Intravascular ketamine infusion for the treatment of chronic pain and depression. Case report

Infusão intravascular de cetamina para o tratamento de dor crônica e depressão. Relato de caso

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ABSTRACT

BACKGROUND AND OBJECTIVES: Chronic pain and depression are two comorbidities that correlate at the molecular level in the central nervous system and cause suffering to the patient, being difficult to be managed. In recent years, several studies have shown significant analgesic and antidepressant effects from intravascular infusion of ketamine, being a promising alternative option for refractory patients. Thus, the aim of the study was to report the case of a patient with refractory chronic pain and depression submitted to serial ketamine single dose infusions.
CASE REPORT: Female patient, 33 years old, diagnosed with interstitial cystitis 13 years ago with refractory chronic pain and depression, submitted to serial infusions of intravascular ketamine. Three serial infusions were performed, providing a significant improvement in pain and mood. However, the patient could not tolerate the adverse effects, particularly, the transient sensation of impending death and panic attack, and abandoned the treatment.
CONCLUSION: Ketamine is a safe and promising treatment option for chronic pain and depression and can promote significant, albeit transient, pain and mood relief using subanesthetic dosage. However, its adverse effects can be an important limitation for therapeutic success. Standardized clinical studies are needed to better understand the relationship between chronic pain and depression and to establish the best therapeutic approach.

Keywords: Chronic pain, Depression, Interstitial cystitis, Ketamine.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor crônica e a depressão são duas comorbidades que se correlacionam em nível molecular no sistema nervoso central e promovem sofrimento ao paciente, sendo de difícil manejo. Nos últimos anos, diversos estudos demonstraram efeitos analgésicos e antidepressivos significativos a partir da infusão intravascular de cetamina, sendo uma opção alternativa para pacientes refratários ao tratamento convencional. Assim, o objetivo do estudo foi relatar o caso de uma paciente com dor crônica e depressão refratária submetida a infusões seriadas de doses únicas de cetamina.
RELATO DO CASO: Paciente do sexo feminino, 33 anos, diagnosticada com cistite intersticial há 13 anos com refratariedade no manejo da dor e da depressão, submetida a infusões seriadas de cetamina intravascular. Foram realizadas 3 infusões seriadas que proporcionaram uma melhora significativa na dor e no humor. Entretanto, a paciente não tolerou os efeitos adversos, particularmente, de sensação de morte iminente e ataque de pânico, e abandonou o tratamento.
CONCLUSÃO: A cetamina é uma opção de tratamento promissora para dor crônica e depressão e pode promover alívio significativo, embora transitório, da dor e humor utilizando dose subanestésica. No entanto, seus efeitos adversos podem ser uma limitação para o sucesso terapêutico. Estudos clínicos padronizados são necessários para compreender melhor a relação entre dor crônica e depressão e para estabelecer a melhor abordagem terapêutica.

Descritores: Cetamina, Cistite intersticial, Depressão, Dor crônica.

INTRODUCTION

Pain is an important public health problem. The World Health Organization's (WHO) Global Burden of Disease Study 2016 revealed that pain (lumbar and cervical, migraine and musculoskeletal disorders) is among the top 10 disability causes in Brazil. In the same WHO study, depressive disorders are the fifth largest cause of years lived with disability[1]. Depression, like chronic pain, has a multidimensional character and requires specialized approach. Depression and pain are often interconnected and can aggravate physical and psychological conditions, leading to poor treatment outcomes and longer duration of symptoms. The common mechanisms and pathways of these effects are not yet very enlightened, but several studies have demonstrated that depression intensifies symptoms or reduces pain tolerance capacity[2].
Conventional treatment of depression includes pharmacotherapy and psychotherapy, and various other approaches are in-

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HIGHLIGTS
- Ketamine is a safe and promising treatment option for chronic pain and depression and can promote significant, albeit transient, pain and mood relief using subanesthetic dosage.
- The present study observed that a single infusion at low doses of ketamine can quickly relieve depressive symptoms, thoughts, and suicidal actions in patients with refractory depression.
- It is noteworthy that the serial infusion of ketamine for a certain period is a safer and more effective alternative to the treatment of pain and depression when compared to a single IV infusion regimen.

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tended for treatment-resistant patients. In recent years, there has been great interest in the treatment of mood disorders due to its morbidity and refractory nature. Therefore, different studies have found promising effects of ketamine infusion for the treatment of both chronic pain and depression. In this way, the American Society of Regional Anesthesia and Pain Medicine and the American Academy of Pain Medicine developed a consensus guideline on the use of ketamine for the treatment of chronic pain[3]. Likewise, the American Psychiatry Association published in 2017 a statement of consensus on the use of ketamine for the treatment of refractory mood disorders[4].

Ketamine is a phencyclidine derivative substance available as a racemic mixture developed in the 1960s and has anesthetic, analgesic and antipsychotic properties. It is a safe drug due to its anesthetic and analgesic potential, rapid effect and hemodynamically stable sedation by sympathetic stimulus without affecting respiratory function. Among its limitations, oral administration implies low bioavailability and high side effects due to the first-pass hepatic metabolization, which makes intravenous (IV) administration the best choice[5]. The main contraindications for its use include poorly controlled cardiovascular disease, hepatic dysfunction, psychoses, delirium, and active substance abuse[6,7].

Thus, the present study seeks to better understand the relationship between these complex clinical conditions and the effects of IV infusion of ketamine.

CASE REPORT

The CARE (Case Report) guidelines for case reports was used in an attempt to reduce risk of bias and increase transparency[8].

The female patient, 33-year-old, with interstitial cystitis (IC), has a progressive history of chronic pain and resistant depression. She was diagnosed with IC at the age of 20, when she started to receive specialized urological treatment. Since then, she has been through several urological treatments with no significant improvement, and currently requires regular follow-up.

At the same time of IC diagnosis, the patient began pain management with amitriptyline, followed over the years by the gradual use of initial to optimal doses of codeine-paracetamol combination, tramadol and eventually, oxycodone, all without persistent improvement. Over time, there was a progressive worsening of pain and the intrathecal morphine via implanted infusion pump was suggested. The patient reported a relative pain relief after the procedure, however, there was a need to further increase the dose of drugs as the disease progressed.

Faced with a complex treatment resistant condition of both IC and depression, the patient sought our care for chronic pain and depression management. The neurological examination was normal and showed no sign of cognitive, motor or sensitive dysfunction. She referred progressive mood aggravation, anxiety, insomnia, significant weight gain, fatigue, adynamia and persistent pelvic pain. In addition, she reported suicidal ideation and history of attempted prior suicide. She was in use of quetiapine (600 mg/day), escitalopram (20 mg/day), sodium valproate (1.5 g), clonazepam (75 mg), intrathecal morphine (2.1 g/day) and oral morphine (720 mg/day).

After evaluation, the patient was proposed weekly sessions of intravenous (IV) infusion of ketamine (dose) for eight weeks for the treatment of chronic pain and depression considering resistance to conventional pharmacological treatment. The infusions were held in a secure hospital environment and consisted of a single dose of ketamine (1 mg) diluted in physiological serum (100 mL of 0.9%) without use of other medications immediately before and after infusion.

The score on the Hamilton Depression Rating Scale (HAM-D) before the first infusion was 40 and pain intensity was 9 on the visual analog scale (VAS). There were no documented adverse effects during the first ketamine infusion session and the patient reported significant improvement in mood and pain perception, as well as suicidal ideation immediately after the procedure. From the improvement, it was possible to reduce the oral morphine dose. In turn, during the second session, she presented transient symptoms of nausea, dissociative symptoms, dyspnea, and panic attack, describing it as one of the worst sensations of her life.

Improvement in mood and pain perception persisted after the second infusion and it was possible to continue the decrease in oral morphine dosage to 600 mg/day and further decrease intrathecal morphine dosage (0.8 g/day). During the third session, the same adverse effects reported earlier were observed, and the improvement in mood and perception of pain persisted. The antidepressant and analgesic effect of ketamine was documented by a decrease on the HAM-D and VAS to 14 and 4, respectively, during treatment.

However, the patient abandoned the treatment after the third session due to significant intolerance to the adverse effects, particularly, due to the sensation of impending death and panic attack during infusion, despite the beneficial analgesic and antidepressant effects documented. She returned for a follow-up two weeks after the third session of ketamine reporting progressive pain and deterioration of mood with the need to readjust the morphine dosage to the baseline before the infusion of ketamine and remains in regular follow-up to the time of the study.

The patient signed a Free Consent Informed Term (FICT) and the study was approved by the Ethics and Research Committee in Human Beings of *Pontifical Catholic University of Goiás* (CAAE: 33852820.4.0000.0037), which is in accordance with the Declaration of Helsinki.

DISCUSSION

IC is an unusual chronic disease characterized mainly by pelvic pain and urinary symptoms with or without an identified cause and has high impact on patients' quality of life[9]. The pathophysiology is not completely elucidated and involves the sensory dysregulation of bladder awareness, associated with the disruption in the urothelium's apical cell layer. Its presentation and severity can vary, however, due to its chronic nature. Patients typically progress toward worsening symptoms and prognosis

can be disabling. Together with specialized urological treatment, IC approach involves early pain management for improving quality of life[10].

In line with the exposed case, the pharmacological pain treatment must be individualized and involves antidepressants, antiepileptics, analgesics and opioids. However, only about 30-40% of the patients with chronic pain, in general, have an improvement with pharmacological treatment[11-13]. In parallel, chronic pain and depression are usually interconnected and can intensify the symptoms and decrease the threshold of pain[2]. Considering this complex comorbidity, the treatment approach can be long and difficult and, therefore, makes the analgesic and antidepressant effects of IV ketamine infusion described in several studies a promising finding[4,14-16].

Ketamine has a complex mechanism of action and acts primarily as a non-competitive antagonist of the N-Methyl-D-Aspartate receptors (NMDA) in the central nervous system, intervening directly on the sensory input, mediating the responses of pain, memory, and emotions, with dissociative properties. It promotes effects on multiple other receptors that have a relationship in pain and mood regulation, such as the opioid receptor agonist, antagonist of nicotinic and muscarinic receptors, blockade of sodium and potassium channels, has high affinity with dopamine D2 receptors and calcium dependent channels, increases the activity of aminobutyric acid (GABA) and enhances descending modulatory pathways[3].

In preclinical studies, ketamine has shown to reduce opioid tolerance and hyperalgesia[17]. Moreover, ketamine infusions were associated with significant reductions in chronic pain and can generate a decrease of 2 points or 30% in the pain score, corresponding to a clinically important improvement, considering that pain parameters are not linear[18]. Accordingly, this case presented an improvement of 5 points on the VAS, comparable to a clinically significant relief of approximately 55% during treatment.

Several published studies were able to demonstrate the antidepressant effects of ketamine, as it was initially shown by the study[15], with the standard IV dose of 0.5mg/kg per 40 minutes of ketamine. The antidepressant effect of the studies, on average, presented greater efficacy with 24h post-infusion and had a mean transitional duration of 1-2 weeks. Additionally, it was observed that single dose IV infusions of ketamine in subanesthetic doses entail response rates of approximately 37 to 71% in patients with treatment resistant depression[16]. The duration of the antidepressant effect has been quite variable in clinical studies, ranging from hours to weeks, and most patients eventually relapse. In this sense, several studies have exploited the serial and weekly IV ketamine infusion trial for a certain period, to maintain the short and transient analgesic and antidepressant effect[19].

The present study observed that a single infusion at low doses of ketamine can quickly relieve depressive symptoms, thoughts, and suicidal actions in patients with refractory depression. In accordance with clinical trials, the patient showed an improvement of 65% in mood during treatment, leaving a very severe depression score (40 points) to moderate depression (14 points) on HAM-D.

Another relevant fact in the case presented was the significant and gradual decrease in opioids during the treatment period. The decrease in the use of intrathecal and oral morphine used during serial treatment with ketamine infusion represents lesser systemic, nephro and hepatotoxicity, in addition to improving the patient's quality of life. Furthermore, it has been demonstrated that the antidepressant effects of ketamine can be prolonged with serial and intermittent infusion schemes, generating more significant therapeutic effects when compared to a single infusion[20]. This effect has special relevance considering refractory depressive patients and patients at risk for suicide, since ketamine has shown rapid, safe, and effective therapeutic potential for this situation.

However, one major disadvantage and obstacle of its use is the adverse effects caused, namely: rising respiratory rate, hallucinations, diplopia, dissociative symptoms, agitation, nausea, and vomiting[7]. Its long-term use is related to the risks of serious and persistent urinary diseases, cognitive impairment, chemical dependence, and these are dose and exposure time dependent. Nevertheless, there is still a lack of studies demonstrating the long-term effects and serial infusions of ketamine, both for the treatment of pain and depression. The patient presented dissociative symptoms, sensation of impending death and inexplicable fear from the second session to the third infusion, which was crucial for the intolerance to treatment despite the significant improvement in mood and pain.

Finally, it is noteworthy that the serial infusion of ketamine for a certain period is a safer and more effective alternative to the treatment of pain and depression when compared to a single IV infusion regimen. In fact, treatments with a standard IV dose of 0,5 mg/kg per 40 minutes presented better clinical results, allowing greater tolerance to adverse effects[3,4,16,17].

The strengths of this case are related to the possibility of applying serial ketamine infusions as an alternate treatment for treatment resistant depression, however, in low doses and through continuous infusion for a certain period compared to a single dose application. Nevertheless, there were limitations related to the follow-up immediately after treatment as the patient decided to abandon the therapy after the third session, which could better determine the transient effect of the analgesic and antidepressant properties of ketamine.

CONCLUSION

Ketamine is a promising treatment option for chronic pain and depression and can promote considerable but temporary pain and mood relief using a subanesthetic dose. However, the adverse effects can be a considerable limitation.

AUTHORS' CONTRIBUTIONS

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Statistical analysis, Funding acquisition, Data Collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Software, Supervision, Validation, Visualization

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Statistical analysis, Funding acquisition, Data Collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Software, Supervision, Validation, Visualization

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