

Intravenous Lysine Clonixinate for the Acute Treatment of Severe Migraine Attacks: A Double-Blind, Randomized, Placebo-Controlled Study

Aouch Valenty Krymchantowski, MD, PhD, and Marcus Tullius T. Silva, MD

Department of Neurology, Universidade Federal Fluminense, Instituto de Neurologia Deolindo Couto, Headache Center of Rio de Janeiro, Rio de Janeiro, Brazil

ABSTRACT

Background: Several nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective in the treatment of migraine. However, few commercially available NSAIDs can be administered IV. Lysine clonixinate (LC), an NSAID derived from nicotinic acid, has been proved effective in various algescic syndromes (eg, renal colic, muscular pain, nerve compression, odontalgia). The oral formulation of LC has been shown to be effective in the treatment of migraine of moderate severity.

Objective: The aim of this study was to assess the efficacy and tolerability of the IV formulation of LC in the treatment of severe migraine.

Methods: This double-blind, randomized, placebo-controlled, prospective study enrolled patients with severe migraine (without aura) as defined by the criteria of the International Headache Society. When patients presented to a neurology hospital with an outpatient headache unit (Instituto de Neurologia Deolindo Couto, Rio de Janeiro, Brazil) with a severe migraine attack that had lasted <4 hours, they were randomized to 1 of 2 groups (IV placebo [25 mL of 0.9% saline] or IV LC [21 mL of 0.9% saline plus 4 mL of LC 200 mg]). Headache intensity and adverse effects (AEs) were assessed before (0 minute) and 30, 60, and 90 minutes after study drug administration. Rescue medication was available 2 hours after study drug administration, and its use was compared between groups.

Results: Thirty-two patients (23 women, 9 men; mean [SD] age, 32 [2] years; range, 18–58 years) entered the study. Twenty-nine patients (21 women, 8 men; mean [SD] age, 32 [2] years; range, 18–56 years) completed the study. Three patients (all in the placebo group) did not complete the study (1 patient was unable to rate the pain severity after drug administration and 2 patients refused IV drug administration). Among study completers, 17 patients received LC and 12 placebo. At 30 minutes, 1 patient (8.3%) in the placebo group and 5 patients

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(29.4%) in the LC group were pain free; the between-group difference was not statistically significant. At 60 and 90 minutes, respectively, 3 (25.0%) and 5 (41.7%) patients in the placebo group and 12 (70.6%) and 14 (82.4%) patients in the LC group were pain free ($P = 0.021$ and $P = 0.028$ between groups at 60 and 90 minutes, respectively). Six patients (50.0%) in the placebo group and 1 patient (5.9%) in the LC group required rescue medication at 2 hours ($P = 0.010$ between groups). Three patients (25.0%) in the placebo group experienced AEs, including vomiting, dizziness, and malaise (1 patient [8.3%] each); 11 patients (64.7%) in the LC group experienced ≥ 1 AE, including burning pain at the injection site (5 patients [29.4%]), heartburn (4 patients [23.5%]), and dizziness and malaise (1 patient [5.9%] each) ($P = 0.025$).

Conclusions: NSAIDs administered by the IV route cannot be used routinely in an outpatient environment, although an attempt to improve drugs in this class is clearly justified. This study demonstrated that IV LC was effective and well tolerated in the treatment of severe migraine attacks. This finding differs from results with the oral formulation, which is effective only in migraine of moderate severity. (*Curr Ther Res Clin Exp.* 2003;64:505–513) Copyright © 2003 Excerpta Medica, Inc.

Key words: lysine clonixinate, migraine, severe attacks, acute treatment.

INTRODUCTION

Migraine is a prevalent (18%–20% of women and 4%–6% of men worldwide) disorder that manifests clinically as moderate to severe headache attacks with frequent frontotemporal unilateral location and associated symptoms.^{1–3} The pain is pulsating and/or pressure type and is usually associated with nausea, photophobia, phonophobia, and osmophobia. The attacks cause disability and generally worsen with physical activity. An attack may last from 4 to 72 hours when not treated or treated ineffectively,³ and the frequency varies, with some individuals experiencing migraine on a weekly basis, and others having an attack less than once a month.⁴ The disability of migraine results in considerable economic and social losses.⁵

Serotonergic agonists known as *triptans* have recently been shown to be effective for the acute treatment of migraine.⁶ However, due to the high cost of the triptans (average cost, \$4–\$7 per tablet and \$20 per injection), some emergency facilities in developing countries do not have these drugs available. In most of these facilities, common analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and even opioids are the basic components of the therapeutic arsenal.⁷ In addition to the high cost, clinical experience suggests that the moderate pain-free rate (~40% at 2 hours) and sustained pain-free rate (<60% at 24 hours), as well as headache recurrence within 24 hours, may limit the use of triptans.⁸

Several drug options and different formulations are available to treat migraine attacks. The choice of specific medication type depends on individual characteristics such as pain intensity, speed of onset of action, presence of associated symptoms, the degree of incapacitation, and the patient's response.⁹

Some patients find relief using simple analgesics alone or in combination with caffeine or barbiturates.^{10,11} In addition, some NSAIDs have proved effective for treating migraine, and they are still widely used in many countries despite the potential for gastrointestinal adverse effects (AEs) and the availability of agents developed specifically to treat migraine, such as triptans.^{8,10,12-14} However, few commercially available NSAIDs can be administered intravenously (IV).

Lysine clonixinate (LC) is an NSAID derived from nicotinic acid, with a chemical structure similar to that of flufenamic acid.^{15,16} LC has been studied for the acute treatment of migraine in controlled and open-label trials.¹⁷⁻¹⁹ Its chemical structure (2-[3-chloro-o-toluidine]piridino-3-carboxilate) allows rapid absorption. LC is 96% to 98% protein bound, and its hepatic metabolism results in 4 different inactive metabolites. Seventy-five percent of its excretion is renal and 25% is fecal.²⁰

The aim of this study was to assess the efficacy and tolerability of the injectable formulation of LC in treating severe migraine attacks.

PATIENTS AND METHODS

This double-blind, randomized, placebo-controlled, prospective study was conducted at a neurology hospital with an outpatient headache unit (Instituto de Neurologia Deolindo Couto, Rio de Janeiro, Brazil) from March 15 to December 10, 1998. We studied male and female patients aged 18 to 65 years with the diagnosis of migraine without aura according to the International Headache Society criteria (Table).³ The patients were either already receiving treatment at the unit or they were being seen for an initial assessment.

The institutional review board at the Universidade Federal Fluminense (Rio de Janeiro, Brazil) approved the study and all patients provided written informed consent to participate.

Patients receiving treatment for any other medical condition; pregnant, possibly pregnant, or breast-feeding women; and patients who used any type of migraine symptomatic medication within the previous 6 hours were excluded.

Patients were assigned to the placebo or the LC group when they presented to the headache unit with a severe migraine attack lasting <4 hours. Due to the logistics of preparing the medications for administration, the patients were randomized to the treatment groups following a 2-3-3 order (ie, the first 2 patients were placed in the LC group, the next 3 patients were placed in the placebo group, the next 3 in the LC group, and so forth).

Patients rated the severity of the attack on a 4-point visual analog scale (VAS) ranging from 0 (no pain) to 3 (severe headache). Patients were placed in the supine position and a peripheral vein in the right forearm was catheterized; 25

Table. Diagnostic criteria of migraine without aura according to the Headache Classification Committee of the International Headache Society (IHS).³

- A. ≥ 5 Attacks fulfilling criteria B–D
- B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
- C. Headache has ≥ 2 of the following characteristics:
 - Unilateral location
 - Pulsating quality
 - Moderate or severe intensity (inhibits or prohibits activities of daily living)
 - Aggravation by walking stairs or similar routine physical activity
- D. ≥ 1 of the following:
 - Nausea and/or vomiting
 - Photophobia and phonophobia
- E. ≥ 1 of the following:
 - History, physical, and neurologic examinations do not suggest one of the disorders listed in groups 5–11 of the IHS classification
 - History, physical, and/or neurologic examinations suggesting such a disorder, but the disorder is ruled out by appropriate investigations
 - Such a disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

mL of 0.9% saline (placebo) or 21 mL of 0.9% saline plus 4 mL of LC (200 mg) were injected freely through a microdrop system in a double-blind fashion. Study drug administration lasted an average of 5 minutes (approximate rate, 96 drops/min). An auxiliary nurse and the primary author (A.V.K.) administered the drug. The secondary author (M.T.T.S.) prepared the medications, thereby maintaining the blinding throughout the study. Because a burning sensation at the injection site is common with LC, we diluted the drug in saline and informed all of the patients that the sensation could occur with either of the medications.

The primary author assessed headache intensity and AEs before (0 minute) and 30, 60, and 90 minutes after drug administration. Use of the rescue medication (indomethacin 100 mg rectally, available after 2 hours) was compared between groups by the primary author.

Statistical Analysis

Statistical comparisons were performed using the nonparametric chi-square test or the Fisher exact test (when applicable) to verify the between-group differences in responses at 30, 60, and 90 minutes; the use of rescue medication at 2 hours; and the incidence of AEs. We used GraphPad Prism version 3 (GraphPad Software, Inc., San Diego, California) for statistical analysis. $P < 0.05$ (2-tailed) was considered significant.

RESULTS

Thirty-two patients (23 women, 9 men; mean [SD] age, 32 [2] years; range, 18–58 years) entered the study. Twenty-nine patients (21 women, 8 men; mean [SD]

age, 32 [2] years; range, 18–56 years) completed the study. Among those who completed the study, 27 patients (93.1%) had been treated for periods ranging from 2 weeks to 4 months with drugs other than NSAIDs and 2 patients (6.9%) had presented to the headache unit for the first time. Three patients (all in the placebo group) did not complete the study (1 patient was unable to rate the pain severity after drug administration and 2 patients refused IV drug administration). Among those who completed the study, 12 patients (8 women [66.7%], 4 men [33.3%]; mean [SD] age, 35 [2] years) received placebo and 17 patients (13 women [76.5%], 4 men [23.5%]; mean [SD] age, 35 [2] years) received LC.

Thirty minutes after drug administration, 1 patient (8.3%) in the placebo group and 5 (29.4%) in the LC group were pain free (VAS score = 0); the between-group difference was not statistically significant. At 60 minutes, 3 patients (25.0%) in the placebo group and 12 (70.6%) in the LC group were pain free ($P = 0.021$). At 90 minutes, 5 patients (41.7%) in the placebo group and 14 (82.4%) in the LC group were pain free ($P = 0.028$) (Figure 1). Rescue medication was required at 2 hours by 6 patients (50.0%) in the placebo group and by 1 (5.9%) in the LC group ($P = 0.010$) (Figure 2). Two patients (16.7%) in the placebo group and 3 (17.6%) in the LC group had mild or moderate pain (VAS score = 1 or 2) at 2 hours but did not request rescue medication.

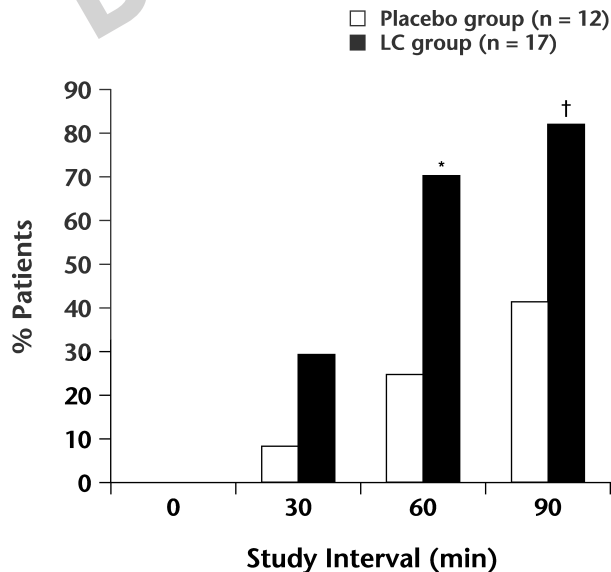


Figure 1. Percentages of pain-free patients at each study interval, by treatment group. * $P = 0.021$ versus placebo. † $P = 0.028$ versus placebo. LC = lysine clonixinate.

The following AEs occurred: vomiting, dizziness, and malaise (1 patient [8.3%] each) were reported by 3 patients (25.0%) in the placebo group; burning sensation at the injection site (5 patients [29.4%]), heartburn (4 patients [23.5%]), and dizziness and malaise (1 patient [5.9%] each) were reported by 11 patients (64.7%) in the LC group ($P = 0.025$) (Figure 2).

DISCUSSION

This double-blind, randomized, placebo-controlled study demonstrated that LC, an inexpensive injectable NSAID (average cost, \$1.50 per dose), was effective for the treatment of severe migraine attacks. We assessed pain intensity at T_0 and 30, 60, and 90 minutes after study drug administration, and use of rescue medication at 2 hours, as suggested by the guidelines of the International Headache Society.²¹

Although it might be argued that the blinding was lost due to the pain at the injection site, we believe we avoided this problem by informing the patients, prior to drug administration, that they might experience that sensation with either treatment. However, the study deserves criticism because we did not assess associated symptoms and sustained pain-free measures at 24 hours. In fact, we limited our assessment to 2 hours, as did, in part, Bigal et al,²² because of the large numbers of patients seen each day in the public health unit of

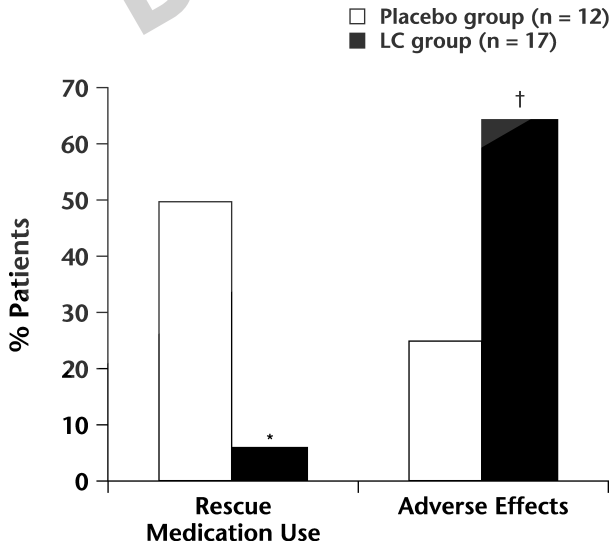


Figure 2. Percentages of patients using rescue medication and experiencing ≥ 1 adverse effect, by treatment group. * $P = 0.010$ versus placebo. † $P = 0.025$ versus placebo. LC = lysine clonixinate.

the developing country in which the study was conducted. In addition, we did not ask the patients whether they would use this treatment again, which represents another methodologic flaw limiting the efficacy analysis of this study.

LC has proven efficacy in the treatment of several pain syndromes (eg, renal colic, muscular pain, nerve compression, odontalgia) and migraine.^{15-18,20} Other classes of NSAIDs also have demonstrated effectiveness in the acute treatment of migraine compared with placebo and even with ergotamine.^{12-14,23,24} Although the exact mechanism by which NSAIDs function in the treatment of migraine and other headaches remains controversial, these agents seem to inhibit the synthesis of prostaglandins, free radicals, and superoxide and to promote partial inhibition of platelet aggregation secondary to the inhibition of thromboxane A₂. In addition, serotonin release from platelets was inhibited and a central pharmacologic action, specifically in the thalamus and spinal cord, also was demonstrated. LC also interacts directly with the central serotonergic system and indirectly with opioid receptor systems in thalamic nuclei, dentate gyrus, and layers of the parietal cortex in rats.^{6,15,16,20,25}

Furthermore, some NSAIDs effective in the treatment of migraine reveal high affinity binding to nociceptive structures in the dorsal horn and brain stem nuclei.²⁶ Taken together, LC and the other NSAIDs may act in migraine through a combination of central and peripheral mechanisms.

With the exception of the 30-minute time point, the values for LC are comparable to the results observed by Bigal et al,²² who found that IV dipyrone was significantly more effective than placebo in reducing pain, associated symptoms, and rescue medication use in migraineurs with and without aura. In that trial, the pain-free rate at 30 minutes, 60 minutes, and 24 hours was 11.4%, 43.2%, and 70.8%, respectively. Our results also may be comparable to those of subcutaneous sumatriptan. This serotonergic agonist is considered one of the most efficacious acute treatments for migraine, and its use resulted in a 72% headache relief rate at 1 hour and a pain-free rate >60% at 2 hours.²⁷ However, because we did not analyze headache recurrence and sustained pain-free values, conclusions in comparing efficacy parameters could not be reached.^{27,28} Other NSAIDs have been compared with sumatriptan, either early in the attack or during moderate or severe headache, and were found to be as effective as that drug.^{29,30}

The tolerability profile of LC is favorable. In this study, patients in the LC group had significantly more AEs than patients in the placebo group, but these AEs were moderate and transient. LC has no formal contraindications for its use in patients with coronary artery disease or uncontrolled hypertension, conditions that contraindicate the use of ergots and triptans. In addition, nephrotoxicity is not an issue with LC.^{15,17}

CONCLUSIONS

NSAIDs administered by the IV route cannot be used routinely in an outpatient environment, although an attempt to improve drugs in this class is clearly

justified. This study demonstrated that IV LC was effective and well tolerated in the treatment of severe migraine attacks. This finding differs from results with the oral formulation, which is effective only in migraine of moderate severity.

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Address correspondence to:

Abouch Valenty Krymchantowski, MD, PhD
Headache Center of Rio de Janeiro
Av das Américas 1155 sala 1608 Barra
Rio de Janeiro 22631.000
Brazil
E-mail: abouchkrym@globo.com