

Therapeutic Values of Ketamine for COVID-19-Cared Patients: An Expert's Point of View

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Ketamine has long been used in the field of anesthesia [1]. Its rapid and long-acting analgesic effects associated with its dissociative properties have also established its use in pre-hospital and emergency department patients [2]. Both the D- and the S-ketamine enantiomers are included in the list of narcotic drugs, and therefore ketamine is legally administered under surveillance. The drug has been widely accepted for its effectiveness, and has been deemed to be advantageous even during the COVID-19 pandemic [3,4]. Ketamine has also been shown to possess antidepressant properties and to be effective for even major depressive disorders. This brief opinion review describes the beneficial use of ketamine for pandemic-associated depressive states during hospitalization and its modes of administration.

COVID-19-infected patients suffer from overwhelming hyper-inflammatory syndrome induced by the SARS-CoV-2 virus. This proinflammatory burst contributes to generalized disease at various severities enough to lead to mortality [5]. Specifically, COVID-19 patients will suffer from an increased respiratory rate (>30 breaths/min), blood oxygen saturation $\leq 93\%$ at rest, or arterial oxygen tension ratio to fractionated inspired oxygen tension (P_aO_2/F_iO_2) ≤ 300 mmHg. The most severe patients will then require mechanical ventilation or even ECMO installation. They frequently succumb from shock (heart failure, diffused coagulopathy) or from combined organ failure [6,7]. In addition to these severe pathologies, patients also sustain mental stress and depression. While the physical manifestations require the provision of advanced, intensive care, little is discussed about the manner of handling patients' depression and fear of death when they become severely weakened or when facing the need for invasive respiratory aid or ECMO installation. Even when surviving such experiences, but still under care in ICU, depression and anxiety will reign

their state of mind.

Objective-oriented or pathology-targeted psychological or psychiatric aids have been scarcely tested among patients in the ICU corona suites, not even in reports on those with pre-existing mental illnesses (in particular, psychosis or mood disorders) [8]. Most of the known sedatives, as well as hypnotics or opioids are respiratory and cardiovascular depressants; their actions would deteriorate a patient's fragile condition. Their use does not enable the ensuring of physical and mental conditions, nor does it facilitate the patient's acceptance of a grave condition. Common antidepressants may provide help in bringing about a state of calm, but data on their therapeutic dose-related effects among stressful COVID-19 patients are still lacking. Furthermore, if antidepressants are given either at unestablished or unverified dosages (due to SAR-2 effects on gastric or parenteral absorptions), most pharmaceuticals may interfere with respiratory and cardiovascular functions or even exacerbate mental function, and therefore their administration may result counterproductive [9]. In contrast, the role of ketamine in similar conditions is better known [10].

Ketamine, given mainly IV or parenterally, is a unique and safe drug that enables well-controlled, dose-dependent and timely calculated sedation, analgesia and anesthesia [11]. It is now acknowledged that the drug also attenuates gloominess and mitigates suicidal thoughts [12]. All of these responses are free of negative interference with respiratory or cardiovascular processes. Furthermore, ketamine induces positive effects on the respiratory and the cardiovascular systems. Among the properties worth mentioning are bronchodilation, stable respiration rate and oxygenation, and maintenance of upper airway reflexes, as well as preservation (and even raising) of blood pressure and counteraction of bradycardia. Ketamine increases blood pressure and heart rate by releasing endogenous catecholamines, while blood saturation is

maintained stable [13,14]. Nevertheless, if used at an excessive dose, ketamine can result in thin bronchial secretions and negligible hallucinations. Ketamine is also free of negative effects as those induced by narcotics on the gastrointestinal tract motility, thus reducing the need for aggressive bowel regimens. Importantly, a somewhat less well-known action of ketamine is its anti-inflammatory effect [15,16]. Inflammatory markers, in particular IL-6 and CRP, are significantly reduced after the administration of ketamine in general and cardiac surgical patients in particular [16,17].

Various reuptake inhibitors are used to treat depressive states [18,19]. However, their therapeutic effects manifest only after several weeks of administration. Thus, their use would hardly be suitable in cases of hospitalized COVID-19-infected patients. Given that the glutamatergic system is involved in pain and anesthesia as well as in the depression-antidepressant course, the adjunctive use of ketamine, which acts at various neural networks [20], exerts potent and rapid pharmacological effects and ameliorates these patients' depressive mood states [21-23]. Ketamine exerts its properties mainly through NMDA receptors, although it also acts on other receptor sites as well [11]. It decreases synaptic ascending and descending neuroactivities, and modulates synaptic neurotransmissions via either brain-derived neurotrophic factors or the prefrontal cortex [20]. Sustained efficacy of ketamine was evidenced in patients suffering from lasting depression and in those who were treatment-resistant [24,25]. Adverse events that had led to reluctance to use it in the past, such as abuse potential or psychomimetic events, seem not to have had elicited comparable concern with regard to patients who need a reliable, quick-acting and dose-adjustable drug with short-lasting effects after its withdrawal [1,4,26].

The role of ketamine in the treatment of mechanically ventilated patients in the OR or ICU has recently been suggested by Ortoleva [27]. Comparably, its recently documented anti-depressive effects has led to its use in the field of psychiatry and to its now proposed use in ICU-COVID-19 patients [3,28]. Pharmacologically, the combination of parenteral and enteral use of ketamine would enhance and prolong the pharmacologic outcomes in the latter patients [29]. For example, its therapeutic effects were proven devoid of adverse effects on either pain, anxiety or depression when given at 40 mg/d orally to treat the latter condition [30]. A significant proof of concept of usability and efficacy was reported by Irwin and colleagues when administering oral ketamine at a daily dose of 0.5 mg/kg for 28 days; no adverse events were recorded among the depressed patients [31]. A combination of both routes of administrations, i.e., parenteral and enteral ones, could bring about a quick start followed by a stable and durable pharmacologic anti-depressive and analgesic results in these patients [29]. As for dosing, the current subanesthetic IV bolus doses of ketamine range between 0.15-0.5 mg/kg. Ketamine infusion, ranging

between 0.15-0.3 mg/kg/h, would properly relieve acute pain, depression and discomfort after an initial bolus dose [1,11]. Smooth awakening is regained upon slow dialing down the drug's infusion rate [11]. The adjustable and predictable duration of action, and the lack of significant side effects were proven in general intensive care patients as well [13,32-35]. Although not yet introduced as part of the COVID-19 treatment protocol, ketamine would be safe and effective when administered by oral, sublingual, transmucosal, intranasal, intravenous, intramuscular, intraosseous and subcutaneous routes [11,36]. Importantly, bioavailability is best when ketamine is administered IV, IM, or intranasally; oral, subcutaneous, or rectal applications would be of less predicted pharmacokinetics in ICU-COVID-19 patients. It was suggested that (as for analgesia) the starting parenteral effective dose of ketamine would be as low a dose as 40-60 mg over 24 hours (not necessarily coadjuvated with a benzodiazepine), followed by an initial conversion dose of oral ketamine of 30-40% of the effective parenteral dose [29]. An in-depth discussion of the pharmacology and clinical portrayal of ketamine, including suggested doses, can be found in the report by Zanos et al. [37].

Summary

The values of ketamine's use for various situations in COVID-19 hospitalized patients can be summarized as follows:

- it is a well-studied and safe drug that is relatively inexpensive
- it devises anti-proinflammatory capabilities
- it provides antidepressant effects and potentiates control of suicidal ideation
- it provides smooth start and optimal sedation, amnesia and, when necessary, a safe and deep state of anesthesia
- it enables slow and controlled downgrading mode of administration, especially when combining enteral and parenteral applications
- it allows for easy parenteral dose (mainly IV) adjustments as well as conversion into oral administration. Note: excessive doses may induce adverse effects
- it has optimal bioavailability when administered parenterally or intranasally. Oral, subcutaneous or intraosseal deliveries may, in rare cases, prove practical in COVID-19 in depressed patients
- it affords stabilization of hemodynamic conditions
- it preserves the automaticity and mechanics of the respiratory system and blood saturation
- it is free of uncontrolled hyperalgesia-induced agitation

that frequently characterizes awakening from specific sedatives and anesthetic drugs [38]

- its treatment sessions can be repeated as needed (at adjustable doses) to re-elicite its pharmacological response even if refractoriness seems to have taken place.

The criteria of patients who may benefit from ketamine administered parenterally or parenterally then converted enterally:

- patients verbally expressing sadness or depression
- patients verbally expressing anxiety or restlessness
- patients diagnosed with mixed anxiety and depression
- patients visibly restless, not complying with staff orders or requiring restraint
- patients emotionally or mentally hard to calm.

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