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LYSINE CLONIXINATE VERSUS DIPYRONE (METAMIZOLE) FOR THE ACUTE TREATMENT OF SEVERE MIGRAINE ATTACKS

A single-blind, randomized study

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Abstract – Background and Objective: Nonsteroidal anti-inflammatory drugs (NSAID) are effective to treat migraine attacks. Lysine clonixinate (LC) and dipyrone (metamizol) have been proven effective to treat acute migraine. The aim of this study was to evaluate the efficacy and tolerability of the intravenous formulations of LC and dipyrone in the treatment of severe migraine attacks. **Method:** Thirty patients (28 women, 2 men), aged 18 to 48 years with migraine according the International Headache Society (IHS) (2004) were studied. The patients were randomized into 2 groups when presenting to an emergency department with a severe migraine attack. The study was single-blind. Headache intensity, nausea, photophobia and side effects were evaluated at 0, 30, 60 and 90 minutes after the drug administration. Rectal indomethacin as rescue medication (RM) was available after 2 hours and its use compared between groups. **Results:** All patients completed the study. At 30 minutes, 0% of the dipyrone group 13% of the LC group were pain free (p=0.46). At 60 and 90 minutes, 2 (13%) and 5 (33%) patients from the dipyrone group and 11 (73%) and 13 (86.7%) patients from the LC group were pain free (p<0.001). At 60 minutes, significantly more patients from the LC group were nausea-free (p<0.001). Regarding photophobia, there were no differences between groups at 60 minutes (p=0.11). The use of RM at 2 hours did not differ among groups (p=0.50). Pain in the site of the injection was reported by more patients of the LC group compared to the dipyrone group (p<0.0001). **Conclusion:** LC is significantly superior to dipyrone in treating severe migraine attacks. LC promotes significantly more burning at the site of the injection.

KEY WORDS: lysine clonixinate, dipyrone (metamizole), migraine, severe attacks, acute treatment.

Clonixinato de lisina versus dipirona (metamizol) para o tratamento agudo de uma crise intensa de enxaqueca: estudo monocego e randomizado

Resumo – Contexto e Objetivo: Antiinflamatórios não esteroidais (AINE) são eficazes no tratamento de crises de enxaqueca. O objetivo deste estudo foi comparar a eficácia e a tolerabilidade das apresentações injetáveis do clonixinato de lisina (CL) e da dipirona no tratamento de crises intensas de enxaqueca. **Método:** Trinta pacientes (28 mulheres, 2 homens), com idades entre 18 e 48 anos e enxaqueca de acordo com a Classificação Internacional de Cefaléias (2004) foram estudados. Os pacientes foram randomizados em 2 grupos ao se apresentarem em uma unidade de emergência, com uma crise intensa de enxaqueca. O desenho do estudo foi monocego. A intensidade da cefaléia, a presença de náusea e fotofobia e os efeitos colaterais foram avaliados e comparados na administração das drogas e após 30, 60 e 90 minutos. Indometacina retal foi disponibilizada como droga de resgate (DR) e seu uso comparado entre os grupos. **Resultados:** Todos os pacientes completaram o estudo. Após 30 minutos, 0% do grupo da dipirona e 13% do CL encontravam-se sem cefaléia (p=0,46). Após 60 e 90 minutos, 2 (13%) e 5 (33%) do grupo da dipirona e 11 (73%) e 13 (86,7%) do grupo do CL encontravam-se sem cefaléia (p<0,001). Após 60 minutos, o CL foi mais eficaz que a dipirona em eliminar a náusea (p<0,001), mas não houve diferença quanto à melhora da fotofobia entre os grupos (p=0,11). Não houve diferenças entre os grupos que utilizaram DR (p=0,50). Dor no local da injeção foi apresentada por mais pacientes que usaram CL comparados aos da dipirona (p<0,001). **Conclusão:** O CL é significativamente superior a dipirona no tratamento de uma crise intensa de enxaqueca, mas resulta em mais queimação no local da injeção.

PALAVRAS-CHAVE: clonixinato de lisina, dipirona (metamizol), enxaqueca, tratamento agudo, crise intensa.

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Migraine is a highly prevalent neurological disorder manifesting as moderate or severe intermittent headache attacks with associated symptoms. Migraine attacks worsen with routine physical activities and may last 4 to 72h if not properly treated[1-3]. The burden of migraine results in considerable economic and social losses[4,5]. Recent options for the acute treatment have been based on effective serotonergic agonists known as triptans[6]. However, due to the high cost of the triptans in developing countries (average US$ 4-7 per tablet, US$ 20 per injection), some of the emergency facilities do not have access to specific antimigraine drugs. In most, common analgesics, nonsteroidal anti-inflammatory drugs (NSAID), and even opioids are the basic components of the therapeutic arsenal[7,8]. In addition, clinical experience suggests that high prices, moderate pain free rates and sustained pain free as well as headache recurrence within 24 hours may also represent limiting prescription factors for the triptans use[9].

Several patients find relief using simple analgesics or its combinations with caffeine or barbiturates[6,10]. Additionally, various NSAID were also proved effective in treating patients with migraine attacks and are still widely used in many countries despite its potential for gastrointestinal side effects and current availability of more specific agents[6,8,11-14]. Although commonly used in emergency departments, injectable formulations of different NSAID are scarce and there are only few options which may be used for those patients with severe headache and nausea or vomiting[15].

Lysine clonixinate (LC) is an anthranilic derivative resembling the chemical structure of the flufenamic acid[15,16]. LC was already suggested for the acute treatment of migraine in controlled and in open trials[15-17]. Its structural formula (2-(3-chloro-o-toluidine) piridino-3-carboxilate) allows a fast absorption. LC is 96-98% protein-bounded and its hepatic metabolism results in four different inactive metabolites. Seventy-five percent of its excretion is renal and 25% fecal[18,20].

Dipyrone is a pyrazolone derived non-opiate analgesic drug with antipyretic and spasmolitic properties first introduced for therapeutic use in 1922. It is an effective analgesic with proven efficacy in pain relief for post-surgical pain, toothache, oncologic surgery and migraine with and without aura[8,21]. Regarding migraine, dipyrone is a well established and highly used drug to treat acute attacks in emergency settings in Brazil[7,8]. It is a highly hydrophilic compound that in solution is quickly hydrolyzed to methyl-aminoantipyrine. Its analgesic effect starts almost immediately and reaches its peak 20 to 45 minutes after intravenous administration. Its active metabolites are methyl-amino-antipyrine and aminoantipyrine. The half-life of the methyl-amino-antipyrine complex is about 2.7 hours. Excretion is predominantly renal[8,21,22].

Both pharmacological agents are not selective COX 2 inhibitors but have a good profile of tolerability and a short number of contraindications, mostly related to gastro-intestinal tract as common NSAID[16,20,21].

The aim of this study is to compare the efficacy and tolerability of the injectable formulations of LC and dipyrone in treating severe migraine attacks in an emergency department setting.

METHOD

The study was conducted at the emergency department of a general hospital (Hospital Mater Dei) in the City of Belo Horizonte, during the period January – September of 2006. Thirty patients (28 women, 2 men), aged 18 to 48 (mean 31) with the diagnosis of migraine according to the International Headache Classification (ICHD-II)[3] were prospectively studied. The study was single-blind. The patients were randomized to dipyrone or LC when presenting with a severe migraine attack, by the order of arrival.

The severity of the attack was based on a verbal categorical scale, ranging from 0 (no pain) to 1 (mild headache), 2 (moderate headache) and 3 (severe headache). The severity of the associated symptoms nausea and photophobia were also scored using a verbal scale ranging from 0 (no nausea/no photophobia) to 3 (severe nausea/severe photophobia). The patients were placed in a supine position and a peripheral vein of the right forearm was catheterized. Twenty-three milliliters of 0.9% saline plus two milliliters of dipyrone (1000 mg) or twenty-one milliliters of 0.9% saline plus 4 milliliters of LC (200 mg) were injected freely through a micro drop system in a single-blind fashion. The duration of the drug administration lasted an average of 5 minutes (approximate rate of 96 drops per minute).

Because burning at the site of injection is common with LC[15,20], dilution in saline was used and all patients were informed that it could happen with both of the studied medications. Headache intensity and side effects at 0 (T_0), 30, 60 and 90 minutes after the drug administration were evaluated and compared between groups. The presence of nausea and photophobia was also evaluated at these time points and compared between groups. The consumption of rescue medications, suppositories of 100mg indomethacin were available after 2 hours and its use compared between groups. Patients with known intolerance or formal contra-indications to the use of lysine clonixinate as well as dipyrone were not included. Moreover, patients under treatment for any other medical conditions, women in childbearing age not using contraceptive methods as well as those having used any type of migraine symptomatic medications within the previous 3 hours were excluded. An institutional review board approved the study and all patients gave written informed consent.

The statistical comparisons were done by non-parametric χ^2 test or Fisher exact test (when applicable), to verify the association differences between treatment responses at 30, 60 and 90 minutes, consumption of rescue medication at 2 hours, and incidence of side effects found in the two patient groups. The

analysis of variance and co-variance for repeated measures were performed by CATMOD® procedure from SAS system package. Mc Nemar statistical test, corrected at the level of 1.3%, was also used for confirming differences encountered among groups. We used SAS statistical system version 6.04 and adopted two-tailed p value <0.05 for significance levels.

RESULTS

All patients completed the study. Tables 1 and 2 show the efficacy results regarding pain measures, nausea and photophobia for both drugs. At 30', no patients from the dipyrone group and 2 (13%) patients form the LC group were pain free (p=0.46). At 60 and 90 minutes respectively, 2 (13%) and 5 (33%) patients from the dipyrone group and 11 (73%) and 13 (86.7%) patients from the LC group were pain free (p<0.001 for both endpoints).

Regarding nausea, which was present at baseline in 12 patients of each group, at 60 minutes, 7 patients of the dipyrone group and 11 patients of the LC group were nausea-free (p<0.001). At 90 minutes, 11 patients of each group were nausea-free. Both drugs were effective in alleviating nausea at 90 minutes and there was no difference between treatments (p=0.084).

With regard to relieving photophobia, which was present in 15 patients of each group at baseline, both drugs were effective at 60 and 90 minutes (p<0.001, compared to baseline, for both treatments) although no difference was encountered between groups (p=0.11 and p=0.59, respectively). Eight patients from dipyrone group and 13 patients of the LC group were photophobia-free at 60 minutes whereas 13 patients from the dipyrone group and 14 subjects from the LC patients were photophobia-free at 90 minutes.

Three (20%) patients from the dipyrone group and 2 (13.4%) patients from the LC group required rescue medication at 2 hours (p=0.50). Side effects were pain in the site of the injection, which was reported by 3 patients of the dipyrone group while burning pain in the site of injection and/or in the upper limb (13 patients), heartburn (2 patients) and chest pressure (1 patient) were presented by the LC group (p<0.0001).

DISCUSSION

This is a single-blind, parallel-group study with patients having treated one migraine attack of severe intensity. The doses were 200 mg of LC and 1000 mg of dipyrone and the method of randomization was bellow

Table 1. Longitudinal analysis of the symptoms for dipyrone group.

Symptoms	Endpoints				p value[a]	Significant differences[b]
	Baseline	30'	60'	90'		
Headache (%)	100	100	86.7	66.7	0.073	
Nausea (%)	80.0	53.3	33.3	6.7	< 0.0001	Baseline ≠ 90'
Photophobia (%)	100	80.0	46.7	20.0	< 0.0001	Baseline ≠ 60' Baseline ≠ 90' 30' ≠ 90'

[a]Level of significance for the analysis of variance for repeated measures using CATMOD procedure; [b]Significant differences according to Mc Nemar test, corrected at the level of 1.3%.

Table 2. Longitudinal analysis of the symptoms for lysine clonixinate group.

Symptoms	Endpoints				p value[a]	Significant differences[b]
	Baseline	30'	60'	90'		
Headache (%)	100	86.7	33.3	20.0	< 0.0001	Baseline ≠ 60' Baseline ≠ 90' 30' ≠ 60' 30' ≠ 90'
Nausea (%)	80.0	26.7	6.67	6.7	< 0.0001	Baseline ≠ 30' Baseline ≠ 60' Baseline ≠ 90'
Photophobia (%)	100	53.3	13.3	6.7	< 0.0001	Baseline ≠ 60' Baseline ≠ 90'

[a]Level of significance for the analysis of variance for repeated measures using CATMOD procedure; [b]Significant differences according to Mc Nemar test, corrected at the level of 1.3%.

carried out through arrival order. Although the number of patients and attacks may be low and the absence of a placebo arm may counteract conclusions, the study was powered by treating severe attacks, which usually are excluded from most trials of acute migraine. In addition, it may be speculated that single-blindness do not allow for definitive conclusions but this design was chosen since LC commonly provokes burning pain in the site of injection. Therefore, the blindness was kept mainly directed to the patients through the emphatic orientation that both drugs could provoke this symptom. Moreover, it may be argued of whether sequence effect on treatment had a role in the outcome. It has to be emphasized that the patients were clearly oriented to report other drugs taken up to three hours prior to the arrival at the emergency department.

This study demonstrated that both LC and dipyrone are effective in eliminating the nausea and the photophobia associated with a migraine attack within 60'. The results are similar to those observed by Bigal et al.[8,22], who used dipyrone in a dose of 1000 mg as well, and treated headache attacks of migraine without aura, migraine with aura and tension-type headache. Compared to placebo, these authors encountered significant relief of nausea and photophobia ($p<0.001$) but they did not look at the absence of these associated symptoms at the studied time points. Rather, they emphasized the relief of the symptoms. In addition, the outcomes for headache intensity were evaluated focusing on pain relief rather than on pain-free status, which, in one of the trials[8] showed indeed absence of headache at 60 minutes in 43.2% of the patients. The results of the present study were different since 33% of the patients who used dipyrone were pain-free at 60 minutes.

However, when the numbers for pain-free outcome were evaluated, dipyrone was not effective in eliminating the headache of a severe migraine attack within the studied timeframes in most of the subjects, despite its high use profile in Brazilian emergency departments throughout the country. It may be argued of whether dipyrone does really promote pain-free status or only relief of a severe migraine attack.

In fact, although dipyrone previously showed a highly effective analgesic effect on migraine with and without aura[8], with figures achieving respectively 43.2% and 50% at 2 hours, the authors did not specify whether the headache was severe at the time of drug administration. In the present study only patients with a severe migraine attack were included. In addition, it is common, at least in Brazilian migraineurs, the habit of self-medication which may lead to the use of numerous over-the-counter medications prior to the arrival in the emergency unit. Again, in our study, only patients not having used rescue medications in the 3-hour period before the drug administration were included.

Regarding the adverse event profile, dipyrone is known as a well tolerated drug[22-24] and all patients from its group revealed a low incidence of adverse. It does not cause thrombophlebitis in clinical practice[23]. LC, however, provoked mostly burning sensation at the site of injection in nearly all patients who received it, but it is not a common cause of thrombophlebitis as well[19]. A caution has to be emphasized in this trial since it was not evaluated of whether the patients were satisfied with the drug received despite the presence of the aforementioned adverse event.

Patients receiving migraine acute treatments seek for several attributes of their medications[25]. In around 90% of the patients, the rapid relief of the headache with no side effects is the most desirable characteristic of a migraine acute treatment. It is therefore, useful to compare drugs regarding not only effectiveness but tolerability and patient preference as well.

The mechanism of action by which dipyrone exerts its efficacy in migraine is uncertain. It may act in two ways, peripherally and centrally. The turning off of nociceptors sensitive to pain activation is the potential site for peripheral action whereas the effect on the periaqueductal gray matter (PAG) and the activation of pain inhibitory pathways may be the central mechanism[26,27]. Regarding the beneficial effects of dipyrone in nausea and photophobia, its action on the PAG and on medial rostrobulbar areas, as well as on the interaction between the trigeminal and visual pathways may explain why dipyrone was effective in relieving these associated symptoms[28,29]. The expected duration of action for dipyrone in migraine is short (nearly 6 hours) and although considered effective and comparable with injectable NSAIDs, it is one of the most used antimigraine drugs in Brazil due to its considerable low cost[21,23,28,29].

Although the exact mechanism by which LC and other NSAIDs function in the treatment of migraine and other headaches remain a matter of controversy, these agents seem to inhibit the synthesis of prostaglandins, the synthesis of free radicals and superoxide as well as to promote partial inhibition of platelet aggregation secondary to the inhibition of thromboxane A2. In addition, the serotonin release from platelets is inhibited and a central pharmacological action, specifically in thalamus and spinal cord, was demonstrated as well. LC also interacts directly with the central serotonergic system and indirectly with opioid receptor systems in thalamic nuclei, gyrus dentate, and layers of parietal cortex of rats[6,17,20,30].

Furthermore, some NSAIDs effective in the treat-

ment of migraine reveal high affinity binding to nociceptive structures in the dorsal horn and brain stem nuclei[31]. Taken together, LC, other NSAIDs and dipyrone may act in migraine through a combination of central and peripheral mechanisms.

In conclusion, despite the limitations of a single-blind study with no placebo arm, this trial showed that dipyrone and LC may be similarly effective in treating the associated symptoms of a severe migraine attack. However, regarding headache severity, LC was significantly more effective. In addition, both drugs presented good tolerability and may be good candidates to be used alone in emergency settings. Brazil and other developing countries need inexpensive medications to be used in its health public system. Dipyrone has been used frequently so far, but perhaps LC may represent an even better option for those with a severe migraine attack to whom it is not adequate or effective. Double-blind studies are necessary to confirm these observations.

REFERENCES

1. Stewart WF, Schechter A, Lipton RB. Migraine heterogeneity, disability, pain intensity and attack frequency and duration. Neurology 1994;44(Suppl 4):S24-S39.
2. Rasmussen BK. Epidemiology of headache. Cephalalgia 1995;15:45-68.
3. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2.Ed. Cephalalgia 2004;24(Suppl 1):S16-S149.
4. Stewart WF, Lipton RB, Simon D. Work-related disability: results from the American migraine study. Cephalalgia 1996;16:231-238.
5. Lipton RB, Stewart WF. Prevalence and impact of migraine. Neurol Clin 1997;15:1-13.
6. Peroutka SJ. The drug treatment of migraine. In Hardman JG, Limberd LE, Molinoff PB, Ruddon RW, Giman AG (Eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9.Ed. London:Pergamon; 1996:487-502.
7. Bigal ME, Bordini CA, Specialli JG. Tratamento da cefaléia em uma unidade de emergência da cidade de Ribeirão Preto. Arq Neuropsiquiatr 1999;57:813-819.
8. Bigal ME, Bordini CA, Tepper SJ, Specialli JG. Intravenous dipyrone in the acute treatment of migraine without aura and migraine with aura: a randomized, double-blind, placebo-controlled study. Headache 2002;42:862-871.
9. Krymchantowski AV. Acute treatment of migraine: breaking the paradigm of monotherapy. BMC Neurology 2004;4:4.
10. Limmroth V, Przywara S. Analgesics. In Diener HC (Eed). Drug treatment of migraine and other headaches. Monogr Clin Neurosci, Vol 17. Basel:Karger, 2000:30-43.
11. Lipton RB, Stewart WF, Ryan RE, Saper J, Silberstein SD, Sheftell F. Efficacy and safety of nonprescription combination of acetaminophen, aspirin and caffeine in alleviating headache pain of an acute migraine attack: three double-blind, randomized, placebo-controlled trials. Arch Neurol 1998;55:210-217.
12. Dahlof C, Bjorkman R. Diclofenac-K (50 and 100mg) and placebo in the acute treatment of migraine. Cephalalgia 1993;13:117-123.
13. Nestvold K, Kloster R, Partinen M, Sulkava R. Treatment of acute migraine attack: naproxen and placebo compared. Cephalalgia 1985;5:115-119.
14. Kloster R, Nestvold K, Vilming S. A double-blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. Cephalalgia 1992;12:169-171.
15. Pereyra Quintana JR, Levy DE, Brocato N. Comparacion del efecto analgésico del clonixinato de lisina com um hipnoanalgesico. El Dia Medico 1978;50:6-23.
16. Sierralta F. Clonixinato de lisina: interacciones com el sistema serotoninérgico y naloxona. Proc 9th Latinoamerican Congress of Pharmacology and Therapeutics, Abstracts. Santiago;1982:64.
17. Krymchantowski AV, Barbosa JS. Clonixinato de lisina injetável intravenoso para o tratamento agudo das enxaquecas: um estudo piloto aberto. Arq Neuropsiquiatr 1999;57:606-609.
18. Krymchantowski AV, Barbosa JS, Cheim C, Alves LA. Oral lysine clonixinate in the acute treatment of migraine: a double-blind, placebo-controlled study. Arq Neuropsiquiatr 2001;59:46-49.
19. Krymchantowski AV, Silva MT. Intravenous Lysine clonixinate for the acute treatment of severe migraine attacks: a double-blind, randomized, placebo-controlled study. Curr Therap Res 2003;64:505-513.
20. Paredes H, Solis R, Palacios J. The use of intravenous lysine clonixinate for rapid pain relief: an open clinical study. Curr Therap Res 1996;40:86-91.
21. Insel PA. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In Hardman JG, Limbird LE, Molinoff PB, Ruddon LW, Gilman AG (Eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics. Nxinth Edition. New York:McGraw Hill, 1996:617-657.
22. Bigal ME, Bordini CA, Speciali JG. Intravenous metamizol (dipyrone) in acute migraine treatment and in episodic tension-type headache headache: a placebo-controlled study. Cephalalgia 2001;21:90-95.
23. Stankov G, Schmieder G, Lechner FJ, Schinzel S. Observer-blind multicentre study with dipyrone versus tramadol in postoperative pain. Eur J Pain 1995;16:56-63.
24. Garcia-Alonso F, Gonzales de Suso MJ, Lopes-Alvarez M, Palop R. Comparative study of the efficacy of dipyrone, diclofenac sodium and pethidine in acute renal colic. Eur J Clin Pharmacol 1991;40:543-546.
25. Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from acute migraine treatment?. Headache 2002;42(Suppl 1):S3-S9.
26. Lorenzetti BB, Ferreira SH. Mode of analgesic action of dipyrone: direct antagonism of inflammatory hiperalgesia. Eur J Pharmacol 1985;114:375-381.
27. He X, Neugebauer V, Schaible Hg, Schmidt RF. New aspects of the mode of action of dipyrone. New Pharmacologial and Epidemiological Data in Analgesics Research. Adelaide, 3 Apr 1999. 1999:9-18.
28. Carlsson KH, Helmreich J, Jurna I. Activation of inhibition from the periaqueductal gray matter mediates central analgesic effect of metamizol (dipyrone). Pain 1986;27:373-390.
29. Tortorici V, Vanegas H. Putative role of medullary off- and on-cells in the antinociception produced by dipyrone (metamizol) administered systemically or microinjected into PAG. Pain 1994;57:197-205.
30. Orti E. Site-specific effects of the nonsteroidal anti-inflammatory drug lysine clonixinate on rat brain opioid receptors. Pharmacology 1999;58:190-199.
31. Kaube H, Hoskin KL, Goadsby PJ. Acetylsalicilic acid inhibits cerebral cortical vasodilatation caused by superior sagittal sinus stimulation in the cat. Eur J Neurol 1994;1:141-146.