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Title	**The Benefit of Adding Lidocaine to Ketamine During Rapid Sequence Endotracheal Intubation in Patients with Septic Shock: A Randomised Controlled Trial**
Citation	Fathy S, Hasanin A, Mostafa M, Ramzy E, Sarhan K, Almenesey T, Safina AG, Hosny O, Hamden GA, Gado AA, Mokhtar A. The benefit of adding lidocaine to ketamine during rapid sequence endotracheal intubation in patients with septic shock: A randomised controlled trial. Anaesth Crit Care Pain Med. 2020 Sep 5.
Introduction	Patients with septic shock commonly require endotracheal intubation in emergency departments and intensive care units and also frequently need urgent surgical intervention. The current sepsis guidelines recommend rapid implementation of source control surgical interventions, which are usually performed under general anesthesia.[1] Most of the drugs used for induction of anesthesia negatively impact patient hemodynamics and positive pressure ventilation decreases the venous return and aggravates the hypotensive effect of induction drugs. Thus, endotracheal intubation is usually associated with hypotension. [2,3] Post-intubation hypotension is associated with organ dysfunction and increases 30-day postoperative mortality rates.[4] Ketamine is considered an induction agent that provides positive hemodynamic profile; therefore, it had been suggested for use in hypotensive patients.[7] However, ketamine had shown direct inhibitory effect on cardiac muscle in vitro. Thus, caution was recommended when using ketamine in hemodynamically vulnerable patients [8,9] Possibly using lower doses of ketamine during induction of anesthesia might result in better hemodynamic response during this critical period. [10] The available data for lidocaine had not shown any negative hemodynamic effect with sedative doses in humans, thus, it's hypothesized that its use as an adjuvant to ketamine during induction of anesthesia in patients with septic shock could provide a better hemodynamic profile compared to full-dose ketamine. [11] Both groups of patients also received 0.05 mg/kg of midazolam prior to intubation.
Objective	The primary objective was to evaluate the clinical benefit of using ketamine in combination with lidocaine vs ketamine alone for rapid-sequence-intubation in patients with septic shock.

Study Design	A 7-month randomized, double-blinded, controlled study was conducted in Cairo University Hospital in Egypt. Inclusion criteria: Ages 18-65, with septic shock scheduled for emergency surgery. All patients were also on norepinephrine drips. Exclusion criteria: Patients with; cardiac arrhythmias, head trauma, burns, or skin lesions which impaired placement of cardiometry electrodes. Primary outcomes: Average MAP through invasive blood pressure monitoring during the first 5 minutes after induction of anesthesia. Other outcomes: Frequency of post-intubation hypotension Frequency of bradycardia Cardiovascular data: heart rate and cardiac output Serum lactate Central venous blood gas levels: pH, O_2 saturation, and HCO3
Statistical Analysis	Continuous data were analyzed using the unpaired t-test (for normally distributed data) and using the Mann–Whitney test. Categorical data was expressed as frequency (%) and were analyzed using the Chi squared test or the Fisher's exact test. Continuous data were tested for normality using the Shapiro-Wilk test and were presented as either mean (standard deviation), or median (quartiles). For repeated measures, general linear model was used to run mixed Analysis of Variance (ANOVA) test. Post-hoc pairwise comparison was performed using the Bonferroni test. H_0= No significant difference found in either arm from baseline or after completion. H_A= Significant difference found in either arm from baseline or after completion. A P value of < 0.05 was considered statistically significant.

Results	<u>Baseline characteristics:</u> Total patients enrolled = 43 patients Intervention arm (ketamine and lidocaine) (n=21); control arm (ketamine) (n=22) Patient demographics (Table 1): Mean age: 47 (intervention arm) 49 (control arm) Mean weight: 76 kg (intervention arm) 77 kg (control arm) Baseline MAP: 78 (intervention arm) 75 (control arm) Heart rate: 107 (intervention arm) 110 (control arm) Baseline cardiac output (L/min): 6 (intervention arm) 6 (control arm) Baseline norepinephrine dose (mcg/kg/min): 0.26 (intervention arm) 0.17 (control arm) Overall, the patients in both arms were comparable in all baseline parameters. Primary outcome: Average MAP in the first 5 minutes s/p induction (Table 2) The MAP was 82.8 in the intervention arm and was 73 in the control arm. In the intervention arm, the MAP was elevated by roughly 10 mmHg. Secondary outcome: Frequency of hypotension (Table 2) Hypotension only occurred in 1 patient in the intervention arm and occurred in 17 patients in the control arm. Baseline SCvO2, HCO3, lactate and pH were comparable between the two groups. Hemodynamic variables cardiac output and heart rate were comparable between both study groups.
Author's Conclusion	The use of the lidocaine-ketamine combination was associated with a better hemodynamic profile compared to ketamine full-dose when used for endotracheal intubation in patients with septic shock.
Strengths	Appropriate study design – prospective review The study had clear objectives and the primary and secondary outcomes were appropriate for the goals of the study. The tests analyzed were appropriate for the measured outcomes. The patient population analyzed was appropriate. The author listed several limitations of the study. The statistical analyses performed were appropriate and the Mann-Whitney U test, a nonparametric test, allows for both arms to be compared without assuming the values are distributed normally.

Limitations	Authors Limitations: It is a single center study with a relatively small sample size. The study included septic shock patients, mostly abdominal sepsis . The mean dose of norepinephrine in our patients was 0.2 mcg/kg/min. High dose norepinephrine was previously mentioned > 0.3 mcg/kg/min; therefore, patients with higher dose of norepinephrine might show different response to our intervention. We used a non-invasive method for cardiac output measurement; however, the validity of electrical cardiometry was acceptable as a trend monitor in various previous reports. We did not use a monitor for depth of anaesthesia such as bispectral index to guide induction of anaesthesia. However, it had been recently reported that lidocaine confounds bispectral index readings; this was explained by the subcortical actions of lidocaine, which are not revealed by bispectral index. The study was conducted in Cairo, Egypt and only studied patients within the region. The data collected from this study may be only applicable to the population in which the study was conducted.
Evaluator's Conclusion / Clinical Application	This study is, for the most part, an adequate study. I would prefer it if this study was conducted for a longer period of time which would allow its sample size to increase. Based on current literature and the results of this study, the use of ketamine and lidocaine in combination for RSI would be very beneficial in preserving hemodynamics for the patient. Future prospective studies: Future studies are warranted to confirm our findings to other categories of shock. Further studies are also required in elderly population who were excluded in the current study. Further studies in different geographical regions.

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