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Ketamine Use for Sedation in Critically Ill Patients with Coronavirus Disease 2019 (COVID-19) Infection: A Case Series

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Abstract

Introduction: Ketamine has been previously used as an add-on analgesic and a sedative agents for the treatment of critically ill surgical patients, resulting in a reduced opioid consumption. During the Coronavirus Disease 2019 (COVID-19) pandemic, a surge of critically ill patients with Acute Respiratory Distress Syndrome (ARDS) requiring mechanical ventilation with deep sedation and paralysis lead to the overuse of first line sedative medications like benzodiazepines and Propofol, exposing them to serious shortages, especially in view of worsening national economic crisis. This dilemma pushed the critical care teams to explore new medications for sedation, resulting in shifting away from the first line therapies to the use of other sedatives, like Ketamine. We describe our experience using Ketamineto maintain an adequate sedation when Midazolam was not available and Propofol contraindicated.

Methods: Ketamine was used on four critically ill patients with severe COVID-19 ARDS requiring paralysis. We focused on vital signs variation and quality of sedation during Ketamine use in comparison to Midazolam/Propofol. During the transition period from Midazolam/Propofol to Ketamine, our patients had an acute increase in blood pressure, respiratory rate and heart rate, a drop in their oxygen saturation with ventilator dyssynchrony. Other deteriorations witnessed included new respiratory acidosis and cardiac arrhythmia.

Discussion: In comparison to previous successful uses of Ketamine in the Intensive Care Unit ICU, its limited efficacy in our population could be explained by the requirement for neuro-muscular blockade, the high ventilatory drive and the fact that it was used alone.

Conclusion: Our experience with Ketamine during drug shortage of first-line sedatives in critically ill patients with COVID-19 ARDS was shown to be insufficient when used alone as an alternative sedative agent compared to Propofol and Midazolam. Further studies with larger sample size are advised before drawing a final conclusion.

Keywords: Ketamine; Critical care; First-line sedative; Synchrony

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Introduction

During the Coronavirus Disease 2019 (COVID-19) pandemic, severely ill patients with severe lung injury and respiratory difficulties were admitted to the Intensive Care Unit ICU and put on ventilators (breathing machine) to be able to breathe. Mega doses of sedatives (medications that calm and tranquilize patients) used to help patients tolerate the ventilator were massively used worldwide exposing them to severe shortage. Nationally, that came on top of an economic crisis causing a total depletion of the first line classical sedatives that we usually use in the ICU (Midazolam and Propofol). We were left with Ketamine, a sedative known to be successfully used in the ICU, however, at low doses and always combined with other pain medications and sedatives; but never alone. Sequentially, we had to use very high doses in order to achieve the same level of comfort for patients. We started Ketamine on four patients and, as we were going up with the dose, we noticed that patients were becoming more agitated, experienced significant elevation in blood pressure, heart rate and respiratory rate. They were also not able to breathe properly through the ventilator and the amount of oxygen was dropping in their blood and lungs. Because of this instability, we had to immediately stop Ketamine. Luckily, we received a stock of Midazolam and were able to resume proper sedation and stability for patients. We assume that, failing with Ketamine, is due to the severity of illness of our patients, who required very high doses of sedatives that Ketamine couldn't achieve without complications; and very high ventilator settings. We concluded that Ketamine, used alone, can not to assure the comfort of severely ill COVID-19 patients on ventilators. Nevertheless, our sample size is small and before reaching a final conclusion, further studies on a larger sample size are needed.

Ketamine has previously been used as an analgesic and a sedative agent for the treatment of critically ill surgical patients, resulting in reduced opioid consumption [1]. The addition of Ketamine to Propofol for procedural sedation in the emergency department has also been described as effective, safe, and satisfying for the providers [2]. During the Coronavirus Disease 2019 (COVID-19) pandemic, a surge of critically ill patients with Acute Respiratory Distress Syndrome (ARDS) requiring mechanical ventilation with deep sedation and paralysis, and where it was impossible to apply the standard light sedation guidelines [3], lead to the overuse of first line sedative medications like benzodiazepines and Propofol, worldwide [4-6] and in Lebanon, resulting in serious shortages [7], especially in view of the economic crisis that hit the country [8]. This dilemma pushed the critical care team to explore new medications for sedation, resulting in a shift away from these first line therapies to the use of other sedatives, like Ketamine. It has already been established that Ketamine can be used as adjunct to high doses of benzodiazepines or Propofol in COVID-19 patients [9,10].

However, due to severe shortages, and for a short period of time, Ketamine was used at the American University of Beirut Medical Center as the main sedative agent (with or without very low doses of benzodiazepines). We aim to describe our experience in the use of Ketamine to maintain adequate sedation either alone or in combination with very low doses of Midazolam (during periods of shortage), when Propofol was contraindicated due to adverse reactions and at a time of severe shortage of Midazolam.

We conducted a retrospective case series on four critically ill patients with severe COVID-19 ARDS, to describe our experience with Ketamine use as the main or sole sedative in terms of baseline characteristics like vital signs variation, oxygen saturation, Richmond Agitation Sedation Scale (RASS) variation and synchrony with ventilator during Ketamine use.

Cases

A total of four patients who were admitted to our Intensive Care Unit (ICU) were prescribed Ketamine. The median age was 66 years (54-66.5) and the sex distribution was 3 males and 1 female. They were all intubated due to ARDS secondary to COVID-19 infection. Three out of the 4 had previously been paralyzed with Rocuronium which had to be withheld once the switch to Ketamine was decided awaiting the achievement of deep sedation. In terms of paincontrol, they were all on very high rates of Fentanyl (reaching 300 microgram/hour). In all 4 patients, Propofol (reaching 30 microgram/kg/min), was used for sedation but due to elevated triglyceride levels, it had to be stopped. This imposed switching to the only available sedative at that time: Ketamine. Meanwhile, Fentanyl was kept at the same rate. Ketamine rate ranged from 0.2 mg/kg/hour to 4.5mg/kg/hour. Patients were started at the rate of 0.2 mg/kg/hour and up titration was quick, to achieve same RASS and ventilator synchrony. With the rapid up-titration of Ketamine, there was a statistically significant increase in the blood pressure, heart rate and respiratory rate of the patients when the shift from Propofol to Ketamine was done (Table 1) (Figures 1 & 2).

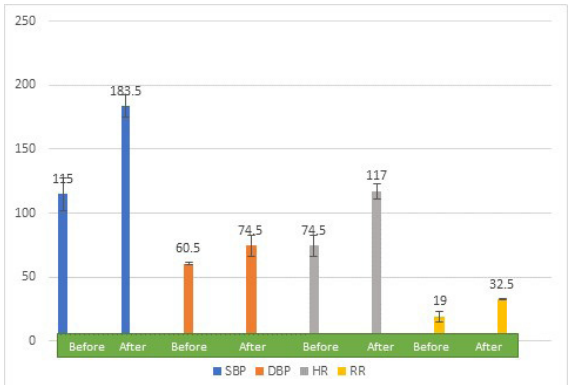

Figure 1: Variations and standard deviations in vital signs before and after the start of Ketamine.
Abbreviations: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; RR: Respiratory Rate.

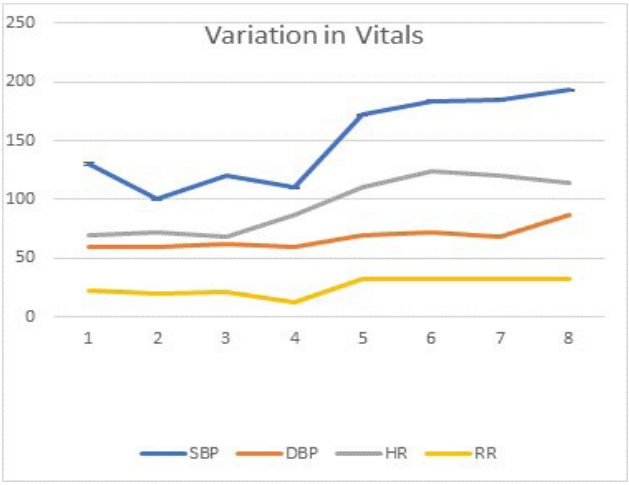

Figure 2: Variations of vital signs before (times 1 2 3 and 4) and after (times 5 6 7 and 8) the start of Ketamine.
Abbreviations: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; RR: Respiratory Rate.

Table 1: Vital signs variation in terms of blood pressure, heart rate and respiratory rate before and after Ketamine use for sedation (Numbers shown are median, lower range and higher range respectively).

Median SBP before Ketamine (on Propofol)	Median SBP after Ketamine	Median DBP before Ketamine (on Propofol)	Median DBP after Ketamine	Median HR before Ketamine (on Propofol)	Median HR after Ketamine	Median RR before Ketamine (on Propofol)	Median RR after Ketamine
115 (105-125)	184.5 (178-189)	60.5 (60-61)	86.5 (84-93)	71 (69.5-79.5)	117 (112-122)	20.5 (16.5-21.5)	32.5 (32-33)

Abbreviations: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; RR: Respiratory Rate.

These sudden changes in vitals were accompanied by dyssynchrony with the ventilator and drop in oxygen saturation to an extent that one of the patients needed the addition of inhaled nitric oxide as salvage therapy after adequately increasing both the positive end-expiratory pressure and the administered fraction of inspired oxygen through the ventilator. One patient developed an episode of Premature Atrial Contraction (PAC) and non-sustained Ventricular Tachycardia (VT) for which he was prescribed Amiodarone and Bisoprol and responded. Other deteriorations witnessed included a new respiratory acidosis. Finally, for all patients, Ketamine failed to achieve the targeted RASS.

As evident by the RASS and other vital signs changes, all trials to achieve adequate sedation with Ketamine and Fentanyl failed. Other variables goals were not met either and the use of Ketamineas an alternative to other sedatives or to significantly minimize their use did not work. Luckily, we were able to secure and to reintroduce Midazolam few days later.

Discussion

Our findings show that the use of Ketamine as the main sedative agent in critically ill patients with COVID-19 ARDS, instead of first line sedatives like Midazolam and Propofol, is insufficient to maintain a similar level of deep sedation.

In order to achieve the goal RASS in our patient population, and to minimize patient ventilator desynchrony, Ketamine titration reached very high doses of 4.5 mg/kg/hour which is higher than was previously reported in the literature (up to 2.5 mg/kg/min for the treatment of ARDS patients) [11]. This may have contributed to the increase in blood pressure and cardiac arrythmias as side effects.

In comparison with previous satisfying uses of Ketamine in the critically ill patient following abdominal surgery, successfully reducing opioid requirements [1] as an adjunct for sedation in mechanically ventilated adults [10] and for procedural sedation in the emergency department in addition to Propofol [2], the limited efficacy of this medicationen countered in our population could be explained by several factors. First are the requirement for neuro-muscular blockade for the management of severe ARDS patients, frequently encountered in critically ill patients with acute respiratory failure due to COVID-19 infection, and its accompanying need for a deeper sedation compared to mild ARDS cases. Another factoris the presence of increased ventilatory drive, possibly leading to additional patient-ventilator dyssynchrony and necessitating deeper sedation [12]. Lastly, when used in mechanically ventilated adults and with previous studies showing favorable results with an ability to decrease the requirements for other sedatives while achieving a desirable sedation scale, Ketamine was mainly used as an adjunct medication to Propofol and/or Midazolam, rather than alone [9,11].

Conclusion

Our experience with Ketamine use during drug shortage of first-line sedatives in the management of critically ill patients with COVID-19 ARDS was shown to be insufficient when used alone as an alternative sedative agent compared to Propofol and Midazolam. This is also important when targeting an acceptable safety profile with a reasonable dosage range, in an extremely sick population with a high mortality rate, risk of complications, and fears of multiple drug interaction; target that Ketamine failed to achieve. Finally, and before any specific recommendation can be concluded, larger randomized-control studies involving the use of Ketamine at specific doses, as an alternative or adjunct agent for the sedation of critically ill patients with COVID-19 ARDS are needed.

Conflict of Interest

There are no conflicts of interest.

Ethical Consideration

Informed consent was waived by our Institutional Review Board because all our subjects were considered non-human (deceased).

Availability of Data and Materials

All data are available on the Electronic Health Record at AUBMC

Competing Interests

The authors declare that they have no competing interests

Authors' Contributions

D.G. conceived the presented idea and participated in writing the manuscript, S.K. participated in writing the manuscript, I.B. reviewed and supervised the manuscript. All authors read and approved the final manuscript.

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