

# Feasibility of intravenous ketamine infusion for refractory headache

## Viabilidade da infusão intravenosa de cetamina para cefaleias refratárias

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### ABSTRACT

**Background:** Ketamine intravenous infusion has been used safely to several chronic pains and it is a good option to refractory chronic headaches. It is a noncompetitive NMDA receptor antagonist that blocks glutamate, responsible for the dissociation between thalamus-neocortical and limbic systems, leading to changes in patients' pain perception. Due to this theoretical mechanism and results in reducing cortical spreading depression, Ketamine has been proposed as a treatment for migraine. **Methods:** We conducted a retrospective medical chart review study at Hospital Israelita Albert Einstein including three patients. All of them were diagnosed previously with refractory chronic headache. **Results:** Of participants included (n = 3), two were woman. The median duration of the disease was 21 years and 12 previous treatment's failures. All the patients were currently in use of more than 4 preventive drugs. Treatment-emergent response was seen in all patients, requiring 1, 3 and 4 sessions to complete plain remission. They presented good tolerability to the treatment. One patient complained of tinnitus and mild dizziness at the end of the last session, which lasted less than 30 minutes. **Conclusion:** Ketamine is well tolerated and an effective treatment for patients with refractory chronic headache.

**Keywords:** Ketamine, chronic headache, refractory headache

### RESUMO

**Justificativa:** A infusão intravenosa de cetamina tem sido utilizada com segurança em diversas dores crônicas e é uma boa opção para dores de cabeça crônicas refratárias. É um antagonista não competitivo do receptor de NMDA que bloqueia o glutamato, responsável pela dissociação entre os sistemas tálamo-neocortical e límbico, levando a alterações na percepção da dor dos pacientes. Devido a esse mecanismo teórico e redução da depressão cortical alastrante, a cetamina foi proposta como tratamento para enxaqueca. **Métodos:** Realizamos um estudo retrospectivo de revisão de prontuários no Hospital Israelita Albert Einstein, incluindo três pacientes. Todos foram diagnosticados previamente com cefaleia crônica refratária, enxaqueca crônica. **Resultados:** Dos participantes incluídos (n = 3), dois eram do sexo feminino. A duração média da doença foi de 21 anos e 12 falhas do tratamento anterior. Todos os pacientes estavam atualmente em uso de mais de 4 medicamentos preventivos. A resposta emergente ao tratamento foi observada em todos os pacientes, exigindo 1, 3 e 4 sessões para concluir a remissão simples. Eles apresentaram boa tolerabilidade ao tratamento. Um paciente apresentou queixa de zumbido e tontura leve no final da última sessão, que durou menos de 30 minutos. **Conclusão:** A cetamina é bem tolerada e um tratamento eficaz para pacientes com cefaleia crônica refratária.

**Descritores:** cetamine, cefaleias crônicas, cefaleias refratárias

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## INTRODUCTION

Refractory chronic headache is responsible for high financial costs to the health system, considering the frequent use of services and disability in the economically active population. One of the currently used treatment options is ketamine<sup>1</sup>. This drug has been used to treat several chronic pains with good results, and some reports on refractory headaches also indicate good response<sup>2-4</sup>.

Ketamine is a dissociative anesthetic that acts on glutamate binding sites at the N-methyl-D-aspartate receptor (NMDA), as well as at opioid, monoaminergic, cholinergic, nicotinic, and muscarinic receptors<sup>5,6</sup>. There is a theory of functional and electrophysiological dissociation between thalamus-neocortical and limbic systems: sensory afferences may reach cortical receptor areas, but are not observed in some areas of association with ketamine use<sup>7,8</sup>. Analysis of the effects of dose-dependent ketamine on pain processing showed reduced activation of the secondary somatosensory cortex, insula and anterior cingulate, which has been associated with the affective component of pain<sup>9</sup>. This theoretical mechanism of action of ketamine has been shown to decrease central sensitization and allodynia, which has motivated physicians to use it as a treatment for migraine. Ketamine also reduces cortical spreading depression in animal models. The most common known side effects may include cardiovascular instability, respiratory changes, and psychiatric symptoms, including acute psychosis, hallucinations, anxiety, but are generally dose dependent<sup>4</sup>.

Although Ketamine infusions has been widely used in depression and chronic pain conditions, limited information is available in Brazil regarding this option in refractory headache patients.

## METHODOLOGY

We conducted a retrospective medical chart review study. In 2018, a total of three patients were admitted to a day hospital for continuous intravenous ketamine treatment at Hospital Israelita Albert Einstein, in São Paulo. Data were collected from medical records obtained from electronic medical records. Prior to admission, patients were already diagnosed with refractory chronic headache by a specialist neurologist for headache.

Patients were evaluated by neurologists (HFA, MFPP) monitored by a team of anesthetists (UCD, LSFM, BSA), who repeated the same infusion procedure in all cases. The protocol used was 30 mg IV ketamine diluted in 0.9% saline 100 ml, with a one-hour continuous infusion pump infusion time. Number of previous treatments, headache history time, pain intensity before and after infusion (visual analog scale), tolerability (adverse effects) and number of applications were evaluated in the patients.

## RESULTS

The age ranged from 39 to 53 years and two out of three patients were women. EVA scores at admission were nine or ten. All patients were Brazilian, born in São

Paulo. The median duration of the disease was 21 years (range 20-24). The average number of failures in previous treatments was 12 and were currently in use of more than 4 preventive treatments. Two out of three patients receiving ketamine had a previous psychiatric diagnosis (depression and panic syndrome). All three patients were on at least one of the following medications: muscle relaxant, NSAID, opioid, antiepileptic, antidepressant, benzodiazepine, triptan, beta blocker or antiemetic.

Responses from 3 patients, one man and 2 women were evaluated. Patient 1, 50 years old, required 3 sessions for complete pain remission, evolved with good tolerability, no comorbidities. Patient 2, 53 years old, previously diagnosed with depression and chronic neck pain, required 4 sessions for complete pain relief (1 session per week), tinnitus and mild dizziness lasting less than 30 min only at the end of the last session. Patient 3, 39 years old, previously diagnosed with panic syndrome, underwent only 1 session of IV ketamine with complete pain remission, with no reports of adverse events.

## DISCUSSION

Intravenous ketamine has been proposed for the treatment of headache disorders. Despite the small number of patients in the case series and the absence of a comparative placebo group, we have demonstrated short-term success in pain relief in patients with chronic headache with tolerable and short-term adverse effect. It is biologically plausible that ketamine may be an effective treatment for intractable headaches. Since Ketamine has been used for depression and severe headache patients are likely to present with comorbid depression, its use may have multiple benefits.

Ketamine use has been very effective, has variable durability and has side effects with anomalous body and consciousness sensations but not reported as uncomfortable. Its application is feasible in our environment, the use of infusion pump makes the procedure expensive and is in our opinion unnecessary. Despite the fear of the side effects profile, they are all easy to handle.

## CONCLUSION

Intravenous infusion ketamine protocol is feasible, safe, and effective. It can be done in a non-hospitalized infusional environment, alleviates pain without substantial adverse effects. Future studies are necessary to stablish the role of ketamine infusion in other headache conditions.

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