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•CASE REPORT•

A Case Report of A Patient with Treatment-Resistant Depression Successfully Treated with Repeated Intravenous Injections of A Low Dosage of Ketamine

Shikai WANG, Mincai QIAN*, Liang LI, Qi YANG

Summary: Depression is a highly prevalent and severely disabling disease. The treatment effects, intensity and onset time of antidepressants have been highlighted in many studies. Recent studies on the rapid-onset of antidepressant response focused on the effect of a single low dose of intravenous ketamine. However, there are still some problems with treatment, including safety, efficacy, ethics, dose, frequency of administration and their effect in treatment-resistant depression. In the present study, we treated one case of treatment resistant depression with repeated intravenous injections with a low dosage of ketamine.

Key words: Treatment-resistant depression, Ketamine

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1. Introduction

Depression is a kind of disorder with core symptoms of low mood, decreased interests and anhedonia, and can also be accompanied by a variety of somatic symptoms as well as negative thoughts and behaviors. However, the current rate of effectiveness for antidepressants is only 60% to 80%,[1] and it takes about two weeks for them to be effective; furthermore, residues of symptoms are common after treatment. Therefore, achieving rapid relief of depression symptoms within a short period of time has attracted increasing attention in the current research field. Previous research[2] has stated that the antagonist of N-methyl-D-aspartic acid receptor (NMDA) represented by ketamine can relieve the depression symptoms of patients effectively, but mostly with a single intravenous injection of a low dose; even though the curative effect is guaranteed, it does not last long. We treated one case of treatment-resistant depression with repeated intravenous injections of low dose ketamine in our department with satisfying results. Now the case is reported as below:

2. Medical history

The patient was a 27-year old single, male, with a junior high education, surnamed Wang. Wang was a blue collar worker from Huzhou, Zhejiang province. Patient's depression had a duration of over 8 years. He was admitted to our hospital on 29th August 2016 with principle complaints being "trouble sleeping, feeling unhappy, worried and fatigued". Over 8 years ago this patient gradually developed sleep difficulties, as well as low mood, loss of interest, speaking less, loss of movement and excessive worries. At that time he sought treatment in our out-patient department, and was diagnosed with depressive disorder. After taking Seroxat 40 mg every morning, his symptoms improved with normal intermissions. However, after he stopped

Third People's Hospital, Huzhou, Zhejiang Province, China

*correspondence: Mincai Qian. Mailing address: No. 2088 East Shaoxi Road, Wuxing District, Huzhou, Zhejiang Province, China. Postcode: 313000. E-Mail: 1311956613@qq.com

taking medication on his own, he started to feel unable to be happy, have no motivation to do things, have prominent anxiety and a tendency to uncontrollably over-think situations. He returned to our hospital for treatments multiple times, and during the treatment, he took many medications, such as "paroxetine (Seroxat), Sertraline (Zoloft), Fluvoxamine (Luvox), Venlafaxine (Efexor RX), clorimipramine, etc." He tried both single-drug-use and multiple-drug-use of antidepressant medications with different mechanisms, and "Olanzapine (Zyprexa) or Quetiapine (Seroquel)" were also used as supplemental drugs to improve the curative effect. Even though during the period of treatment, he was treated with a systematic antidepressant procedure accompanied with sufficient doses and time, his symptoms were not fully relieved. Moreover, they became greatly aggravated in the month leading up to the treatment reported here. He became depressed all day, was fatigued, had no motivation to do anything, had decreased interest in life, and experienced difficulties working normally, and felt distressed. Therefore, he was hospitalized with a diagnosis of "recurrent depression disorder, current as major depressive episode without psychotic symptoms". The patient had an appendicitis operation two years ago, and denied any other major medical conditions or a history of allergies. The patient was an only child and reported a normal childhood and development. He had a middle school education, and reports being an average student. After growing up the patient began working in a delivery company and reports having good relationships with his coworkers and no problems with his work ability. Client denied any drug or alcohol use, and is a non-smoker. Individual history was unremarkable and family history of mental illness was negative.

Physical examination at the time of hospitalization revealed that his height was 181 cm and his weight was 80 kg. His vital signs were all normal, and no abnormal results were found from his cardiopulmonary auscultation. There was a 10 cm long surgical scar on his lower right quadrant. The result of the neurological examination was negative. The mental status examination indicated that his consciousness was clear, that he was cooperative during contact, and that he was able to stay on topic during conversations. There were no signs of hallucinations and delusions. His mood was low, and his facial expressions were sad. He showed obvious anxiety, and he was worried that he could not get better. Decreased interests were present. He had little energy all day long, and felt difficulty concentrating. He had low self-assessment and distressed feelings. Even though negative thoughts were present, he did not show any negative behavior. His volitional behavior was diminished, but his insight about the illness existed.

After hospitalization, his results of routine blood tests, blood biochemistry tests, thyroid function tests, electrocardiogram, chest radiograph, abdominal color Doppler ultrasound and head CT were all within normal limits. The initial treatment was Venlafaxine release capsules (150 mg every morning) and Olanzapine tablets (2.5 mg every evening) orally. After two weeks of treatment, the effect was not satisfactory. Therefore, Escitalopram (the dose was increased to 20 mg/d for 2 weeks) tablets were added; but the effect was still not significant. The patient lay and sighed with sad expressions all day long. Then he was given with 6 consecutive sessions of MECT with propofol anesthesia (3 times a week), but it did not improve his symptoms either. His mood and interests were low, and his movements diminished. His HAMD-17 score was 28. And his score on the Beck Scale for Suicide Ideation-Chinese version (BSI-CV) [3] was 11. During his hospitalization, he was discussed as a difficult case multiple times, and the diagnosis was always treatment-resistant depression.[4] Considering that regular drugs did not improve symptoms and he did not react well to MECT, we planned to have an anesthesiologist conduct MECT with ketamine intravenous injection anesthesia under supervision after the patient and his family provided written consent. The initial injection was a one-minute-long fast intravenous injection with a subclinical dose of 70 mg (<1 mg/kg).[5] A few minutes later, the patient's depressive symptoms were completely gone; instead, he experienced comfort which he had never felt before. He commented that "this is so much better than electroshock therapy", and that "now we have entered the 25th century" and so on. His expression became happy, and he felt relaxed. Hence, the following MECT electrical stimulation was canceled and he was put on observation. At the 40, 80, 120, 230 minutes, the first and the second day after the injection, the scores of HAMD-17 were consistently under 7, and those of BSI were consistently under 5. The patient was able to communicate with other patients in the ward, but he still worried that the effect of the drug would not last. Three days later, he was given another 40 mg (the dose was based on 0.5 mg/kg) [2] ketamine intravenous injection using a micro pump and lasted for 40 minutes. He was injected every other day and three times in total. Evaluations with HAMD-17 and BSI-CV were conducted before and after every ketamine infection. After the injection treatment, his symptoms disappeared and he was discharged from the hospital with a prescription of "Venlafaxine release capsules 150 mg every morning and Escitalopram tablets 20 mg every morning". During the ketamine injection treatment, no other adverse reactions other than light dizziness were found. No cognitive impairment was detected in the neuropsychological tests. However, the patient reported that the pleasant experiences felt after the last three ketamine injections were far less than what he felt after the first injection. During that time, he wanted to accept fast intravenous injection treatment of ketamine again, but this request was denied because ketamine has a potential risk of being abused and addictive.[6] In the outpatient follow-ups during the two weeks after he was discharged, his symptoms of depression were improved, and he was able to work. Besides worrying about the recurrence of depression disorder, he did not show any other symptoms.

3. Discussion

Ketamine is a kind of phencyclidine drug with a complex mechanism, and it may involve NMDA receptors, opioid receptors, monoamine receptors, acetylcholine receptors, voltage-gated channels and so on. Due to its rapid and strong effect against depression, it has become a hot research topic in recent years. The mechanism of this drug's rapid effect on improving depression remains unclear, but it may be related to the biological factors including neural plasticity (slow waved electrical activities of brain, brain-derived neurotrophic factor (BDNF), Val166Met gene polymorphism, Shank 3 protein expression), neurological factors (anterior cingulate gyrus activities, glutamate/glutamine concentration), inflammatory factors (IL-6 concentration), and metabolic factors (VitB12 concentration, D-/L-serine, mitochondria β-fatty acid oxidation changes).[7] Because of the potential psychoactive effect of this drug and the ethical issues involved, the clinical use of it is limited.[8] However, the current evidence-based medicine studies have shown that using it to treat major or treatment -resistant depression does not violate medical ethics.[9]

This patient had multiple antidepressant treatments with adequate dosage and duration, and six consecutive MECT treatments, but his depressive symptoms did not improve significantly. In this situation, employing ketamine intravenous injection treatment produced a satisfying outcome. His depressive symptoms were relieved to the clinically cured level, and there was a significant improvement in his self-experience. However, this patient was followed up for only two weeks outside the hospital. In order to explore the effect that ketamine has on treating difficult-to-treat depressive disorder, future studies should include larger samples and longer follow-up durations.

During the ketamine injection treatment, the patient was able to experience a rapid relief of negative emotions. What was different about this case was that this patient received ketamine treatments with two different dosages and injection methods. During the initial rapid intravenous anesthesia with 70 mg ketamine before MECT, this patient experienced the relief of his depressive symptoms; in the meantime, he also experienced pleasure that he had never experienced before. However, when he was treated three times with micro-pump intravenous injections with 0.5 mg/kg ketamine as it was indicated in the literature on ketamine, this phenomenon did not appear again. Furthermore, it was not seen among other depressed patients who also received ketamine treatments. This suggests that high dosage treatments are highly likely to cause dissociative symptoms and an increase in blood pressure. Moreover, it can also make patients want to seek "pleasure" again,[10] thereby potentially leading to drug-seeking or drug-abusing behavior. Therefore, we recommend using slow intravenous injections with low dosages for treatment, and there is research recommending an even lower ketamine dosage (0.1 mg/kg) to treat difficult-to-treat depressive disorder.[11] This should be noted for future clinical research or practice.

Adverse reactions to ketamine in clinical practice are usually hallucinations, delirium, nightmares, fear or cataleptic state. But in this case, the patient only felt a light dizziness during ketamine injection treatment, which was tolerable. Moreover, the adverse reaction disappeared after bed rest. This indicates that the adverse reaction of this drug is related to the dosage and tolerance of the individual. In fact, if the dosage of ketamine for antidepressant use is the dosage (0.5 mg/kg) indicated by the current published research, the patient's consciousness will be clear, and there will not be obvious respiratory effect or cognitive impairment. Furthermore, in terms of improving depressed emotion and negative thoughts, its effect is strong and rapid, and it may be more effective than MECT in some cases. Therefore, under careful observation and with full informed consent, this could be an alternative treatment for treatment -resistant depression.

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Conflicts of interests statement

None.

Informed consent

The patient and his family provided written informed consent.

Authors' contribution

Shikai Wang was responsible for coordinating the study and writing up the paper. Mincai Qian participated in the revision of the paper. Liang Li was responsible for delivering the specific treatment. Qi Yang was responsible for the evaluations with scales during treatment.

低剂量氯胺酮重复静脉注射成功治疗难治性抑郁症患者 1 例

王世锴，钱敏才，李良，杨奇

概述：抑郁症是一类患病率高且危害严重的疾病，抗抑郁药物的疗效强度及起效时间一直备受关注，目前在抗抑郁治疗的快速起效方面研究热点是以低剂量氯胺酮静脉注射治疗，但在氯胺酮使用过程中仍有较多问题，包括安全性、疗效、伦理、给药剂量及频次、在难治性抑郁症患者中的应用等。本研究采用重复低剂量氯胺酮静脉注射的方式成功治疗了一例难治性抑郁症患者，结果安全有效。

关键词：难治性抑郁症；氯胺酮

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Shikai Wang graduated from the Medical School of Peking University in June 2007 with a master's degree in psychiatry. He is currently a psychiatry PhD candidate at the Anding Hospital of Capital Medical University. He has been working in the Huzhou Third People's Hospital in Zhejiang Province since March 2008. He is currently the director of the Open Psychiatry Department in the Huzhou Third People's Hospital. His research interests are biological psychiatry and psychopharmacology.