ORIGINAL ARTICLE

Comparison of Norepinephrine and Terlipressin vs Norepinephrine Alone for Management of Septic Shock: A Randomized Control Study

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Abstract

Purpose: To compare norepinephrine and terlipressin vs norepinephrine alone for management of septic shock.

Materials and methods: In this prospective, randomized control trial, 50 adult patients with septic shock were randomized into two groups. Group I received a combination of injection terlipressin 0.02 µg/kg/min (fixed dose) infusion and injection norepinephrine 0.01 µg/kg/min infusion and group II received injection norepinephrine 0.01 µg/kg/min infusion alone. Dose of noradrenaline in both the groups was titrated to achieve the target MAP of 65–70 mm Hg. The data collected were the dose of norepinephrine required to maintain an MAP of above 65 mm Hg, urine output, serum lactate, procalcitonin level, C-reactive protein, sequential organ failure assessment (SOFA) score, total duration of vasopressor support, and incidences of the adverse effects.

Results: The norepinephrine dose in group I vs group II at 12 hours was found to be 0.141 ± 0.067 vs 0.374 ± 0.096 µg/kg/min ($p \leq 0.005$). The serum lactate was lower, and urine output was higher in group I than group II ($p < 0.05$). Group I had a significantly greater reduction in SOFA score in 12 hours than group II. Group I patient also had a significant decrease in the duration of vasopressor administration than group II patients being discharged from the ICU. However, there was no difference in the mortality between the two groups during their ICU stay.

Conclusion: A low-dose continuous infusion of terlipressin and norepinephrine could help attain early resuscitation goals for managing patients with septic shock.

Keywords: Norepinephrine, Septic shock, Terlipressin.

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Introduction

Sepsis is a potentially life-threatening disorder that arises when the body's immune system, in response to an infection, attacks its tissues, thus hampering the normal functioning of the organs. 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%.[1,2]

Norepinephrine has long been the first-line recommended vasopressor to treat hypotension after initial fluid resuscitation in septic shock.[3] On the other hand, high-dose catecholamine therapy may have unintended consequences such as increased myocardial oxygen requirements, fatal tachyarrhythmia, immune paralysis, increased cellular energy expenditure, and bowel ischemia.[4–9] Therefore, it becomes extremely crucial to find other vasoactive drugs as an alternative or accessory to norepinephrine to incur its benefits while avoiding its side effects in septic shock.

Vasopressin is a peptide hormone released by the posterior pituitary gland that causes vasoconstriction via stimulating mainly the V1a receptors present on the smooth muscles of blood vessels. The endogenous levels of vasopressin tend to get inappropriately low in cases of sepsis, thus leading to vasodilatation induced hypotension.[10–13] As it causes aggregation of platelets and release of von Willebrand's factor, vasopressin is known to have procoagulant properties. Furthermore, it leads to the release of coagulation factors due to stimulation of extrarenal V2 receptors. It also tends to cross-activate oxytocin receptors and purinergic receptors and is also known to cause hyponatremia and hyperbilirubinemia.[13–15]

Terlipressin (triacyl-lysine vasopressin), a long-acting synthetic analogue of vasopressin, has a similar pharmacodynamic profile but exerts higher selectivity for the V1 receptor.[16] Hence, terlipressin produces potent vasoconstriction of blood vessels without causing damaging side effects like that of vasopressin. It restores vascular reactivity in the vasodilated blood vessels of a patient with sepsis and thus enhances their sensitivity to endogenous and exogenous catecholamines.[17] It is currently being used in specific settings as

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a last resort vasopressor in the late stages of septic shock when a high dosage of catecholamines cannot treat hypotension.[9,17–19]

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. We hypothesized that the use of terlipressin reduces the requirement of norepinephrine to achieve target MAP and subsequently improves organ perfusion. The present study aimed to estimate the dose of injection of norepinephrine in micrograms/kg/min after 12 hours of starting the vasopressor (terlipressin) infusion to keep an MAP of above 65 mm Hg.

Materials and Methods

Study Design and Settings

This prospective, open-label, randomized control study was conducted in a tertiary care center's adult intensive care unit. Approval was taken from the Institutional Ethics Committee of All India Institute of Medical Sciences, Jodhpur, India (IEC Reg No.—AIIMS/IEC/2019-20/815 dated June 20, 2019), and the study was registered with Clinical Trial Registry—India (CTRI Reg. No. CTRI/2019/10/021484 dated 01 October 2019). Enrollment of patients started in October 2019 and ended in January 2021. Patients 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 [cardiac index (CI) less than 2.2 L/min/m^2], unstable coronary artery disease (acute angina or myocardial infarction in the course of septic shock, based on history, cardiac biomarkers and electrocardiogram), 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.

Clinical criteria given by the third international consensus definitions for sepsis and septic shock were used to diagnose patients included in the trial. Patients who were suspected or microbiologically documented to have an infection and showed a rise of SOFA score by two or more points were diagnosed with sepsis. 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.

Interventions

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. Dose of noradrenaline in both the groups was titrated to achieve the target blood pressure of 65–70 mm Hg at the earliest keeping in line with the recommendations of the Hour-1 bundle of Surviving Sepsis Campaign guidelines.[2]

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.

Intravenous fluids, empirical antibiotics depending on the microbiological epidemiology of our institute, and eventual modification based on the patient's culture positivity were all part of standard ICU medical treatment apart from the vasopressor as mentioned earlier therapy. Slow low-efficient dialysis (SLED) was used for renal replacement therapy in refractory acidosis, progressive azotemia, hyperkalemia, or anuria.

Outcome Measures

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).

Data Collection

To achieve the aims and objectives of this study, various parameters were observed for the study period of 12 hours. 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.

Sample Size Calculation

The sample size was determined using data from a TERLIVAP study done by Morelli et al.[18] In their study, the norepinephrine requirement in the norepinephrine group was found to be 1.2 ± 1.4 µg/kg/min as opposed to 0.2 ± 0.4 µg/kg/min in the terlipressin group. Using this data, taking a confidence level of 95 and 5% level of significance, the sample size was computed to be a total of 44 (22 in each group) and adding 10% of patients as a loss to follow up; the sample size was determined to be 25 in each group.

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). The comparison of the quantitative and not normally distributed variables was analyzed using the Mann–Whitney test (for two groups). The comparison of the variables that were ordinal in nature was analyzed using Mann–Whitney test (for two groups). The odds ratio was used to see the association of any adverse events with the intervention. 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, IBM manufacturer, Chicago, USA, version 21.0.

Results

In the present study, 70 patients were assessed for eligibility; 14 were excluded at the beginning of the study as they did not meet the inclusion criteria. Total fifty-six patients were enrolled and randomized for the study. However, six patients were not included for data analysis due to the initiation of additional vasopressors besides norepinephrine and terlipressin. Finally, fifty patients were analyzed, and the results were computed (Flowchart 1). Both the groups were matched for age, weight, and gender distribution (Table 1).

At the Beginning of the Study

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 0.141 ± 0.067 {95% CI (0.113–0.169)} vs 0.374 ± 0.096 {95% CI (0.335–0.415)} µg/kg/min ($p < 0.001$) (Fig. 1). Reduction in blood lactate concentration in 12 hours was significantly higher in group I [1.275 ± 1.24 {95% CI (0.762–1.789)}] than group II [0.060 ± 1.30{95% CI (0.601–(−0.479))}] mmol/L ($p = 0.002$). Increase in the urine output of the patients in 12 hours in Group I [0.512 ± 0.276 {95% CI (0.398–0.626)}] than group II [0.250 ± 0.230 {95% CI (0.155–0.346)}] mL/kg/hour ($p = 0.001$) (Tables 2 and 3).

Both the groups were comparable with respect to heart rate, serum creatinine, and serum hs-CRP after 12 hours of initiation of

Flowchart 1: Consolidated standards of reporting trials (CONSORT) diagram representing the enrolment and randomization of cases

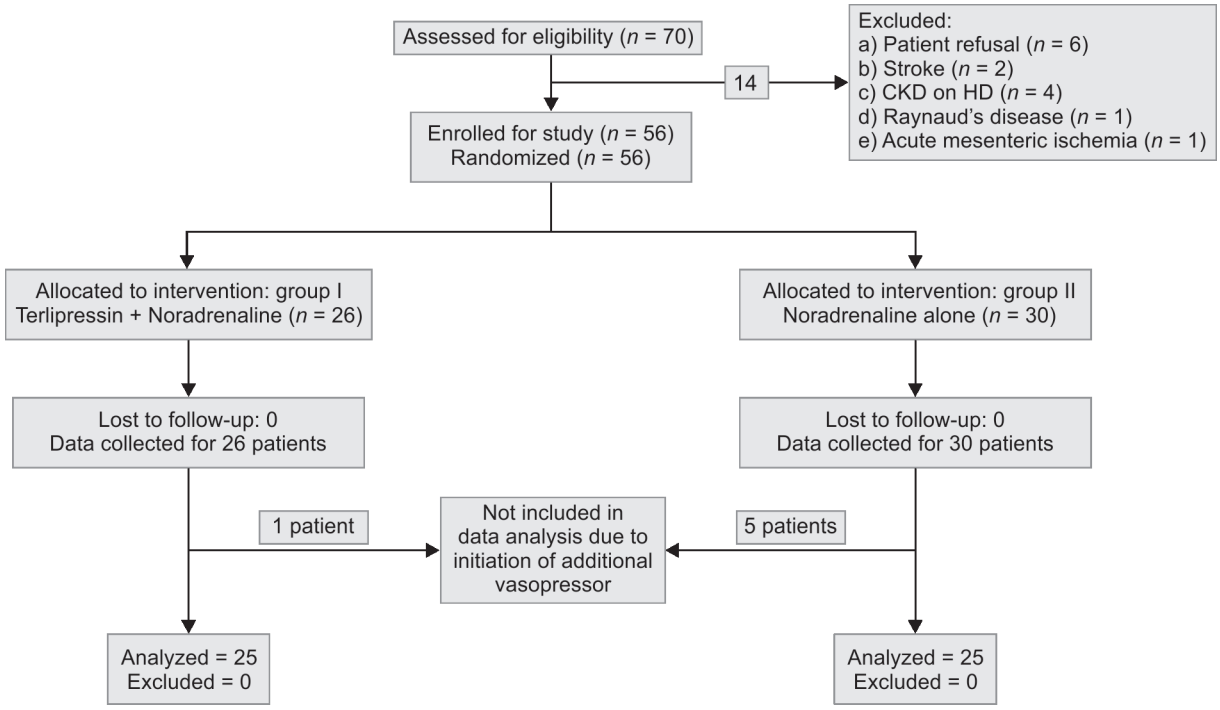

Table 1: Patient's demographic data

Parameter	Group I (n = 25)	Group II (n = 25)	p value	95% confidence interval of mean	
				Group I	Group II
Age (years) Mean ± SD	48.88 ± 17.98	48.84 ± 19.08	0.994	41.46–51.30	40.96–56.72
Weight (kg) Mean ± SD	65.76 ± 10.22	62.12 ± 10.86	0.229	61.54–69.98	57.63–67.61
Gender	Male: 8 Female: 17	Male: 5 Female: 20	0.333	—	—

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 ICU (Tables 2 and 3).

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 (Table 4).

Incidence of death was 11 out of 25 patients in group I and 9 out of 25 in group II ($p = 0.564$); that is, both groups were comparable for mortality during their ICU stay.

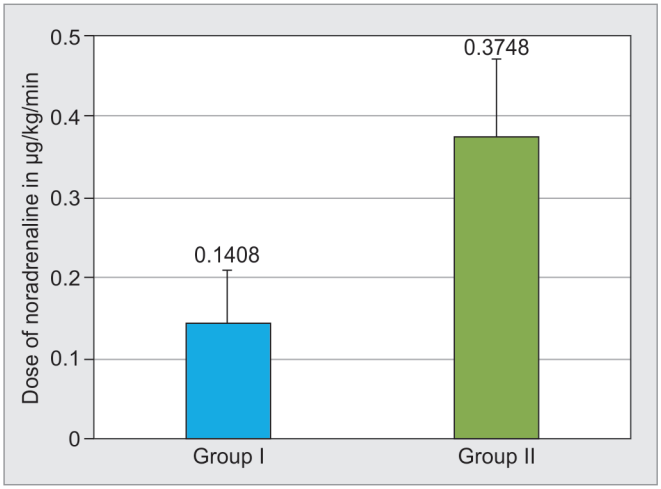

Fig. 1: Bar diagram comparing the mean of dose of noradrenaline after 12 hours of initiation of vasopressors in the two groups

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.

Vasopressin causes efferent arteriolar vasoconstriction (V1 receptor agonism) but does not affect the afferent arterioles, thus boosting the renal blood flow and glomerular filtration rate, leading to increased urine output.[13,19–22] The VANISH trial found that using vasopressin early in the management of adult patients with septic shock lowered the need for renal replacement therapy as opposed to norepinephrine.[19] 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.[19] Liu et al., 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. However, no reduction in the need for renal replacement therapy or incidence of acute kidney injury was appreciated with the use of terlipressin in their study.[23] Since the study period of our study was as short as 12 hours, a significant change in serum creatinine in the terlipressin + norepinephrine could not be demonstrated. However, there was a significant improvement in urine output with the addition of terlipressin, and lesser patients in the T + N group needed renal replacement therapy during their stay in ICU as compared to the N group. It was in consistency with the results of the study by Morelli et al. and Xiao et al.[18,24,25] This draws attention to the role of terlipressin in the improvement of renal functions and prevention of renal injury.

In harmony with results from previous studies,[18,25] 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.

Currently, the SOFA score is widely accepted and utilized to assess the severity and prognosticate in patients with septic

Table 2: Comparison of mean arterial pressure, dose of noradrenaline, blood lactate concentration, and urine output between the study groups at the time of initiation and after 12 hours of initiation of vasopressor therapy as well as change in blood lactate concentration and urine output after the study duration

Parameter					*95% confidence interval for mean*	
Mean ± SD	*Time of study*	*Group I (n = 25)*	*Group II (n = 25)*	*p value*	*Group I*	*Group II*
Mean arterial pressure (mm Hg)	0 hour	57.92 ± 2.842	58.72 ± 2.458	0.292	56.75–59.09	57.71–59.73
	12 hours	69.44 ± 2.78	69.12 ± 2.22	0.655	68.29–70.59	68.20–70.04
Dose of noradrenaline (µg/kg/min)	0 hour	0.205 ± 0.075	0.244 ± 0.079	0.080	0.174–0.236	0.212–0.277
	12 hours	0.141 ± 0.067	0.374 ± 0.096	<0.001*	0.113–0.169	0.335–0.415
Blood lactate concentration (mmol/L)	0 hour	4.408 ± 1.410	4.180 ± 1.112	0.534	3.822–4.986	3.720–4.639
	12 hours	3.129 ± 1.261	4.119 ± 1.032	0.004*	2.606–3.601	3.693–4.545
	Reduction in 12 hours	1.275 ± 1.24	0.060 ± 1.30	0.002*	0.762–1.789	0.601–(−0.479)
Urine output (mL/kg/hour)	0 hour	0.245 ± 0.132	0.288 ± 0.122	0.237	0.191–0.300	0.238–0.339
	12 hours	0.758 ± 0.352	0.539 ± 0.247	0.015*	0.612–0.903	0.437–0.641
	Increase in 12 hours	0.512 ± 0.276	0.250 ± 0.230	0.001*	0.398–0.626	0.155–0.346

*p value <0.05; The difference between both the groups is statistically significant

Table 3: Comparison of heart rate, serum creatinine, serum procalcitonin, serum hs-CRP, and total duration of vasopressors in patients discharged from ICU were not normally distributed in the study; they are being represented as median (IQR)

Parameter median (IQR)	*Time of study*	*Group I (n = 25)*	*Group II (n = 25)*	*p value*
Heart rate (beats/min)	0 hour	96 (89.5, 111)	98 (94, 108.5)	0.768
	12 hours	84 (79.5, 93)	89 (86, 92)	0.144
	Decrease in 12 hours	13 (7, 19.5)	8 (4, 14)	0.082
Serum creatinine (mg/dL)	0 hour	1.12 (0.88, 1.39)	1.17 (0.97, 1.31)	0.764
	12 hours	1.13 (96, 134)	1.48 (1.18, 1.86)	0.091
Serum procalcitonin (ng/dL)	0 hour	8.10 (3.96, 13.56)	8.91 (4.90, 17.81)	0.337
	12 hours	9.31 (5.77, 16.08)	13.13 (8.14, 22.47)	0.044*
Serum hs-CRP (mg/L)	0 hour	103.1 (85.90, 128.85)	96.50 (85.00, 123.70)	0.541
	12 hours	98.1 (84.7, 128.5)	113.80 (85.9, 12.82)	0.535
Total duration of vasopressors among survivors (hours)	—	40.50 (33–52)	89.50 (71.50–108)	<0.001*
SOFA score	0 hour	9 (8, 10)	9 (8.50, 10)	0.230
	12 hours	7 (6, 9.5)	9 (8, 11)	0.004*
	Reduction in 12 hours	2 (1, 2)	0 (−1, 1)	0.002*
	At discharge from ICU	2.50 (1, 3.25)	3 (2, 4)	0.294

SOFA score and APACHE II score between the study groups at the time of initiation and after 12 hours of initiation of vasopressor therapy. *p value <0.05; The difference between both the groups is statistically significant

Table 4: Comparison of adverse events between the two groups

Adverse events	*Yes/no*	*Group I (n = 25)*	*Group II (n = 25)*	*Odds ratio*	*95% confidence interval of odds ratio*
Digital ischemia	Yes	7 (28%)	1 (4%)	9.33	1.05–82.78
	No	18	24		
Cardiac arrhythmia	Yes	1 (4%)	6 (24%)	0.132	0.015–1.19
	No	24	19		
Upper GI bleed	Yes	1 (4%)	1 (4%)	1.000	0.059–16.928
	No	24	24		
Need for RRT	Yes	1 (4%)	6 (24%)	0.132	0.015–1.192
	No	24	19		
Diarrhea	Yes	2 (8%)	7 (28%)	0.224	0.041–1.210
	No	23	18		

shock.[1] 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.[26–28] 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.

The abovementioned organ-protective effect of terlipressin was initially thought to be connected to improving cardiac functions by enhancing myocardial contractility.[18,24] Furthermore, Xiao et al. demonstrated that terlipressin increases the vascular tone and optimizes the hemodynamic in septic shock patients.[25] This action of terlipressin is linked to it enhancing the vascular reactivity by activation of Rho-kinase. The Rho-A-Rho kinase signal pathway and protein kinase C pathway are activated by vasopressin and terlipressin, enhancing MLC20 phosphorylation and calcium sensitivity.[29] This can be the reason for the improvement in urine output and clearance of lactate levels with the use of terlipressin, as found in our study.

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.[18,24,25,30] 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. It might have happened because of the lack of monitoring of pulmonary artery occlusion pressure or IVC collapsibility index as a marker of adequate fluid volume resuscitation, and the sufficiency of fluid administration was left to the judgment of the ICU doctor on duty. Hence, the level of fluid resuscitation might not have been adequate or similar in all patients. Moreover, the background of smoking, tobacco intake, alcohol intake, and atherosclerosis status were not checked. Radial and ulnar artery Doppler was also not done routinely. This re-emphasizes the need for aggressive fluid resuscitation as early as possible in treating septic shock-induced systemic vasodilation[1–3] and adequate monitoring for the same via either pulmonary artery occlusion pressure monitoring or IVC collapsibility index as done in previous studies.[18,25]

In our study, the mean age of the patients who developed digital ischemia in group I was a decade higher than the overall mean age of that group (58.28 vs 48.88 years). Ischemic diseases are commonly associated with aging, implicating that terlipressin may have led to more severe digital ischemia in the older population. None of the patients having digital ischemia in our study needed any surgical intervention.

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.

This study has important limitations. The sample size was limited. The duration of the study was restricted to 12 hours as the primary outcome was to observe the effect of terlipressin on the dose of noradrenaline after 12 hours, and long-term terlipressin infusion may have deleterious effect on organ perfusion and on microcirculation.[23] However, a need is felt to plan a large-scale RCT to observe the effects of long-term dual vasopressor infusion on organ perfusion and mortality of the patients. The sufficiency of fluid administration was left to the judgment of the ICU doctor on duty and was not monitored. The cause of sepsis and septic shock was varied in the patient population, which might have affected the outcome of the patients. A longer study duration is required to evaluate the effect of terlipressin on the patients' overall outcome and assess its adverse effects.

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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