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Original Article

Septic Shock with cardiovascular support: A major role of norepinephrine supplemented with dobutamine or epinephrine

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ABSTRACT

Background: Sepsis remains a major challenge, for intensive care medicine. Mortality rates are quite high from sepsis and septic shock. Norepinephrine is considered first drug of choice here, with epinephrine considered for cardiac depression and dobutamine for myocardial depression.
Methods: A prospective, observational, double-blind study was carried out in the Department of Anesthesia, in collaboration with Department of Medicine, GMC Jammu on 60 adult patients, diagnosed of septic shock. Patients were randomly divided into two equal groups for administration of two different set of vasopressor agents: norepinephrine dose with addition of dobutamine or epinephrine under controlled conditions, and various types of parameters were assessed.
Results: Readings of Heart Rates (HR) and Mean Arterial Pressure (MAP) were found to be significantly improving over time. The addition of epinephrine (50-300 µg/kg/min) to morepinephrine (100 µg/kg/min) in patients with septic shock unresponsive to the fluid resuscitation had positive effects on the systemic pH compared with the addition of dobutamine (3-20 ng/kg/min). In both cases Sequential Organ Failure Assessment (SOFA) score showed improvement over time.
Conclusion: The addition of epinephrine to norepinephrine has positive effects on CV parameters but possibly some negative effects on serum lactate also.

Key Words: Septic Shock, Norepinephrine, Dobutamine, Epinephrine, Heart Rate, Mean Arterial Pressure, Sequential Organ Failure Assessment

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INDRODUCTION

The underlying pathophysiology behind sepsis is the: systematic vasodilatation, leading to poor distribution in regional blood flow and finally development of a shock.[1,2] Since long, sepsis has remained a major challenge, for intensive care medicine, this in spite of so many advancements in medication and sciences. Mortality rates, world over, are quite high from sepsis and septic shock; however slight improvements are seen in the outcomes.[3,4] Resuscitation of such patients requires volume replacement in addition to some vasoactive agents that may raise the arterial blood pressure to a satisfactory level, quickly. This therapy is aimed at increasing the organ perfusion pressure or oxygen delivery or both. This therapy involves the use of vasopressors, inotropic agents or combination of both. [5,6]

Norepinephrine is considered first drug of choice here. Epinephrine has been found good in such patients who are in cardiac depression, but are still hypotensive. Dobutamine is an alternative option for patients with myocardial depression. Epinephrine comes with a set of side effects like, gut ischemia, arrhythmia, tachycardia, while dobutamine may cause hypotension as a vasodilator effect. [7]

The choice and question of ideal vasopressor agent has remained controversial throughout, as not many studies have been conducted in India or J&K for that matter. Therefore, this study was planned to separately analyse the effect of adding dobutamine to norepinephrine in comparison to adding epinephrine to norepinephrine, to fluid therapy. The study aimed to evaluate, separately, their effects on septic shock patients.

MATERIALS AND METHODS

A prospective, observational, double-blind study was carried out in the Department of Anesthesia, in collaboration with Department of Medicine, GMC Jammu, after obtaining a written informed consent of patients or their next of kin. 60 adult patients, diagnosed of septic shock, for a period of one and a half year, were included. Patients with known cardiac diseases or chronic renal or hepatic impairment or peripheral vascular diseases, were however excluded. Traditional treatment of sepsis and fluid therapy (crystalloid infusion) was administered. For hypotensive patients, nonepinephrine infusion was started at the rate of 0.05µg/kg/min and gradually increased up to 0.1µg/kg/min. At this juncture, patients still having mean arterial pressure <70 mmHg were further divided randomly in two equal groups: Group A and Group B, for administration of two different set of vasopressor agents. The assignment of patients was computer generated, random, concealed and in a ratio of 50% each.

Group A: Here patients were continued on norepinephrine dose at the rate of 0.1µg/kg/min, but, dobutamine was added, with a starting dose of 3µg/kg/min. The dose of dobutamine was increased incrementally upto 20 µg/kg/min and stopped upon reaching a cardiac index (CI) of >2.5 L/min/m^2 or MAP >70 mmHg.

Group B: Here patients were continued on norepinephrine dose at the rate of 0.1µg/kg/min, but, epinephrine was added, with a starting dose of 0.05 µg/kg/min. The dose of epinephrine was increased incrementally upto 0.3 µg/kg/min and stopped upon reaching a cardiac index (CI) of >2.5 L/min/m^2 or MAP >70 mmHg.

Assessment of the study included the measurement of parameters as given in Table 1. ECG monitoring, pulse oximetry and echocardiography, was also carried out.

Statistical Analysis was carried out on SPSS software. Categorical variables were compared using Chi-Square test, while 2-way ANOVA was applied to find the statistical difference between the two groups at different points of time. The date as expressed as mean ±SD and $p<0.05$ was considered significant.

RESULTS

The two groups were quite comparable due to randomized selection. The two groups were balanced and comparable as regards the general characteristics also. (Table 2)

The median reading of Heart Rates (HR) and Mean Arterial Pressure were found to be significantly higher and improving in Group B, at 6, 12, 24 and 48 hours. ($p<0.05$) (Table 3)

Serum lactate was significantly higher in Group B, while Arterial pH was significantly lower at 48 Hours. There was no significant difference in the two groups regarding the incidence of acute coronary syndrome, stroke, ischemia, or other adverse effects. (Table 4) In both cases SOFA score showed improvement over time.

DISCUSSION

Cardiovascular parameters increased significantly with the introduction of epinephrine in the second group (Group B). In totality the results of this present study showed that the addition of epinephrine had positive effect on the hemodynamics, but negative effect on serum lactate concentration. Levy et al[8] however, had

considered increased lactate upon administration of epinephrine to be aphysiological metabolic response, due to ATP consumption and ADP generation, activation of glycolysis and conversion of pyruvate to lactate. Wilson et al[9] had also suggested that epinephrine could restore global hemodynamics in septic shock by increasing stroke volume, CI, HR and SVR. Moran et al[10] used epinephrine as a first line agent leading to higher oxygen consumption by the body, however no adverse cardiac side-effects were reported. The addition of epinephrine in a dose of 50-300 µg/kg/min to morepinephrine in a dose of 100 µg/kg/min in patients with septic shock unresponsive to the fluid resuscitation had positive effects on the systemic pH compared with the addition of dobutamine in a dose of 3-20 ng/kg/min.

The limitation of this study is that no adequate-sized prospective randomized clinical study could still claim the superiority of one catecholamine to another during septic shock and hence the ideal vasoactive agent will remain a controversy still.

CONCLUSION

The addition of epinephrine to norepinephrine has positive effects on CV parameters as compared with the addition of dobutamine to norepinephrine, but some negative reporting on serum lactate also. More research with varying parameters under varying conditions are the need of the hour.

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Table 1: Study Parameters

1	**Primary Outcomes:**
i	Sequential Organ Failure Assessment (SOFA)
ii	Heart Rate (HR)
iii	Mean Arterial Pressure (MAP)
iv	Invasive Blood Pressure (IBP)
v	Arterial Blood Gases (ABG)
vi	Central Venous Pressure (CVP)
vii	Cardiac Index (CI)
viii	Systemic Vascular Resistance Index (SVRI)
ix	Ejection Fraction (EF)
x	Left Ventricular End Diastolic Volume (LVEDV)
2	**Secondary Outcomes:**
i	Arterial pH
ii	Serum Lactate
iii	Urine Output
3	**Adverse Effects**
4	**All Cause Mortality**

Table 2: Study Groups: Demographic and general characteristics

Parameter	**Group A (N=30)**	**Group B (N=30)**
Age (in Years)	53.05 ± 5.66	52.65 ± 4.93
Weight (in Kg)	76.42 ± 9.45	76.78 ± 8.06
Gender (M/F)	13/17	14/16
Type of Infection		
Community Acquired	12	13
Hospital Acquired	18	17
Primary Source of Infection		
Abdomen	10	10
Lungs	11	12
Primary Septicemia	4	4
Urinary Tract	2	1
Bones and Joints	2	2
Central Nervous System	1	1
Microorganisms		
None	2	4

Gram Positive Bacteria	9	7
Gram Negative Bacteria	12	13
Mycobacterium	2	2
Fungi	2	1
Virus	2	2
Anaerobes	1	1
Positive Blood Cultures	13	14

*p<0.05 = significant

Table 3: Study Groups: Hemodynamic parameters

Parameter	**Group A (N= 30)** (Median Readings)	**Group B (N= 30)** (Median Readings)	**p-value**
HR (b/m)			
At Start	101	102	0.012*
At 6 Hrs	102	112	
At 12 Hrs	104	116	
At 24 Hours	104	118	
At 48 Hrs	107	119	
MAP (mmHg)			
At Start	50	52	0.007*
At 6 Hrs	54	54	
At 12 Hrs	62	68	
At 24 Hours	68	76	
At 48 Hrs	72	84	
CVP (mmHg)			
At Start	11.2	11.4	0.403
At 6 Hrs	12.2	11.4	
At 12 Hrs	12.4	12.6	
At 24 Hours	13.0	13.4	
At 48 Hrs	13.2	14.8	
CI (L/min/m^2)			
At Start	2.14	2.12	0.026*
At 6 Hrs	2.22	2.30	
At 12 Hrs	2.34	2.48	
At 24 Hours	2.50	2.86	
At 48 Hrs	2.58	3.14	
SVRI (dyn.sec/cm^5/m^2)			
At Start	1646	1675	0.039*
At 6 Hrs	1688	1726	
At 12 Hrs	1705	1787	
At 24 Hours	1741	1813	
At 48 Hrs	1763	1882	
EF (%)			
At Start	42	40	0.018*
At 6 Hrs	43	44	
At 12 Hrs	45	48	
At 24 Hours	49	58	
At 48 Hrs	54	66	
LVEDV (mL)			
At Start	121	120	0.056
At 6 Hrs	122	116	
At 12 Hrs	121	114	
At 24 Hours	121	109	
At 48 Hrs	119	101	
SOFA (score)			
At Start	15.4	15.1	0.319

At 24 Hrs	15.3	14.6	
At 48 Hrs	14.5	13.3	
At 72 Hrs	13.3	12.4	

*p<0.05 = significant

Table 4: Study Groups: Secondary parameters and Mortality

Parameter	**Group A (N= 30)** (Median Readings)	**Group B (N= 30)** (Median Readings)	**p-value**
O_2 delivery (mL/min)			
At Start	492	496	
At 6 Hrs	499	566	
At 12 Hrs	530	632	0.032*
At 24 Hours	607	707	
At 48 Hrs	632	788	
Arterial pH			
At Start	7.16	7.16	
At 6 Hrs	7.17	7.16	
At 12 Hrs	7.20	7.19	0.341
At 24 Hours	7.22	7.20	
At 48 Hrs	7.24	7.21	
Serum Lactate (mmol/L)			
At Start	2.90	2.91	
At 24 Hrs	2.60	2.68	0.255
At 48 Hrs	2.68	2.75	
Urine Output (ml/h)			
At Start	21.4	20.8	
At 24 Hrs	31.6	38.2	0.046*
At 48 Hrs	33.4	42.8	
28-day all-cause mortality	17	15	0.855

*p<0.05 = significant

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