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Original Contribution

Is magnesium sulfate effective for pain in chronic postherpetic neuralgia patients comparing with ketamine infusion therapy?

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Abstract

Background: Postherpetic neuralgia (PHN) is a frequent debilitating complication and one of the most intractable pain disorders, particularly in elderly patients. Although tricyclic antidepressants, topical capsaicin, gabapentin, and oxycodone are effective for alleviating PHN, many patients remain refractory to current therapies. Here, the analgesic effects of ketamine or magnesium for PHN were assessed in an open prospective study.

Method: Thirty patients with severe, intractable PHN who were unresponsive to conservative therapy participated. The effects of ketamine hydrochloride (Ketara, Parke Davis) 1 mg/kg and magnesium sulfate (Magnesin) 30 mg/kg were investigated. The patients were randomly divided into 2 groups of 15 patients each, and ketamine 1 mg/kg or magnesium 30 mg/kg was administered intravenously for 1 hour after midazolam sedation. Pain was rated on a visual analog scale (VAS) during a 2-week follow-up. All patients also completed the Doleur Neuropathique 4 questionnaire at baseline and final visits.

Results: Response to treatment, defined as a 50% reduction in VAS score 2 weeks after, was recorded in 10 of 15 patients in the ketamine group and 7 of 15 patients in the magnesium group. The difference in VAS reduction was not significant between the 2 groups.

Conclusions: Ketamine and magnesium showed significant analgesic effects in patients with PHN.

1. Introduction

Postherpetic neuralgia (PHN) is one of the most intractable pain disorders, particularly in elderly patients. Although various procedures aimed at pain relief have been devised and tested, no established treatment for PHN has yet been identified. The mechanism for pain in PHN may be associated with direct neuronal damage to both peripheral and central nervous systems [1]. The clinical features of PHN are accompanied by allodynia, burning, aching, and continuous pain [2].

The N-methyl-D-aspartate (NMDA) receptor plays an important role in mechanisms underlying central sensitization (wind-up) and expansion of receptive fields in the spinal cord [3-5]. Eide et al [6]. showed that NMDA receptors are involved in the control of PHN, including allodynia and wind-up–like pain. Ketamine, a noncompetitive NMDA antagonist to the phencyclidine site of the NMDA receptor for the excitatory

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neurotransmitter glutamate, has been reported to reduce neuropathic pain and allodynia in patients with chronic PHN [6-10]. Another NMDA antagonist, magnesium sulfate, is a physiological blocker of NMDA calcium channels, blocking calcium influx into the cell and contributing to secondary neuronal changes. It has also been shown to be effective in the treatment of several neuropathic pain such as PHN, CRPS, and phantom limb pain [11-15].

The present study assessed and compared the efficacy of intravenous (IV) ketamine, well known to be effective in the treatment of several neuropathic pain disorders, or magnesium sulfate in PHN patients.

2. Materials and methods

The study had a randomized double-blind, uncontrolled design. Thirty patients with severe, intractable PHN who had not previously responded to conventional treatment with pharmacologically based interventional therapies participated. The patients reported pain resistant to conventional treatments, including stellate ganglion block, local anesthetic infiltration, epidural block, and systemic administration of anticonvulsants and antidepressants. Spontaneous pain with a visual analog scale (VAS) score >7 and lasting for ≥6 months was consistently reported. The ketamine and magnesium solutions used in the study were similar in appearance and volume, and the patients were randomly assigned to receive one or the other by sealed envelope technique.

The study protocol was approved by the hospital's ethical committee. Informed consent was obtained from each patient.

Patients were excluded if they had hypermagnesemia, hypercalcemia, abnormal electrocardiogram, asthma, any degree of heart block, or renal impairment (blood urea >12 mmol/L and creatinine >150 μmol/L) or were taking digoxin. During the entire study period, the patients continued with their regular medication, including analgesics. Local infiltration and nerve blocks were not allowed in the 2 weeks before this study.

Ketamine hydrochloride (Ketara, Parke Davis) or magnesium sulfate (Magnesin) was administered in a double-blind fashion with respect to the assessor and patient. They were given midazolam intravenously (0.1 mg/kg) to render them unconscious. Ketamine (1 mg/kg per hour) and magnesium sulfate (30 mg/kg per hour) were diluted in 0.9% normal saline to a final volume of 100 mL and infused by syringe pump over 1 hour. The drugs were administered on 3 sessions: and each session was performed consecutively every other day. At each of the 3 time points, an electrocardiogram was obtained, and heart rate, noninvasive blood pressure, and pulse oximetry were monitored throughout the drug infusions. Serum magnesium concentrations were measured before the study and at its conclusion and were within normal limits in all patients.

Pain intensity was evaluated just before drug treatment, 2 weeks after the third ketamine or magnesium infusion using a VAS in which pain was rated on a 0- to 10-cm scale, with 0 for no pain and 10 for the worst pain imaginable. Response to treatment was defined as a >50% reduction in VAS score compared with baseline; otherwise, the patient was classified as a nonresponder. All patients also completed the Doleur Neuropathique 4 (DN4) questionnaire for evaluation of the neuropathic components of pain at baseline and final visits. Mechanical stimulation with a brush to test for mechanical dynamic allodynia was performed before and 2 weeks after the infusions. Painful cold of DN4 items assessed by touching an alcohol swab on the painful region. The Wilcoxon signed rank test was used to compare pain scores between the ketamine and magnesium groups.

3. Results

Of the 30 patients who participated, 9 were male and 21 were female. Their mean age was 69 years (65-83 years), and the average pain duration was 21 months (range, 6-53 months). All patients had previously tried a variety of pharmacological and nonpharmacological interventions, such as tricyclic antidepressants, anticonvulsants, sympathetic nerve block, nerve root block, and pulsed radiofrequency thermocoagulation. All patients suffered significant pain despite ongoing pain therapy, as reflected in an initial mean VAS score for continuous pain of 8 (1.94) in the ketamine group and 7.7 (1.55) in the magnesium group. Visual analog scale score in 2 weeks after ketamine of 4.33 (2.15) or VAS score in 2 weeks after magnesium infusion therapy of 3.1 (1.45) were significantly lower than the initial VAS score ($P < .001$). The mean value for pain reduction from baseline was 51% for patients receiving ketamine and 39.6% for those receiving magnesium. The difference in VAS score reduction between the ketamine and magnesium groups was not significant ($P = .4018$) (Table 1).

According to our definition of drug responder (>50% reduction in VAS score), 10 of 15 patients responded to ketamine, and 7 of 15, to magnesium (Figure). Twelve for patients receiving ketamine and 11 for patients receiving magnesium had a decrease in the VAS score of >30%. The

Table 1 The VAS scores for pain assessment just before the initiation of ketamine or magnesium infusion and at 2 weeks after the third ketamine or magnesium infusion in patients with PHN

Time	Ketamine group	Magnesium group	*P*
DN4 questionnaire, mean (SD)	4.38 (1.0)	4.64 (1.6)	>.05 *
VAS 1	8 (1.94)	7.7 (1.55)	>.05 *
VAS 2	4.33 (2.15)	3.1 (1.45)	>.05 *
P	<.05 †	<.05 †	

VAS 1 = baseline VAS score; VAS 2 = VAS score in 2 weeks after the third ketamine or magnesium infusion.

* Compared ketamine group with magnesium group.

† Compared VAS 1 with VAS 2.