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The effects of the use of ketamine on suicide ideation in patients with treatment-resistant depression

Fernanda Moreira Franco[1], Ana Julia Modesto Lima[2], Natana Carol Alves[3], Rafaela Beatriz Silva[4], Talita Braga[5]

[1] *School of Medicine, Centro Universitário de Anápolis – UniEVANGÉLICA, Brazil*
[2] *School of Medicine, Centro Universitário de Anápolis – UniEVANGÉLICA, Brazil*
[3] *School of Medicine, Centro Universitário de Anápolis – UniEVANGÉLICA, Brazil*
[4] *School of Medicine, Centro Universitário de Anápolis – UniEVANGÉLICA, Brazil*
[5] *Psychiatrist at Pax- Instituto de Psiquiatria. Professor at School of Medicine, Centro Universitário de Anápolis – UniEVANGÉLICA, Brazil*

Abstract: Approximately one third of people affected with depression do not respond to treatments known until then, and one of the main complications in these patients is suicidal ideation. Studies have shown that ketamine, an antagonist of glutamatergic receptors, in subanesthetic doses, has antidepressant action in a few hours, especially in patients who are resistant to treatment, in addition to exhibiting a good safety profile. Therefore, this research aims to analyze the use of ketamine and its effects on suicidal ideation in patients with depression resistant to conventional treatments by comparing the scores on the Hamilton Depression Assessment Scale (HAM-D), evaluating them in the beginning and during the treatment. This is a descriptive, quantitative, cross-sectional study, carried out at Pax Clínica Psiquiatrica – Neurosciences Institute, located in Goiânia - Goiás, in patients diagnosed with a Depressive Episode and resistant to treatment. In the results with significant improvement in 83.3% of the patients in the symptom of suicidal ideation (p-value = 0.038) and 83.3% of the patients reported a reduction in the total score of the scale (p-value = 0.046). From the preliminary results, it can be concluded that ketamine provided a benefit in reducing the suicidal ideation of these patients, in addition to offering a clinical improvement of depressive symptoms. The realization of new research is of significant importance in order to provide greater statistical evidence and subsidies to offer a concrete option to the biology of depression.

Keywords: ketamine, suicide, depression, treatment-resistant depression

1. Introduction

Depression is a condition of chronic, recurrent and highly prevalent in the world population, often associated with functional disability and impaired physical health of those affected [1]. Depressive conditions are characterized by the presence of depressed mood and / or loss of pleasure or interest, added to the presence of some or all of the following symptoms: altered sleep, altered weight and eating behavior, psychomotor alteration, fatigue or loss of energy, impairment of cognitive functions, feeling of lack of worth or excessive feeling of guilt and suicidal ideation [2]

The World Health Organization (WHO) has classified depression as the fourth leading cause of disability worldwide and projects it to be the second largest cause in 2020. According to definition, it affects about 120 million people worldwide. In Brazil, a WHO estimate that 15.8% of the population suffers from some subtype of depression [3]. The WHO estimates that every 40 seconds a person commits suicide in the world, not just in developed countries [4].

Response rates of drugs known to be used in the treatment of depression usually range from 50 to 70% in most randomized controlled trials (RCTs) [5]. Of the patients that do not induce treatment, 10% to 30% are resistant to treatment with difficulties in social function and occupational, decline in physical health, suicidal thoughts and increased use of health services [6].

Treatment-resistant depression (TRD) is defined as severe depression with a weak or unsatisfactory response from two drugs (in optimal and medium dosage) from two different classes of antidepressants. Usually these patients respond to change combination of antidepressants, electroconvulsive therapy (ECT) or psychotherapy [6]. Thus, 9 to 10% of patients with depression have TRD. Some studies have found that ketamine has rapid antidepressant effects in patients with TRD [7].

The emergence of intravenous ketamine therapy was celebrated by the NIMH (National Institute of Mental Health) as perhaps "the most important advance in antidepressant treatment in decades". In 2000, a first report of the antidepressant action of a subanesthetic dose of ketamine occurring in hours, even in a sample of patients, was a reference work in the field of research on mood disorders [8]. Since this first report of the

antidepressant effects of subanesthetic doses of ketamine, studies have repeatedly confirmed its therapeutic benefits in major depressive disorder, as well as in depressive episodes in patients with bipolar disorder [9].

The antidepressant effects of ketamine result from the increased presynaptic release of glutamate, with an increase in cell signaling at the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamatergic receptor to the relative N- methyl-D-aspartate (NMDA) [10]. Two characteristics of this antidepressant response are noteworthy: first, it can manifest within minutes or hours after transient mental dissociation, and second, it occurred mainly in treatment-resistant patients. The response rate has been around 50% in placebo-controlled studies. The main disadvantage is that its antidepressant effects generally do not last more than a week. Studies unchanged, however, that repeated administration can maintain and prolong the response [11].

Although the use of ketamine to treat depression has not yet been approved in Brazil, the Regional Council of Medicine of the State of São Paulo (CREMESP), in 2014, issued opinion number 167761 (Consultation No. 167.761 / 2013) stating that: National Health Surveillance Agency (ANVISA) Regulation the use of unfulfilled drugs (Ketamine is only authorized for anesthetic purposes) only in research protocols and "off label" use, respecting the laws of the institution's Research Ethics Committee; the “off label” use of medication approved for another purpose is, by definition, not authorized by the ANVISA regulatory agency, but this does not imply that it is incorrect; the use is made at the risk and expense of the doctor who prescribes it, and may eventually characterize a medical error [12].

The present study aims to analyze the use of ketamine and its effects on suicidal ideation in patients with depression resistant to conventional treatments by comparing the scores on the Hamilton Depression Assessment Scale (HAM-D), evaluating them in the beginning and during the treatment.

2. Materials and Methods

This is a descriptive, cross-sectional, quantitative study, carried out at Pax Clínica Psiquiatrica - Neuroscience Institute, located in Goiânia - Goiás, in patients diagnosed with a depressive episode and resistant to treatment, from September 2019 to January 2020.

Data were collected using the Hamilton Depression Assessment Scale (HAM-D) at two different times, before treatment with subcutaneous ketamine (SC) and after at least two applications of the drug. This instrument investigates how the patient has been feeling in the last seven days, including the day of application. The symptoms are scored according to the intensity of the symptoms, from 0 to 2, 0 to 3 or from 0 to 4.

There are no cutoff points in the literature determined by the author of the scale, accepting, in clinical practice, scores above 25 points as characteristic of severely depressed patients; scores between 18 and 24 points, patients moderately depressed; and scores between 7 and 17 points, patients with mild depression [13].

Inclusion criteria were patients undergoing care and treatment at the co-participating institution, over 18 years old, diagnosed with treatment-resistant depression, who agreed to sign the Free and Informed Consent Form (TLCE) and who had a prescription for ketamine SC from the date of data collection. Exclusion criteria were patients who had already started treatment with ketamine SC or who refused to sign the informed consent form.

The Microsoft® Excel 2007 program was used for data tabulation and statistical analysis was performed using the Statistical Package for Social Sciences (SPSS®) for Windows®, version 21.0. To perform the descriptive statistical analysis, the chi-square test ($\chi 2$) was adopted. The level of significance was set at 5% ($p < 0.05$) for all analyzes.

The work was submitted to the Research Ethics Committee (CEP) of the University Center of Anápolis (UniEVANGÉLICA) and approved with the opinion number 3,552,645.

3. Results

This study involved the participation of six patients, five women and one man, with a mean age of 36 years, with a standard deviation of 17,064 years.

To analysis of the total HAM-D score, among the patient patients, 83.3% (5/6) reduced the score in this parameter, while 16.7% (1/6) showed worsening due to the increase in the score. Before using ketamine, there was an average of 24.17 (standard deviation of 5.04) without a total score; when applying a scale in the course of treatment, 16.00 was obtained as an average (standard deviation of 4.47). From this comparison, a statistically significant difference was observed for the total score, before and during the treatment with ketamine (p-value = 0.046).

Regarding the symptoms of suicidal ideation, 83.3% (5/6) of the patients reported improvement and 16.7% (1/6) maintained the score (p-value = 0.038). The other symptoms analyzed in HAM-D with statistically significant differences were: somatic symptoms in general, 66.7% (4/6) of the sample reported improvement, while 33.3% (2/6) maintained the score reported before treatment (p-value = 0.046); diurnal variation, 83.3% (5/6) reported improvement and 16.7% (1/6) maintained the score (p-value = 0.038); depersonalization and

derealization, 66.7% (4/6) reported improvement and 33.3% (2/6) maintained the score reported before the applications (p-value = 0.046).

Regarding the classification of depression as to its severity (severe, moderate, mild), it was observed, when comparing the Total Score of each patient, obtained by the application of HAM-D before starting and during the treatment with ketamine, that 16.7% (1/6) progressed from severe to moderate depression, 33.3% (2/6) from severe to mild, another 33.3% (2/6) from moderate to mild, while the others 16.7% (1/6) went from mild depression to moderate depression (Table 1).

Table 1: Classification of patients' depression assessed according to the HAM-D Total Score.

Patient	**Before**		**After**	
	Score	Classification	Score	Classification
P1	24	Moderate	12	Mild
P2	27	Severe	11	Mild
P3	22	Moderate	15	Mild
P4	25	Severe	16	Mild
P5	16	Mild	19	Moderate
P6	31	Severe	23	Moderate

4. Discussion

This study sought to describe the use of ketamine and its effects in patients with depression resistant to conventional treatments, by comparing the scores on the Hamilton Depression Assessment Scale, evaluating them at the beginning and during the treatment.

The reduction in the total HAM-D score suggests a general improvement in depressive symptoms, which support the antidepressant effect of ketamine, in line with the results of other research. In one review, a significant improvement was noted in the assessment of HAM-D of 21 items with ketamine compared to placebo at all times, from 110 minutes to 7 days. The authors showed that individual symptoms of HAM-D, depressed mood, guilt, work and interests, psychological anxiety, suicide, insomnia, general somatic symptoms, genital symptoms and hypochondria improved significantly with ketamine [14]. Findings observed in another study also demonstrated a significant improvement in terms of depression, anxiety and disease severity after one hour of application of the drug compared to baseline results [15].

The effectiveness of ketamine, defined by a significant difference in the severity score of depression before and after treatment, assessed by validated depression classification scales, shows results in favor of ketamine over placebo, from 40 minutes to 6 weeks [16]. However, not all patients respond to ketamine and the duration of the antidepressant effect is variable between individuals [17].

The results of several studies indicate that some patients may benefit from serial ketamine infusions, even if they have not had a marked response to the first treatment9. When analyzing patients with treatment-resistant depression and the response to ketamine treatment, with single or repeated doses, it was concluded that repeated ketamine infusions have cumulative and sustained antidepressant effects and that the reduction in depressive symptoms was maintained among those who responded through infusions performed once a week [18].

Most studies with ketamine for treatment-resistant depression administered the drug as an intravenous infusion of 0.5 mg / kg for 30-40 min [19]. Comparing, in a placebo-controlled group, the administration of ketamine in the intravenous (IV), intramuscular (IM) and subcutaneous (SC) routes, it was possible to conclude that the injection of ketamine by SC appeared to be the most advantageous of the three routes of treatment studied [20]. The results were that the SC and IM pathways had less psychomimetic effects when compared to the IV pathway, coupled with this, the SC pathway also had a lower risk of cardiovascular effects, in addition to being the simplest to administer.

Suicide is a serious public health problem and is among the top ten causes of death in the world population in all age groups [21]. Thus, the decrease in the score observed in this item is a great achievement. In a first analysis published in a study of 26 patients with treatment resistant to treatment who received ketamine intravenously, using the suicidal item of the Montgomery-Asberg Depression Classification Scale (MADRS); it was observed that a single subanesthetic dose of ketamine was associated with a significant reduction in suicidal thoughts within 24 hours, demonstrated by the reduction in MADRS scores. In addition, a subsample of these patients (n = 9) repeated doses of ketamine over 12 days, and as reductions in MADRS values were maintained [22].

In a study, the regional metabolism of cerebral glucose was evaluated in three areas of interest in relation to suicidal thoughts: the amygdala, the infra-limbic cortex (Brodmann area 25) and the subgenual anterior cingulate. Basal suicidal thoughts were associated with regional cerebral glucose metabolism in the infra-limbic

cortex, while basal mood was not associated with metabolism in that area. In addition, reductions in suicidal thoughts, but not in depression, have been associated with reduced metabolism in the infra-limbic córtex [23]. Therefore, it is possible that brain regions, such as the infra-limbic cortex, are associated with the presence and changes in suicidal thoughts, but not in mood, which would provide further evidence of the specific anti-suicidal effects of ketamine [24].

When analyzing the use of single and repeated ketamine infusions to reduce suicidal ideation in patients with treatment-resistant depression, we observed a reduction in these thoughts in single and repeated infusions, with cumulative effects noted with repeated infusions three times a week and maintenance of the effects of ketamine with infusions once a week. The findings suggested that the effects of ketamine on suicidal ideation and depression are partially independent, supported by the fact that 60% of the variation in the overall change in suicidal ideation was not explained by the change in depressive symptoms. It was also noticed that several desires that do not meet the criteria for an antidepressant response with ketamine still experienced a relief from the symptoms of suicidal ideation with repeated infusions. This partial independence required the potential use of ketamine as a treatment for suicidal ideation outside the context of treatment-resistant depression [25].

As for the limitations of the study, the small number of participants, the lack of randomization regarding the other diagnoses of mental disorders and previous or concomitant treatments, as well as the lack of evaluation of the immediate effects of ketamine after the application were the factors found.

As treatment with ketamine for antidepressant purposes is very pioneering and innovative, it becomes financially expensive for the patient, since it is self-funded, the sample was limited to a small number. The evaluation of the immediate effects after ketamine applications proved to be unfeasible, both due to the patient's condition and willingness to answer the questions, as well as the waiting time necessary to start the effects of the medication, causing the patient to leave the hospital before the ideal time for evaluation.

5. Conclusion

The present study analyzed the use of ketamine and its effects on suicidal ideation in patients with depression resistant to conventional treatments by comparing the scores of the Hamilton Depression Assessment Scale, evaluating them at the beginning and during the treatment.

It was found that ketamine provided a significant improvement in suicidal ideation in patients resistant to the treatment of depression; in addition to a considerable decrease in the total score in HAM-D, representing a clinical improvement of depression in these patients. These results are quite expressive and promising in the face of a pathology responsible for generating numerous disabilities for the patient, which are still difficult to manage and cope with.

Treatment-resistant depression is a chronic disease and longer-term studies are needed to fully characterize whether the clinical benefits of ketamine are maintained and, if any, whether they can be sustained despite reductions in dosing frequency during chronic treatment.

In this sense, the authors intend to continue the research, which will provide greater statistical evidence and support to offer a new window to the biology of depression, in order to unveil new therapeutic targets to achieve rapid relief of depressive symptoms, especially to those who suffer and are refractory to conventional treatments.

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