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Master thesis | Original study

Ketamine Infusion Therapy in chronic pain

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Abstract

Background: **Ketamine has been used for several years in the treatment of therapy-resistant chronic pain. The effects on multiple receptors that participate in the perception of pain are shown both in vivo and in vitro. Nevertheless, only a few clinical studies, often in relatively small populations, support the efficacy of ketamine in chronic pain.**
Objectives: **This study aimed to investigate the efficacy of ketamine infusion therapy in a relatively large population at our center. Furthermore, we report the side effects and complications in this population.**
Design: **Retrospective cohort study.**
Setting: **General Hospital AZ Sint-Blasius, Dendermonde, Belgium.**
Methods: **Between January 1, 2015, and December 31, 2019, 74 patients with chronic pain were treated with ketamine infusions at our center. After an initial test dose of 75 mg, patients were treated with 150 mg of racemic ketamine. Forty-five patients were included in the study and were treated according to the protocol. Data were extracted retrospectively from the patient files and analyzed.**
Main outcome measures: **A favorable outcome was defined as a ≥50% reduction in pain from baseline and when the patient did not discontinue treatment because of lack of effect.**
Results: **23/45 (51.1%) had a favorable outcome as defined. No significant difference in efficacy was observed for neuropathic, nociceptive, or nociplastic pain. Side effects were generally mild and easily treated. No major complications related to ketamine infusion therapy were observed in this population.**
Conclusions: **Overall, the results of this study were positive, especially considering that first- and second-line treatments did not benefit these patients. Ketamine is therefore a valuable therapeutic option for treatment-resistant chronic pain. Further research should include infusions of isolated S-ketamine, which may provide additional benefits regarding its effects and side effects.**

Keywords: **Ketamine, Chronic Pain, Pain Management.**

Introduction

Ketamine (Ketalar®) entered the market in 1970 as an intravenous anesthetic in the hope of using it as a monoanesthetic[1,2]. It is a structural analog of phencyclidine but is ten times less potent[3]. Since the introduction of other intravenous anesthetics, it has rapidly lost its popularity. Its main use as an anesthetic is now limited to patients with hemodynamic shock, intramuscular induction of anesthesia in uncooperative patients, and sedation in short and painful procedures. Ketamine hydrochloride is commercially available as a racemic mixture of R(−) and S(+) optical enantiomers, with benzethonium chloride as a preservative[1].

Despite its declining popularity as a monoanesthetic, an increased interest in ketamine for other indications has emerged in recent decades. Specifically, ketamine is becoming more popular as an analgesic given its unique mechanism of

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action, with the main effect being noncompetitive antagonization of the N-methyl-D-aspartate (NMDA) receptor[1]. The affinity of the isolated S-stereoisomer for the NMDA receptor is three to four times greater than that of the R-isomer[4,5]. The analgesic properties of ketamine were first described by Weisman in 1971[6]. Ketamine provides excellent analgesia in acute pain, comparable to opioids[7-9].

With an extraction ratio of 0.9, ketamine is extensively absorbed by the liver and metabolized by the cytochrome p450 system. This explains the relatively short elimination half-life T½b of two hours. Norketamine, one of these metabolites, also exhibits an anesthetic effect and may contribute significantly to prolonged analgesia[1,3]. Besides antagonism at the NMDA receptor level, ketamine also inhibits some non-NMDA glutamate receptors, such as the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors[10,11]. Furthermore, a limited portion of the analgesic effects of ketamine appear to be mediated by the stereoselective activation of opioid receptors. However, the affinity of ketamine for μ- and κ-receptors is 10 and 20 times smaller than that for the NMDA receptor, respectively[11,12]. In addition, ketamine inhibits the reuptake of norepinephrine, serotonin and dopamine[13-15].

Its action on different receptors accounts for its various side effects. Cardiovascularly, ketamine increases systemic and pulmonary arterial blood pressure, stroke rate, myocardial work, and cardiac output[3,16,17]. Ketamine causes only minimal respiratory depression. The reported sialorrhea may be limited by the association of an anticholinergic[3,18,19]. Ketamine-mediated emesis is thought to be caused by impaired serotonin reuptake since ondansetron inhibits the action of ketamine on the 5HT-receptor[14,15].

Several urological syndromes involving dysuria, hematuria, and proteinuria have been described with chronic ketamine use. These uropathies manifest mainly at higher doses and high-frequency exposures. Consequently, they are observed far more frequently in recreational abuse than in controlled medicinal use[20,21].

Psychotomimetic effects such as nightmares and delirium are also important side effects. These effects can be prevented by premedication with benzodiazepines or a continuous infusion of propofol[3]. In clinical practice, psychotomimetic effects appear to be more pronounced in patients who are already anxious before drug administration[22].

Ketamine infusion therapy in chronic pain

When a large number of afferent nociceptive stimuli reach the spinal cord, the 'wind-up phenomenon' leads to sensitization and hyperexcitability[23]. NMDA receptors are thought to be involved in pain memory. NMDA antagonists prevent the onset of central sensitization and can remedy previously developed hypersensitivity[24]. Ketamine modulates nociceptive transmission through activation of the brainstem, insulae, and specific cortical areas. The analgesic effect appears to persist much longer than can be assumed from pure receptor binding based on the plasma half-life[25]. For example, Dahan et al. demonstrated this in a placebo-controlled study of 60 patients with complex regional pain syndrome (CRPS). In this study, S-ketamine was infused for 100 h. Subsequently, the plasma concentrations of ketamine and its metabolites decreased rapidly. Nevertheless, analgesia was found to last longer. 63% of patients receiving S-ketamine experienced prolonged analgesia compared to 23% in the placebo group. The study showed an onset/offset half-life of 10.9 days, with the analgesic effect only fading out after 55 days[26]. Based on this theory, ketamine infusion therapy (KIT) has been developed, in which patients are administered ketamine over the course of several hours or days at quasi-regular intervals[25].

Another theory suggests that the effects of ketamine on chronic pain may rely on the antidepressant effects of ketamine. Zhou et al. published a study in which half of patients with treatment-resistant depression reported at least one pain symptom. Ketamine proved to be more effective as an antidepressant in patients with comorbid pain[27].

In their review, Hocking et al. demonstrated evidence for use of KIT in various types of chronic pain, but the included studies covered relatively small populations (n=1-31)[22]. In 2017, Maher et al. compared the duration of analgesia for neuropathic pain among different KIT protocols from various institutions. They found a correlation between prolonged analgesia and higher total doses of ketamine, longer infusion durations, and the use of midazolam and/or clonidine. Nevertheless, they described a lack of solid evidence and called for further scientific support for an optimized protocol[25].

Objective

The meta-analyses by Hocking et al. and Maher et al. depicted varying effects of KIT. The studies included in each group used separate protocols. These protocols differed greatly from one another in terms of total duration and dose, infusion rate, and co-administration of active additives. These studies used different inclusion criteria and outcomes. Furthermore, most investigators have included only 10–20 patients.

This study aimed to analyze a larger patient population that received ketamine following a uniform infusion protocol. A subhypnotic propofol infusion was chosen to reduce psychotomimetic side effects. By choosing the very short-acting propofol, we attempted to avoid confounding of the results by the longer-acting benzodiazepines.

As the primary outcome, we examined the effectiveness of the KIT protocol in the treatment of chronic pain. Second, we aimed to investigate whether this protocol is more effective based on the origin of chronic pain, distinguishing between neuropathic, nociceptive, and nociplastic pain. Adverse effects were also reported.

Methods

Patient selection and inclusion criteria

Prior to starting the study, approval was obtained from the Medical Ethics Committee of AZ Sint-Blasius (Kroonveldlaan 50, B-9200 Dendermonde, Belgium, Chair: Dr. S. Serry) under internal reference number 502207. The study was registered nationally under number B0122021000002.

The patients were selected from the treatment lists of the Pain Center of the General Hospital Sint-Blasius Dendermonde. Patients were included in the study if they received at least one treatment using the ketamine infusion protocol at the center. Patients who were minors at the start of the therapy were excluded from the study. Further exclusion was made in patients with oncologic pain and those who deviated from the infusion protocol described below. All patients were evaluated by a psychologist and in those with predominant 'yellow', 'blue' or 'black flags' or significant psychiatric comorbidities, ketamine treatment was not initiated. From January 1, 2015, to December 31, 2019, 74 treated patients were identified. Because of the impact of the COVID-19 pandemic on consultations and treatments, further inclusion was discontinued in 2020.

Data collection

Data were collected in a database using clinical reports from electronic health records. The Numeric Rating Scale (NRS) scores were recorded by a nurse at the multidisciplinary pain center before the initiation of therapy. From the second session onwards, the self-reported percentage of pain improvement after the first full dose was recorded. The nurses were not blinded to the treatment. For each patient, we determined whether the pain for which ketamine treatment was initiated was best characterized as nociceptive, nociplastic, or neuropathic. Two physicians within our center with several years of experience in pain medicine retrospectively reviewed the cases and independently scored the type of pain that best described each patient's primary pain. Only the results in which both physicians came to the same conclusion were accepted. When no unanimous results were obtained, the opinion of an external, independent physician was requested to be the deciding factor.

The reported side effects and complications were documented in the database. All patients who received ketamine at the pain center during this period were followed up six-monthly with a blood test to detect hepatic complications. Any new elevation in liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and alkaline phosphatase (AF)) was recorded in the database. The database was anonymized at all times to protect the patients' confidential data.

It was reported whether therapy was continued after the first two trial doses. If therapy was discontinued, it was specified whether it was due to a lack of effect, disturbing side effects, or other reasons.

Successful therapy was defined as a patient reporting a pain reduction of at least 50%, and if the record did not indicate that the therapy was stopped because of a subjective lack of effect.

Therapy protocol

All the patients included in this study received a standardized infusion protocol. During the first session of therapy, a total dose of 75 mg racemic ketamine (Ketalar®, 50 mg ml-1, Pfizer) was administered intravenously over 4 h. If this was well-tolerated by the patient, the dose was doubled to 150 mg for the second therapy. Treatment was scheduled approximately every four weeks. To prevent psychotomimetic effects, an intravenous infusion of 1 mg kg-1 h-1 propofol (Propolipid® 1%, 10 mg ml-1, Fresenius Kabi) was administered. Patients were monitored during the entire treatment with transcutaneous oxygen saturation measurement, electrocardiography, and noninvasive blood pressure measurement in accordance with current standards according to the American Society of Anesthesiologists. During administration, the patients stayed in a private, darkened, low-stimulation room. For safety reasons, patients needed to be escorted when leaving the hospitals, and were told that they were unfit to participate in traffic or operate heavy machinery for the remainder of the day.

Statistics

A database was created using SPSS® (IBM Corp. Published 2020. IBM SPSS Statistics for Windows,

Version 27.0. Armonk, New York) and completed with the obtained data. Descriptive statistics were extracted after data collection. Logistic regression was used to detect a possible correlation between the baseline NRS score and the outcome. A 2 × 3 cross-tabulation of outcomes according to the pain type was prepared. Because the conditions for the Pearson χ^2 test were not met, Fisher's exact test was used for statistical analysis. The significance level for P was set at $\alpha = 0.05$.

Reporting

This study was conducted in accordance with the STROBE guidelines for cohort studies. The STROBE checklist is available online.

Results

Descriptive statistics

During the inclusion period, 74 patients were treated with ketamine, 61 of whom met the inclusion criteria. In the remaining 13 patients, ketamine was started before the study period or at another center; therefore, insufficient information was available about the condition before and after the first dose. Sixteen patients were lost to follow-up after the first administration. Thus, in these patients, the study protocol was not followed and insufficient information on the effect was available. Adverse events were also recorded in this population (Figure 1).

The 61 included patients consisted of 14 men (23.0%) and 47 women (77.0%). The age at the first treatment ranged from 27 to 84 years, with a median age of 54 years (IQR: [46.50-58.50]; Shapiro-Wilk test: p=0.538).

Effectiveness

Of the 45 patients in whom ketamine was administered according to the predetermined protocol, 23 (51.1%) had a successful outcome.

Six patients (13.3%) discontinued therapy after administration of the first full dose, and eight patients (17.8%) discontinued therapy after a total of three administrations. Thirty-one of the included patients (68.9%) continued therapy after the first three doses. The mean pain reduction was 43.85% (CI-95%: [35.54-52.15]) (Figure 2).

The median NRS score before the first therapy session was 7 (IQR [6-8]; Shapiro-Wilk test: p=0.005). No significant correlation between baseline NRS and chance of treatment success was observed (Wald test: p=0.863; OR 0.975 (CI-95%: [0.729-1.304])).

Eighteen patients were categorized as having neuropathic pain type. The largest proportion of favorable therapeutic effects was observed in this group (61.1%). Only two of the included patients had nociceptive pain, and both had no favorable outcomes after KIT. Nociplastic pain was observed in 25 patients. Twelve (48.0 %) patients with nociplastic pain had good outcomes after KIT (Table I). No significant difference was demonstrated between the outcomes of the different types of pain (Fisher's exact test: p=0.280).

Safety

Side effects were recorded in 61 patients who received at least one dose of ketamine. The treatment of side effects was not protocolized and was left to the judgement of the supervising anesthesiologist.

Three patients reported nausea associated with the therapy. In two of these patients, nausea improved after intravenous administration of 4 mg ondansetron and therapy was continued without further issues. The third patient was lost to follow-up after the first trial dose for unknown reasons. Four other patients experienced dizziness. No further specific interventions were performed on these patients.

Psychotomimetic side effects have been reported in several patients. Four patients experienced hallucinations. In one patient, the hallucinations disappeared spontaneously without therapy, and in two others, they disappeared after the administration of midazolam. The fourth patient stopped the follow-up after the first trial dose. One patient spoke

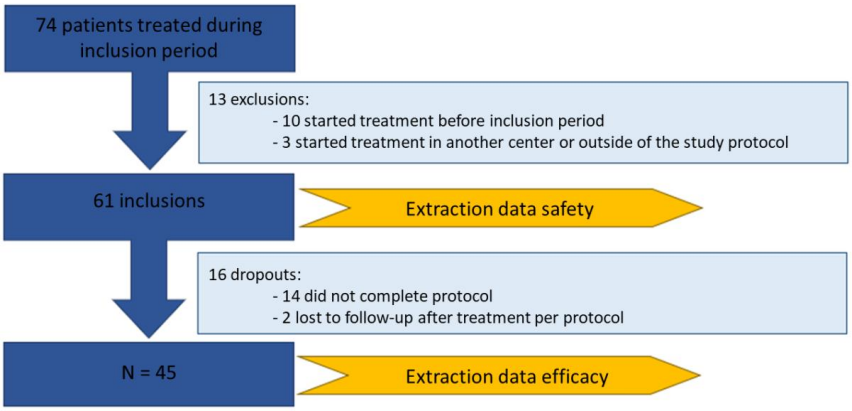

Fig. 1 — Patient inclusion flowchart.

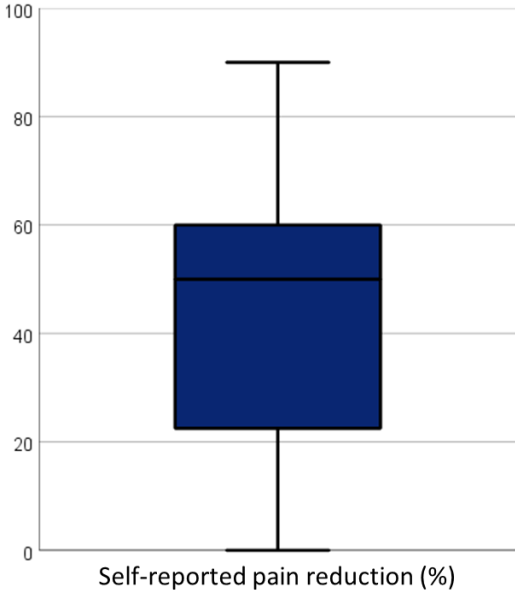

Fig. 2 — Box and Whisker plot: self-reported pain reduction.

deliriously when 75 mg ketamine was administered, but not at 150 mg. She subsequently left the center for undetermined reasons. Another patient described nightmares during therapy, but these could be treated with the intravenous administration of 30 mg of additional propofol.

Disturbed liver enzymes were only observed in one patient after the study period. This case involved a GGT of 39 U L-1 (laboratory normal values: <36 U L-1). After this point, KIT was discontinued. Eight months later, cholecystitis based on choledocholithiasis was diagnosed, and cholecystectomy was performed with full recovery of the liver enzymes to baseline. One patient disappeared from follow-up after an initial test dose of 75 mg and was confirmed to have deceased two months later. Unfortunately, the patient was diagnosed with oncological disease while being treated with ketamine. The cancer was discovered later and was unrelated to pre-existing pain. Based on the file review, no relationship to KIT could be discerned.

Intolerance was reported in four other patients without further definition.

Discussion

We present an analysis of one of the largest series of ketamine infusion therapies for chronic pain to date. The number of patients included in this retrospective single-center cohort study was large compared to that in the available literature. The fact that patients were selected as is common in real-world clinical pain practice is an additional strength of this study. Of course, the design of this retrospective cohort study has some limitations. For example, some patients came to our center after exhausting every possible treatment at several other centers, without success. They then sometimes disappeared from follow-up after one or more sessions, and it often proved impossible to determine the outcomes and reasons for therapy discontinuation. Future studies in this area would therefore benefit from prospective, controlled research. In the past, however, placebo comparisons proved difficult because the sedative effects of ketamine almost always nullify blinding.

A possible overestimation of therapeutic effects due to selection bias should be considered when interpreting the results. Patients who received only the trial dose and disappeared from follow-up before undergoing the full protocol were excluded, although these patients possibly disappeared because of a lack of effect. However, patients who were already receiving KIT at another center or before the start of the study were deliberately excluded to avoid positive selection bias, as they had a previously proven positive effect.

Few studies have been found in the literature that allow direct comparisons. The protocols used had notable differences in the total dose, additives, infusion duration, and frequency of administration. Furthermore, different outcomes were examined, and the timing of pain reduction evaluation varied.

Patil and Anitescu conducted the most comparable study. They also retrospectively examined a population of patients receiving ketamine infusions in one-day admission over a five-year period and included 49 patients with various chronic pain conditions. 0.5 mg kg-1 of racemic ketamine was administered at the initial treatment and increased afterwards in case of insufficient effect (mean 0.9 (±0.4) mg kg-1). Pain reduction based on the Visual Analog Scale (VAS) was found to be significant. The probability of long-term pain reduction was 59-85% (23-51% reduction over three weeks)[11].

Table I. — Outcome by type of pain.

		Pain type			Total
		Neuropathic	Nociceptive	Nociplastic	
Outcome	Unsuccesful	7 (38,9%)	2 (100,0%)	13 (52,0%)	22 (48,9%)
	Succesful	11 (61,1%)	0	12 (48,0%)	23 (51,1%)
Total		18	2	25	45

Graven-Nielsen et al. and Noppers et al. conducted the largest studies on the effect of KIT in fibromyalgia. Graven-Nielsen et al. demonstrated pain relief during infusion, but did not examine long-term analgesia as an outcome[28]. Noppers et al. conducted a randomized study of 24 patients, comparing ketamine (n=12) and midazolam (n=12). Although a pain reduction of more than 50% was demonstrated shortly after infusion, the effect was significantly reduced after several hours. However, only 0.5 mg kg-1 ketamine was administered over 30 min[29].

Kang et al. treated 103 Korean patients with a loading dose of 0.2 mg kg-1 ketamine followed by an infusion of 0.5 mg kg-1 h-1 for two hours. These sessions were repeated every two days for a total of three treatments in patients with therapy-resistant chronic neuropathic pain. Two weeks after the infusion, significant pain reduction was confirmed. The main side effects were ronchopathy and dizziness[30].

While the literature reports better outcomes in neuropathic pain and we also noticed this trend, we were unable to demonstrate it with statistical significance. This may be explained by the small sample size. The main side effects were nausea, dizziness, and hallucinations; however, most often, these side effects were benign and easily treated. Mildly elevated GGT was observed in one patient during routine screening, but this was presumably not caused by KIT. No cardiovascular, respiratory or urological complications were observed. When compared with the rates of adverse effects described in the systematic review by Guimarães Pereira et al., we note that side effects in our study were far less common[31]. Therefore, an underestimation due to patients not consistently reporting side effects should be considered, although this may also be explained by a difference in the definition of certain side effects.

In conclusion, this study showed that a relatively high proportion of patients treated according to the KIT protocol at our center over the past five years experienced good results. Considering that these patients often already underwent most conventional treatments without sufficient effects, these findings are consequently very positive. However, a significant proportion of our patients were lost to follow-up, and the lack of a control group limited the strength of our conclusions. Nevertheless, we conclude that KIT is a valid therapeutic option for chronic pain that does not improve sufficiently with first- and second-line therapies. An important advantage of this protocol is that treatment can be provided through same-day admission, which is important in the current economic climate. However, extramural treatment remains strongly discouraged for safety reasons.

At the end of the inclusion period, our center switched to a protocol using isolated S-ketamine instead of racemic ketamine. Theoretically, this could be associated with a more favorable ratio of effects and side effects, but future research is warranted.

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