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Comparison of Norepinephrine & Terlipressin vs Norepinephrine Alone for Management for Septic Shock

Madhav Navlekar[1], Harshil Mehta[2]

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Abstract

Introduction: Sepsis is a clinical syndrome that has physiologic, biologic, and biochemical abnormalities caused by a dysregulated inflammatory response to infection. The present study aimed to estimate the dose of injection of norepinephrine in micrograms/ kg/min after 12 hours of starting the vasopressor infusion to keep an MAP of above 65 mm Hg.

Materials & Method: The study was done for the period of two years. Patients who were 18 years and above; who were diagnosed with septic shock during their ICU course and whose relatives gave informed written consent were included in the study.

Resuly: Total of 12 patients were lost during the study period and so in total 100 patients were enrolled for the study. Both the groups were comparable with respect to the MAP (p = 0.655). The norepinephrine dose in group I vs group II at 12 hours was found to be 0.163 ± 0.089 vs 0.396 ± 0.18 µg/kg/min (p <0.001). Reduction in blood lactate concentration in 12 hours was significantly higher in group I [1.479 ± 1.46] than group II [0.08 ± 1.50] mmol/L (p = 0.002). Increase in the urine output of the patients in 12 hours in Group I [0.72 ± 0.44] than group II [0.47 ± 0.460] mL/kg/hour (p = 0.001).

Conclusion: A low-dose continuous infusion of terlipressin may have a significant role in ensuring better organ perfusion, preventing renal injury, and improving the SOFA score of the patients when used in adjunct to norepinephrine, early in the management of septic shock.

Keywords: norepinephrine; terlipressin; septic shock.

Author's Affiliation: [1]Associate Professor, [2]Assistant Professor, Department of Emergency Medicine, Gujarat Adani Institute of Medical Science, Bhuj, Kutch-370001, Gujarat, India.

Corresponding Author: Harshil Mehta, Assistant Professor, Department of Emergency Medicine, Gujarat Adani Institute of Medical Science, Bhuj, Kutch-370001, Gujarat, India.

E-mail: researchguide86@gmail.com

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INTRODUCTION

Sepsis is a clinical syndrome that has physiologic, biologic, and biochemical abnormalities caused by a dysregulated inflammatory response to infection. This syndrome, especially in the absence of early recognition and prompt treatment, may evolve into septic shock, which is a more severe illness with a much higher mortality rate despite the broad implementation of life support measures

in the intensive care unit.[1-3]

In the background of sepsis, when patients are unable to maintain mean arterial pressure (MAP) of 65 mm Hg despite adequate fluid resuscitation by crystalloids (30 mL/kg) and have elevated blood lactate levels of more than or equal to 2 mmol/L, diagnoses of septic shock is made. This combination has been linked to hospital death rates of more than 40%.[3,4]

For septic shock, vasoactive drugs are important means to maintain the stability of hemodynamics and ensure the perfusion of major organs. Norepinephrine (NE) is the first-line drug for septic shock (Singer et al., 2016).[5] However, NE mainly acts on the alpha-adrenergic receptor (alpha-receptor) of peripheral vascular resistance, which can increase cardiac after-load and thus reduce the volume responsiveness of patients. What's more, NE may induce life-threatening arrhythmia.[4,6]

Vasopressin is an endogenously released peptide hormone and exerts vasoconstriction effect via stimulating specific receptors mainly V1 receptors. A previous study indicated the survival benefit in terlipressin.[7]

Recent guideline also referred the use of vasopressin as potential rescue agents in catecholamine-refractory septic shock. However, in the vasopressin and septic shock trial (VASST), low-dose AVP failed to reduce overall mortality compared with norepinephrine in patients with septic shock. Therefore, terlipressin (tricyl-- lysine vasopressin), a synthetic analog of vasopressin, has attracted attention for its similar pharmacodynamic profile but greater selectivity of V1 receptor.[7]

Hence, there lies the potential for starting a low-dose continuous infusion of terlipressin early in the management of septic shock and norepinephrine to attain better organ perfusion and MAP without significantly increasing the dose of either of them, thus avoiding their dose-dependent deleterious side effects.[7-9] The present study aimed to estimate the dose of injection of norepinephrine in micrograms/kg/min after 12 hours of starting the vasopressor infusion to keep an MAP of above 65 mm Hg.

MATERIALS & METHOD

The present study is the randomized control study that was done in the medical college and associated hospital. The institutional ethical committee was informed about the study procedure and the ethical clearance certificate was obtained prior to the start of the study. The study was done for the period of two years. Patients who were 18 years and above; who were diagnosed with septic shock during their ICU course and whose relatives gave informed written consent were included in the study.

The following patients were excluded from the study:

Lack of consent, known cardiovascular impairment, unstable coronary artery disease, stroke or head injury, chronic renal failure on maintenance dialysis, advanced stages of malignancy, acute mesenteric ischemia, Raynaud's disease, pregnant women, patients with transplanted organs, and known hypersensitivity to norepinephrine or terlipressin. When patients were unable to sustain a mean arterial blood pressure of 65 mm Hg despite requisite fluid resuscitation by crystalloids (30 mL/kg) and had elevated blood lactate levels, more than 2 mmol/L were diagnosed to have septic shock.

The participants were recruited and randomized by using a computer-created random number technique using the allocation ratio 1:1. The group allocation numbers were concealed in sealed opaque envelopes, each of which was opened just before starting the vasopressor.

Patients belonging to group I received a combination of injection terlipressin 0.02 µg/kg/min (fixed dose) infusion and injection norepinephrine (0.01–3) µg/kg/min infusion. Patients allocated to group II received an injection of norepinephrine (0.01–3) µg/kg/min infusion. If the maximum dose of injection norepinephrine (3 µg/kg/min) infusion was reached, and administration of any other vasopressor was warranted, the concerned patient was excluded from the study and managed as per the standard ICU guidelines of using multiple vasopressors in septic shock patients.

In group I, when the MAP of 65–70 mm Hg was achieved, the vasopressors were tapered down, and while tapering down the vasopressors, injection norepinephrine was tapered down first. It was titrated to keep the MAP of 65–70 mm Hg. The infusion of terlipressin was discontinued at the end of 12 hours of study, while the infusion of norepinephrine was continued to achieve the target MAP.

The primary outcome was to study the dose of norepinephrine required to achieve target MAP (65–70 mm Hg) after 12 hours of starting the infusion. The secondary outcomes were duration of vasopressor requirement, changes in lactate level at 12 hours post-initiation of the vasopressor infusion, urine output in mL/hour at 12 hours post-initiation

of the vasopressor infusion, changes in the SOFA score at 12 hours post-initiation of the vasopressor infusion, and incidence of serious adverse events like digital ischemia, cardiac arrhythmias, the incidence of diarrhea, and upper gastrointestinal bleed (GI bleed).

Parameters observed every 2 hours were dose of injection norepinephrine required to maintain an MAP of above 65 mm Hg, heart rate, MAP, and urine output. The parameters observed at the beginning of the study and at the end were serum lactate level, serum procalcitonin, serum creatinine, C-reactive protein value, and SOFA score. The total duration of vasopressor support and the SOFA score of the survivors at discharge from the ICU were noted. Incidences of the adverse effects of terlipressin like ischemia of digits, arrhythmias, diarrhea, and bleeding manifestations were also noted.

Statistical Analysis

The data normality was checked by using Shapiro–Wilk test. The quantitative data with normal distribution were presented as the means ± SD, and the data with non-normal distribution as median with 25th and 75th percentiles (interquartile range). The comparison of the quantitative and normally distributed variables was analyzed using independent test (for two groups). For statistical significance, a p-value of less than 0.05 was considered statistically significant. The data entry was done in the Microsoft EXCEL spreadsheet, and the final analysis was done using Statistical Package for Social Sciences (SPSS) software.

RESULTS

In the present study, 140 patients were assessed for eligibility; 28 patients were excluded at the beginning of the study as they did not meet the inclusion criteria. Total of 12 patients were lost during the study period and so in total 100 patients were enrolled for the study. Both the groups were matched for age, weight, and gender distribution.

Both the groups were comparable concerning the heart rate, MAP, serum creatinine, serum lactate, serum procalcitonin, serum hs-CRP, dose of norepinephrine, urine output, and SOFA score at the beginning of the study.

After 12 hours of Initiation of Vasopressor Therapy Both the groups were comparable with respect to the MAP (p = 0.655). The norepinephrine dose in group I vs group II at 12 hours was found to be 0.163 ± 0.089 vs 0.396 ± 0.18 μg/kg/min (p <0.001). Reduction in blood lactate concentration in 12 hours was significantly higher in group I [1.479 ± 1.46] than group II [0.08 ± 1.50] mmol/L (p = 0.002). Increase in the urine output of the patients in 12 hours in Group I [0.72 ± 0.44] than group II [0.47 ± 0.460] mL/kg/hour (p = 0.001).

Both the groups were comparable with respect to heart rate, serum creatinine, and serum hs-CRP after 12 hours of initiation of vasopressors. However, serum procalcitonin level was higher in group II as compared to group I. The combination of terlipressin and norepinephrine caused a more significant reduction in SOFA score in 12 hours than norepinephrine alone, but both groups were comparable with respect to SOFA score at discharge from ICU among the survivors. The combination of terlipressin and norepinephrine caused a more significant reduction in total duration of vasopressor administration than norepinephrine alone in patients being discharged from IC.

The incidence of digital ischemia was significantly higher in group I as compared to group II. However, the incidence of cardiac arrhythmias and the requirement of renal replacement therapy were significantly higher in group II than in group I. p-value could not be calculated as more than two cells had an expected count of less than 5. Incidence of death was 22 out of 50 patients in group I and 18 out of 50 in group II (p = 0.42); that is, both groups were comparable for mortality during their ICU stay.

DISCUSSION

Our study emphasizes that a low-dose continuous infusion of terlipressin could help norepinephrine in attaining early resuscitation goals for management of patients with septic shock without causing the side effects related to catecholamines.

Terlipressin is a synthetic analogue of vasopressin which has greater affinity for the V1 receptor that is the mechanism of vascular smooth muscle vasoconstriction in response to vasopressin and thus could be associated with less side effects than vasopressin.[10,11] Therefore, terlipressin, a selective V1 agonist, when used in treating septic shock patients, can lead to an increase in urine output. According to animal studies, terlipressin might preserve the functionality of organs by enhancing myocardial contractility, kidney function, and altering vascular permeability in septic shock.[12,13]

Liu et al.14, in the post hoc analysis of their trial, reported a higher reduction in serum creatinine

in the terlipressin group on days 5 and 7 than the norepinephrine group after randomization. In harmony with results from previous studies, our study showed a more significant reduction in blood lactate levels when terlipressin was added to the vasopressor therapy. Since serum lactates are a surrogate marker of end-organ perfusion, it can be safely said that incorporating a low-dose continuous infusion of terlipressin improves organ perfusion to a large extent.[15]

A high SOFA score is associated with significantly increased mortality, and a swift improvement in SOFA score has been linked with a reduced probability of death. Our study demonstrates that compared to baseline (zero hours of study), the SOFA score at 12 hours of study improved significantly in the patients administered the combination of terlipressin and norepinephrine as compared to norepinephrine alone. This signifies that low-dose terlipressin, when added to norepinephrine, helped in better organ perfusion and hence better organ functionality.

One of the most important findings in the study by Liu et al. was that patients who received terlipressin combined with norepinephrine had a greater frequency of digital ischemia than those who received norepinephrine alone. According to them, the reason is that the maximum amount of terlipressin they administered (4 mg/day) was higher than the maximum dose (1–2 mg/day) reported in previous trials. Excessive vasoconstriction and, as a result, peripheral ischemia may have resulted from this high dose of terlipressin. Our study demonstrated a higher incidence of digital ischemia (28%) in the terlipressin group than in the abovementioned study.

Though the mortality of patients administered with the combination of terlipressin and norepinephrine (44%) was higher than in patients administered norepinephrine alone (36%), the difference between the two groups was statistically nonsignificant ($p > 0.05$). Double-blinded randomized control trials including a higher number of participants and a more extended study period are needed to assess the effects of using the combination of terlipressin and norepinephrine on the mortality of the patients with septic shock.

CONCLUSION

A low-dose continuous infusion of terlipressin may have a significant role in ensuring better organ perfusion, preventing renal injury, and improving the SOFA score of the patients when used in adjunct to norepinephrine, early in the management of septic shock.

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