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Ketamine and Acute Pain Management in Vaso-Occlusive Crisis in Sickle Cell Patients: Case Report and Literature Review

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Abstract **Case Report**

Sickle cell disease is an autosomal recessive genetic disease by mutation of the β globin gene. The painful crisis is the clinical manifestation most frequently encountered in adults with sickle cell disease. It is manifested by the sudden onset of very intense joint or bone pain. Despite a multimodal analgesic strategy, some patients in vaso-occlusive crisis have severe pain, even after gradually increasing opioid doses. Ketamine offers an additional potentially effective therapeutic possibility in this particular clinical context. We report a case of vaso-occlusive crisis in an adult with sickle cell disease, in whom low-dose ketamine infusion resulted in clinically significant pain relief.

Keywords: Ketamine, vaso-occlusive crisis, sickle cell patients.

1. INTRODUCTION

Sickle cell disease is an autosomal recessive genetic disease by mutation of the β globin gene [1]. This mutation induces the synthesis of abnormal hemoglobin (Hb) HbS, mainly responsible for all clinical vaso-occlusive manifestations and chronic hemolysis with anemia of varying degrees [1, 2]. The main manifestation is vaso-occlusive crisis, which corresponds to bone pain linked to bone infarction following the occlusion of blood capillaries by sickled red blood cells [3]. Analgesic treatment must be rapid and includes taking morphine given the intensity of the pain. Despite an optimal analgesic strategy combining opioids and correction of the factors responsible for the sickling of red blood cells, the pain is sometimes rebellious [4, 5]. We report a case of vaso-occlusive crisis in an adult with sickle cell disease, in whom low-dose ketamine infusion resulted in clinically significant pain relief. The interest of this presentation is to demonstrate the interest of the association of a ketamine infusion with opioid analgesia for the relief of painful crises in adults with sickle cell disease.

2. CASE DESCRIPTION

This is a 22-year-old patient, homozygous SS sickle cell patient, weighing 70 kg. He was admitted to intensive care at the Essos hospital center for the management of very intense pain in the right hip, associated with bilateral gonalgia. The history of the disease found an onset that dated back to 5 days before admission to the service, marked by the occurrence of hip pain of moderate intensity motivating self-medication based on the association paracetamol (1g every every 6 hours) and tramadol (100mg every 6 hours) orally. The evolution was made towards the increase of the painful intensity and the addition to the initial clinical picture of a bilateral gonalgia exacerbating the pain intensity. On admission, the patient was afebrile, pain intensity was rated 9/10 on the visual analog scale. Breathing was calm, pleuropulmonary auscultation normal. The abdomen was soft and depressible without a palpable mass, the cardiovascular examination normal. Consciousness was clear, the rest of the somatic examination unremarkable. The additional assessment was non-contributory, apart from moderate anemia at 8.7g/dl for a hematocrit rate of 24%.

Initial management consisted of: rehydration with saline serum, oxygen therapy at 2 l/minute, treatment of anxiety (hydroxyzine 100 mg per day per os), prevention of stress ulcer (omeprazole 40 mg per day IV), prevention of venous thromboembolic disease (enoxaparin sodium 4000 IU per day subcutaneously). The initial analgesic strategy combined: paracetamol 1g every 6 hours IV, nefopam 20 mg every 6 hours IV, ketoprofen 100 mg every 8 hours IV. Morphine was administered at a dose of 8 mg every 6 hours subcutaneously after IV titration which reduced the pain score to 3-4/10. The evolution, in the first 24 hours, was marked by the persistence of the intensity of the pain with a VAS = 7-8/10 despite a well-conducted analgesic treatment according to the medical prescription. The patient then received a transfusion of two units of packed cells to optimize the hemoglobin level to 10g/dl. Continuous infusion of ketamine was added to the analgesic protocol, initially at a dose of 0.1mg/kg/h, then readjusted to 0.2mg/kg/h to obtain a pain score of less than 4/10 on the visual analogue scale. The clinical evolution was satisfactory on the 5th day of treatment with complete pain relief, and discharge was authorized.

3. DISCUSSION

Sickle cell disease has the highest prevalence rates in Africa, where between 150,000 and 300,000 homozygous births are recorded per year [6]. Its clinical aspects are known by African populations long before its clinical description in America [6]. Bone vaso-occlusive crisis is the most frequent extremely painful clinical manifestation [1, 2, 7]. It is the leading cause of emergency hospitalization due to the sudden onset of very intense joint or bone pain [2]. Despite the spectacular progress recorded in knowledge of the disease, the management of vaso-occlusive crisis, which represents the most frequent manifestation of the disease, remains paradoxically insufficient in intensive care units [7]. We report a case of vaso-occlusive crisis in a homozygous SS patient who presented with very intense pain not relieved by a multimodal analgesia protocol, combining the optimal doses of the drugs involved. Despite the correction of other risk factors for sickling of red blood cells and the addition of morphine to the initial therapeutic strategy, the pain remained severe. During the vaso-occlusive crisis, the pains are multiple, they most often affect the long bones, the spine, the pelvis, the thorax and the abdomen [8,9,10]. Painful crises can be frequent and this repetition induces a decrease in the threshold of pain sensitivity with risks of neuronal plasticity which can evolve towards a chronicization of the pain [11, 12]. Regular pain assessment is the basis for effective management of pain caused by vaso-occlusive crises.

The management of pain related to vaso-occlusive crises can be difficult due to other associated factors such as the state of hyperalgesia linked to the repetition of pain since childhood and the anxious context induced by this pain [4, 13]. Hyperalgesia reflects sensitization of the nervous system, it combines phenomena of allodynia and hyperalgesia. According to the International Association for the Study and Treatment of Pain (IASP), hyperalgesia is defined as a more intense pain response to a nociceptive stimulus and allodynia as a painful sensation triggered by a normally non-nociceptive stimulus [14]. There are two types of hyperalgesia, primary and secondary. Primary hyperalgesia results from peripheral sensitization phenomena, and secondary hyperalgesia reflects central hyperexcitability. In the case of our patient, the indirect signs of hyperalgesia associated increased pain, overconsumption of analgesics and prolonged pain. The addition to the initial therapeutic protocol of a low dose of ketamine in continuous infusion, made it possible to obtain effective pain relief. The analgesic effect of ketamine results primarily from antagonism of N-methyl-D-aspartate (NMDA) receptors in the brain and spinal cord, which are involved in opiate tolerance, chronic pain, and central sensitization [15]. Low dose ketamine (≤ 0.5 mg/kg) is a non-competitive NMDA receptor antagonist [15, 16].

Alshahrani *et al.*, [17] have reviewed the evidence from published reports on the efficacy and safety of ketamine in the management of vaso-occlusive pain crises in patients with sickle cell disease. Fourteen studies were included in the analysis. Ketamine has been shown to significantly reduce pain scales and opioid use in both populations [17]. The only randomized controlled trial available showed that ketamine was non-inferior to morphine in reducing pain scores, but had a higher incidence of non-fatal reversible adverse effects [17].

4. CONCLUSION

Vaso-occlusive crisis is an acute complication of sickle cell disease that may justify intensive care management. Despite a multimodal analgesic approach, some patients in vaso-occlusive crisis keep intense pain, even after the progressive increase in morphine doses. Low-dose ketamine infusion would represent an effective alternative, as an adjuvant to morphine and non-morphine analgesics in the management of vaso-occlusive crisis. The minimum effective dose, to avoid side effects, remains to be defined through multicenter studies.

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