

Brief Communications

Ketamine Infusion Combined With Magnesium as a Therapy for Intractable Chronic Cluster Headache: Report of Two Cases

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Background.—Chronic cluster headache (CH) is a rare, highly disabling primary headache condition. As NMDA receptors are possibly overactive in CH, NMDA receptor antagonists, such as ketamine, could be of interest in patients with intractable CH.

Case reports.—Two Caucasian males, 28 and 45 years-old, with chronic intractable CH, received a single ketamine infusion (0.5 mg/kg over 2 h) combined with magnesium sulfate (3000 mg over 30 min) in an outpatient setting. This treatment led to a complete relief from symptoms (attack frequency and pain intensity) for one patient and partial relief (50%) for the other patient, for 6 weeks in both cases.

Conclusion.—The NMDA receptor is a potential target for the treatment of chronic CH. Randomized, placebo-controlled studies are warranted to establish both safety and efficacy of such treatment.

Key words: cluster headache, ketamine, NMDA

Abbreviations: CH cluster headache, NMDA *N*-methyl-D-aspartate

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INTRODUCTION

Cluster headache (CH) is characterized by severe strictly unilateral headaches lasting 15–180 min, accompanied by agitation and ipsilateral autonomic phenomena, including rhinorrhea, lacrimation, and conjunctival injection.¹ The chronic

form of CH is rare, and its attacks recur over more than 1 year without remission periods or with remission periods lasting less than 1 month.¹ Some chronic CH patients become drug-resistant and continue to suffer almost daily attacks for long periods. When medically intractable, occipital nerve stimulation can offer effective treatment.² Nonetheless, new pharmacological options are needed to avoid or to wait for surgery. Ketamine seems to be effective in a variety of chronic pain conditions³ including refractory headache⁴ and could be even more analgesic when combined with magnesium.⁵ Indeed, extracellular magnesium ions can bind to

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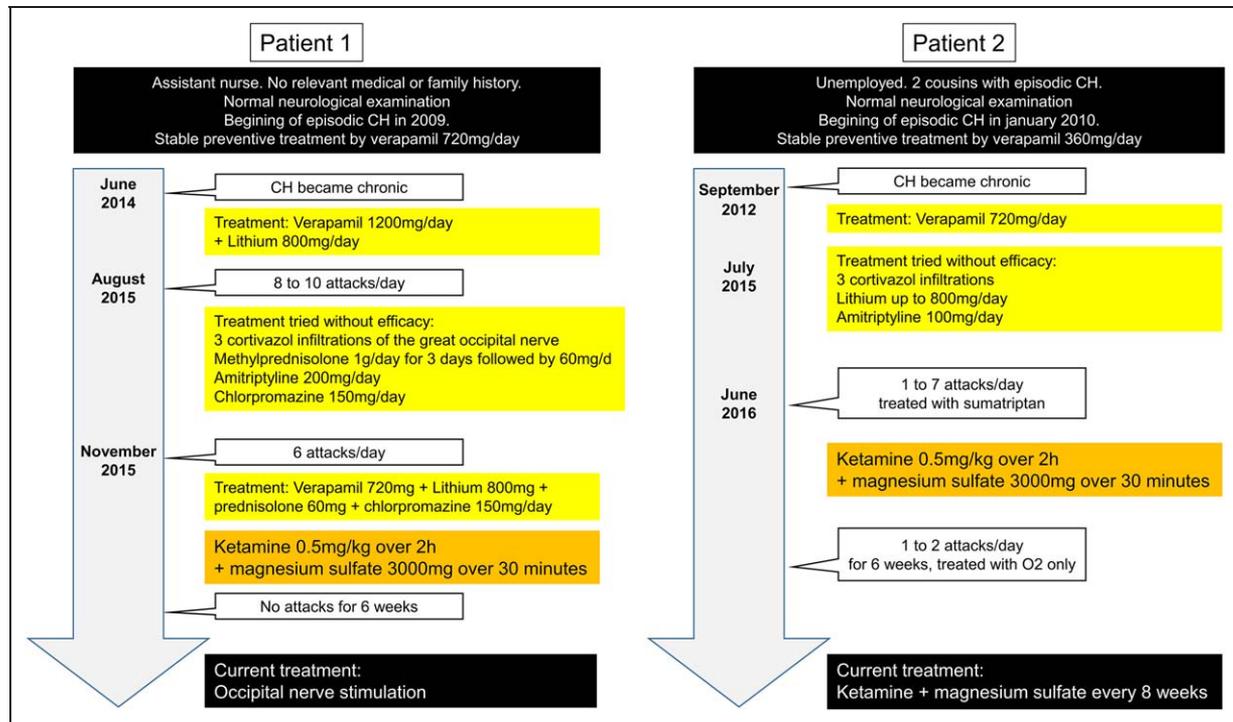


Fig. 1.—Timeline of interventions and outcomes. CH = cluster headache. [Color figure can be viewed at wileyonlinelibrary.com]

specific sites on the *N*-methyl-D-aspartate (NMDA) receptor, blocking the passage of other cations (Na^+ , Ca^{2+}) through the open ion channel. Therefore, both ketamine and magnesium could participate in NMDA blockade. Thus, we decided to try ketamine (NMDA antagonist) combined with magnesium sulfate in two patients with severe and intractable chronic CH.

CASE REPORTS

We report the case of a 45-year-old Caucasian male who was suffering from CH for 6 years, with a chronic form for 1 year despite maximal tolerated doses of prophylactic drugs (verapamil 1200 mg/day combined with lithium 800 mg/day, see Fig. 1). The patient has been presenting between 8 and 10 attacks per day for the last 3 months and he was performing one subcutaneous sumatriptan injection during each attack. He had suicidal ideation. A series of three corticosteroid 3.75 mg infiltrations of the great occipital nerve was performed without any pain reduction.⁶ Methylprednisolone infusions of 1 g per day for 3 consecutive days allowed an

attack-free period of 3 days only, despite oral treatment continuation with 60 mg per day. Amitriptyline was tested up to 200 mg per day during 3 weeks without any efficacy on either pain or mood. Chlorpromazine was used at a dose of 150 mg per day allowing a reduction of attack frequency of 20%. After 14 days with a stable pharmacological treatment associating 720 mg verapamil, 800 mg lithium, 60 mg prednisolone, and 150 mg chlorpromazine, the patient was still presenting six attacks per day. A single ketamine infusion of 0.5 mg/kg over 2 h combined with 3000 mg of magnesium sulfate infused over 30 min was performed without any adverse event. This procedure resulted in total pain relief the very next day that lasted for 6 weeks. This pain relief enabled the patient to wait for great occipital nerve stimulation. Suicidal ideation disappeared in the same time. The electrical stimulation was turned on 8 weeks after the ketamine infusion, as the patient was once again presenting between 6 and 10 attacks per day. This led to an immediate reduction of 75% of attacks frequency (2 attacks

per day) and after further tuning, to a complete cessation of attacks.

The second patient was a 28-year-old male who had also been suffering from CH for 6 years and chronic CH for 4 years, with 1-7 attacks per day (mean of 4) treated by subcutaneous sumatriptan (Fig. 1). Daily treatment was verapamil 720 mg per day (higher doses were not tolerated). Previous treatment with lithium, cortivazol infiltrations, and amitriptyline were ineffective. Ketamine infusion (combined with magnesium sulfate) was performed without any adverse event and allowed a 50% decrease in attack frequency and intensity for 6 weeks, enabling him to treat CH with oxygen therapy only. Since then, three infusions have been performed, 8 weeks apart, with the same efficacy and duration. Greater occipital nerve stimulation was proposed, but this was declined by the patient.

DISCUSSION

Cluster headache is rare, but the most severe of the primary headache disorders, which is occasionally refractory to conventional treatment. Very few preventive treatments have proven effective,⁷ and there is need for additional therapeutic options. Although repeated ketamine administration seems to be effective in a variety of chronic pain conditions including refractory headache,^{3,4} we reported for the first time that a single infusion of ketamine and magnesium is effective in chronic CH. The effect was almost immediate and lasted for 6 weeks for both patients. We can wonder how ketamine works on both pain and depression. It is known that ketamine acts as a NMDA-antagonist, but also enhances the descending inhibiting serotonergic pathway.⁸ Moreover, recent findings are in favor of reduced levels of kynurenic acid (an NMDA receptor antagonist) in patients affected by CH, supporting the hypothesis that NMDA receptors are overactive in CH.⁹ In addition to pain relief, a single ketamine infusion seems to be effective to very rapidly reduce suicidal ideation,¹⁰ which can be a major issue in patients with CH. Nonetheless, side effects can occur during acute ketamine infusion and long term use of intermittent ketamine must be prescribed with caution,¹¹ and delayed-onset

suicidal ideation after ketamine infusion have even been reported.¹² We can wonder if magnesium, also needed in the function of NMDA receptor, can favor this very positive and rapid effect of ketamine. Moreover, an old study suggested that magnesium infusion could have analgesic properties in CH patients with low ionized magnesium level,¹³ but we did not measure the magnesium in these two patients. Ketamine is already labeled for anesthesia and is used by several pain practitioners for chronic pain.³ Thus, it seems feasible to conduct clinical trials with this drug for refractory chronic CH, for example comparing this therapeutic with invasive approaches. We can also wonder if other treatments acting on NMDA, such as memantine or riluzole, could have a place in preventive CH treatment.

KEY FINDINGS

A single ketamine infusion combined with magnesium induces a sustained symptom relief in two patients with refractory CH.

The NMDA receptor is a potential target for the treatment of chronic CH.

Randomized, placebo-controlled studies are warranted to establish both safety and efficacy of ketamine infusion combined with magnesium in CH patients.

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