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The Clinical Impacts Of Ketamine versus Morphine as an Analgosedative Agents in Mechanically Ventilated Critically ILL

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Abstract

Objective: Intravenous analgosedative agents are used widely in the critical care units to achieve the target Richmond agitation sedative scale in mechanically ventilated patients. Ketamine is a rapid-acting dissociative anesthetic with analgosedative properties. However, there are limited data on the safety and efficacy of Ketamine. The purpose of this study is to determine the clinical impacts of Ketamine versus Morphine as an analgosedative agents in septic and non-septic mechanically ventilated critically care patients.

Method: A retrospective analysis was conducted in our institution between April 2017 and Sep 2018. Our sample was stratified into six groups (Group I-VI). Analysis values were compared among the six tested groups by using ANOVA test for continuous variables and Chi Square test for nominal data in which the continuous variables of all patients were expressed as Mean±SD and nominal data were expressed as numbers with percentages.

Result: The mean age of our studied critically ill patients was 58.94±10.37. 131 patients of the eligible sample were male (69.7%) while 57 were female (30.3%). Critically ill patients who received Ketamine had significantly higher hemodynamic pressure parameters compared with Ketamine/Morphine and Morphine alone in which the hemodynamics were significantly higher in septic than in non-septic patients. The incidence of convulsive seizure was significantly lowest in non-septic critically ill patients who received Ketamine as analgosedative and highest in septic critically ill patients who received Morphine as analgosedative.

Conclusion: Ketamine infusion as analgosedative in mechanically ventilated critically ill patients appears as an effective and well-tolerated agent with positive effects on hemodynamics, vasopressor requirements and gastric residual volume. However, it did not appear to affect overall ICU length of stay or mortality.

Keywords: Analgosedative, Critical care, Ketamine, Morphine, Mechanical ventilation.

Introduction

Continuous infusion of analgosedative with or without sedative agents are a fundamental component and are widely used in intensive care units (ICUs) to achieve the target Richmond Agitation Sedative Scale (RASS) in mechanically ventilated critically ill patients. There has

been a great interest toward analgosedation for the management of agitation and anxiety; thus reducing the overall oxygen consumption.[1] Undesirable acute and longstanding consequences can occur with the administration of analgosedatives.[2] Although commonly used opioid analgosedatives are effective, they cause unwanted adverse effects, including delirium, constipation, and negative hemodynamic effects. [2,3] Recent studies have shown that 40% of the critically ill are at risk of over-sedation; leading to elevated infection rates, increased mechanical ventilation time, and lowered respiratory drive.[4]

Ketamine has gathered momentum due to its propensity to preserve cardiovascular stability, respiratory effort, and airway reflexes.[5] Unlike other sedatives, Ketamine is a rapid-acting dissociative anesthetic with analgosedative properties and does not reduce mean arterial pressure (MAP) or impair gastrointestinal motility. It serves as a dissociative agent by antagonizing N-methyl-D-aspartate (NMDA) receptor causing both analgesia and amnesia with no reducing effect on the respiratory drive.[6] On the other hand, Morphine has the tendency to cause hypotension resulting from histamine release[7], in addition to opioid-induced constipation which many patients develop during their ICU stay.[8] This makes it an attractive alternative to conventional opioid agents. However, there are limited data on the safety and efficacy of Ketamine to support its use as a continuous infusion for sedation in mechanically ventilated ICU patients. This study challenges the continuous Ketamine infusion in septic or non-septic mechanically ventilated critically ill patients compared to Morphine in terms of the total vasopressors requirement (NE_{rate}), the hemodynamic parameters of MAP, systolic blood pressure (SBP), and diastolic blood pressure (DBP), the risk of opioid-induced constipation (OIC), the incidence of convulsion, the ICU and overall hospital length of stay (LOS), and the overall 28-day ICU mortality.

Material and Methods

This was a single-center observational retrospective study conducted in the departments of King Hussein Medical Center (KHMC) at Royal Medical Services (RMS) in Jordan between Apr 2017 and Sep 2018. This study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. This study included a 188 septic and non-septic mechanically ventilated critically ill patients. Flow chart of our studied patients' selection and data collection process is fully illustrated in Figure 1. Our sample was stratified into six groups: Group I (Septic critically ill patients who were on Ketamine infusion), Group II (Non-Septic critically ill patients who were on Ketamine infusion), Group III (Septic critically ill patients who were on Morphine infusion), Group IV (Non-Septic critically ill patients who were on Morphine infusion, Group V (Septic critically ill patient who were on Morphine/Ketamine infusion), Group VI (Non-Septic critically patients who were on Morphine/Ketamine infusion). Analysis values were compared among the six tested groups by using ANOVA test for continuous variables and Chi Square test for nominal data in which the continuous variables of all patients were expressed as Mean±SD and nominal data were expressed as numbers with percentages. Statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤ 0.05 were considered statistically significant.

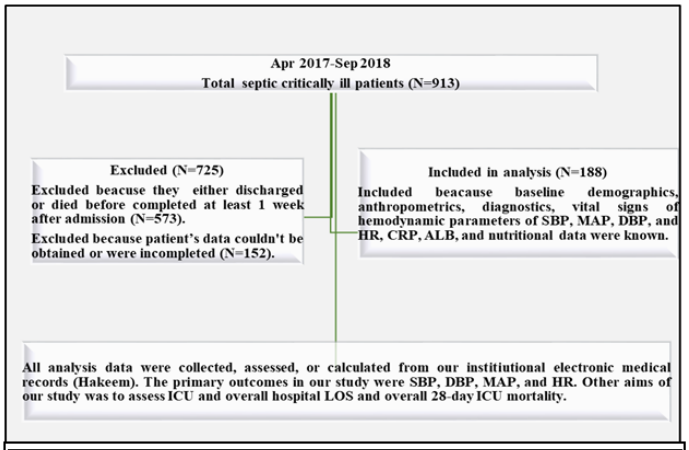

Fig 1. Flow chart of septic and non-septic critically ill patient's selection and data collection process.

Apr: April. Sep: September. DBP: Diastolic blood pressure. CRP: C-reactive protein. LOS: Length of stay MAP: Mean arterial pressure. SBP: Systolic blood pressure. ALB: Albumin. HR: Heart rate.

Results

The mean age of our studied critically ill patients was 58.94±10.37. 131 patients of the eligible sample were male (69.7%) while 57 were female (30.3%). There were insignificant differences across the six groups regarding anthropometrics of body weight (BW) and body mass index (BMI), nutritional indices of total calorie input (TCI) and protein density (PD), acute phase reactants of c-reactive protein (CRP) and CRP to ALB ratio (CRP:ALB), laboratories of blood glucose level (BG) and blood urea nitrogen (BUN), liver functionality, admission length of stay (LOS) days, and overall 28-day ICU mortality. Critically ill patients who received Ketamine had significantly higher SBP, DBP, and MAP compared with Ketamine/Morphine and Morphine alone in which the hemodynamics were significantly higher in septic than in non-septic patients with Mean±SD of (119.2±11.0 mmHg, 116.11±10.9 mmHg, 111.61±11.4 mmHg, 104.2±11.5 mmHg, 99.08±10.65 mmHg, and 90.56±7.41 mmHg), (72.04±5.69 mmHg, 70.85±6.00 mmHg, 69.54±6.54 mmHg, 63.89±7.95 mmHg, 60.36±5.92 mmHg, and 56.69±4.07 mmHg), and (93.54±9.21 mmHg, 91.70±9.42 mmHg, 87.04±9.86 mmHg, 80.81±9.98 mmHg, 78.00±9.22 mmHg, and 70.79±6.33 mmHg) for Group I, Group V, Group II, Group VI, Group III, and Group IV, respectively. The analgosedative infusion rate of Morphine was significantly higher in Group III, followed by Group IV, Group V, and lastly Group VI which was accompanied by a significantly higher NE_{rate} in Group III followed by Group V and finally, Group I. (4.16±0.32 ml/hr,4.12±0.34 ml/hr, 2.07±0.24 ml/hr, and 2.02±0.2 ml/hr) and $NE_{rate\ of}$ (11.22±1.70 mcg/min, 6.17±0.76 mcg/min, 3.48±0.43 mcg/min). The incidence of convulsive seizure was significantly lowest in non-septic critically ill patients who received Ketamine as analgosedative and highest in septic critically ill patients who received Morphine as analgosedative with number (%) of 1 (3.6%), 2 (7.4%), 3 (10.7%), 6 (22.2%), 14 (35.9%), and 19 (48.7%) for Group II, Group VI, Group I, Group V, Group IV, and Group III, respectively. Regarding consumption rate of prokinetic (PROK) of either erythromycin or metoclopramide, the PROK rate was significantly lowest in Group II followed by Group I, Group VI, Group V, Group IV, and Group III with number (%) of 9 (32.1%), 16 (57.1%), 19 (70.4%), 22 (81.5%), 37 (94.9%), and 39 (100.0%), respectively. Demographics, anthropometrics, nutritional indices, laboratory data, hemodynamics, analgosedative and vasopressor infusion rate, and other primary and major clinical outcomes of GRV, convulsive incidence, LOS, and overall 28-day ICU mortality are fully described in **Table 1-2**.

Discussion

A total of 188 patients were included in this study divided into six different groups as septic or non-septic and the type of analgosedative administered, Group I, II, III, IV, V, and VI with 28, 28, 39, 39, 27, and 27 patients in each group, respectively. The anthropometric data for the patients included in the study is illustrated in **Table 1**, with a mean age of 58.94±10.37 years and BMI of 25.90±3.97 Kg/m^2 for the total number of patients and no

significant difference in age or BMI between the six groups. Some clinical data that may affect the interpretation of the results were taken into consideration and recorded, such as the Total fluid input, BG, CRP, and CRP:ALB. The differences in these measurements between the different groups were statistically insignificant (P-value > 0.05), as shown in **Table 1**.

Qualitative assessment of Ketamine infusion effects on hemodynamics was described in multiple studies to be favorable. MAP was reported to be higher in patients receiving Ketamine continuous infusion while vasopressors requirements were reduced or unchanged, and were never reported to be increased. [9] In our study, three of the studied groups were already off vasopressor infusion (Group II, IV, VI), while the other three groups were on vasopressor (Group I, III, V), mainly NE. By comparing the results, the patients who were on Ketamine continuous infusion recorded a noticeable increase in MAP compared to baseline measurements, in addition to, decreased requirements of NE. Norepinephrine infusion rate needed to maintain hemodynamic stability in Group I was lower than Group III followed by Group V with the highest Norepinephrine requirements (3.48±0.43 mcg/min, 6.17±0.76 mcg/min, and 11.22±1.70 mcg/min, respectively). These findings are consistent with findings from previous studies that demonstrated that Ketamine does not negatively affect hemodynamics and may actually decrease vasopressor requirements and support vasopressor weaning effects when used as a continuous infusion in mechanically ventilated ICU patients. [3]

Other clinical outcomes were measured such as GRV which was increased in all groups but variably with magnitude increase the lowest among patients receiving Ketamine as sole analgosedative agent, Group I and II, as illustrated in **Table 2**. This conclusion was further confirmed by the percent of patients administered Prokinetics within Group I, II, III, IV, V, VI being the following (57.1%, 32.1%, 100.0%, 94.9%, 81.5%, and 70.4%, respectively). Interestingly, the incidence of convulsion seizure, the requirement of Morphine to maintain the target RASS, and the requirement of vasopressor to maintain the target MAP were lowest in mechanically ventilated critically ill patients who were on Ketamine analgosedative. These observations may strength the theories surrounding the triple advantages of Ketamine as anti-convulsive, anti-hyperalgesia, and hemodynamic supporter. Overall hospital/ICU length of stay and survival were not significantly different among the six groups. This study is limited by its retrospective design, using single-center data, and the lack of multiple comparisons of various significant variables across Group I-VI. Nonetheless, our center is an experienced and high-volume unit, so our data may be useful in other centers. A larger, multisite, and prospective study is needed to control for multiple confounders.

Table 1. Demographics, anthropometrics, laboratory values, nutritional indices, and admission days.

Variable		Total (N=188)	Group I Mean ±SD (N=28)	Group II Mean ±SD (N=28)	Group III Mean ±SD (N=39)	Group IV Mean±SD (N=39)	Group V Mean±SD (N=27)	Group VI Mean ±SD (N=27)	P-value
Gender	M	131 (69.7%)	21 (75.0%)	19 (67.9%)	29 (74.4%)	27 (69.2%)	21 (77.8%)	14 (51.9%)	0.211 (NS)
	F	57 (30.3%)	7 (25.0%)	9 (32.1%)	10 (25.6%)	12 (30.8%)	6 (22.2%)	13 (48.1%)	
Age (Yrs)		58.94±10.37	61.25±8.78	58.46±10.47	56.56±11.05	59.56±11.71	59.59±10.27	58.93±8.94	0.59 (NS)
BW (Kg)		74.05±10.23	73.00±8.50	73.64±11.60	75.08±10.03	75.67±9.15	72.85±11.48	72.93±11.3	0.796 (NS)
BMI (Kg/m^2)		25.90±3.97	25.13±3.23	25.75±4.85	26.12±4.08	26.87±3.73	25.12±3.71	25.92±4.13	0.471 (NS)
CRP (mg/dl)		13.19±4.27	14.06±3.86	13.10±3.49	12.42±3.72	12.46±3.72	12.47±4.02	15.27±6.24	0.054 (NS)
ALB (g/dl)		2.37±0.18	2.33±0.16	2.37±0.15	2.40±0.15	2.41±0.18	2.41±0.20	2.30±0.19	0.045 (S)
CRP:ALB		5.72±2.45	6.18±2.17	5.64±1.94	5.29±2.12	5.32±2.03	5.34±2.21	6.94±3.81	0.058 (NS)

TCI (Cal/Kg/day)	9.50±0.70	9.31±0.64	9.47±0.60	9.62±0.62	9.63±0.74	9.65±0.80	9.18±0.76	0.044 (S)
TCI (Cal/day)	651.6±79.5	640.3±59.4	650.9±81.2	666.5±64.6	662.2±85.6	663.9±97.4	615.0±80.1	0.107 (NS)
PD (g/100 Cal)	1.45±0.68	1.32±0.58	1.36±0.73	1.56±0.71	1.43±0.62	1.35±0.62	1.65±0.80	0.371 (NS)
BUN (mg/dl)	14.87±5.27	16.07±4.81	15.26±4.79	13.74±4.76	14.34±5.44	14.58±5.64	15.88±6.23	0.438 (NS)
∑FLUD I (ml/day)	2709±422	2654±362	2693±446	2781±369	2774±451	2749±470	2550±419	0.250 (NS)
Pre ICU Days	4.32±3.95	5.07±3.23	4.39±3.60	3.85±3.51	3.69±3.07	3.85±3.93	5.52±6.10	0.367 (NS)
ICU Days	12.76±4.95	14.04±4.92	12.00±4.23	12.26±4.73	12.72±5.19	11.52±4.70	14.22±5.64	0.222 (NS)
Hospital Days	17.07±6.98	19.11±6.63	16.39±6.36	16.10±6.59	16.41±7.14	15.37±7.23	19.74±7.44	0.096 (NS)
Mg (mg/dl)	2.31±0.01	2.31±0.00	2.31±0.00	2.32±0.02	2.32±0.02	2.31±0.00	2.31±0.01	0.018 (S)
BG (mg/dl)	188.7±6.7	190.1±6.1	188.3±5.3	187.5±4.7	188.0±6.8	187.2±6.8	191.8±9.8	0.087 (NS)
K (mEq/l)	2.84±0.19	2.79±0.17	2.85±0.14	2.88±0.19	2.89±0.18	2.86±0.18	2.75±0.27	0.020 (S)
Temp (ºC)	7.95%±2.7%	8.7%±2.9%	7.80%±2.4%	7.56%±2.4%	7.95%±2.8%	7.63%±2.8%	8.2%±2.8%	0.623 (NS)

Data were presented as Mean±SD by using ANOVA Test. Also, data were presented as Number (Percentage) by using Chi Square Test.

Group I: Septic critically ill patients who were on Ketamine infusion.
Group II: Non-Septic critically ill patients who were on Ketamine infusion.
Group III: Septic critically ill patients who were on Morphine infusion.
Group IV: Non-Septic critically ill patients who were on Morphine infusion.
Group V: Septic critically ill patients who were on Morphine/Ketamine infusion
Group VI: Non-Septic critically patients who were on Morphine/Ketamine.

N: Number of Patients.
SD: Standard Deviation.
S: Significant.
NS: Non-Significant.
0: Baseline at admission.
BW: Body Weight.
BMI: Body Mass Index.
CRP: C-reactive protein.
Mg: Magnesium.
BG: Blood glucose.
K: Potassium.
Temp: Temperature.
M: Male.
F: Female.
ALB: Albumin.
CRP:ALB: CRP to ALB Ratio.
TCI: Total Calorie Input.
PD: Protein density input.
BUN: Blood Urea Nitrogen.
ICU: Intensive care unit.
∑FLUD I: Total fluid input.

Table 2. Hemodynamics, analgosedative and vasopressor infusion rate, prokinetic and convulsive rate, and overall ICU mortality.

Variable		Total(N=188)	Group I Mean±SD (N=28)	Group II Mean ±SD (N=28)	Group III Mean ±SD (N=39)	Group IV Mean±SD (N=39)	Group V Mean±SD (N=27)	Group VI Mean ±SD (N=27)	P-value
NE_{rate} (mcg/min)		3.73±4.50	3.48±0.43	0.00±0.00	11.22±1.70	0.00±0.00	6.17±0.76	0.00±0.00	0.000 (S)
Ketamine (mg/hr)		11.99±10.23	20.66±1.67	20.58±1.90	0.00±0.00	0.00±0.00	20.63±2.25	20.08±2.04	0.000 (S)
Ketamine (ml/hr)		2.40±2.05	4.13±0.33	4.11±0.38	0.00±0.00	0.00±0.00	4.13±0.45	4.02±0.42	0.000 (S)
Morphine (mg/hr)		2.30±1.75	0.00±0.00	0.00±0.00	4.16±0.32	4.12±0.34	2.07±0.24	2.02±0.21	0.000 (S)
Morphine(ml/hr)		2.30±1.75	0.00±0.00	0.00±0.00	4.16±0.32	4.12±0.34	2.07±0.24	2.02±0.21	0.000 (S)
GRV_0 (ml)		144.43±8.42	143.21±7.6	143.29±9.43	146.33±6.51	145.10±9.44	144.22±8.57	143.37±9.1	0.586 (NS)
GRV_1 (ml)		160.99±14.3	150.42±7.9	146.81±9.67	175.65±7.70	170.50±11.0	158.62±9.46	154.10±9.8	0.000 (S)
SBP_0 (mmHg)		105.07±11.3	108.39±9.9	101.39±10.4	110.05±11.9	100.59±8.26	110.63±10.5	99.15±10.9	0.000 (S)
SBP (mmHg)		105.36±14.5	119.2±11.0	111.61±11.4	99.08±10.65	90.56±7.41	116.11±10.9	104.2±11.5	0.000 (S)
DBP_0 (mmHg)		64.53±6.39	65.43±5.07	63.21±5.97	67.00±6.70	62.85±4.68	67.44±5.77	60.93±7.76	0.000 (S)
DBP (mmHg)		64.72±8.34	72.04±5.69	69.54±6.54	60.36±5.92	56.69±4.07	70.85±6.00	63.89±7.95	0.000 (S)
MAP_0 (mmHg)		82.32±9.64	85.00±8.34	79.11±8.89	86.59±10.23	78.69±6.79	87.37±8.99	76.93±9.48	0.000 (S)
MAP (mmHg)		82.54±12.03	93.54±9.21	87.04±9.86	78.00±9.22	70.79±6.33	91.70±9.42	80.81±9.98	0.000 (S)
HR_0 (bpm)		87.11±8.02	85.71±6.64	88.82±7.99	84.21±8.04	89.44±6.72	83.85±6.99	90.85±9.47	0.001 (S)
HR (bpm)		93.32±10.92	102.82±8.1	97.68±8.86	92.64±8.94	80.59±6.06	96.33±7.93	95.33±10.0	0.000 (S)
CPS	A	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.1%)	2 (7.4%)	0 (0.0%)	0.631 (NS)
	B	177 (94.1%)	28(100.0%)	27 (96.4%)	38 (97.4%)	36 (92.3%)	23 (85.2%)	25 (92.6%)	
	C	7 (3.7%)	0 (0.0%)	1 (3.6%)	1 (2.6%)	1 (2.6%)	2 (7.4%)	2 (7.4%)	
Convulsive $Incidence_0$	NO	188 (100%)	28 (100%)	28 (100%)	39 (100%)	39 (100%)	27 (100%)	27 (100%)	0.000 (S)
	YES	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Convulsive Incidence	NO	123(65.4%)	25(89.3%)	27 (96.4%)	20 (51.3%)	25 (64.1%)	21 (77.8%)	25(92.6%)	0.000 (S)
	YES	65 (34.6%)	3 (10.7%)	1 (3.6%)	19 (48.7%)	14 (35.9%)	6 (22.2%)	2 (7.4%)	
Overall ICU Survival		112 (59.6%)	12 (42.9%)	19 (67.9%)	27 (69.2%)	24 (61.5%)	18 (66.7%)	12 (44.4%)	0.955 (NS)
Overall ICU Mortality		76 (40.4%)	16 (57.1%)	9 (32.1%)	12 (30.8%)	15 (38.5%)	9 (33.3%)	15 (55.6%)	
$PROK_0$	NO	146 (77.7%)	23 (82.1%)	24 (85.7%)	28 (71.8%)	28 (71.8%)	20 (74.1%)	23 (85.2%)	0.754 (NS)
	YES	42 (22.3%)	5 (17.9%)	4 (14.3%)	11 (28.2%)	11 (28.2%)	7 (25.9%)	4 (14.8%)	
PROK	NO	46 (24.5%)	12 (42.9%)	19 (67.9%)	0 (0.0%)	2 (5.1%)	5 (18.5%)	8 (29.6%)	0.002 (S)
	YES	142 (75.5%)	16 (57.1%)	9 (32.1%)	39 (100.0%)	37 (94.9%)	22 (81.5%)	19 (70.4%)	

Data were presented as Mean±SD by using ANOVA Test. Also, data were presented as Number (Percentage) by using Chi Square Test.

Group I: Septic critically ill patients who were on Ketamine infusion.
Group II: Non-Septic critically ill patients who were on Ketamine infusion.
Group III: Septic critically ill patients who were on Morphine infusion.
Group IV: Non-Septic critically ill patients who were on Morphine infusion.
Group V: Septic critically ill patients who were on Morphine/Ketamine infusion
Group VI: Non-Septic critically ill patients who were on Morphine/Ketamine.

N: Number of Patients.
SD: Standard Deviation.
S: Significant.
NS: Non-Significant.
0: Baseline at admission.
NE: Norepinephrine.
SBP: Systolic Blood Pressure.
DBP: Diastolic Blood Pressure.
MAP: Mean Arterial Pressure.
HR: Heart Rate.
ICU: Intensive care unit.
GRV: Gastric residual volume.
CSP: Child Pugh Score.
PROK: Prokinetic.

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