Original Article

Efficacy of phenylephrine versus noradrenaline in management of patients presenting with septic shock in the intensive care unit

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Objective: To evaluate the efficacy of phenylephrine in comparison to nor-epinephrine in patients presenting with septic shock in the intensive care unit of a tertiary care hospital in Pakistan.

Methodology: This study was conducted at the Intensive care Unit of Holy Family Hospital, Rawalpindi Medical College, Rawalpindi, Pakistan over a period of 1 year from Jan 2011 till December 2011. A total of 42 patients presenting with septic shock, were recruited in the study. They were randomly divided in to two groups: Group A included those who received Phenylephrine while group B received Noradrenaline. The aim was to achieve SBP >90 mm Hg and/or MAP >75 mm Hg. The response was considered significant if the subjects achieved and maintained the pre-de?ned targets of therapy for a period of continuous 4-6 hours, in the speci?ed dose range.

Results: There was no considerable difference in amount of ?uid infusion given in both groups. Maximum infusion requirement of Phenylephrine and Noradrenaline were 4.37±1.87µg/kg/min and 3.98±1.31 µg/kg/min, respectively. There was significant increase in post-treatment levels of SBP (75.41±3.22 vs. 103.24±12.32, P<0.05 in group A and 73.89±5.60 vs112.45±3.64, P<0.05 in group B), mean arterial pressures (48.35±4.28 vs. 77.38±3.17, P<0.05 in group A and 47.15±5.02 vs. 75.45±8.24, P<0.05 in group B) and the urine output (0.22±0.02 vs. 0.51±0.04, P<0.05 in group A and 0.19±0.06 vs. 0.55±0.07,P<0.05 in group B) in both the groups. The drop in heart rate was not significant in group B, (post treatment heart rate in group A 114.23±4.86 vs. 145±8.65 in group B) indicating that Phenylephrine did not result in tachycardia.

Conclusion: Phenylephrine infusion was better as compared to Noradrenaline in reversing hemodynamic and metabolic parameters and maintaining a hemodynamic stability without any negative outcomes in intensive care with septicemia. (Rawal Med J 2014;39: 136-140).

Key words: Septic shock, septicemia, phenylepherine, noradrenaline.

INTRODUCTION

Shock is a final common pathway that has been linked with conditions like myocardial infarction, microbial sepsis, pulmonary embolism, significant trauma, and anaphylaxis.[1] It leads to impaired tissue perfusion, cellular hypoxia, and metabolic derangements which in turns cause cellular injury causing progressive organ dysfunction, and death. In septicemia, septic shock has intravascular volume depletion, inadequate and non-uniform distribution of regional blood flow,[2,3] reduced peripheral resistance along with hypotension.[1,3]

Aggressive volume resuscitation along with antibiotics has been the first-line treatment in of sepsis.[4,5] However, the mortality remains high with severe arterial hypotension and organ failure refractory to antibiotic therapy, fluid expansion, and vasopressor treatment.[5] The prime reason for this may be substantial peripheral vasodilatation in these patients.[6] Recent data suggest that tissue oxygenation is a major predictor of morbidity and mortality in patients of septic shock.[6,7]

In order to restore systemic vascular tone so as to ensure adequate tissue perfusion, vasoactive agents are recommended in such patients,[2-4] which have been used to treat the hemodynamic changes associated with shock for a long time.[8] It is used to manipulate the relative distribution of blood flow and restore tissue perfusion.[7-9] Dopamine has been considered as the first-line vasoactive agent, in the management of septic shock. However there are concerns regarding tachyarrhythmia, elevated myocardial oxygen requirements, associated gut ischemia and undesirable endocrine effects with the

use of dopamine.[10] Through dopamine receptors, dopamine increases cardiac output by improving myocardial contractility and at certain doses increasing heart rate. Some studies, however, recommend the use of other presser agents only in patients who are "dopamine-resistant.[11,12]

Noradrenaline is considered to be better than phenylephrine in terms of improvement in myocardial contractility due to additional action on β1-receptors in volume- resuscitated patients.[9-11] However, additional β1-receptor stimulation in the presence of ongoing dopamine infusion will maintain an increased heart rate and the consecutive increase in cardiac output will not be achieved, in absence of adequate cardiac filling. Phenylephrine on the other hand, increases systemic vascular resistance at the expense of decrease in heart rate without any consecutive improvement in cardiac output.[11-13] Phenylephrine has pure alpha activity thus causing veno-arterial vasoconstriction. It causes minimal effects on heart contractility or conductivity.[14] It can lead to an increased systolic, diastolic, and mean arterial pressure. It has little effect on heart rate or contractility thus arrhythmia potentiation is minimal.[13,14] The associated increased oxygen demand may induce coronary ischemia in vulnerable patients, although this is largely theoretic. Phenylephrine's vasoconstrictive effects have been associated with decreased renal and splanchnic perfusion.[1] The aim of this study was to evaluate the efficacy of phenylephrine in comparison to nor-epinephrine in patients with septic shock in the intensive care unit of a tertiary care hospital in Pakistan.

METHODOLOGY

This study was conducted at the Intensive care Unit of Holy Family Hospital, Rawalpindi Medical College, Rawalpindi, Pakistan over a period of 1 year from Jan 2011 till December 2011. Internal Medicine, Critical care and the department of Anesthesia coordinated simultaneously to conduct the research. A total of 42 participants presenting with septic shock were included in the study. The study was approved from the Ethical Committee of the hospital and a written informed consent was obtained from the immediate relatives of the study participants. Septic shock was defined as persistent hypotension, evidence of one or more end organ dysfunction, infection along with two or more additional sepsis clinical features.

Persistent hypotension was labeled as systolic arterial blood pressure (SBP) <90 mm Hg or mean arterial pressure (MAP) <60 mm Hg, despite adequate fluid resuscitation and continuous infusion of pharmacological doses of dopamine 25 μg/kg/min over 45-60 minutes. The additional sepsis criteria included body temperature higher than 38ºC or less than 36ºC, heart rate (HR) greater than 90/min, respiratory rate greater than 20/min, or arterial CO2<32 mm Hg on arterial blood gas, White cell count >12000/ mm3, or < 4000/ mm3. Patients with acute coronary artery disease (CAD), chronic liver disease (CLD), chronic renal failure (CRF) and uncorrected shock due to blood loss were excluded from the study.

The baseline demographic details along with age, gender, weight, height and cause of sepsis were recorded. All subjects were mechanically ventilated with the target to maintain PaO2 more than 60 mm Hg and PaCO2 in a range of 35-40 mm Hg on ABGs. Sedation and analgesia was given by nalbuphine and midazolam. Hemodynamic monitoring was done using continuous electrocardiogram (ECG) and invasive arterial pressure. The systolic, diastolic and MAP were measured at end expiration. Maximal infusion requirement of studied drug, number of responders and urine output (UO) were recorded.

The participants were then randomly divided in to two groups: Group A included participants who received Phenylephrine while group B received Noradrenaline. Each group had 21 (50%) patients. The details of doses were according to table below.

Parameter	Group A	Group B
Dose (Range)	0.5-8ug/Kg/min	0.5-3.5ug/Kg/min
Time (Min)	30	30
Increments	1ug/Kg/min	0.5ug/Kg/min

Baseline parameters were recorded when the infusion of drug was initiated. The assessment of outcome and the response was done at the study end, if achieving the target of therapy among the subjects. Blood pressures, Pulse, Oxygen saturation and ECG recordings were obtained right from the

beginning of the study.

The target of therapy was to achieve stable hemodynamics in terms of SBP >90 mm Hg and/or MAP >75 mm Hg. All the parameters were recorded every 30 min and increment in dose of studied drug was done if targets were not achieved. Serial IV fluid challenges so as to maintain CVP in the normal range along with dopamine infusion at a rate of 25µg/kg/min were continued throughout the study duration. The response was considered significant if the subjects achieved and maintained the pre-defined targets of therapy for a period of continuous 4-6 hours, in the specified dose range.

All the statistical analyses were performed by using SPSS version 15, StatXact 6, and SAS version 8.2. Student's t-test was used to test for differences in ordinal and continuous variables. The chi-square test was used to compare proportions. A p-value <0.05 was considered statistically significant.

RESULTS

The basic parameters had no differences in two study groups (Table 1). ARDS and abscess were commonest causes of shock (Table 2). There was no significance difference in pretreatment parameters in two groups (Table 3).

Table 1. Basic characteristics of Study Participants.

Parameters	Group A Phenylephrine	Group B Noradrenaline	95%CI	P Value
Sex/Total	21	21	NS	NS
Male	16(%)	14(%)		
Female	5(%)	7(%)		
Age(Years)	47±4.2	48±3.3	0.01	0.21
Weight (Kg)	59±3.1	61±2.7	0.02	0.18
Height (cm)	168.3±1.8	163.8±3.5	0.01	0.11
BMI (Kg/m2)	21.4±0.8	20.3±1.1	0.01	0.14

Table 2. Cause of Sepsis in Study Participants.

Prime Cause of Sepsis	Group A (n=21)	Group B (n=21)	P-Value
ARDS	8	9	N.S
Abscess	6	5	N.S
Pneumonia/RTI	3	2	N.S
Polytrauma	2	3	N.S
Fascitis	2	2	N.S

There was no considerable difference in amount of fluid infusion given during the study phase in both groups. Maximum infusion requirement of Phenylephrine and Noradrenaline were 4.37±1.87 µg/kg/min and 3.98±1.31 µg/kg/min, respectively.

Table 3. Pre-Treatment parameters.

Pretreatment Parameters	Group A (n=21)	Group B (n=21)	P-Value
Systolic BP	75.41±3.22	73.89±5.60	N.S
Heart Rate	145.74±6.85	148.21±2.43	N.S
Mean.Art. Pressure	48.35±4.28	47.15±5.02	N.S
Urine Output	0.22±0.02	0.19±0.06	N.S
Serum Lactate	3.28±0.47	3.35±0.39	N.S

There was significant increase in post-treatment levels of SBP (75.41±3.22 vs. 103.24±12.32, P<0.05 in group A and 73.89±5.60 vs112.45±3.64, P<0.05 in group B), MAP (48.35±4.28 vs. 77.38±3.17, P<0.05 in group A and 47.15±5.02 vs. 75.45±8.24, P<0.05 in group B) and urine output (0.22±0.02 vs. 0.51±0.04, P<0.05 in group A and 0.19±0.06 vs. 0.55±0.07,P<0.05 in group B) in both the groups (Tables 4 and 5).

Table 4. Pre and post-treatment parameters in Group-A (Phenylephrine).

Parameter	Pre-Treatment	Post-Treatment	P-Value
Systolic BP (mmHg)	75.41±3.22	103.24±12.32	<0.05*
Heart Rate (rate/Min)	145.74±6.85	114.23±4.86	<0.05*
MAP	48.35±4.28	77.38±3.17	<0.05*
Urine Output	0.22±0.02	0.51±0.04	<0.05*
Serum Lactate	3.28±0.47	2.85±0.42	<0.05*

Table 5. Pre and post treatment parameters in Group-B (Noradrenaline).

Parameters	Pre-Treatment	Post-Treatment	P-Value
Systolic BP	73.89±5.60	112.45±3.64	<0.05*
Heart Rate	8.21±2.43	145±8.65	N.S
MAP	47.15±5.02	75.45±8.24	<0.05*
Urine Output	0.19±0.06	0.55±0.07	<0.05*
Serum Lactate	3.35±0.39	2.79±0.35	<0.05*

There was statistically significant post-treatment reduction of heart rate in group A. The drop in heart rate was not significant in group B, making this study significant (post treatment heart rate in group A 114.23±4.86 vs. 145±8.65 in group B) in terms of conclusion that Phenylephrine is much significant in controlling the tachycardia existing among patients of septicemia (Table 6).

Table 6. Pre and Post treatment parameters in both Groups.

Parameters	Group A	Group B	P-Value
Systolic BP	103.24±12.32	112.45±3.64	N.S
Heart Rate	114.23±4.86	145±8.65	<0.05*
MAP	77.38±3.17	75.45±8.24	N.S
Urine Output	0.51±0.04	0.55±0.07	N.S
Serum Lactate	2.85±0.42	2.79±0.35	N.S

DISCUSSION

Dopamine has been considered as the first-line vasoactive agent, in the management of septic shock.[15-17] However, there are concerns regarding tachyarrhythmia, elevated myocardial oxygen requirements, associated gut ischemia, and undesirable endocrine effects with the use of dopamine.[1] In our study, no difference was observed between phenylephrine and noradrenaline, in terms of improvement in post-treatment SBP, MAP and urine output reflecting renal perfusion. It is primarily due to the α1 agonistic effect of both agents.[18] Noradrenaline is considered to be better than Phenylephrine in terms of improvement in myocardial contractility because of the β1-receptor stimulation.[19,20] Its primary mechanism is to enhance organ perfusion while maintaining the hemodynamic parameters. It is also the drug of choice for patients presenting with either severe sepsis or septic shock at our center.

In contrast to noradrenaline use in the intensive care units, phenylephrine is primarily used in the obstetric anesthesia cases of our hospital. Its prime use is to boost, maintain and stabilize the blood pressures of obstetric patients with tachycardia undergoing cesarean section under regional anesthesia. We use to give intravenous bolus doses of phenylephrine after regular intervals in according to blood pressure. The response is excellent.

Thus, while considering the use of phenylephrine in the intensive care units, particularly in patients of sepsis and septic shock, our goal was to evaluate the efficacy in comparison to noradrenaline in maintaining the hemodynamic stability. In our study, baseline tachycardia along with persistent hypotension was present in both groups. There were statistically significant improvements in tachycardia thus leading to heart rate nearly towards normal with Phenylephrine in comparison to Noradrenaline group. Thus, heart rate stabilization while maintaining blood pressures in our study with phenylephrine was considered to be a major positive outcome.

There was significant increase in the urine output in both the groups. It may be due to increase in glomerular filtrate as a result of efferent arteriolar vasoconstriction with the use of both agents. Further studies are recommended to make a direct relationship between the two and it has been considered as one of the study limitation.

CONCLUSION

Phenylephrine infusion was better as compared to noradrenaline in reversing hemodynamic and metabolic parameters and maintaining a hemodynamically stability without any negative outcomes of patients in intensive care with septicemia.

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