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The Nutritional Impacts of Using Ketamine Infusion Adjunctively For Mitigation Hemodynamics and Constipation Negative Impacts of Morphine in Septic Mechanically Ventillated Critically Ill Patients

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Abstract— Objective: *Intravenous opioids are widely used as an analgosedative agents in the intensive care units (ICUs) to approach the recommended Richmond Agitation Sedative Scale (RASS) level in septic and nonseptic mechanically ventilated critically ill patients. Ketamine is a dissociative anesthetic with a positive hemodynamic and gastrointestinal properties that can be used at a lower dose as an analgosedative. The purpose of this study is to determine the nutritional and clinical impacts of ketamine/morphine versus morphine alone as analgosedative agents.* ***Method:*** *A retrospective analysis was conducted in our institution between April 2017 and Sep 2018. Our sample was stratified into two groups (Group I and II). Analysis values were compared among the two tested groups by using independent T-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 57.94±9.37. 106 patients of the eligible sample were male (69.74%) while 46 were female (30.26%). Critically ill patients who received ketamine/morphine had a significantly higher hemodynamics and nutritional indices and a significantly lower vasopressor and morphine dependency, gastric residual volume, ICU and overall hospital admission days, and overall 28-day ICU mortality compared with morphine alone.* ***Conclusion****: Co-infusion of fixed analgosedative dose of ketamine (5 mcg/kg/min) with targeted RASS guided morphine in septic mechanically ventilated critically ill patients appears as an effective and well-tolerated agent with a positive nutritional and a positive nutritional and clinical impacts in septic mechanically ventilated critically care patients who are taken norepinephrine (NE).*

Keywords— *Analgosedative, Ketamine, Morphine, Mechanical ventilation, Septic patients*.

I. INTRODUCTION

Intermittent or continuous infusion of either opioids, ketamine, or dexmedetomidine (Analgosedatives) with or without either benzodiazepines or propofol (sedatives) are a fundamental component in septic or non-septic mechanically ventilated critically ill patients in order to approach the pre-specified desired RASS. There has been a great interest in analgosedation monotherapy or in combination to keep the RASS between -2 to -1 (mild-moderate sedation) and for acutely or proactively management of agitation and anxiety; thus reducing the overall oxygen consumption.[1] Undesirable acute and chronic complications can occur with the administration of analgosedatives.[2] Although commonly used opioid analgosedatives are effective, they are commonly associated with negative nutritional and clinical impacts, including but not limited to delirium, opioid induced constipation (OIC), elevated gastric residual volume (GRV), aspiration pneumonia, and negative hemodynamic outcomes.[2,3] Recent studies have shown that 40% of the critically ill are at risk of over-sedation (RASS <-2); leading to elevated infection rates of multi and extensively drug-resistant gram-negative bacteria (MDR and XDR-GNB) , decreased ventilation free days (VFDs), decreased mechanical ventilation independency, and elevated respiratory muscle dystrophy.[4]

Ketamine has gathered momentum due to its favorable pharmacokinetic and pharmacodymics characteristics, including but not limited to its propensity to preserve cardiovascular stability (does not reduce mean arterial pressure) and airway reflexes (maintain spontaneous responses), rapid-acting dissociative anesthetic (at higher dose) and analgosedative (at lower dose) by antagonizing N-methyl-D-aspartate (NMDA) receptor, does not impair gastric emptying and overall gastrointestinal motility. [5-6] On the other hand, morphine, the most commonly used opioid, has the tendency to cause hypotension resulting from histamine release[7], in addition to OIC and delaying gastric emptying rate which subsequently leads to overall negative nutritional outcomes.[8] This makes it attractive to use ketamine at analgosedative dose to mitigate the negative nutritional and clinical outcomes of conventional opioid agents. However, there are limited data on the safety and efficacy of ketamine to support its use as a continuous co-infusion with morphine for analgosedation in mechanically ventilated ICU patients. This study challenges the continuous of fixed dose ketamine co-infusion with target RASS guided morphine in septic mechanically ventilated critically ill patients compared to

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morphine in terms of the total NE requirement, the hemodynamic parameters of MAP, systolic blood pressure (SBP), and diastolic blood pressure (DBP), the GRVs and overall prokinetics using rate, the ICU and overall hospital length of stay (LOS), and the overall 28-day ICU mortality.

II. 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 152 eligible septic mechanically ventilated critically ill patients admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medical or surgical problem. Totally, 761 ICU patients were excluded because they either discharged, extubated, or died before completed at least 1 week after ICU admission (601 participants) or because the required data couldn't be recruited (160 participants). Patients' demographics, anthropometrics, hemodynamic parameters and NE rates, nutritional indices, ICU LOS, and overall 28-day ICU mortality were recorded retrospectively through our institutional electronic medical records (Hakeem).

Our sample was stratified into two groups: Group I (Septic critically ill patients who were on titratable Morphine infusion to achieve the target RASS level), Group II (Septic critically ill patients who were on co-infusion of fixed analgosedative Ketamine dose and titratable Morphine to achieve the target RASS level. Analysis values were compared among the two tested groups by using independent T-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. All statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA); P-values ≤0.05 were considered statistically significant.

III. Results

The mean age of our studied critically ill patients was 57.94±9.37. 106 patients of the eligible sample were male (69.74%) while 46 were female (30.26%). There were insignificant differences between the two groups regarding anthropometrics of body weight (BW) and body mass index (BMI), 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). In contrast, there were significant differences between Group I vs II in terms of nutritional indices of total calorie input (666.5±64.6 Cal/day vs 615.0±80.1 Cal/day), albumin level (2.40±0.15 g/dl vs 2.25±0.19 g/dl), and protein density (1.65±0.80 g/100 Cal vs 1.56±0.71 g/100 Cal)), ICU and overall hospital LOS days (14.22±5.64 days vs 12.26±4.73 days and 19.74±7.44 days vs 16.10±6.59 days), and overall 28-day ICU mortality (20 (27.03%) vs 41 (52.56%)), respectively.

Critically ill patients who received ketamine/morphine co-infusion (Group II) had significantly higher SBP, DBP, and MAP compared with morphine infusion monotherapy (Group I) with Mean±SD of (104.2±11.5 mmHg vs 99.08±10.65 mmHg), (63.89±7.95 mmHg vs 60.36±5.92 mmHg), and (80.81±9.98 mmHg vs 78.00±9.22 mmHg), respectively. The overall infusion rates of morphine and vasopressor (NE) were significantly higher in Group I compared with Group II (4.16±0.32 ml/hr vs 2.02±0.21 ml/hr) and (11.22±1.70 mcg/min vs 3.33±2.61 mcg/min), respectively. Regarding consumption rate of prokinetics (PROK) of either erythromycin or metoclopramide, the PROK rate and GRVs were significantly lower in Group II compared with Group I (21 (28.38%) vs 47 (60.26%)) and (154.10±9.8 ml vs 175.65±7.70 ml), 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.

IV. Discussion

A total of 152 patients were included in this study divided into two different groups according to the titratable morphine co-infusion with or without ketamine fixed dose at rate of 5 mcg/kg/min, Group I and II, with 78 participants and 74 participants in each group, respectively. The anthropometric data for the patients included in the study is illustrated in Table 1, with a mean age of 57.94±9.37 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. 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. Hemodymanics were reported to be higher in patients receiving ketamine continuous infusion while vasopressors' requirements (mostly norepinephrine) were reduced or unchanged. [9] In our study, the two studied groups were norepinephrine as a vasopressor. By comparing the results, the patients who were on ketamine co-infusion recorded a noticeable increase in MAP compared to baseline measurements, in addition to, decreased requirements of NE. NE_{rate} needed to maintain hemodynamic stability in Group I was significantly higher than Group II. 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 the two tested groups but variably with magnitude increase the lowest among patients receiving ketamine co-infusion with morphine, as illustrated in Table 1. This conclusion was further confirmed by the percent of patients administered Prokinetics within Group I and Group II.

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The aforementioned conclusions may be primarily explained by the significant lower requirement of morphine to maintain the target RASS, and the requirement of vasopressor to maintain the target MAP in Group II vs Group I. These observations may strength the theories surrounding the dual advantages of ketamine as anti-hyperalgesia, and hemodynamic supporter. 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-II. 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, hemodynamics, admission days, mortalities, and other measurable variables.

Variable		Total (N=152)	Group I Mean±SD (N=78)	Group II Mean±SD (N=74)	P-value
Gender	M	106 (69.74%)	58 (74.36%)	48 (64.86%)	0.211 (NS)
	F	46 (30.26%)	20 (25.64%)	26 (35.14%)	
Age (Yrs)		57.94±9.37	56.56±11.05	58.93±8.94	0.59 (NS)
BW (Kg)		74.05±10.23	75.08±10.03	72.93±11.3	0.796 (NS)
BMI (Kg/m^2)		25.90±3.97	26.12±4.08	25.92±4.13	0.471 (NS)
CRP (mg/dl)		13.19±4.27	15.27±6.24	12.42±3.72	0.054 (NS)
ALB (g/dl)		2.31±0.18	2.25±0.19	2.40±0.15	0.045 (S)
CRP:ALB		5.72±2.45	6.94±3.81	5.29±2.12	0.058 (NS)
TCI (Cal/day)		651.6±79.5	615.0±80.1	666.5±64.6	0.037 (S)
PD (g/100 Cal)		1.45±0.68	1.56±0.71	1.65±0.80	0.041 (S)
BUN (mg/dl)		14.87±5.27	13.74±4.76	15.88±6.23	0.438 (NS)
∑FLUD I (ml/day)		2709±422	2781±369	2550±419	0.250 (NS)
Pre ICU Days		4.32±3.95	3.85±3.51	5.52±6.10	0.367 (NS)
ICU Days		12.76±4.95	12.26±4.73	14.22±5.64	0.002 (S)
Hospital Days		17.07±6.98	16.10±6.59	19.74±7.44	0.046 (S)
BG (mg/dl)		188.7±6.7	187.5±4.7	191.8±9.8	0.087 (NS)
Temp (°C)		7.95%±2.7%	7.56%±2.4%	8.2%±2.8%	0.623 (NS)
NE_{rate} (mcg/min)		7.73±4.50	11.22±1.70	3.33±2.61	0.000 (S)
Morphine (mg/hr)		2.30±1.75	4.16±0.32	2.02±0.21	0.000 (S)
GRV_0 (ml)		144.43±8.42	146.33±6.51	143.37±9.1	0.586 (NS)
GRV_1 (ml)		160.99±14.3	175.65±7.70	154.10±9.8	0.000 (S)
SBP_0 (mmHg)		105.07±11.3	110.05±11.9	99.15±10.9	0.000 (S)
SBP (mmHg)		105.36±14.5	99.08±10.65	104.2±11.5	0.000 (S)
DBP_0 (mmHg)		64.53±6.39	67.00±6.70	60.93±7.76	0.000 (S)
DBP (mmHg)		64.72±8.34	60.36±5.92	63.89±7.95	0.000 (S)
MAP_0 (mmHg)		82.32±9.64	86.59±10.23	76.93±9.48	0.000 (S)
MAP (mmHg)		82.54±12.03	78.00±9.22	80.81±9.98	0.000 (S)
HR_0 (bpm)		87.11±8.02	84.21±8.04	90.85±9.47	0.001 (S)
HR (bpm)		93.32±10.92	92.64±8.94	95.33±10.0	0.000 (S)
Overall ICU Survival		91 (59.87%)	37 (47.44%)	54 (72.97%)	0.001 (S)
Overall ICU Mortality		61 (40.13%)	41 (52.56%)	20 (27.03%)	
$PROK_0$	NO	118 (77.63%)	56 (71.79%)	62 (83.78%)	0.754 (NS)
	YES	34 (22.37%)	22 (28.21%)	12 (16.22%)	
PROK	NO	84 (55.26%)	31 (39.74%)	53 (71.62%)	0.002 (S)
	YES	68 (44.74%)	47 (60.26%)	21 (28.38%)	

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

Group I: Septic critically ill patients who were on Morphine infusion. **Group II: Septic critically ill patients who were on Morphine/Ketamine co-infusion**

Ketamine infusion was prepared according to our institutional protocol by mixing 400 mg of Ketamine with 100 ml normal saline to yield a Ketamine solution ready for infusion at a fixed rate of 5 ml /hr which is equivalent to approximately 5 mcg/kg/min.

N: Number of Patients.
SD: Standard Deviation.
S: Significant.
NS: Non-Significant.
0: Baseline at admission.
BW: Body Weight.
BMI: Body Mass Index.
NE: Norepinephrine.
SBP: Systolic Blood Pressure.
DBP: Diastolic Blood Pressure.
CRP: C-reactive protein.
Mg: Magnesium.
BG: Blood glucose.
K: Potassium.
Temp: Temperature.
M: Male.
F: Female.
MAP: Mean Arterial Pressure.
HR: Heart Rate.
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.
ICU: Intensive care unit.
GRV: Gastric residual volume.
PROK: Prokinetic.

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REFERENCES

[1] McGrane S, Pandharipande PP. Sedation in the intensive care unit. Minerva Anestesiol. 2012;78:369–80.
[2] Groetzinger LM, Rivosecchi RM, Bain W, Bahr M, Chin K, Mcverry BJ, et al. Ketamine Infusion for Adjunct Sedation in Mechanically Ventilated Adults. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2018;38:181–8.
[3] Garber PM, Droege CA, Carter KE, Harger NJ, Mueller EW. Continuous Infusion Ketamine for Adjunctive Analgosedation in Mechanically Ventilated, Critically Ill Patients. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2019;39:288–96.
[4] Wiatrowski R, Norton C, Giffen D. Analgosedation: Improving Patient Outcomes in ICU Sedation and Pain Management. Pain Management Nursing 2016;17:204–17.
[5] Patanwala AE, Martin JR, Erstad BL. Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. Journal of Intensive Care Medicine 2015;32:387–95.
[6] Reese JM, Sullivan VF, Boyer NL, Mount CA. A Non-Comparative Prospective Pilot Study of Ketamine for Sedation in Adult Septic Shock. Military Medicine 2018;183.
[7] Tedders KM, Mcnorton KN, Edwin SB. Efficacy and Safety of Analgosedation with Fentanyl Compared with Traditional Sedation with Propofol. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2014;34: 643–7.
[8] Sizar O, Gupta M. Opioid Induced Constipation. [Updated 2019 Jun 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-.
[9] Miller, A. C., Jamin, C. T., and Elamin, E. M. Continuous intravenous infusion of ketamine for maintenance sedation. *Minerva Anestesiol*. 2011;77: 812–820.

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