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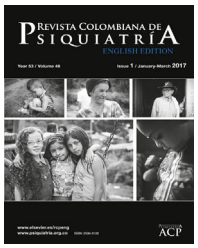

Case Report

Successful treatment for serious depression with suicidal risk in a heart transplant patient

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ABSTRACT

Introduction: Major depressive disorder is related to unfavourable outcomes in patients with severe comorbidities. In transplant patients, major depression is associated with worse clinical outcomes.

Case report: We present the case of a 55-year-old man with a heart transplant due to heart failure of ischaemic origin. Six months after the transplant he developed depressed mood, anhedonia and suicidal ideation with a score of 20/27 on the PHQ-9 depression screening scale. After receiving mirtazapine 30 mg/night for a week and persisting with a high suicide risk, it was decided to administer ketamine infusion for 24 h, with which a significant improvement in mood was observed, and the disappearance of suicidal ideation 24 h after the infusion.

Discussion: Depression in transplant patients is a factor associated with graft loss and post-transplant mortality, in addition to favouring other negative outcomes such as deep vein thrombosis.

Conclusions: Ketamine infusion was shown to be an effective and safe option to treat major depression with suicidal risk in a heart transplant patient.

Tratamiento Exitoso para la Depresión Grave con Riesgo Suicida en un Paciente Trasplantado de Corazón

Palabras clave:
Trasplante de corazón
Trastorno depresivo
Riesgo suicida
Ketamina

RESUMEN

Introducción: El trastorno depresivo mayor se relaciona con desenlaces desfavorables en pacientes con comorbilidades graves. En pacientes trasplantados, la depresión mayor se asocia con peores desenlaces clínicos.

Reporte de caso: Se presenta el caso de un varón de 55 años, con trasplante de corazón por insuficiencia cardiaca de origen isquémico, que 6 meses después del trasplante presentó

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ánimo deprimido, anhedonia e ideación suicida, con un puntaje de 20 sobre 27 en la escala para tamizar depresión PHQ-9. Luego de recibir mirtazapina 30 mg/noche durante 1 semana y persistir con alto riesgo suicida, se decidió administrar infusión de ketamina durante 24 h, con lo cual se observó mejoría significativa en el ánimo y desaparición de la ideación suicida 24 h tras la infusión.

Discusión: La depresión en pacientes trasplantados es un factor asociado con la pérdida del injerto y la mortalidad postrasplante, además de favorecer otros desenlaces negativos como trombosis venosa profunda.

Conclusiones: La infusión de ketamina se ha demostrado como una opción efectiva y segura para tratar la depresión mayor con riesgo suicida en un paciente trasplantado de corazón.

Introduction

Transplant patients have a higher prevalence of depression than the general population.[1] While in the general population the prevalence is 3%–10%,[2] in organ recipients it is 14%–63%.[3] Depression has the potential to decrease the overall success after transplantation, and leads to a significant increase in morbidity and mortality. According to the meta-analysis by Dew et al.,[1] depression is associated with a 65% higher risk of graft rejection and post-transplant mortality. Patients with depression have greater social isolation[4,5] and poorer adherence to diet, physical rehabilitation[6,7] and the immunosuppressive medication regimen required post-transplant.[8] Depression has also been associated with high concentrations of C-reactive protein and proinflammatory cytokines, each of which increases the risk of death in the general population and in cohorts of patients with end-stage organ disease.[9,10]

Available oral antidepressant treatments have two main limitations, delay in onset of action and undesirable effects.[11,12] However, there is now a drug treatment which has been proven to rapidly reduce suicidal ideation and severe depressive symptoms.[13] Ketamine, an N-methyl-D-aspartate receptor antagonist, has evidence from 10 systematic reviews and clinical trials that conclude it significantly reduces severe symptoms of depression and suicidal ideation in a matter of hours or a few days.[14,15]

Ketamine has been shown to be an effective option for treating suicidal ideation and major depression in patients in hospital or Accident and Emergency department settings.[14,16] However, despite multiple studies indicating that ketamine is effective for treating severe depressive episodes,[14,15] there is no reported experience and there are no clinical practice guidelines for prescribing it in the context of post-transplant patients. This study presents a case report of a patient with severe depression and suicidal ideation who was administered ketamine by intravenous infusion.

Case report

This was a 55-year-old married man, who lives with his wife and children. He was retired due to heart disease, having worked in the financial sector. Fig. 1 shows the timeline.

Previous medical history

Heart transplant six months earlier, due to heart failure of ischaemic origin. He was admitted to the Accident and Emergency department due to orthopnoea and fatigue. After being medically assessed, he was diagnosed with subacute right infrapopliteal deep vein thrombosis and acute bilateral lobar and segmental pulmonary embolism, predominantly affecting the right. Before the transplant, he had a history of systemic hypertension, dyslipidaemia and type 2 diabetes mellitus, and had suffered a stroke resulting in mild right hemiparesis.

Diagnostic aids

Transthoracic cardiac ultrasound showed myocardial contractility with diffuse hypokinesis and remodelling of the basal segment of the inferior wall, with an ejection fraction of 38%. Myocardial biopsy ruled out acute cellular rejection of the graft. Electrocardiogram revealed sinus tachycardia, right bundle branch block, and altered repolarisation in V_1.

Laboratory tests

D-dimer and troponins were elevated. Blood count, kidney function, liver tests, electrolytes, thyrotropin, Vitamin B_{12} and folic acid were normal; serology for human immunodeficiency virus and syphilis were negative.

Psychiatric interview

While in the Accident and Emergency department, he was assessed through an unstructured psychiatric interview. Depressive and suicidal ideas were identified, and so he was referred for Psychiatric assessment. The assessment by Liaison Psychiatry identified a six-month history of depressive symptoms, characterised by sadness for most of the day every day, anhedonia, overall insomnia, decreased appetite with unquantified weight loss, irritability, easy crying, memory problems and depressive and suicidal ideas. He was also markedly sedentary and anergic, resulting in him spending

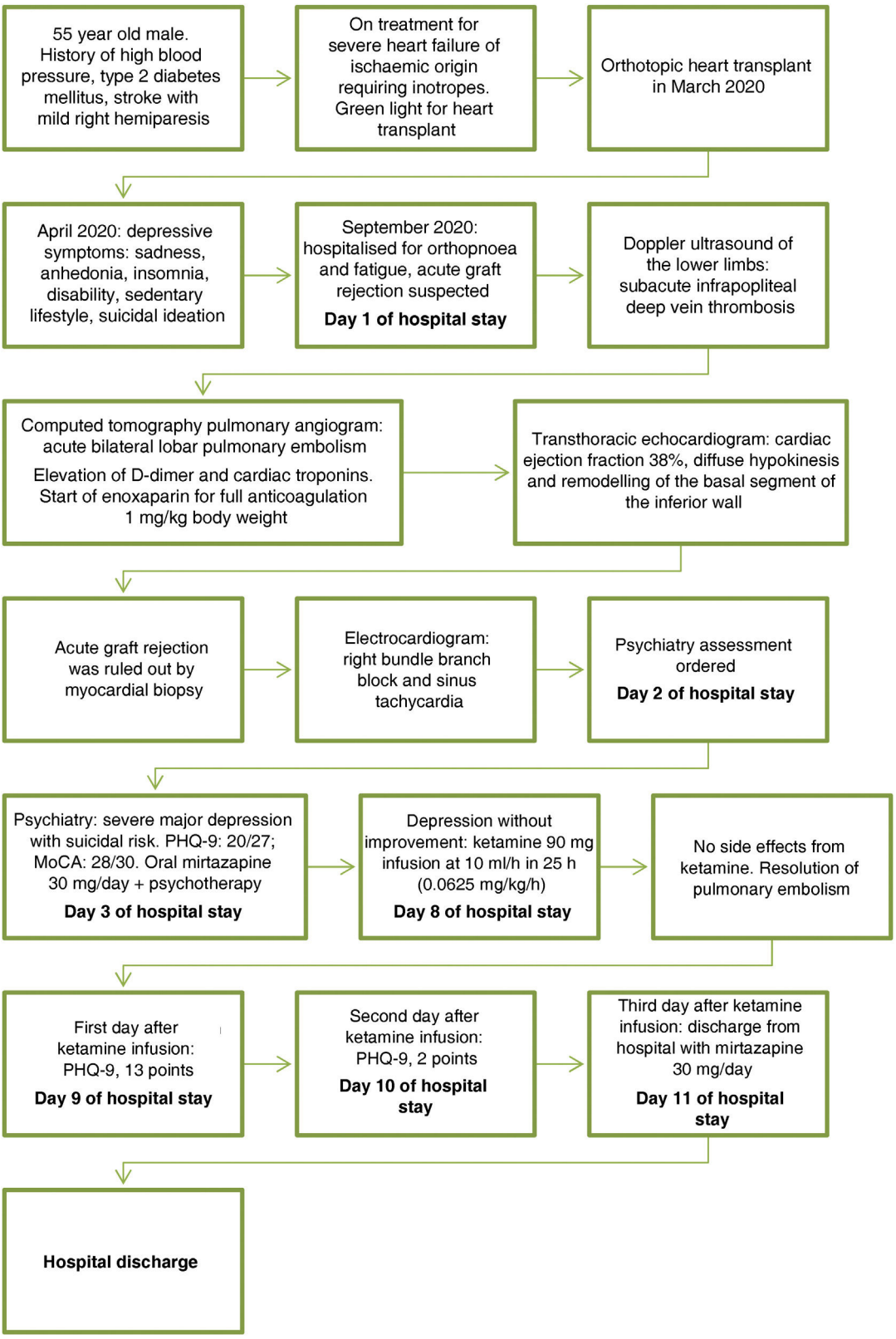

Fig. 1 – Timeline.

Table 1 – Assessment for the appropriate use of ketamine infusion in the patient.

Component	Recommendation
1	Psychiatric interview: no history of smoking, alcohol or other drugs. No history of psychotic symptoms or disorders
2.	Baseline and post-infusion assessment of depressive symptoms using the depression scale (PHQ-9), which includes the nine depression criteria according to the DSM-IV
3.	History of taking psychotropic drugs: the patient had never taken any antidepressant or other psychotropic drug. This is the first depressive episode he has ever had in his life. He has no family history of depression or other mental disorders
4.	Check contraindications for the use of ketamine: the patient was hypertensive, but blood pressure is controlled with medication. He has no history of hypersensitivity to ketamine
5.	Clinical and laboratory screening: the heart transplant staff discussed the case and it was assessed by Anaesthetics, which approved the procedure. Lab tests normal
6.	Review of the patient's medical records, in addition to corroborating the history with his wife: no history of allergies or previous use of opiates or benzodiazepines
7.	Informed consent process, which included: conversation about the procedure (benefits, risks, questions) the day before the ketamine infusion and the day of the infusion: checking that the information had been understood, resolving of doubts and written informed consent obtained.

Prepared by the authors based on Sanacora et al.[17]

most of the day and night in bed when he was having symptoms.

Psychiatric history

He had no history of depression or suicidal behaviour, either personal or family, or psychotic symptoms or disorders. No previous substance abuse. In terms of personality traits, he was described by his wife as an extroverted, cheerful person who had always been effective at resolving problems and difficulties.

Mental examination

Alert, orientated overall, establishing eye contact, appropriate attention, no motor restlessness, depressive affect, fluent and well-articulated language, with a quiet tone of voice and normal language processing. His thinking was coherent and logical, with depressive cognitions of disability and hopelessness, thinking about death and suicidal ideation, without delusions. He denied sensory-perceptive disorders and had his memory intact, appropriate judgement but negative prospection. On admission to hospital, his score on the PHQ-9 scale was 20 and on the MoCA, 28. Physiotherapy and assessment by a hospital nutritionist and neurologist were ordered.

Hospital follow-up

The major depression in this patient met severity criteria (sedentary lifestyle that led to deep vein thrombosis and pulmonary embolism, in addition to suicidal ideation and high risk of graft loss), so it was decided to start mirtazapine, which, in addition to treating his depression, could help with insomnia and hyporexia. Eight days after starting mirtazapine, while still within the therapeutic window before the onset of the full action of the antidepressant, the patient was discussed at a case conference with the transplant cardiologists. At the meeting, the benefits and risks of ketamine were presented to the medical group, with a proposal to administer it to the patient, which was approved. The reasons for deciding on this option for the patient were the persistence of suicidal risk, the rapid onset of the antidepressant action of ketamine compared to antidepressants, and the ease of application and monitoring of the patient as he was already in a hospital environment.

Pre-procedure assessment for appropriate ketamine administration

In 2017 Sanacora et al.[17] published a consensus document on ketamine for the treatment of affective disorders, which includes seven recommendations for the assessment of the candidate before infusion of the drug. Table 1 shows the assessment carried out on the patient.

Anaesthetics

Liaison Psychiatry made a referral to the Anaesthetics department to request support in the infusion of ketamine to a patient recently having had a heart transplant. Working together, we found systematic reviews and meta-analyses which enabled us to identify various doses of ketamine administration (from 0.5 to 7.0 mg/kg) and infusion frequencies (single, 1–3 times per week, once a month).[18,19] In other clinical settings, continuous ketamine drips are common, such as in intensive care for sedation/analgesia,[20] on hospital wards to treat acute[21] and chronic pain,[22] and in Accident and Emergency departments for pain and as an alternative to opioids.[23]

In a recent systematic review and meta-analysis[24] which included 28 studies in the systematic review and 19 in the meta-analysis, nine studies were identified that assessed the effects of multiple infusions of 0.5 mg/kg of ketamine in 269 participants. No studies with continuous ketamine infusion were identified. According to the consensus for the use of ketamine in affective disorders,[17] the most frequently administered antidepressant dose in clinical studies with ketamine is 0.5 mg/kg in venous infusion over 40 min,[25] which does not produce anaesthetic effects. However, an average increase of 13.4 mmHg[9] in systolic pressure has been reported, with BP values of 180/100 mmHg or heart rates >110 bpm in 30% of treated patients.

The use of ketamine infusion for depression has been associated with the following side effects[26,27]: psychiatric in 72% of studies assessing it (anxiety, agitation, irritability, delusions, panic, derealisation, depersonalisation); cardiovascular in 38% (increased blood pressure, arrhythmias, palpitations, chest pain, increased heart rate); neurological (headache, dizziness, poor motor coordination, tremor and involuntary movements); and in other systems (gastrointestinal, respiratory, urological, ocular). Consequently, in addition to the particular situation of our patient (heart transplant) and the fact that we were unable to find any reported cases in similar patients, the Anaesthetics department proposed a total dose of 90 mg of ketamine diluted in 250 ml of 0.9% saline solution to infuse over 25 h at a rate of 10 ml/h, which provided ketamine 1.5 mg/kg body weight. This method of infusing ketamine was chosen to extend the infusion time and reduce the potential dissociative and cardiovascular symptoms reported with high doses of the drug.[28]

Procedure

The day before the ketamine infusion, they spoke with the patient and his wife; his clinical situation was explained from a psychiatric perspective, along with the option of administering ketamine to treat his depression. On the day of the ketamine infusion, just beforehand, a conversation was held with the patient and his wife about the previous day's conversation. The patient's understanding of the clinical situation was verified, doubts were resolved, and informed consent was signed. The patient's weight and height were checked (60 kg and 170 cm; body mass index, 20.7). The patient's vital signs were taken and he was asked to lie down on the bed. The ketamine infusion was administered through a venous catheter in his left forearm. His initial blood pressure was 130/85 mmHg; heart rate, 72 bpm; respiratory rate, 14 rpm; and temperature, 36.5°C. Continuous blood pressure monitoring showed a maximum of 155/92 mmHg and a minimum of 105/82 mmHg, with a maximum heart rate of 90 bpm and a minimum of 69 bpm.

Side effects

The patient did not report any side effects during the ketamine infusion, which his wife corroborated, as she had been with him the entire time.

Interview and mental examination after ketamine infusion

The day after the ketamine infusion, the patient reported increased appetite and better mood. He said the suicidal thoughts had almost completely disappeared and he had slept better. Two days after receiving the infusion, the patient reported feeling "very well", with no sadness, with a perception of well-being and optimism, without negative thoughts about himself, and with a desire to live and share with his family. His wife said she saw him in very good spirits, smiling, with spontaneous displays of affection towards her and the children, spontaneously talking about returning home and showing affection through hugs and kisses to his family members.

Changes in the PHQ-9 score after the infusion

The PHQ-9 prior to ketamine infusion was 20. The next day, when the infusion was stopped, the PHQ-9 was 13; the day after the score was 2. The initial changes in the score were found in the desire to die, sadness and anhedonia, and 48 h later, the almost complete disappearance of depressive symptoms.

Hospital discharge

The patient was discharged four days after completing the ketamine infusion. He reported a complete improvement in his depressive symptoms. His wife described him as fully recovered from the depression. She said she saw him "full of energy, without negative or hopeless thoughts, optimistic about the future and with plans to do repairs at home".

Outpatient follow-up

Due to the health restrictions imposed by the SARS-COV-2 pandemic, the patient received psychiatric follow-up by telephone. The psychiatry resident (MMA) called him every eight days to conduct the hospital follow-up. The telephone interview was semi-structured. First, the patient was asked about personal and family events during the last week, and then a check was made on mood and associated cognitive functions. He was then asked to complete the PHQ-9 and send it in via his mobile phone. The patient continues to take mirtazapine 30 mg orally every night.

His wife reported by telephone that her husband continues to be in good spirits, is more physically active, does household activities, is in a better mood, makes jokes, starts conversations spontaneously, sleeps well, has a better appetite, and is making plans for the future. The follow-up continued in this form for the next 12 weeks, with affective stability and persistence of euthymia observed. Eleven months after the ketamine infusion, the patient continues on treatment with mirtazapine 30 mg/night. He says he feels in good spirits, able to enjoy his daily activities and without suicidal thoughts. His wife and children see him in better spirits and with more physically active during the day. The transplant cardiologist describes an overall clinical improvement, including improvement in mood.

Discussion

The admission of a patient with deep vein thrombosis and pulmonary embolism, which subsequently generated cardiac hypokinesis and put the patient's life at risk, was the indirect consequence of symptoms such as sadness, anhedonia, anergy and a sedentary lifestyle in a heart transplant patient with comorbid severe depression.

In transplant patients, major depression doubles the risk of graft rejection and post-transplant mortality,[29,30] in addition to reducing heart rate variability and contributing

to the development of deep vein thrombosis, as occurred in our patient.[31] The symptoms of depression are often confused with those generated by immunosuppressive medications, such as insomnia, anergy, difficulty concentrating and anorexia, but other symptoms such as hopelessness and suicidal ideation are not considered part of the normal trajectory of the post-transplant patient.[32]

Depression is a medical disorder for which there are numerous pharmacological and psychotherapeutic interventions available, but most antidepressant medications take between two and six weeks to begin their therapeutic effect. Therefore, in the context of a patient at risk of suicide and short-term graft loss, ketamine emerges as a valid therapeutic option.

There is increasingly more literature supporting the clinical utility of ketamine in patients with depression and other serious comorbidities. This indication is based on the rapid and powerful antidepressant effect. Typical dosing regimens for ketamine in these cases are sub-anaesthetic doses of 0.5 mg/kg in 40 min of infusion. This case report is novel in two aspects: first, it concerns a heart transplant patient and second, the dose used has not been reported before and shows a robust and positive antidepressant effect.

Irwin et al.[33] reported two cases of hospice patients, seriously ill with other clinical problems, who had rapid and persistent improvement in depression and anxiety after ketamine infusion. The patients had no adverse effects in either case, and the improvement persisted for weeks. In another report, ketamine 0.5 mg/kg was infused in 60 min in a patient with metastatic prostate cancer and produced rapid improvement in depressive symptoms.[34]

To the best of the authors' knowledge, the use of ketamine as an antidepressant has been little explored in transplant patients. We hope that this report will help awaken interest and motivate the setting up of studies, such as clinical trials, with more structured research methodologies, which would enable a better level of evidence to be obtained. As far as we are aware, this is the first reported case of ketamine infusion in a severely depressed heart transplant patient with suicidal ideation.

Conclusions

This case report shows the successful and side effect-free administration of ketamine infusion for the treatment of severe depressive symptoms and suicidal ideation in a heart transplant patient.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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