Randomized Trial

Management of Neuropathic Chronic Pain with Methadone Combined with Ketamine: A Randomized, Double Blind, Active-Controlled Clinical Trial

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: The authors state that there are no conflicts of interest regarding this work. We acknowledge CNPq and CAPES (Brazil) for fellowships. F.K. Rigo is Postdoctoral Fellows of the Capes Toxinology Program.

Manuscript received: 04-18-2016
Revised manuscript received: 08-24-2016
Accepted for publication: 10-14-2016

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Background: Methadone and ketamine are used in neuropathic pain management. However, the benefits of both drugs association are uncertain in the treatment of neuropathic pain.

Objective: Our primary objective was test the hypothesis that oral methadone combined with oral ketamine is more effective than oral methadone or ketamine alone in reducing neuropathic pain.

Study Design: We conducted a randomized, double blind, active-controlled parallel-group clinical trial.

Methods: Forty-two patients with neuropathic pain refractory to conventional therapy were randomly assigned to receive oral methadone (n = 14), ketamine (n = 14), or methadone plus ketamine (n = 14) over a 3-month period.

Results: During these 90 days, we observed pain scores using a visual analogical scale (VAS), allodynia, burning/shooting pain, and some side effects. All treatments were effective in reducing pain scores by at least 40%. However, a significant improvement in pain was observed only in the ketamine alone group compared with both the methadone or methadone/ketamine groups. No significant differences were observed among the treatment groups for the reduction of burning or shooting pain, while ketamine alone was more effective than methadone or methadone/ketamine for the reduction of allodynia.

Limitations: Formal assessment for awareness of the allocation was not performed, some co-intervention bias may have occurred, our results could be only relevant to the patient population investigated and the use of VAS as the primary outcome detect changes in pain intensity but not to assess neuropathic pain symptoms.

Conclusion: This study indicates that ketamine was better than methadone or methadone/ketamine for treating neuropathic pain.

Key words: Multimodal analgesia, refractory pain, NMDA receptor, opioid

Pain Physician 2017; 20:207-215

Pain resulting from neuropathy is most likely the most challenging and difficult painful state to manage (1). Neuropathic pain has numerous possible causes, including infection, metabolic diseases, chemotherapy, and trauma, and is often associated with common alterations in the pain response, such

as allodynia, and burning or shooting pain (2,3). The dysfunctional mechanisms involved in neuropathic pain are diverse and poorly understood, making the clinical management of this condition difficult. Despite limited knowledge, there is evidence of dysfunction in the opioid (μ-opioid receptor – MOR) and glutamatergic systems (N-methyl-D-aspartate receptor – NMDA) in neuropathic pain (4,5). Thus, drugs capable of modulating these systems, such as methadone and ketamine (alone or in combination), present a potential way to treat neuropathic pain.

During the last decade, sub-anesthetic doses of ketamine (NMDA blocker) have been used as an alternative to treat neuropathic pain (6,7). However, oftentimes the effective analgesic dose of ketamine induces severe adverse effects such as floating sensations, hallucinations, delirium, and drowsiness (7). Similarly, the synthetic opioid methadone inhibits NMDA receptors in addition to its action on MOR (8). Methadone is often used to treat severe pain (9,10) and has been successful against neuropathic pain resistant to conventional analgesics (11,12). Nevertheless, typical opioid adverse effects such as somnolence, nausea, constipation, vomiting, and analgesic tolerance sometimes limit the use of methadone (13,14).

To avoid these therapeutic limitations and to increase analgesic efficacy, multimodal analgesia (drug combination therapy) has been successfully used in pain therapy (15). In our previous report, we demonstrated that oral methadone plus ketamine was efficient to treat refractory neuropathic pain, reducing pain and decreasing several side effects (16).

These promising results must, however, be confirmed through a clinical trial. Hence, we designed this double-blinded, parallel-group, randomized clinical trial to compare the effects of oral treatment with methadone, ketamine, or methadone plus ketamine in neuropathic pain not responsive to conventional therapies (e.g., antidepressants, anticonvulsants, opioids, and anti-inflammatories).

Methods

Design Overview, Setting, and Participants

The Methods and Results sections are reported according to the Consolidated Standards of Reporting Trials — CONSORT guidelines (17).

All patients provided written informed consent before participating in this randomized, double-blind, parallel 3-group, clinical trial, which was approved by the Research Ethics Committee at the Federal University of Santa Maria, Santa Maria, Brazil (N° 0050.0.243.000-07) in accordance with the Declaration of Helsinki (Resolution 196/96 of the National Health Council).

We recruited 42 patients who had experienced neuropathic pain for more than 6 months (2007 – 2008) who were poorly responsive to drugs used to treat neuropathic pain (e.g., opioids, non-opioid pain relievers, anticonvulsants, and antidepressants) and who were 22 to 77 years old from the Clinical Care & Pain Management of Santa Maria University Hospital (HUSM). The neuropathic pain diagnosis was made according to the following diagnostic algorithm:

Step 1. A clinical history of disease or lesion of the somatosensory system was obtained by an independent clinician with more than 10 years of experience in a pain clinic.

Step 2. Either clinically reproducible signs or investigations (light touch, temperature, painful stimulus, vibration, and proprioception) confirmed neuropathic pain. In the clinical exam, the patient was tested on both sides to grade the symptoms as decreased or increased. In addition, we performed motor testing to determine whether there was abnormal tone, strength, reflexes, or coordination, as well as autonomic changes, such as color, temperature, sweating, and swelling.

Step 3. If the history, clinical examination, and investigations were positive, the neuropathic pain diagnosis was definite (18). We assessed the site and etiology by clinical history and clinical exam. All patients had the diagnosis confirmed by a senior physician with extensive experience in a pain clinic (GC). Patients with a history of severe psychiatric disorder, misuse of illegal drugs, or hepatic disease were excluded (Fig. 1).

Sample Size Justification

We estimated the minimum number of patients needed for this project based on the incidence of chronic moderate-severe pain in the Brazilian population (19,20). An a priori estimate indicated that a total sample size of 37 patients, at least, would be needed, thus we recruited a total amount of 42. After, we divided the total number of patients into 3 different groups in a way that each group presented a similar initial VAS score, based on the overall VAS score of all patients taken together (19,20).

Randomization and Masking

The treatment allocation method used was advanced simple randomization without blocking or

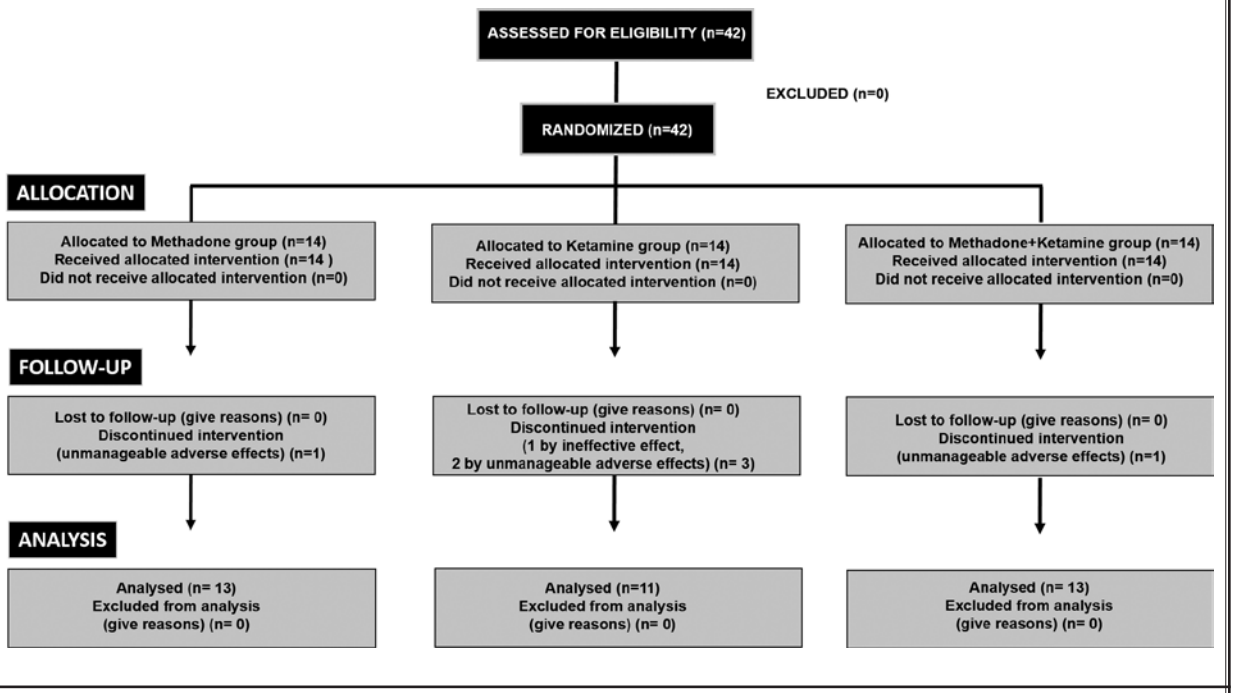

Fig. 1. *Representative flowchart of the randomization process and exclusion of patients.*

stratification. Before the recruitment phase of the study, envelopes containing all protocol materials were prepared and numbered sequentially and then grouped so that each envelope had an independent 50% probability of being included in either group. A sheet indicating the allocated treatment was then placed in the envelope and the envelopes were sealed.

Throughout the course of the study, the sealed envelopes were opened sequentially by a nurse technician who delivered the methadone, ketamine, and ketamine plus methadone solutions only after prospective patients had been screened and had consented to participation. During the entire protocol timeline, blinding and randomization were undertaken by 2 investigators who were not involved in the patients' evaluation. Other individuals involved in the patients' care were unaware of the treatment group to which the patients belonged.

Interventions

The patients were randomly allocated to receive one of the following 3 oral treatments: 3 mg methadone, 30 mg ketamine, or 3 mg methadone plus 30 mg methadone 3 times a day. The treatment schedule was based on a previous work where the doses were titrated to elicit analgesic effect without significant side effects (20 + artigo da celo). The solution of methadone was prepared by mixing 10 mL of methadone hydrochloride (10 mg/mL, Cristália®, São Paulo, Brazil) and 90 mL of saline 0.9% (Baxter, São Paulo, Brazil), obtaining a concentration of 1 mg/mL methadone. The solution of ketamine was prepared by mixing 20 mL of S(+)-ketamine hydrochloride (50 mg/mL, Cristália®, São Paulo, Brazil) and 80 mL of saline 0.9% (Baxter, São Paulo, Brazil), obtaining a concentration of 10 mg/mL of ketamine. Finally, the solution of methadone plus ketamine was prepared by mixing 10 mL of methadone hydrochloride (10 mg/mL, Cristália®, São Paulo, Brazil), 20 mL of S(+)-ketamine hydrochloride (50 mg/mL, Cristália®, São Paulo, Brazil), and 70 mL of saline 0.9% (Baxter, São Paulo, Brazil). The physical aspects of all solutions were identical.

Patients were allowed to use supplementary analgesic medication if necessary. The patients were asked to record their analgesic intake during the treatment period in their pain diaries, which were reviewed during each treatment section. We considered the total analgesic dose taken during treatment for analysis.

Patients' Adherence

The adherence was evaluated as follows: (1) a researcher controlled the volume of solution consumed each medical visit during the study period; (2) the patients were asked to record a diary entry if they failed to use the medication; (3) eligible patients were strongly encouraged to remain on the medication throughout the 12 weeks, during which time they were assessed several times in a visit to the clinical center. Regardless of their decision to continue or discontinue medication at this stage, the patients continued to be assessed during the study period.

Assessment

From each patient, data concerning pain diagnosis, age, gender, and all pharmacotherapies used to manage neuropathic pain were collected. In addition, we evaluated all information regarding how long each patient had neuropathic pain and its intensity at the first clinical evaluation. A physician not involved in the medication management was responsible for collecting all clinical information.

Outcomes

The primary outcome was pain intensity assessed by the 10-point visual analogical scale (VAS). Scores ranged from no pain (zero) to worst possible pain (10 cm) (21). The presence of burning and/or shooting pain, allodynia, and side effects were evaluated as previously described (18). We assessed the side effects using a structured questionnaire with questions about side effects such as sleepiness, dizziness, nausea, vomiting, constipation, visual hallucinations, or any other effect eventually induced by the treatment (18). The assessment of pain and side effects occurred at baseline and 7, 15, 30, 60, and 90 days after the start of the trial during medical visits.

Statistical Analysis

The differences between groups were examined by analysis of variance (ANOVA) with Bonferroni's post hoc test to analyze parametric variables, Kruskal-Wallis test for non-parametric variables, and categorical data were examined by $\chi 2$ or Fisher's exact tests. After first checking assumptions of normality for the outcome measures, the experimental groups were compared for differences in pain and sleepiness by repeated-measures ANOVA, with the treatment group as a factor and time as the repeated measure. One-way ANOVA with Bonferroni's test for post hoc multiple comparisons was used to identify differences between groups at each time point.

We also calculated adjusted mean differences, which were defined as the relative changes in the methadone group combined with the relative changes in the ketamine group compared to the relative changes in the methadone plus ketamine group. This measurement was used to describe the treatment efficacy, which was calculated as the adjusted mean difference divided by the adjusted mean difference in the methadone plus ketamine group and expressed as a percentage (%). The 95% confidence intervals (CI) and associated *P*-values were also calculated. We considered all of the randomized patients as part of the analysis using the intention-to-treat method with the last observation carried forward. For all analyses, statistical significance was set at $P < 0.05$ (2-tailed). Data were analyzed using GraphPad Prism 5.0.

Results

Patients Characteristics and Randomization

The clinical and demographic characteristics of the patients are shown in Table 1. Baseline characteristics were similar across the methadone, ketamine, and ketamine/methadone groups (all *P* values > 0.05) (Table 1).

Forty-two patients were allocated to receive methadone, ketamine, or methadone plus ketamine (Fig. 1). Thirty-seven patients completed the study. During the follow-up (up to 15 days), 4 patients withdrew due to severe side effects (one in the methadone group, 2 in the ketamine group, and one in methadone/ketamine group). Moreover, one patient in the ketamine group withdrew due to treatment inefficacy.

The categories for type of neuropathic pain were lumbar radiculopathy, peripheral neuropathy (i.e., diabetic neuropathy and post herpetic neuralgia), and complex regional pain syndrome I and II. The neuropathic pain categories were similar across the treatment groups (Table 1). The median duration of pain before intervention was similar in the 3 groups (12 months). The number of analgesics used weekly for pain management, such as opioid and non-opioid analgesics, antidepressants, and anticonvulsants, are shown in Table 1. Anticonvulsants and antidepressants were used by more patients than opioids (except methadone) or anti-inflammatory drugs. However, the use of these drugs was not different among treatment groups (Table 1).

Table 1. *Characteristics of the study sample.*

Characteristic	Methadone (n = 13)	Ketamine (n = 11)	Methadone + ketamine (n = 13)	*P* value
Age (years) a	52 ± 13.6	54 ± 12.4	45 ± 8.5	0.19
Weight (kg) a	69 ± 9.8	67 ± 8.3	64 ± 8.2	0.41
Duration of pain (months) b	12 (6 – 33)	12 (6 – 36)	12 (5 – 50)	0.96
Gender (M/F) c	6/7	6/5	5/8	0.73
Diagnosisc,d	6/1/6	6/1/4	6/2/6	0.96
(Co) analgesicsc, e	7/13/11/5	7/11/4/1	9/13/5/4	0.60
Basal VAS a	7.8 ± 1.3	7.1 ± 0.8	7.6 ± 1.0	0.30

Data are shown as a means ± SD, b the medians (interquartile range 75%), or c contingency of proportion. *P* values denote the significance level between groups (a one-way ANOVA, b Kruskal-Wallis test, c $\chi 2$ test). d Lumbar radiculopathy / Complex regional pain syndrome I and II / Peripheral neuropathy. e Anticonvulsants / Antidepressants / Opioids / Nonsteroidal anti-inflammatory drugs.

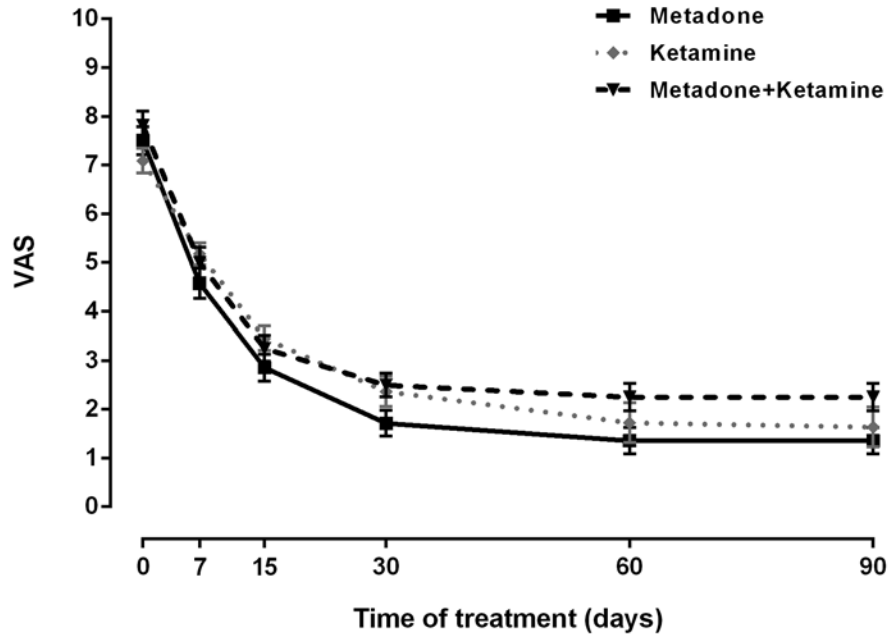

Fig. 2. *Visual analogue scale (VAS) evaluation. Time-course of VAS described by patients during the treatment. Results are shown as mean ± SD, analyzed by 2-way analysis of variance (ANOVA).*

Primary Outcome: Analgesic Efficacy

Oral treatment with methadone, ketamine, or methadone plus ketamine gradually and equally reduced the level of neuropathic pain, measured by VAS. There was no statistically significant difference among the groups in the levels of neuropathic pain in all periods evaluated (Fig. 2). The reduction of pain was approximately 40%, 60%, and 70% after 7, 15, and 30 days of treatment, respectively (Table 2).

We also evaluated the treatment efficacy on allodynia and burning or shooting pain. All treatments induced a significant reduction in the incidence of burning and shooting pain from baseline to the end of treatment. Meanwhile, only ketamine was able to reduce the incidence of allodynia in comparison to basal levels (Table 3).

Secondary Outcomes: Side Effects

The incidence of side effects was similar among the methadone, ketamine, and methadone/ketamine groups (Table 4). However, sleepiness was higher in the methadone group (92%) compared with the methadone/ketamine (46%) and ketamine groups (18%) (Table 4).

Table 2. *Pain evaluation*.

Drug	VAS initial	VAS final	% analgesia	AUC	∑0 -90
Methadone	7.3 ± 1.1	1.3 ± 1.0***	77.9 ± 2.7	193.0	19.4 ± 1.2 (271)
Ketamine	7.1 ± 0.8	1.6 ± 1.3***	73,8 ± 4.1	233.0	21.4 ± 1.4 (236)
Methadone + Ketamine	7.8 ± 1.2	2.2 ± 1.1***	69.2 ± 3.5	259.7	23.0 ± 1.4 (369)

Data are shown as the means ± SD of initial VAS score (before treatment), final VAS score (90 days of treatment), % reduction in VAS score, area under the curve (AUC), and summation of VAS score (∑0 -90). ***$P < 0.001$ according to nonparametric one-way analysis of variance (ANOVA) followed by Kruskal-Wallis posttest.

Table 3. *Sensorial painful changes*.

Painful symptom	Methadone			Ketamine			Methadone + Ketamine		
	Before	After	*P*	Before	After	*P*	Before	After	*P*
Allodynia	3 / 13	1 / 13	0.28	4 / 11	0 / 11	0.02*	4 / 13	3 / 13	0.66
Burning	10 / 13	1 / 13	0.01*	7 /11	2 / 11	0.03*	9 / 13	3 / 13	0.02*
Shooting	8 / 13	3 / 13	0.01*	5 / 11	0 / 11	0.01*	7 /13	3 / 13	0.04*

Data are shown as number of patients who presented the symptom divided by the total number of patients in the group (present the symptom / total in the group). *$P < 0.05$ according to one-way analysis of variance (ANOVA) followed by SNK test; values denote the significance level between groups according to $\chi 2$ test.

Table 4. *Side effects*.

Symptom	Methadone	Ketamine	Methadone + ketamine	*P* value	$\chi 2$
Somnolence	12 / 13 / 92%**	2 / 11 / 19%	6 / 13 / 46%	0.001	13.690
Nausea	4 / 13 / 30%	1 / 11 / 9%	3 / 13 / 23%	0.432	1.677
Vomiting	2 / 13 / 15%	1 / 11 / 9%	2 / 13 / 15%	0.877	0.262
Dizziness	1 / 13 / 8%	2 / 11 / 19%	0 / 13 / 0%	0.266	2.642
Hallucination	0 / 13 / 0%	1 / 11 / 9%	0 / 13 / 0%	0.297	2.429
Constipation	2 / 13 / 15%	0 / 11 / 0%	1 / 13 / 8%	0.387	1.897
Migraine	0 / 13 / 0%	1 / 11 / 9%	0 / 13 / 0%	0.297	2.249

Data are shown as number of patients who presented with the symptom divided by the total number of patients in the group (present the symptom / total in the group / percentage). P values denote the significance level between groups according to $\chi 2$ test, ** indicates $P < 0.001$.

Discussion

In this study, we compared the efficacy of oral methadone, ketamine, and multimodal analgesia using methadone plus ketamine in patients with refractory neuropathic pain. We observed that all treatments reduced neuropathic pain evaluated through VAS. In addition, these treatments also reduced the incidence of burning and shooting pain, while ketamine and methadone plus ketamine also reduced the incidence of allodynia. These treatments also reduced the incidence of some side effects (hallucination, vomiting, nausea, dizziness, constipation, and migraine), while methadone alone presented a higher incidence of somnolence. Overall, these findings demonstrated that long-term treatment of all the tested drugs (methadone, ketamine, or methadone/ketamine) orally had similar analgesic effects in refractory neuropathic pain.

The patients evaluated in this study presented homogeneity (age, weight, gender, and pain duration) and different types of neuropathic pain (lumbar radiculopathy, complex regional pain syndrome I and II, and peripheral neuropathy). The patients had already used different types of medication (listed in Table 1) but did not respond efficiently to any. Thus, they were characterized as refractory neuropathic pain patients and selected for this study.

Initially, we choose to evaluate methadone and

ketamine in the present study mainly because of the known mechanisms of action of these drugs. Both methadone and ketamine present analgesic effects by acting on common targets (opioid receptor and NMDA receptor). Despite these similarities, the drugs present the following different selectivity: methadone presents a higher affinity for the opioid receptor (activator), while ketamine presents a higher affinity for the NMDA receptor (inhibitor) (6,9). It is well known that these systems present a synergistic effect, eliciting a better and safer analgesic effect even in patients with pain refractory to analgesics (16,22-24).

Ketamine is an arylcyclohexylamine derivative, with dissociative, analgesic, and anesthetic properties, due to several mechanisms, mainly the blockade of the NMDA receptor and activation of the opioid system. Ketamine can be administered by different routes with different goals. It can be used as a main analgesic agent or as an adjuvant, but also in anesthetics protocol. The main difference in each route is the quick liver metabolism, which decreases ketamine bioavailability drastically. For instance, intramuscular administration presents a higher bioavailability (93%) in comparison intranasal (50%), sublingual (29%), intrathecal (25%), and oral (10 – 20%) (31). When orally administered, ketamine can be absorbed gastro-intestinally, undergoing liver metabolism (CYP2B6 and CYP3A), forming an active metabolite, nor-ketamine (31). Thus, even with a low bioavailability, it is possible to achieve good analgesic efficacy with non-parenteral ketamine under repeated daily administration due to its active metabolite. Both forms can bind to plasma protein (mainly by α1-acid-glycoprotein) reaching a plasma peak approximately 0.5 hour after administration, with approximately 10% – 20% bioavailability (30). Despite that, it can induce effective analgesic effect due to its active metabolite nor-ketamine, which presents a plasma peak 0.5 hours after oral ketamine administration 10-fold higher than ketamine itself. Even 7 hours after oral ketamine administration, the plasma level of nor-ketamine is still higher than the ketamine plasma level, and it was already described that nor-ketamine is responsible for a significant part of the overall analgesic effect induced by ketamine (32).

Ketamine was only registered as a parenteral anesthetic (intravenous and intramuscular). Despite that, due to its effective sedative and analgesic effect, ketamine is well used clinically off-label by other routes as well (oral, nasal, rectal) due to its efficacy to treat different refractory types of pain, such as neuropathic, in animals and humans (adults and children). Its use is limited by development of psychiatric side effects, such as dissociative disorders and hallucination. It is also possible to develop an addiction after prolonged daily treatment with ketamine. Despite that, addiction is observed more frequently when used as a recreational drug than for pain treatment (33).

Methadone and ketamine also present some similar pharmacokinetics properties. Both bind to plasma proteins (mainly by α1-acid-glycoprotein) and metabolism (by CYP2B6, CYP3A, and CYP2B6). On the other hand, the oral bioavailability is approximately 75% for methadone and 16% for ketamine. Despite this low bioavailability, repeated daily oral administration may be enough to achieve a concentration high enough to induced analgesia. Ketamine also has an active metabolite which presents a longer half-life than ketamine itself, with a better bioavailability. Combined, these facts may explain how a low dose of oral ketamine may induce analgesia. (31-33).

At the beginning of this evaluation, patients presented with similar VAS scores (pain ~7.5). As we divided the patients into 3 groups (methadone, ketamine, and methadone plus ketamine) and started the treatment, we observed that VAS decreased gradually throughout the 90 days until reaching a mean of ~1.5 (Table 2). This result indicates an overall reduction of pain intensity by approximately 80%, indicating a great improvement with a magnitude sufficient to supplant a possible placebo effect (40%) (25). Despite the synergistic effects of opioid and NMDA blockers already described in humans and rodents, our hypothesis failed as we did not observe any difference between the multimodal analgesia (methadone plus ketamine) and the single treatment analgesia (methadone or ketamine) (23,24). Moreover, a similar efficacy of the drugs given alone or in combination indicates that they act on convergent targets or structures to produce analgesia in refractory neuropathic pain. In fact, methadone may inhibit NMDA receptors in addition to activating opioid receptors and, conversely, ketamine may block NMDA receptors as well as stimulate opioid receptors (6-8). Also, part of the analgesic effect elicited by ketamine depends on its active metabolite nor-ketamine. As ketamine and methadone also share metabolic enzymes, the co-administration with methadone may decrease the formation of nor-ketamine, masking a possible synergistic effect between methadone and ketamine (31-33). Maybe the co-treatment of ketamine with a different drug with a similar mechanism of action could

in fact exhibit a synergistic effect.

During neuropathic pain, abnormal activation of the central nervous system, mainly the spinal cord, leads to a plasticity process known as central sensitization. As a result, patients present with a series of sensorial dysfunctions (26). Thus, besides VAS, we also evaluated allodynia and burning or shooting pain. These pain dysfunctions were reported by all patients in the study, and we observed in the baseline data a similar intensity and proportion of allodynia and burning or shooting pain among the 3 groups. While burning and shooting pain was similarly reduced in all the groups, the ketamine-treated group had a better control of this symptom.

The treatment with methadone/ketamine, ketamine, or methadone over a period of 90 days induced some side effects. While side effects such as nausea, vomiting, dizziness, hallucination, constipation, and headache were similar among the groups, sleepiness was higher in the methadone group than methadone/ketamine treated group, a quite common side effect during the first weeks of opioid treatment (18,27). Such an effect is associated with opioid action at central nervous system and tends to disappear throughout the treatment.

It is important to assess the strengths and limitations of this clinical trial. We reported this trial following CONSORT guidelines and using the Delphi List, a list of criteria for quality assessment of randomized controlled trials. Our trial can be considered to have a strong quality, as all 8 items in this scale can be scored positively in our randomized controlled trial (28). However, the trial also has some limitations. First, in this study, the outcome assessor, the care provider, and the patient were blinded (as recommended in the Delphi List for the quality of clinical trials). Although several strategies were used to prevent patients and evaluator teams from unblinding the allocation to cohorts, formal assessment for awareness of the allocation was not performed, and some side effects such as sleepiness could unblind the intervention. Second, some co-intervention bias may have occurred, although it is improbable that this would change the conclusions of our study because the main finding of this study was contrary to our initial hypothesis that the combined methadone/ketamine therapy would be better at improving neuropathic pain symptoms. Third, this finding is important because it demonstrates that the application of therapeutics can be assessed in each particular context to determine whether it provides enough benefit over those already available. Fourth, we emphasize that the results of this study are only relevant to the patient population investigated because the specific characteristics of neuropathic pain may change the impact of these treatments on neuropathic pain. Finally, a possible limitation of this study was that we assessed the primary outcome with the VAS, which is validated to detect changes in pain intensity but not to assess neuropathic pain symptoms. However, when we ran the study, we were in the validation process of the Leeds Assessment of Neuropathic Symptoms and Signs for Patients with Chronic Pain (LANSS) to Brazilian Portuguese (29). For this reason, we used the VAS and specific questions to assess neuropathic symptoms such allodynia and burning or shooting pain.

Collectively, these findings showed that methadone/ketamine was not better than methadone or ketamine for improving refractory neuropathic pain. However, ketamine was more effective in reducing allodynia compared with methadone or methadone/ketamine. Sleepiness was the most prominent side effect when the treatment included methadone. However, further studies are needed to understand the underlying mechanisms to explain the absence of a plausible synergic effect of methadone/ketamine in neuropathic pain treatment.

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