to treat anxiety. Ibuprofen 800mg was administered orally, divided into 2 doses, as an additional analgesic. The reduction of opioids was scheduled to be 150mg oral morphine/24h every week resulting approximately 600mg oral morphine reduction in the 1st month. No opioid-withdrawal symptoms observed or mentioned. Pain levels remained almost the same (NRS 4-8) with allodynia persisting in a same manner. In order to cope with central sensitization so as with the phenomenon of hyperalgesia and, finally, to reduce pain levels, ketamine was decided to be administered being as the most potent NMDA-receptor-channel blocker[9]. An injection solution containing a racemic mixture of ketamine was available for clinical use (50mg/5ml). At first an initial test dose was given to check tolerability and efficacy. Specifically, 50 mg of ketamine were diluted in 100ml N/S 0.9% with the solution administered intravenously in an hour. The result was quite effective with minimum side effects (dizziness and face-flushing). The pain relief was immediate. Subsequently, ketamine was administered systematically orally, directly from the vial (50mg/5ml). The analgesic effect of ketamine administered orally is believed to attribute mainly to norketamine which is a pharmacologically active metabolite[10]. The initial daily oral dose of ketamine was 10mg X 3. At the same time opioid reduction was applied (reduction of 150mg oral morphine/24h per week). Ibuprofen was discontinued. Ketamine augmentation decided to be 10mg every 3 days, always checking analgesic efficacy and side effects. Eventually the best analgesic result with minimum side effects, which were dose-related, was achieved with oral ketamine 120mg/24h divided into 6 doses (20mg X 6) and TTS Fentanyl 100mcg/h every 72h (equi-analgesic dose of oral morphine approximately 350mg/24h). Allodynia was reduced significantly. Side effects that were mentioned and observed were dizziness, sedation, hyper salivation, anorexia and psycho-mimetic ones such as nightmares and impaired attention. Most of them arose while daily dose reached 160mg/24h. Upon hospital discharge pain score was 3 (NRS), with fluctuation during the last week 2-5. In addition, a moderate improvement on depressive symptoms was observed with BDI score upon discharge down to 19. Specifically, significant reduction was recorded on the statements of pessimism, suicidal thoughts, tiredness, sleeping changes and loss of energy.

Discussion

Administration of NMDAR antagonists is referred in the literature as a mean of coping with opioid-induced hyperalgesia[11]. In complex chronic pain settings, especially when other chemical treatments fail to reduce pain, ketamine use seems to achieve adequate pain relief, even when administered for longer periods[12,13]. Long-term adverse effects and efficacy, though, are studied inadequately[14]. The off-label use of ketamine for patients with chronic pain in addition with its psycho-mimetic adverse effects prevents wide clinical use[15]. In our case, a combination of drastic reduction of opioids with the use of oral ketamine in a patient with chronic central pain, opioid tolerance and opioid-induced hyperalgesia, significantly reduced perceived pain. We have to consider, also, the possible antidepressant effect of ketamine that may have contributed to improvement in pain and decrease in opioids[16]. Further research is needed to investigate ketamine efficacy and adverse effects thoroughly in long-term settings as a possible add-on treatment for the pain specialist to consider.

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