Ketamine Prolonged Infusions in the Pediatric Intensive Care Unit: a Tertiary-Care Single-Center Analysis

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OBJECTIVE Ketamine is commonly used as an anesthetic and analgesic agent for procedural sedation, but there is little evidence on its current use as a prolonged continuous infusion in the PICU. We sought to analyze the use of ketamine as a prolonged infusion in critically ill children, its indications, dosages, efficacy, and safety.

METHODS We retrospectively reviewed the clinical charts of patients receiving ketamine for ≥ 24 hours in the period 2017–2018 in our tertiary care center. Data on concomitant treatments pre and 24 hours post ketamine introduction and adverse events were also collected.

RESULTS Of the 60 patients included, 78% received ketamine as an adjuvant of analgosedation, 18% as an adjuvant of bronchospasm therapy, and 4% as an antiepileptic treatment. The median infusion duration was 103 hours (interquartile range [IQR], 58–159; range, 24–287), with median dosages between 15 (IQR, 10–20; range, 5–47) and 30 (IQR, 20–50; range, 10–100) mcg/kg/min. At 24 hours of ketamine infusion, dosages/kg/hr of opioids significantly decreased ($p < 0.001$), and 81% of patients had no increases in dosages of concomitant analgosedation. For 27% of patients with bronchospasm, the salbutamol infusions were lowered at 24 hours after ketamine introduction. Electroencephalograms of epileptic patients ($n = 2$) showed resolution of status epilepticus after ketamine administration. Adverse events most likely related to ketamine were hypertension ($n = 1$), hypersalivation ($n = 1$), and delirium ($n = 1$).

CONCLUSIONS Ketamine can be considered a worthy strategy for the analgosedation of difficult-to-sedate patients. Its use for prolonged sedation allows the sparing of opioids. Its efficacy in patients with bronchospasm or status epilepticus still needs to be investigated.

ABBREVIATIONS AE, adverse event; CAPD, Cornell Assessment of Pediatric Delirium; COMFORT-B scale, Comfort Behavioral scale; IQR, interquartile range; MV, mechanical ventilation; PICU, pediatric intensive care unit; PIM3, Pediatric Index of Mortality-3; WAT-1, Withdrawal Assessment Tool-1

KEYWORDS analgesia; children; ketamine; pediatric intensive care unit; prolonged sedation; safety

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Introduction

Ketamine is an N-methyl-D-aspartate receptor antagonist commonly used during the last decades as an anesthetic and analgesic agent for procedural sedation. The use of ketamine as a prolonged infusion in pediatrics was first described in 1990, in 4 patients who previously experienced hypotension with either benzodiazepines or narcotics and in 1 patient with severe agitation.¹ Prolonged infusions of ketamine have been thereafter described as a successful strategy for the prolonged analgosedation of patients with baseline hemodynamic instability^{1–3} and in patients tested with hypotensive challenges,⁴ as well as in patients who undergo mechanical ventilation and are poorly responsive to conventional drugs⁵ and as a countermeasure for opioid tolerance.⁶ Additionally, the use of ketamine infusions has been proposed in patients with associated bronchospasm.^{7–9} However, as pointed out by recent

reviews,^{10,11} existing studies on the use of ketamine as a prolonged infusion in the PICU are lacking, with those published to date being mainly retrospective or including small sample sizes.^{10,11} Additionally, in the era of the new sedation concept that prioritizes analgesia over sedation to target the minimal yet effective sedation status and minimize benzodiazepine use, the role of this analgesic should be re-discussed.^{12,13}

Here we report a retrospective analysis on the use of ketamine as a prolonged infusion in our tertiary-care academic PICU, designed with the aim of analyzing ketamine modality of use, indications, dosages, infusion duration, concomitant analgosedation management, efficacy, and safety.

Materials and Methods

Study Design and Setting. This is a single-center observational retrospective study developed in our

tertiary-care academic center of Padua University Hospital, Italy. Our PICU is a 10-bed unit that receives about 400 to 450 inpatients/year. Our unit follows an institutional analgesia and sedation physician-driven protocol based on targeting the sedation status to the individual comfort goal while minimizing pain and anxiety, following international recommendations.^{11,13–15} The protocol includes a first-line sedation strategy using a continuous infusion of either an opioid (fentanyl, starting dose 1 mcg/kg/hr), a benzodiazepine (midazolam, starting dose 0.05–0.1 mg/kg/hr) or, more frequently, a combination of both, based on patients' clinical characteristics and their expected trajectory of illness. Neonates receive an opioid-based first-line therapy (fentanyl, starting dose 1 mcg/kg/hr). The analgosedation regimen is then titrated on the sedation level and comfort of the patient, evaluated using a clinical score validated for pediatric age (COMFORT-B scale).¹⁶ In case of suboptimal analgosedation despite the use of high dosages of opioids and benzodiazepines (i.e., fentanyl >2.5 mcg/kg/hr, midazolam >0.25 mg/kg/hr), a second-line analgosedation agent may be started as a continuous infusion, based on the physician's judgment (dexmedetomidine, starting dose 0.4 mcg/kg/hr; ketamine, starting dose 10 mg/kg/min; propofol, starting dose 1 mg/kg/hr). If a second-line agent is started, a loading bolus or supplemental boluses over the infusion may be administered, based on the physician's judgment. No daily sedation interruptions are performed. In case of suboptimal analgosedation despite the use of second-line agents, an opioid-switch strategy may be chosen from fentanyl to morphine, following the equivalence rule of morphine:1 = fentanyl:0.010.¹⁴ In the phase of weaning, if the analgosedation duration is ≥ 5 days, a 20% decrease in drug rate every 24 hours is performed, with careful monitoring of the comfort and withdrawal symptoms (Withdrawal Assessment Tool-1, WAT-1).¹⁷ If a withdrawal syndrome is diagnosed, the weaning is interrupted and a rescue bolus and/or an increase in the rate of the infusion is performed and maintained until resolution of symptoms. The possible onset of delirium is constantly monitored, and suspected cases are assessed with the validated Cornell Assessment of Pediatric Delirium (CAPD).¹⁸ Exclusion criterion for using CAPD is a patient not respondent to voice (deeply sedated) or a patient not respondent to physical stimulation (unarousable).¹⁸ Managing delirium includes the control of pain and environmental triggers, and the administration of a second-generation antipsychotic (i.e., olanzapine). In accordance to previous experiences, in our tertiary care center ketamine may also be used as an adjuvant of bronchospasm treatment in intubated patients,^{7,19} and as an alternative antiepileptic strategy in patients with refractory status epilepticus, titrating its dosages to electroclinical control.^{20,21} Investigations were conducted in accordance with the World Medical Association Declaration of Helsinki and all requested

institutional approvals were collected.

Study Population. We included all critically ill children (<18 years) who were admitted to the PICU and received ketamine prolonged infusions for 24 hours or longer between January 1, 2017, and December 31, 2018. If a patient underwent more than 1 prolonged infusion with ketamine, this information was collected for the cohort description, but only data from the first infusion were included in the statistical analysis.

Data Collection. Data were collected from our institutional electronic system and medical charts by clinical experts using a standardized datasheet.²² The following variables were collected: 1) demographic characteristics, including age, sex, race, and weight; 2) clinical baseline features including primary diagnosis at admission, comorbidities, presence of genetic syndrome, and Pediatric Index of Mortality-3 (PIM3) score²³; 3) characteristics of PICU stay, including mechanical ventilation (MV) modalities during ketamine infusion, length of MV during PICU stay, length of PICU stay, and mortality at discharge; 4) variables regarding ketamine administration including the primary indication for ketamine, use of a loading dose, minimum and maximum infusion dosages, need for additional boluses during the infusion, duration of ketamine infusion, and duration of the infusion weaning; 5) type and dosages of concomitant continuous infusions of analgesics or sedative drugs, collected at ketamine initiation and at 24 hours of ketamine infusion; 6) use of concomitant neuromuscular blockers; 7) cases of withdrawal syndrome (defined as WAT-1 ≥ 3) and delirium (defined as CAPD ≥ 9) throughout the PICU stay^{17,18}; 8) need for any additional analgesic or sedative infusion required to be started within the first 24-hour period of ketamine infusion; and 9) all adverse events (AEs) with onset during the ketamine infusion (those potentially related to ketamine were separately described). To make data comparable among different categories of opioids, dosages of fentanyl were converted as morphine equivalents (morphine:1 = fentanyl:0.010).¹⁴ Values of COMFORT-B score were not registered in the electronic chart and therefore not available for retrospective data analyses.

Outcome Measures. For the purpose of our study, when used as an adjuvant for difficult sedation, ketamine was considered effective if no increases in the dosages of other analgesics and sedatives had been necessary within the 24 hours of ketamine infusion. When ketamine was used as an adjuvant for bronchospasm therapy, a decrease in the dosages of the concomitant bronchospasm therapy after 24 hours of ketamine infusion was evaluated as a secondary outcome measure. When ketamine was used as an alternative therapy of status epilepticus, an electroencephalogram after ketamine introduction was evaluated by an expert neurologist to assess the effect of ketamine on the epileptic status. Finally, ketamine safety profile was evaluated as a secondary endpoint, with

particular attention to the development of hypertension, tachycardia, laryngospasm, hypersalivation, emesis, nystagmus, enhanced skeletal muscle tone or tonic/clonic spasms, anaphylaxis, and erythema.

Statistical Analysis. Descriptive statistics were reported in terms of absolute frequencies, percentages, median, and IQR as appropriate. The variation of drug dosages before and after the introduction of ketamine was tested with the Wilcoxon signed rank test. Pre-post analyses in subgroups with $n < 20$ were performed by using the exact version of the Wilcoxon signed rank test. Demographic, clinical characteristics, and clinical score details were compared between patients who used ketamine as an adjuvant of analgesedation and patients who used ketamine as an adjuvant of bronchospasm. No comparison with the group of patients who used ketamine as an alternative therapy for status epilepticus was possible, owing to the low numbers in this group ($n = 2$). The Pearson chi-squared test was used to test categorical data, and the Fisher exact test was used when expected counts in $>20\%$ of cells were <5 . The Mann-Whitney U test—and its exact version when subgroup $n < 20$ —was used to compare continuous data. All the statistical analyses were performed with IBM SPSS statistical software version 25.0 (IBM Corp, Armonk, NY). Statistical significance was set at a 2-tailed p value <0.05 .

Results

During the course of the study period, 60 consecutive patients <18 years were hospitalized in our PICU and received a prolonged infusion of ketamine ≥ 24 hours. Demographic and clinical characteristics are shown in Table 1. The median age was 12 months (IQR, 2–47). The most frequent primary diagnosis was a respiratory disease (55%). All patients received ventilation during ketamine infusion, and 93% required invasive MV. Twenty-five percent received a concomitant infusion of neuromuscular-blocking agent. The median length of the PICU stay was 17 days (IQR, 12–24). The mortality rate at the time of PICU discharge was 12%.

Details of ketamine administration are shown in Table 2. Seventy-eight percent of patients received ketamine as an adjuvant for analgesedation, 18% as an adjuvant for treating bronchospasm, and 4% as a treatment of status epilepticus. Twelve percent of patients received a loading bolus (1 mg/kg) at the beginning of the infusion. At the time of ketamine start, all patients excluding the 2 patients with status epilepticus were receiving an opioid infusion ($n = 58$, 97%), and 70% an associated midazolam infusion. Fourteen patients (23%) were also receiving dexmedetomidine, and 4 (7%) a propofol infusion (Table 3). The median infusion duration was 103 hours (IQR, 58–159; range, 24–287), with median dosages between 15 (IQR, 10–20; range, 5–47) and 30 (IQR, 20–50; range, 10–100) mcg/kg/min. The infusion was interrupted without weaning in 39 patients (65%)

and gradually weaned in the other 21 (35%) over a median period of 15 hours (IQR, 7–20).

A comparison analysis of ketamine administration details between patients receiving ketamine as an adjuvant of analgesedation and as an adjuvant of bronchospasm is reported in Table 2. Patients using ketamine as an adjuvant of bronchospasm received a significantly longer ketamine infusion ($p = 0.012$), while minimum or maximum dosages/kg/min, the number of additional ketamine boluses, the ketamine weaning modality, and the type of concomitant analgesedation did not differ between groups.

Dosages of concomitant analgesia and sedation registered immediately before the start of ketamine and at 24 hours of ketamine infusion are reported in Table 3. Dosages/kg/hr of opioids significantly decreased at 24 hours after ketamine introduction when compared with dosages registered immediately pre ketamine ($p < 0.001$). Conversely, dosages of benzodiazepines, propofol, and dexmedetomidine did not significantly change at 24 hours of ketamine infusion. Eighty-one percent ($n = 38$) of patients who received ketamine as an adjuvant of analgesedation did not show any need for increasing dosages of concomitant analgesedation within the first 24 hours of ketamine infusion. For 3 of the 11 patients (27%) who received ketamine as an adjuvant for bronchospasm therapy, salbutamol infusion was lowered within 24 hours of ketamine treatment. Patients who received ketamine as an antiepileptic treatment were a 9-year-old female with status epilepticus secondary to anti-N-methyl-D-aspartate-receptor-encephalitis, not respondent to first-line benzodiazepines or phenytoin or midazolam continuous infusion (1 mg/kg/hr), and a 10-year-old male affected by status epilepticus related to pharmacoresistant idiopathic epilepsy not respondent to first-line benzodiazepines, phenobarbital, valproic acid, or midazolam continuous infusion (1 mg/kg/hr). Ketamine dosages ranged from 5 to 20 mcg/kg/min in the first patient, from 10 to 100 mcg/kg/min in the second patient. The electroencephalograms after ketamine administration showed a resolution of status epilepticus in both cases.

Thirteen patients (22%) displayed at least 1 AE during the prolonged infusion. Those events were mostly identified as opioid/benzodiazepines withdrawal symptoms ($n = 13$) and delirium ($n = 1$) and were always reversible (Table 2). Additional AEs likely related to ketamine were systemic hypertension ($n = 1$) and hypersalivation ($n = 1$) and both resolved after stopping the infusion. We did not observe any other ketamine-related AEs. Patients who experienced AEs did not receive significantly different minimum, median, maximum, or cumulative ketamine dosages, compared with patients who did not experience AEs. However, when the analysis was computed by comparing patients with AEs most likely related to ketamine (hypertension, hypersalivation, and delirium) with the others, ketamine median dosages

Table 1. Demographic and Clinical Characteristics of Patients Receiving a Prolonged Infusion of Ketamine in the Pediatric Intensive Care Unit According to Ketamine Primary Indication

Variable	Total (N = 60)	Primary Indication for Ketamine		
		Adjuvant of Sedation (n = 47)	Adjuvant of Bronchospasm Therapy (n = 11)	Treatment of Status Epilepticus (n = 2)
Age, median (IQR), mo	12 (2–47)	14 (2–49)	4 (2–21)	130
Age category, n (%)				
Neonates	7 (12)	6 (13)	1 (9)	0 (0)
Infants	21 (35)	15 (32)	6 (54)	0 (0)
Children	32 (53)	26 (55)	4 (36)	2 (100)
Weight, median (IQR), kg	8.5 (4.0–15.5)	9.3 (4.7–17.0)	4.0 (2.7–8.0)	39
Sex, n (%), male	39 (65)	28 (60)	10 (91)	1 (50)
Race, n (%), white	44 (73)	33 (70)	9 (82)	2 (100)
Primary diagnosis, n (%)				
Respiratory disease	33 (55)	23 (49)	10 (90)	0 (0)
Cardiac disease	11 (18)	11 (23)	0 (0)	0 (0)
Neurologic disease	2 (3)	0 (0)	0 (0)	2 (100)
Sepsis or septic shock	4 (7)	4 (9)	0 (0)	0 (0)
Postsurgical monitoring	4 (7)	4 (9)	0 (0)	0 (0)
Other	6 (10)	5 (11)	1 (9)	0 (0)
Comorbidities, n (%)	34 (57)	25 (53)	8 (73)	1 (50)
Ex-prematurity*	16 (47)	10 (40)	6 (86)	0 (0)
Genetic syndrome	6 (17)	5 (20)	1 (14)	0 (0)
PIM3 score, median (IQR)	0.01 (0.01–0.04)	0.01 (0.00–0.02)	0.01 (0.01–0.04)	0.04
Ventilation type during ketamine infusion, [†] n (%)				
Non-invasive ventilation	8 (13)	6 (13)	1 (9)	1 (50)
Invasive ventilation	56 (93)	43 (91)	11 (100)	2 (100)
High-frequency oscillatory ventilation	1 (2)	1 (2)	0 (0)	0 (0)
Mechanical ventilation length, median (IQR), days	11 (6–18)	11 (6–19)	11 (8–12)	14.5
PICU-stay length, median (IQR), days	17 (12–24)	19 (13–27)	15 (12–17)	16.5
Mortality, n (%)	7 (12)	7 (15)	0 (0)	0 (0)

PIM-3, Pediatric Index of Mortality 3

* Prematurity is defined as gestational age <37 weeks.

† Multiple ventilation types are possible for the same patient during ketamine infusion.

were significantly higher in the group of patients who experienced AEs (median 39 mg/kg/min [IQR, 35–47] vs median 25 mg/kg/min [IQR, 10–50], respectively, $p = 0.046$).

Discussion

To the best of our knowledge, this is one of the largest reports on the use of ketamine prolonged infusions in PICU and shows that a continuous infusion of ketamine may represent an actual strategy in this setting. In our cohort, ketamine was used in patients of all ages, in-

cluding neonates, and in patients with heterogeneous criticality. The main indication for its use was as an additional analgosedation agent in patients who poorly responded to conventional drugs. In those patients, dosages of opioids were significantly decreased after the introduction of ketamine, and, for most patients, no increases in the dosages of other analgosedation drugs were required in the 24 hours after ketamine introduction. In all cases, ketamine was used safely, with the onset of only occasional, minor, and reversible AEs.

Achieving optimal analgosedation is an essential

Table 2. Details of Ketamine Administration and Concomitant Analgosedation, With Comparison Among Groups Based on Ketamine Primary Indication

Variable	Total (N = 60)	Primary Indication for Ketamine			p value*
		Adjuvant of Sedation (n = 47)	Adjuvant of Bronchospasm Therapy (n = 11)	Treatment of Status Epilepticus (n = 2)	
Ketamine loading bolus, n (%)					
Initial dose of 1 mg/kg	7 (12)	5 (11)	1 (9)	1 (50)	1.000
Need for additional boluses during the infusion, n (%)	14 (23)	11 (23)	1 (9)	2 (100)	0.429 [†]
Ketamine infusion dosages, median (IQR), mg/kg/min					
Minimum	15 (10–20)	15 (10–20)	15 (15–20)	7	0.878
Maximum	30 (20–50)	30 (20–50)	30 (30–40)	60	1.000
Ketamine infusion duration, median (IQR), hr	103 (58–159)	92 (52–138)	153 (111–234)	228	0.012
Ketamine weaning					
Time, median (IQR), hr	0 (0–7)	0 (0–4)	0 (0–16)	30	0.491
Suspension without weaning, n (%)	39 (65)	32 (68)	7 (64)	0 (0)	1.000 [†]
Ketamine second infusion during the same PICU stay, n (%)	7 (11)	5 (11)	2 (18)	0 (0)	0.607 [†]
Concomitant analgesia, n (%)					
Fentanyl	60 (100)	47 (100)	11 (100)	2 (100)	1.000 [†]
Morphine	51 (88)	40 (85)	9 (82)	2 (100)	1.000 [†]
	29 (50)	22 (47)	6 (54)	1 (50)	0.644
Concomitant sedation, n (%)					
Midazolam	58 (97)	46 (98)	10 (91)	2 (100)	0.346 [†]
Propofol	55 (95)	43 (91)	10 (91)	2 (100)	1.000 [†]
	16 (28)	14 (30)	0 (0)	2 (100)	0.050[†]
Dexmedetomidine	32 (55)	27 (57)	4 (36)	1 (50)	0.207
Neuromuscular-blocking-agent infusions (rocuronium), n (%)	15 (25)	11 (23)	4 (36)	0 (0)	0.450 [†]
Adverse events during the infusion, n (%) [‡]					
Systemic hypertension	13 (22)	9 (19)	3 (27)	1 (50)	0.681 [†]
Hypersalivation	1 (2)	1 (2)	0 (0)	0 (0)	1.000 [†]
Delirium	1 (2)	1 (2)	0 (0)	0 (0)	1.000 [†]
Opioid/benzodiazepine withdrawal syndrome	1 (2)	0 (0)	1 (9)	0 (0)	0.400 [†]
	13 (22)	9 (32)	3 (37)	1 (50)	1.000 [†]

* p value between the group of patients using ketamine as adjuvant of sedation and the group using ketamine as adjuvant of bronchospasm therapy. The low numbers in the group of patients with status epilepticus precluded any comparison analysis.

[†] Multiple adverse events are possible in the same patient. The patient who developed systemic hypertension was a 4-year-old male, the patient who developed hypersalivation was a 2.5-month-old male, and the patient who developed delirium during ketamine infusion was a 2-year-old male.

[‡] Fisher exact test.

part of the care in critically ill children.^{11,14} The most frequent approach is currently the use of a combination of opioids and benzodiazepines, which are associated with hemodynamic instability, dependence, withdrawal

syndromes, and delirium. The onset of these conditions requires larger dosages of medications, longer time of infusion weaning, and prolonged PICU stay.^{11,14} For all these reasons, the availability of analgosedation

Table 3. Dosages of Concomitant Analgosedation and Clinical Scores Pre and 24 Hours After Ketamine Initiation

Variable	Total (N = 60), n (%)	Primary Indication for Ketamine, n (%)			Pre Ketamine Dosages, Median (IQR), mg/kg/hr	Dosages at 24 Hours of Ketamine Infusion, Median (IQR), mg/kg/hr	p value
		Adjuvant of Sedation (n = 47)	Adjuvant of Bronchospasm Therapy (n = 11)	Treatment of Status Epilepticus (n = 2)			
Opioid*	58 (97)	47 (100)	11 (100)	0 (0)	0.20 (0.06–0.25)	0.10 (0.04–0.20)	<0.001†
Midazolam	42 (70)	41 (87)	0 (0)	1 (50)	0.20 (0.15–0.30)	0.20 (0.15–0.30)	0.426
Dexmedetomidine	14 (23)	13 (28)	0 (0)	1 (50)	0.70 (0.47–1.20)	0.60 (0.15–1.22)	0.072
Propofol	4 (7)	3 (6)	1 (9)	0 (0)	4.5 (3.2–7.0)	2.5 (0.5–4.5)	0.102

* Opioid doses were calculated as morphine equivalents in mg/kg. Morphine:1 = fentanyl:0.01.

† The statistical significance persists when the analysis is stratified by indication: that is, opioid infusive dosages significantly decreased at 24 hours of ketamine infusion both in patients who received ketamine as adjuvant of sedation (n = 36, p < 0.001, Wilcoxon signed rank test) and in patients who received ketamine as adjuvant of bronchospasm therapy (n = 11, p = 0.016, Wilcoxon exact signed rank test).

alternatives for patients who poorly responded to conventional drugs, or experienced withdrawal syndromes, is crucial. Also, recent protocols have proposed to prioritize analgesia over sedation, to achieve optimal comfort status with minimal yet effective sedation.^{12,13} In this context, some retrospective studies (including small sample sizes) on the use of ketamine as prolonged sedation in PICU have been recently reported, confirming increased attention on this topic.^{5,6,24}

In our center, ketamine is used as a second-line analgosedation agent, which is initiated when opioids and/or benzodiazepines are not able to ensure an optimal analgosedation. In our cohort, dosages of conventional analgosedation drugs were at the upper ranges of suggested dosages/kg at the time of ketamine introduction, and more than a quarter of patients were additionally receiving either dexmedetomidine or propofol infusions. Therefore, we can state that patients receiving ketamine as adjuvant of analgosedation in our center represent a unique cohort of difficult-to-sedate patients. Most of these patients did not request any additional increase of analgosedation regimen during the 24 hours after the introduction of ketamine, suggesting that ketamine can represent a worthy strategy for maintaining optimal sedation in this category of patients. This result confirms the findings by Heiberger et al⁵ in a smaller cohort of critically ill patients. Additionally, the introduction of ketamine significantly reduced dosages of opioid infusions, confirming what was previously reported in a smaller study. We could speculate that ketamine improved patients' analgesia and comfort sufficiently to allow a reduction of other analgesic-drug infusions, probably working as a synergic agent with opioids in inducing and stabilizing analgesia at the spinal-cord level.^{25,26} This evidence could be particularly important in the current era in which the opioid crisis has involved also the pediatric population.²⁷ Although few sedation protocols in pediatrics have included ketamine so far, its use has been recently described as a first-line treatment within a rotation sedation protocol²⁸ and has been

highlighted in literature updates,¹¹ suggesting that this strategy should be taken into consideration especially in patients who poorly respond to conventional drugs.

The role of ketamine prolonged infusions for other indications, such as an adjuvant for bronchospasm therapy or as an antiepileptic therapy, is still being discussed. Petrillo et al¹⁹ demonstrated the efficacy of ketamine in patients admitted to the emergency department with status asthmaticus, while Allen and MacIas⁹ stated ketamine was non-superior to placebo in patients who did not respond to bronchospasm treatment. However, studies are missing on patients undergoing mechanical ventilation who received prolonged ketamine infusions as an adjuvant of bronchospasm treatment.⁸ In our experience, the use of ketamine allowed physicians to alleviate bronchospasm, providing analgosedation at the same time, suggesting that ketamine could represent a doubly worthy strategy in the PICU.¹¹ However, no conclusion can be driven from this single-center observational study and randomized controlled trials are needed to define this topic. Finally, we described 2 cases of refractory status epilepticus that efficiently responded to ketamine, confirming what has been previously reported in a case series²¹ and suggesting that this topic could deserve further in-depth investigations.

Adverse events registered during the infusion showed mild severity, were easily reversible, and most were likely related to the concomitant polytherapy rather than to ketamine, as the presence of withdrawal syndromes. Systemic hypertension, hypersalivation, and delirium were more likely related to ketamine and, even if infrequent, their onset should be carefully monitored during a prolonged infusion of ketamine. Also, it is necessary to emphasize that the use of ketamine, especially as a bolus, must be avoided in patients with baseline diminished myocardial contractility and suspected catecholamine-depleted state.^{29,30} Preclinical studies have demonstrated that ketamine has direct negative inotropic properties, and increase

in heart rate and blood pressures are achieved by an indirect sympathomimetic effect from endogenous catecholamine release that generally overrides the negative inotropic effect.^{14,29,30} However, patients with diminished myocardial contractility can miss the catecholaminergic overriding effect and experience hypotension and cardiovascular collapse.^{14,30} Our population did not include any patient with known or suspected baseline diminished myocardial contractility, and no major cardiovascular event was reported. Although those rare events can happen, a recent study involving 82 children receiving ketamine prolonged infusions in PICU reported ketamine to be hemodynamically safe.³¹

Some important limitations should be considered when interpreting these results. The study is retrospective and is therefore subject to pathognomonic biases. Some AEs might not be registered and could have been missed. Validated clinical scores are included in our clinical practice but were not systematically registered in the clinical chart, so we were not able to include them in the analysis. Although the analgosedation management was score driven and we could speculate that a decrease in concomitant drugs could have been possible only when the comfort score improved or remained within optimal levels, this remains speculation and further studies are needed to confirm these results. Additionally, the study could have benefited from collecting data on concomitant analgosedation at 48 hours, 72 hours of infusion, for a more precise evaluation of our patients' outcomes. Finally, since one-fourth of patients were receiving neuromuscular blocker infusions at some point during the ketamine infusion, some delirium cases could have been missed. As a final consideration, the sample size is larger than those reported in literature, but still precludes part of the statistical analyses.

Conclusion

From our single-center experience, we conclude that ketamine can be considered a worthy and relatively safe strategy for the analgosedation of difficult-to-sedate patients who poorly respond to conventional drugs, and has opioid-sparing effect. Ketamine is occasionally used also as adjuvant therapy in patients with severe bronchospasm who receive mechanical ventilation, and it seems to have potential as a treatment of refractory status epilepticus. However, high-quality prospective studies are needed to clearly define the efficacy of ketamine in PICU for those indications.

Article Information

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