

Experiential Learning with Ketamine: A Mixed-Methods Exploratory Study on Prescription and Perception

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Background: Incorporating unfamiliar therapies into practice requires effective longitudinal learning and the optimal way to achieve this is debated. Though not a novel therapy, ketamine in critical care has a paucity of data and variable acceptance, with limited research describing intensivist perceptions and utilization. The Coronavirus-19 pandemic presented a particular crisis where providers rapidly adapted analgesation strategies to achieve prolonged, deep sedation due to a surge of severe acute respiratory distress syndrome (ARDS).

Question: How does clinical experience with ketamine impact the perception and attitude of clinicians toward this therapy?

Methods: We conducted a mixed-methods study using quantitative ketamine prescription data and qualitative focus group data. We analyzed prescription patterns of ketamine in a tertiary academic ICU during two different time points: pre-COVID-19 (March 1–June 30, 2019) and during the COVID-19 surge (March 1–June 30, 2020). Two focus groups (FG) of critical care attendings were held, and data were analyzed using the Framework Method for content analysis.

Results: Four-hundred forty-six medical ICU patients were mechanically ventilated (195 pre-COVID-19 and 251 during COVID-19). The COVID-19 population was more likely to receive ketamine (81[32.3%] vs 4 [2.1%], $p < 0.001$). Thirteen respondents participated across two FG sessions (Pre-COVID = 8, Post-COVID=5). The most prevalent attitude among our respondents was discomfort, with three key themes identified as follows: 1) lack of evidence regarding ketamine, 2) lack of personal experience, and 3) desire for more education and protocols.

Conclusion: Despite a substantial increase in ketamine prescription during COVID-19, intensivists continued to feel discomfort with utilization. Factors contributing to this discomfort include a lack of evidence, a lack of experience, and a desire for more education and protocols. Increase in experience with ketamine alone was not sufficient to minimize provider discomfort. These findings should inform future curricula and call for process improvement to optimize continuing education.

Keywords: analgesation, continuing education, learning theory, ketamine, critical care

Introduction

Ketamine is a potent sedative and anesthetic agent with a favorable hemodynamic profile.¹ Though not a novel therapy, the evidence base guiding ketamine use for analgesation in the critically ill is sparse. While data is limited, studies have demonstrated that ketamine is compatible and safe to use,^{2,3} and systematic reviews have demonstrated that ketamine may reduce analgesic consumption in the ICU.^{4–6} Yet, the Society of Critical Care Medicine guidelines provide little to no mention of ketamine,⁷ and substantial practice variability in the prescription of ketamine in the ICU exists.⁸

In order to incorporate evolving and unfamiliar therapies into practice, effective longitudinal learning is critical. The optimal way to achieve this is debated by varying education theories. Halsted's See One, Do One, Teach One methodology, frequently used in medical education, argues that increased experience alone should be sufficient to achieve competency.^{9,10} More recently, however, Kolb's Experiential learning theory suggests additional components such as abstract conceptualization and reflective observation are needed.⁹⁻¹¹ How providers adapt to novel therapies and respond during a crisis is vital to patient care.

The Coronavirus-19 (COVID-19) pandemic presented a particular crisis where providers had to rapidly adapt to a surge in volume of severe acute respiratory distress syndrome (ARDS) patients who required prolonged, deep sedation.¹²⁻¹⁴ Amidst medication shortages and strains on healthcare capacity, many adjunctive and alternative medications were added to analgesedation algorithms, including ketamine.¹⁵⁻¹⁷

Given the distinct rise in patient volume, we aimed to understand whether experience with ketamine specifically would translate into providers' perceptions of comfort and competence. To this end, we conducted a mixed-methods before-and-after study to quantify potential changes in ketamine prescription and qualify attending physicians' perception through focus groups.

Methods

Study Design

We conducted a mixed-methods study using quantitative ketamine prescription data and qualitative data from focus groups (FG) of attending physicians to explore the relationship between ketamine utilization and physician attitudes and perceptions toward the drug. The initial design was primarily qualitative through FGs to identify the experience (both comfort and use) with ketamine. After preliminary FGs were conducted, the COVID-19 pandemic surged with a rapid rise in ventilated patients requiring deep sedation. The author group hypothesized that this would be a unique opportunity to compare ketamine use before and after the pandemic in the MICU population given their real world lived experiences and the identified discomfort of pulmonary critical care providers. Through this observation, the aim was quickly modified to investigate how an increase in experience with ketamine might affect intensivist perceptions, practice, or analgesedation strategy.

Study Setting

The study was conducted at a single tertiary center in Boston, MA.

Quantitative Data Collection

We performed a retrospective analysis of our institution's administrative and practice patterns of ketamine prescription in the ICU during two different time points: pre-COVID-19 (March 1, 2019, through June 30, 2019) and during COVID-19 surge (March 1, 2020, through June 30, 2020). Patients were included in the study if they were admitted to a MICU and received mechanical ventilation. Extracted data included patient demographics (age, gender), ketamine use, as well as use of other common analgesia and sedative agents (e.g., propofol, midazolam, fentanyl, and dexmedetomidine) and outcomes including length-of-stay and discharge disposition. Data were manually validated and audited by authors AI and JS.

Quantitative Data Analysis

We compared patient characteristics pre-COVID-19 to the COVID-19 population using means and standard deviations for normally distributed data and medians and interquartile ranges (IQRs) for non-normally distributed data. Pairwise comparisons of continuous variables were made using *t*-tests for normally distributed data and rank sum tests for non-normally distributed data. Binary variables, including use vs non-use of each sedative medication, were compared using Fisher's exact tests. Trends over time in sedation use were displayed graphically for ease of comparison. All statistical analyses were conducted using STATA 15 (StataCorp, College Station, Texas).

Qualitative Data Collection

We conducted FGs in order to gain a deeper understanding of physician attitudes towards ketamine, specifically their experiences, comfort, and barriers to use. All pulmonary critical care faculty physicians on staff were recruited via email, and trainees were excluded. No incentives for participation were provided, and participation was entirely voluntary. Authors MMH and AM were trained in FG facilitation and led the FGs. The facilitation guide was created iteratively by authors AI, MMH, and AM based on review of the literature and authors' experiences with ketamine. Author AI was present at each FG as note-taker to ensure consistency and that all verbal and non-verbal information was considered during analysis. All FGs were audio recorded, transcribed, and de-identified.

Qualitative Data Analysis

FG data were analyzed using the Framework Method for content analysis, which allows for both deductive and inductive analysis. This method was chosen as authors had a general sense of physician attitudes towards ketamine but hoped to use an inductive approach to understand the underpinnings of these attitudes. Authors (AI, MMH, JS, and AM) independently read the transcripts, generated potential codes, and met frequently to compare codes and discuss potential themes. Author CB, a non-clinician researcher trained in qualitative methods, individually coded the transcripts before reviewing the thematic codes already established by the other authors, and then compared their coding with the established thematic codes to identify codes that were already created or newly generated. To ensure confirmability, author CB reviewed transcripts and codes to ensure all data were interpreted objectively and to verify that all information was considered.¹⁸ To ensure reflexivity, all authors kept analytic memos and met frequently to discuss the codes together and determine whether they should be added to the codebook.¹⁹ Through this discussion, all authors were able to share their perspectives, experiences, and assumptions. Similar and redundant codes were grouped into higher level codes and defined through team discussion to create a codebook. Having author CB read the transcripts before reviewing the thematic codes generated by the other authors helped to minimize bias as they were reviewing the transcripts individually. This coding structure was then applied to all transcripts by author CB using Dedoose (Version 8.3.45), a web-based application for analyzing qualitative data. These codes were used to inform the main themes and to identify patterns and associations across the FGs.

Study Approval

The Beth Israel Deaconess Medical Center Institutional Review Board (IRB) reviewed the study and provided an exempt designation (Study IRB 2019P000834) with protocols in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained verbally before participation, and consent was audio-recorded in the presence of an independent witness.

Results

Quantitative Results

A total of 4665 patients were included (see [Figure 1](#)). In the pre-COVID-19 population, there were 2173 patients of which 195 required mechanical ventilation, and in the COVID-19 population, there were 2492 patients of which 251 required mechanical ventilation. The mean age was 63 years with 59% female. Characteristics and outcomes of patients are described in [Table 1](#). As compared to the pre-COVID-19 period, patients in the COVID-19 population were more likely to receive ketamine (4 [2.1%] vs 81 [32.3%], $p < 0.001$), midazolam (48 [24.6%] vs 120 [47.8%], $p < 0.001$), and fentanyl (159 [81.5%] vs 225 [89.6%], $p = 0.014$). There was no difference in the use of propofol (88.7% vs 92.0%, $p = 0.15$).

Use of each sedative as well as fentanyl is represented graphically in [Figure 2](#). When used, ketamine was commonly selected as a second or third-line sedative agent (see [Figure 3](#)). In the COVID-19 population, there was a greater median duration of intubation of 199 hours (IQR: 92, 199) compared to 99 hours (IQR: 47, 240) in the pre-COVID population ($p < 0.001$). The ICU and hospital length of stay were longer in the COVID-19 population 8.3 days (IQR: 4.0, 16.8) and 14.1 days (IQR: 7.2, 24.8) compared to 4.8 days (IQR: 2.4, 10.9) and 10.7 days (IQR: 5.0, 19.3) in the pre-COVID population ($p < 0.01$). There was no difference in hospital mortality in the Pre-COVID-19 vs COVID-19 population (30% vs 38%, $p = 0.05$).

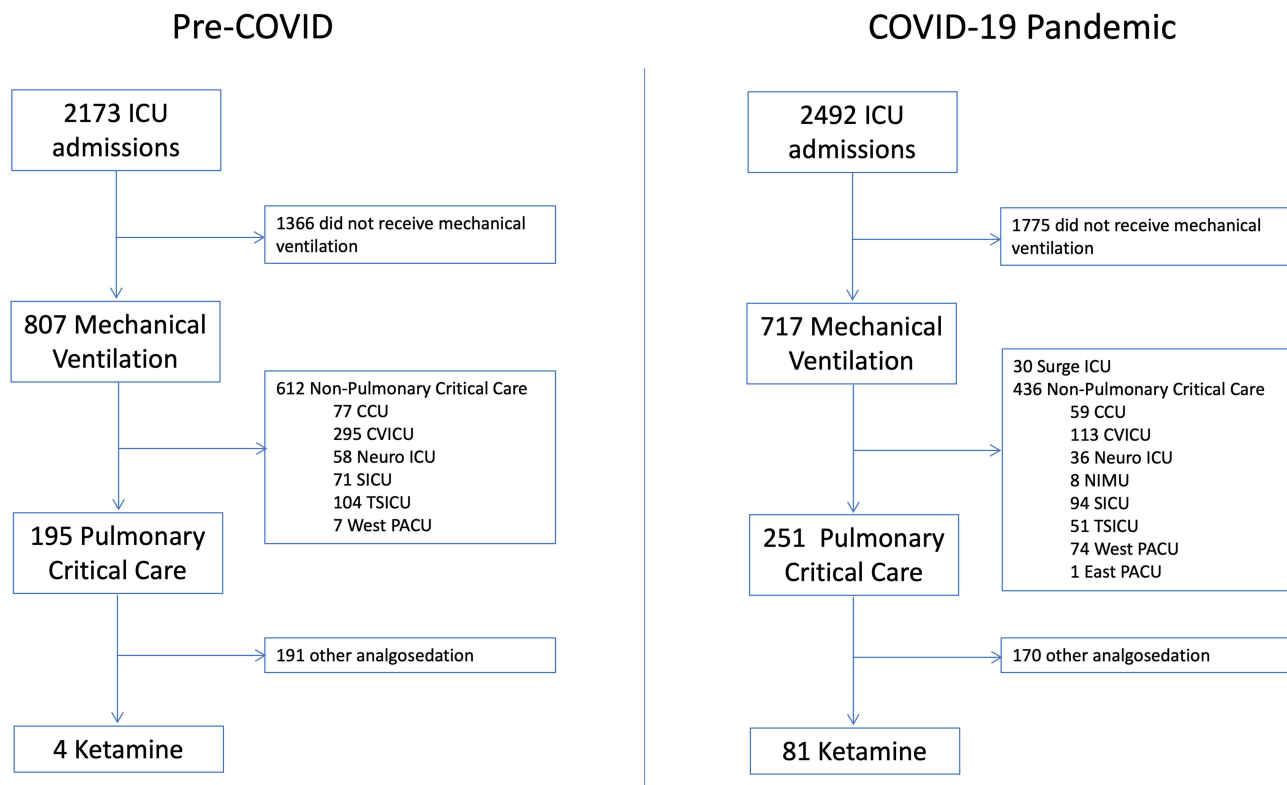


Figure 1 Consort Diagram.

Qualitative Results

A total of 13 respondents participated across two FG sessions (Pre-COVID-19 = 8, During COVID-19 = 5). Participants were all attending physicians who had a range between 7 and 24 years experience (pre-COVID-19 = 7–24 years, During COVID-19 = 10–24 years) creating similar overall FG composition. One FG was conducted in-person in February 2020, while the other session was virtual via Zoom in September 2020 due to the pandemic. Having FGs conducted prior to and after the initial pandemic surge allowed us to assess whether and in what ways there were changes in the attitudes towards ketamine.

Table 1 Patient Demographics, Sedative and Analgesic Medications Received, and Outcomes

Variable	Total (n=446)	Pre-COVID (n=195)	COVID (n=251)	p-value
Demographics				
Age (years, mean, SD)	63.4 (16.7)	63.4 (17.3)	63.3 (16.3)	0.97
Sex (n, %female)	252 (58.7)	80 (41.0)	104 (41.4)	0.5
Sedating medications				
Ketamine (n, % received)	85 (19.1)	4 (2.1)	81 (32.3)	<0.001
Propofol (n, % received)	404 (90.6)	173 (88.7)	231 (92.0)	0.15
Midazolam (n, % received)	168 (37.3)	48 (24.6)	120 (47.8)	<0.001
Analgesic medications				
Fentanyl (n, % received)	384 (86.1)	159 (81.5)	225 (89.6)	0.014

(Continued)

Table 1 (Continued).

Variable	Total (n=446)	Pre-COVID (n=195)	COVID (n=251)	p-value
Outcomes				
Duration of intubation (hours, median, IQR)	153.0 (62.9, 332.0)	99.3 (47.2, 239.9)	198.8 (92.3, 398.5)	<0.001
ICU Length of Stay (days, median, IQR)	6.8 (3.0, 14.0)	4.8 (2.4, 10.9)	8.3 (4.0, 16.8)	<0.01
Hospital Length of Stay (days, median, IQR)	12.2 (6.1, 21.7)	10.7 (5.0, 19.3)	14.1 (7.2, 24.8)	<0.01
Hospital mortality (n, % died)	155 (34.8)	59 (30.3)	96 (38.3)	0.05

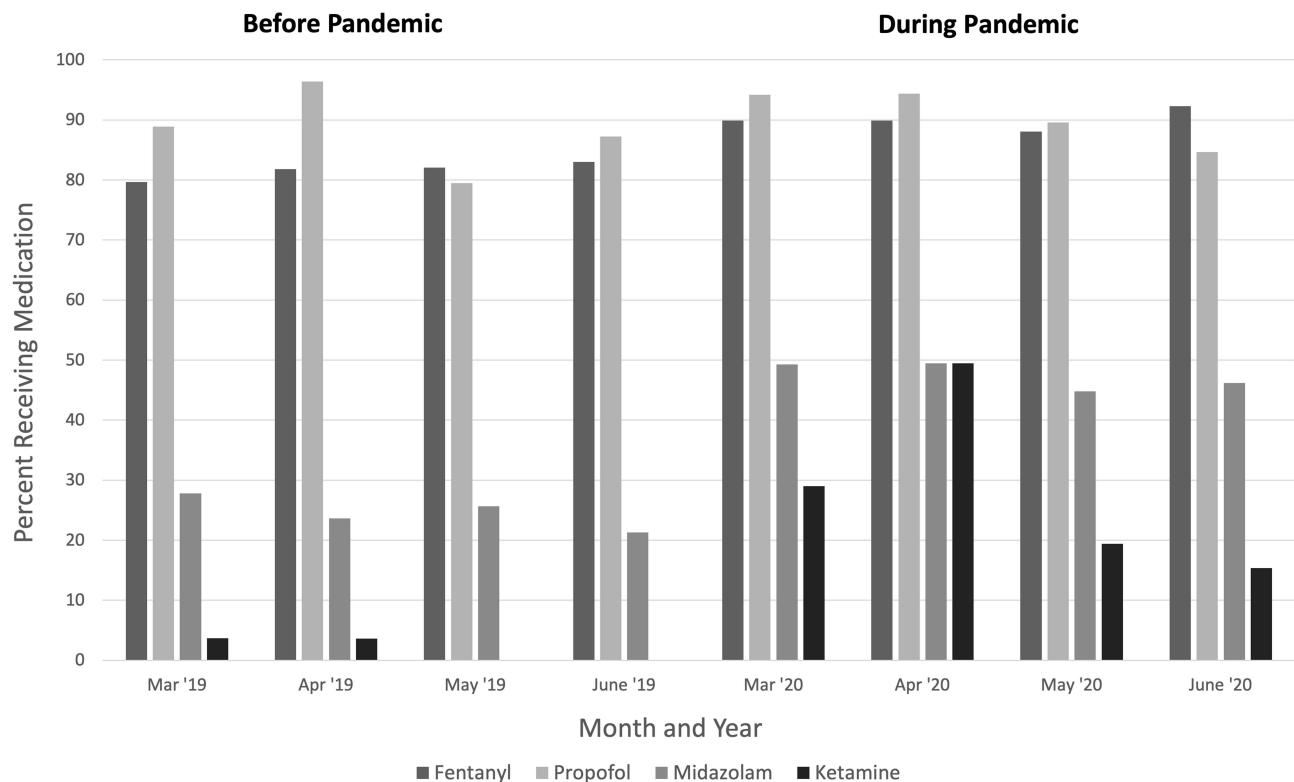
Qualitative Main Results

Overall, the most prevalent attitude among our respondents was a sense of discomfort with ketamine. Even when some respondents in the COVID-19 population group expressed gaining more experience with ketamine, nearly all participants still expressed overall discomfort and uncertainty around its effectiveness. When asked if anyone felt comfortable with ketamine, all respondents indicated they were not comfortable.

We identified 3 key themes related to this discomfort: 1) lack of evidence regarding ketamine use in the ICU, 2) lack of personal experience and familiarity, and 3) desire for more ketamine education and protocols. Table 2 outlines these themes, along with representative respondent quotes. Each quote identifies which FG the respondent participated in (Pre-COVID or COVID-19 population) and their participant number (e.g., P4).

Lack of Evidence

Many participants attributed their discomfort to the general lack of evidence for ketamine in the ICU, which contributed to their infrequent use and lack of comfort and knowledge. As one respondent described,

**Figure 2** Sedation Use by Month.

Sequential Introduction of Sedation

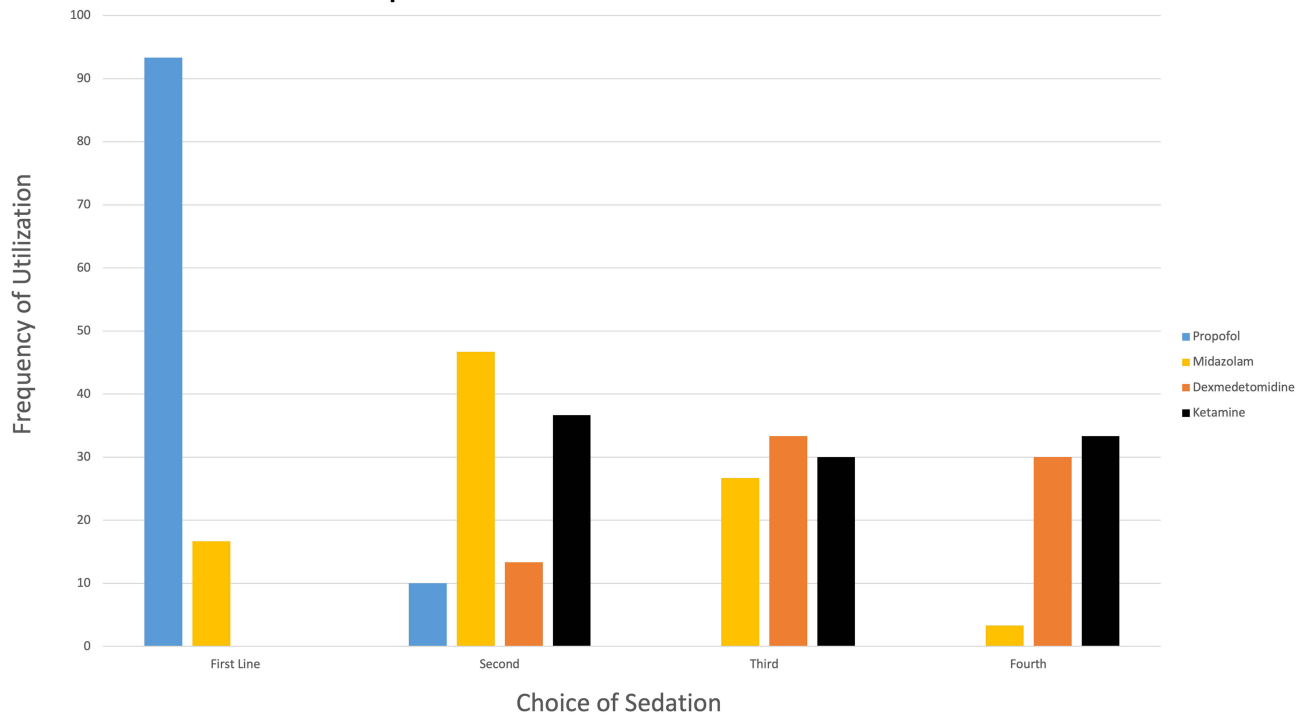


Figure 3 Sequential Introduction of Sedation.

I think in terms of balancing my comfort level and... lack of evidence otherwise to suggest that ketamine is better... there are very few times when I feel like that's exactly what I need. (Pre-COVID-19 FG, P4)

Interestingly, respondents in the COVID-19 population FG expressed uncertainty around effectiveness and hesitancy towards ketamine use in unfamiliar settings, despite gaining more experience throughout the pandemic. One respondent

Table 2 Physician Perspectives on Contributors to Ketamine Discomfort

Theme	Representative Respondent Quotes
Lack of evidence	<p>Lack of evidence otherwise to suggest that ketamine is better. (Pre-COVID FG, P4)</p> <p>There are very few times when I feel like that's exactly what I need. (Pre-COVID FG, P4)</p> <p>There also is not much that I am familiar with in terms of prolonged infusions in critical care as opposed to the procedural setting. (Post-COVID, P5)</p> <p>If there were more clinical data that would also add to, specifically for prolonged infusions cause you know that addressed some of these potential questions or concerns people have. (Post-COVID, P5)</p>
Lack of experience/familiarity	<p>I think every time you use a new drug in a supervised setting, like, will generally make me feel more comfortable (Pre-COVID, P8)</p> <p>You want to feel comfort and mastery of the medicine you are prescribing. (Pre-COVID, P8)</p> <p>I think like a big part of why I chose dex[medetomidine] over ketamine, is I have just used it so much that I am just comfortable with it and the nurses are comfortable with it. (Post-COVID, P1)</p> <p>It's kind of stressful to choose a new agent that I am not as familiar with using. (Post-COVID, P1)</p> <p>I have never really used it as a sole or primary agent. (Post-COVID, P4)</p>
Desire to learn more about ketamine	<p>I would love to see, how do we teach this to residents? How do we approach this for ourselves? (Pre-COVID, P1)</p> <p>As a group to go through the data, and our comfort level, and with pharmacy, and sort of decide. (Pre-COVID, P1)</p> <p>Even our own community coming together to do case reports of common or potentially more unusual and interesting sedation questions. (Post-COVID, P1)</p> <p>At least our own communal and anecdotal data so we can have a little bit more comfort. (Post-COVID, P1)</p>

in the COVID-19 population group expressed discomfort due to the lack of evidence around the effectiveness of ketamine in certain settings, particularly for prolonged infusions in the ICU.

I think part of the reason is that there also isn't much that I'm familiar with in terms of prolonged infusions in critical care as opposed to the procedural setting and so...as another thing that would make me feel more comfortable if there were more clinical data that would add to...specifically for prolonged infusions cause you know that addressed some of these potential questions or concerns. (COVID-19 population, P5)

Lack of Experience/ Familiarity

Respondents also attributed their sense of discomfort to the lack of personal experience and familiarity. One respondent described how their lack of experience contributed to their discomfort with ketamine:

I think every time you use a new drug in a supervised setting will generally make me feel more comfortable getting experienced with it. So when you're an attending and it's your call, ...you want to feel comfort and mastery of the medicine you're prescribing. You know, I had to get that with other drugs that I use— and anything less than that, unless you feel comfortable like in that space, it's a little bit harder. So ketamine is literally the only ICU drug that I've heard about nowadays that I feel that way with. (Pre-COVID-19, P8)

Participants described more familiarity with other drugs (such as propofol and dexmedetomidine), which contributed to them preferring these drugs over ketamine. One respondent described being “a little confused about what it really does” and that “there were so many other drugs and factors involved” (COVID-19 population, P1). Notably, respondents considered not only their own sense of familiarity and experience but also the team's level of comfort and experience. One respondent described, “almost always the right choice is to use whatever the team is most comfortable [with]” (COVID-19 population, P4). When describing a patient case where they chose a different drug over ketamine, another respondent shared:

I consider[ed] using ketamine a couple days ago... I had a post op patient who had raging agitation and it looked kind of like pain after this complicated vascular procedure... I considered ketamine and I ended up using dex[medetomidine]... and I think like a big part of the, why I chose dex[medetomidine] over ketamine is, I've just used it so much that I'm just comfortable with it and the nurses are comfortable with it... it's kind of stressful to choose a new agent that I'm not as familiar with using. (COVID-19 population, P1)

Relatedly, respondents described how ketamine was often utilized as a third-line sedative drug, which limited their experience and familiarity. One physician noted:

Ketamine is always if anything tagged onto the end and that to me also again suggests to me that maybe there's not long term conclusive data that gives them confidence which makes me feel even less confident. (Pre-COVID, P6)

Desire for More Education

In the absence of robust clinical data and literature, many respondents described the desire to learn more about ketamine through group discussion and community decision-making. One respondent brought up the following suggestion:

I would love to see ...in conjunction with how do we teach this to residents— how do we approach this?... What is the rationale approach to.... sedation in ICU? Categories of drugs? When you choose what? As a group to go through the data, and our comfort level, and with pharmacy, and sort of decide... as a core view of a few smart people and put our heads together to come up with this plan. (Pre-COVID, P1)

Respondents described creating institutional guidelines and protocols as one way to mitigate the discomfort and increase confidence and comfort with ketamine. One participant reported:

I think in addition to having data, even our own community coming together to do case reports of ... common or potentially more unusual and interesting sedation questions like... why did you choose what you did, and what other options or alternatives we could've chosen ... So even if it's not great data it's at least our own communal and anecdotal data so we can have a little bit more comfort. (COVID-19 population, P1)

Discussion

To our knowledge, this is the first mixed-methods study on ketamine prescription in the ICU. Our study demonstrated a 15-fold increase in ketamine use during the COVID-19 pandemic contrasted with a consistent feeling of discomfort. Despite a marked increase in use, providers continued to voice concern and uncertainty regarding its effectiveness. Using the Framework method for content analysis, we identified three major themes underlying providers' discomfort: lack of evidence, lack of experience and familiarity, and desire for more education and protocols.

In line with these themes, Bell et al recently published a study describing the perceptions and barriers to use of ketamine in the critically ill and surveyed physicians, pharmacists, nurse practitioners, physician assistants and nurses with 341 respondents.²⁰ Of the respondents, the majority were physicians practicing at academic medical centers. The most common barriers to use identified were adverse effects (42.6%), lack of routine experience and familiarity (41.5%, 33.1% respectively), lack of evidence (33.5%), and lack of hospital guidelines for use (32.3%)²⁰ mirroring the three major themes at the root of provider discomfort described herein: lack of evidence, lack of experience and familiarity, and desire for more education and protocols.

With regard to lack of evidence, currently, there are no formal society guidelines or recommendations for ketamine use in the ICU. However, retrospective studies have shown efficacy as well as opioid-sparing properties.^{21–23} Garber et al²⁴ analyzed 160 patients and found a 20% (interquartile range [IQR] –63.6 to 0.0, $p < 0.001$) relative reduction in total analgesation within 24 hours of ketamine initiation, and moreover, they found that the median percent time within goal RASS improved after ketamine initiation (pre, 7.1% [0–40%] vs post, 25% [0–66.7%], $p = 0.005$). Similarly, Buchheit et al²¹ found a significant decrease in analgesia in morphine equivalent (1 to –0.265 mg/h 12 hours pre- and post-ketamine initiation, $p < 0.001$). In a concise review of the literature, Hurth et al²⁵ provided recommendations on dosing and relative safety for ketamine in the ICU.

Despite these studies demonstrating ketamine can be used to reduce other analgesation requirements, our study found an increasing frequency of other agents, including midazolam and fentanyl. While this observed increase in total analgesation requirements may reflect the uniqueness of the COVID-19 population and demands on the healthcare system,¹⁴ it may also reflect a lack of understanding of the benefits of ketamine.

In terms of experience and familiarity, ketamine use increased 15-fold during the COVID-19 pandemic at our center, with similar increases demonstrated worldwide.^{14,16} Additionally, temporal trends from 2008 to 2018 across 842 US hospitals also showed a 15-fold increase in the utilization of ketamine for continuous infusion in mechanically ventilated patients with substantial variability between hospitals.²⁶ Through experience, the common adage “see one, do one, teach one” has long been relied upon for medical education. However, this theory has recently been called into question,^{9,10} and other learning theories, such as Kolb's experiential learning theory, suggest that in order for there to be effective learning, there has to be reflection and abstract conceptualization in addition to experience.⁷

Many pulmonary critical care physicians utilized ketamine sparingly as a trainee then joined an institutional culture of infrequent use. During the pandemic, and intensivists gained experience with ketamine as nearly one-third of ventilated patients received ketamine. However, despite fulfilling the first two notions: see one, do one, their discomfort persisted. They consistently desired more experience and education, because they did not have the time and space for abstract conceptualization and true experiential learning.

Regarding desire for education and protocols, our center had protocols for ketamine administration for various indications prior to the COVID-19 pandemic. During the pandemic, several iterative guidelines were developed by a multidisciplinary group of physicians, nurses, and pharmacists. Protocols were reviewed and approved through the critical care branch of incident command and distributed via Email to hospital personnel and posted in rounding spaces. Given the time and staffing constraints during the pandemic, no virtual or in-person training regarding analgesation was provided, though an in-person pharmacist was available every day during ICU rounds. Although iterative guidelines were provided, providers still felt uncomfortable with ketamine use because they were not truly learning about it, they were just using it. Although this specific case was due in large part to the pandemic limiting time for learning, this phenomenon is common among attendings and highlights the need for effective continuous medical education (CME).

Trainees have a curriculum and framework to complete Kolb's cycle of experiential learning, but attendings often do not.¹¹ Thus, it is crucial to provide robust opportunities for attending physicians to reflect, conceptualize, and truly learn.

There will always be new medications and procedures to be learned. For example, ECO2Cor Hemolung management, esophageal balloon titration, or andexanet alfa may not have been invented or incorporated during training. Within this knowledge gap lies an opportunity to integrate training modules, simulation, and faculty development sessions to continue growing as lifelong learners. At our institution, now post the pandemic, critical care pharmacists lead annual teaching sessions for attending physicians on ketamine. Additionally, critical care pharmacy leads monthly sessions for attendings, fellows, and resident physicians on sedation with a focus on ketamine use and where difficult analgosedation cases can be reviewed.

This study has several limitations. As a single-center study, our policies and cultures regarding ketamine prescription may be unique to our academic MICU and may limit generalizability to smaller or community institutions. Moreover, ketamine was used as a second-, third-, or fourth-line agent to achieve a target RASS goal, not for other indications, e.g., bronchodilation in status asthmaticus or procedural sedation. The patient population and providers were solely in the MICU which limits generalizability. The quantitative prescription of ketamine was reflective of the pulmonary critical care physicians as a department and may not reflect the individual FG participants. Data regarding ketamine use were limited to initiation of ketamine and did not include duration and de-escalation. Furthermore, FG participation was voluntary which can engender bias and may not reflect the attitudes of all pulmonary critical care physicians. Finally, the pre-COVID-19 FG was held in person, but during the pandemic, the FGs was held virtually which may have introduced unrecognized biases or challenges in participation.

Conclusion

We identified a substantial increase in ketamine prescription through the pandemic, yet intensivists continued to feel a sense of discomfort. The discomfort was tied to lack of evidence, lack of experience, and desire for more education and protocols. Although experience increased and protocols were available, provider discomfort persisted. Institutions should reflect on the notion that solely increasing experience may not be sufficient to achieve comfort or competency. During the absence of adequate data, faculty and medical centers should examine how to create consensus protocols until the necessary data become available. Ultimately, we need to delineate these proceedings to optimize continuing education and clinical competency.

Abbreviations

ARDS, acute respiratory distress syndrome; CME, continuing medical education; COVID-19, Coronavirus-19; FG, focus group; ICU, intensive care unit; MICU, medical intensive care unit; P4, Participant 4.

IRB Approval

Study IRB 2019P000834 approved by BIDMC IRB with protocols in accordance with the World Medical Association Declaration of Helsinki.

Consent

All participants provided verbal informed consent including publication of anonymized responses that was confirmed by an independent witness. The informed consent process was approved by the IRB.

Author Contributions

Margaret M Hayes and Ari L Moskowitz contributed equally to the work as co-principal investigators. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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