

VASOPRESSOR AND INOTROPIC SUPPORT IN SEPTIC SHOCK PATIENTS: A COMPARISON OF VARIOUS DRUGS, ALONE OR IN COMBINATION

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Abstract:

Context: Sepsis has been remained the major cause of mortality in the critical care units. The data about use of inotropes & vasopressors in different combinations is quite limited.

Aim: Our study has been conducted to study these drugs in various combinations to improve morbidity with lesser side effects of the drugs.

Methods: Thirty three adult patients of either sex aged between 20-70 years posted for surgical intervention were included. After thorough pre-anesthetic examination & necessary investigations patients were randomized in to 3 groups. Group I: Dopamine group. Group II – Dobutamine group, Group III – Combination group – Group III was further divided in 3 subgroups viz. A, B and C. IIIA – Dopamine + Dobutamine; IIIB – Dopamine + Noradrenaline. IIIC – Dopamine + Amrinone.

All the patients were stabilized by giving adequate fluid & suitable doses of vasopressors/inotropes. Premedication with inj glycopyrrolate (0.2mg), inj midazolam (1mg iv) and butorphenol/tramadol (100mg,iv) were given and induced with thiopentone (5mg/kg)/Ketamine (2mg/kg iv). Succinylcholine (1.5mg/kg) was used to facilitate intubation. Anesthesia was maintained using N₂O/ O₂, & inj.atracurium. Pulse rate, Blood Pressure, Spo₂, temperature, ECG and urine output were recorded at regular intervals intraoperatively. In addition to these vitals Respiratory rate, condition of chest and mental status were monitored for 3-4 days post operatively.

Statistics: Mortality of different groups was calculated by modified ODIN score. Organ dysfunction variables are selected by multiple logistic regressions.

Results: infusion of inotropes for 3 consecutive days, >50% mortality was observed as follows - Group I - 28.5%; Group II- 20% Group III- IIIA-25%; IIIB-33.3%; IIIC-40%

Conclusion: normo volemic status must be attained, before initiating the vasopressor or inotropic support. The choice of vasopressor or inotropic agent will depend upon the clinical status of the patients. Early surgical intervention and inotropic support especially dobutamine or amrinone along with dopamine make the patients haemodynamically more stable.

Key words: Septicaemia, Septic shock, ODIN Score, Inotropes, Amrinone hydrochloride

Introduction

Sepsis or septic shock is systemic inflammatory response syndrome secondary to a documented infection. This response is a state of acute circulatory failure characterized by persistent arterial hypotension despite adequate fluid resuscitation or by tissue hypoperfusion (manifested by lactate concentration >4mg/dl) unexplained by other causes.

A successful outcome in critically ill patients depends upon the re-establishment of adequate oxygen delivery. Inotropic agents are a crucial component of the management strategy in patients of septic shock.

Material and Methods

The study was conducted on 33 patients of either sex ranging from 20-70 yrs of age having septic shock admitted for surgical intervention in the emergency and critical care unit of Nehru Hospital, BRD Medical College, Gorakhpur after the permission of ethical committee.

After a thorough preanaesthetic checkup, all patients were subjected for routine investigations including haemoglobin, TLC, DLC, platelet count, serum creatinine, serum urea, BUN, serum bilirubin, serum electrolytes Na⁺, K⁺, Ca⁺⁺, Chest X-ray (PA view) and urine output. Other specific investigation advised if needed.

All selected patients under study were randomly divided into 3 groups according to drug given.

Group I - Dopamine group.

Group II - Dobutamine group

Group III - Combination group – it was further divided in 3 subgroups.

IIIA - Dopamine + Dobutamine

IIIB - Dopamine + Noradrenaline

IIIC - Dopamine + Amrinone

All the patients were stabilized haemodynamically by giving adequate fluids and suitable doses of vasopressor or inotrope. After taking written informed consent for operation, all the patients were premedicated with inj. Glycopyrrolate 0.2 mg i.v. and suitable doses of benzodiazepine (inj midazolam) and opioids (inj butorphanol / tramadol) preoperatively.

All the patients were preoxygenated with 100% oxygen for 5 minutes. All patients were induced with suitable

dose of inducing agent (Thiopentone / Ketamine) and tracheal intubation was facilitated using 1-1.5mg/kg. of inj. succinylcholine i.v. in all the cases. Anaesthesia was maintained with N₂O, oxygen and non-depolarising muscle relaxant (Atracurium besylate).

Intraoperative pulse rate, BP, temperature, SpO₂, ECG and urine output were recorded at regular intervals. All the patients were reversed with suitable doses of neostigmine and glycopyrrolate. Good postoperative analgesia was provided to all the patients.

Post operatively all patients were monitored continuously for 3-4 consecutive days and parameters viz. pulse rate, blood pressure, respiratory rate, temperature, SpO₂, urine output were recorded. Condition of chest & mental status were also assessed clinically. All the patients were investigated for Hb, TLC, DLC, serum urea, serum creatinine, serum bilirubin and BUN on daily basis.

Mortality was calculated by using modified ODIN Score (Table 1).

Two most recent version of this system employs 7 binary variables requiring Yes/No response.

Table-1 Modified ODIN Score

Dysfunction	Variable	Value
Respiratory	PaO ₂ <60 mmHg, SPO ₂ <90	Yes-1/No-0
Cardiovascular	SBP<90 mmHg with signs of peripheral hypoperfusion or vasopressure support to maintain SBP > 90mmHg	Yes-1/No-0
Renal	Serum creatinine > 300 μmol/L, or urine output < 500 ml/24 hr or < 80ml/8hr	Yes-1/No-0
Neurological	Glassgow coma scale <6 or sudden onset of confusion or Psychosis	Yes-1/No-0
Hepatic	Serum bilirubin>100 μmol /L or serum Alk. Phosphate > 3times normal	Yes-1/No-0
Haematological	Haematocrit < 20% or white blood cell < 20000 or > 8000 /m ³ or P/C < 40,000/mm ³	Yes-1/No.0
Clinical evidence of infection	present	Yes-1/No.0

Predicted mortality rate was calculated every day with calculation of beta after analyzing the risk stratification of every day and compared with actual mortality.

Group-I - 11 patients.

Group-II - 10 patients.

Group-III; III A– 4 patients ; **III B** –3 patients ; **III C** – 5 patients.

Observations

All 33 selected patients under study were randomly divided into 3 groups.

The details of patients and type of surgery are given in table-2.

Table-2 :
Demographic variations and surgical diagnosis in different groups.

Patients characterization	Group-I	Group-II	Group III			Total
			IIIA	IIIB	IIIC	
Age (in yrs)	43 ±8.64	39±7.64	39 ±9.45	28 ±8.45	54 ±8.64	40 ±8.4
Sex (M/F)%	63.60:36.40	40:60	50:50	33.30:66.6	80:20	55:45
Surgical diagnosis						
Perforation peritonitis	27.3%	50%	25%	33.3%	80%	42.4
Int.obstruction with gangrene	27.3%	10%	25%	0%	20%	18.2
Pyoperitoneum	9.1%	0%	25%	33.3%	05	9.1
Septic abortion	27.3%	30%	25%	33.3%	0%	24.2
Multiple pyaemic abscess	9.1%	10%	0%	0%	0%	6.1
No. of patients	11	10	4	3	5	33

Maximum patients undergone exploratory laparotomy for perforation peritonitis & intestinal obstruction with gangrene as surgical intervention. Other cases were operated for multiple pyemic abscess or septic abortions. Maximum patients were aged between 40-50 years.

Cardiovascular, renal, respiratory, hepatic and neurological insufficiencies were noted and compared for different groups. All tables cannot be published due to limitation of space. Table-3 shows important parameter of cardiovascular insufficiency.

Table-3; above table shows number of patients having cardiovascular insufficiency in different groups. Maximum CV insufficiency was observed in group III-C.

Groups	Total Patients	Patients having cardiovascular insufficiency	
		No	%
I	11	3	27.2
II	10	3	30
III-A	4	1	25
III-B	3	0	0
III-C	5	2	40
Total	33	9	27.27

Mortality of different groups were calculated on different days with the help of modified ODIN score. After calculating mortality comparison was done with other group mortality(table- 4).

Table-4: Showing distribution of mortality of different groups.

Group	Total patients		Patients survived		Patients expired	
	No.	%	No	%	No	%
I	11	33.3	9	81.8	2	18.18
II	10	30.3	7	70.0	3	30
III-A	4	12.12	3	75	1	25
III-B	3	9.09	2	66.6	1	33.3
III-C	5	15.15	3	60	2	40

This table shows that maximum mortality was observed in group III-C and minimum in group-I. Mortality of different groups were also calculated on every day basis from preoperative period to 3rd postoperative day. (Table-5)

Table-5:

Showing predicted mortality of different groups on different days as calculated by modified ODIN score. It shows that maximum predicted mortality was noted in preoperative period.

Predicted mortality range	Group I (n=11)				Group I (n=10)				Group III (n=12)											
									III-A (n=4)				III-B (n=3)				III-C (n=5)			
	Preop	D-1	D-2	D-3	Preop	D-1	D-2	D-3	Preop	D-1	D-2	D-3	Preop	D-1	D-2	D-3	Preop	D-1	D-2	D-3
0-25%	0	0	2	9	2	0	3	7	0	0	2	3	0	0	1	1	0	0	1	3
25-50%	5	9	8	0	3	5	4	0	0	0	1	0	1	1	0	1	0	1	2	0
50-75%	2	0	0	0	3	4	0	0	3	4	1	0	1	1	1	0	1	2	1	0
75-100%	4	2	0	0	2	1	3	1	1	0	0	1	1	1	1	1	4	2	1	0

Discussion

Septic shock usually results in severe decrease in systemic vascular resistance and there is generalized blood flow maldistribution.¹

The commonest effect of septic shock on the cardiovascular system is a haemodynamic profile characterized by an elevated cardiac index and decrease SVR. Myocardial depression in septic shock patients may be due to coronary hypoperfusion or presence of active circulatory myocardial depressant factors in bloodstream.

Dopamine acts on α and β adrenergic and dopaminergic receptors. In the doses between 0.5-3.0 $\mu\text{g}/\text{kg}/\text{min}$ it mainly acts on dopaminergic receptors and leading to natriuresis and increased urine output in septic shock patients². We compared renal insufficiency in different groups. We found that minimum renal insufficiency was noticed in dopamine group (group-1).

In dose of 3.0-5.0 $\mu\text{g}/\text{kg}/\text{min}$, it increases myocardial

contractility with minimal change in heart rate, blood pressure and PSVR. No patient of this group showed signs of hepatic insufficiency (raised serum bilirubin).

Predicted mortality of group I- Out of 11 patients, 7 patients were having more than 50% mortality preoperatively (63.6%). On dopamine infusion for 3 consecutive days, more than 50% mortality was observed only in 2 patients (28.5%). Therefore dopamine infusion led to decrease in 50% mortality by 35.1%.

Dobutamine primarily acts on β_1 adrenergic receptors, and effect on systemic blood pressure is variable in septic shock patients depending upon circulatory volume. Systemic vascular resistance (SVR) may be moderately decreased or unchanged. It markedly increases oxygen delivery and consumption in sepsis. Increase in heart rate is less than dopamine.

Dobutamine infusion was usually started at a dose of 2-3 $\mu\text{g}/\text{kg}/\text{min}$ and gradually increased to achieve the desired effect (maximum dose 5-15 $\mu\text{g}/\text{kg}/\text{min}$).

In a dose range of 0.5 -5 µg/kg/min, it increases SVR and MAP without significantly affecting cardiac output in fluid resuscitated septic shock patients.

Shoemaker WC et al observed a significant increase in cardiac index and heart rate and a decrease in pulmonary vascular resistance (PVR). They also noticed that dobutamine maintains the tissue perfusion more evenly than dopamine. In our study dobutamine group have lowest incidence of respiratory insufficiency which favours the findings of above authors.

Predicted mortality of group-II - out of 10 patients, 5 patients were having > 50% mortality preoperatively (50%). After dobutamine support > 50% mortality was noticed only in 3 patients (30%). Therefore, dobutamine infusion reduced > 50% mortality by 20% reflecting that dobutamine improved the patient's haemodynamically as well as biochemically better than the dopamine.

Noradrenaline is a potent α_1 and α_2 adrenoceptor agonist. It mainly acts as Vasopressor rather inotrope. Systemic blood pressure (SBP) increases because of vasoconstriction in renal, mesenteric and peripheral vascular bed & may cause compensatory bradycardia. It is used to overcome reduction in SVR characteristics of septic shock.³

Predicted mortality of group III A- All the patients of group IIIA were having > 50% mortality preoperatively (100%). On 3rd day infusion of dopamine and dobutamine combination > 50% mortality was observe only in one patient (25%). It reflects that > 50% mortality was reduced by 75%, which is superior outcome than group I as well as group II.

Studies in critically ill septic patients provide strong evidence that noradrenaline improves urine production following restoration of MAP and improves renal function as assessed by serum creatinine and creatinine clearance whether or not noradrenaline is given in combination with low dose dopamine (Martin et al., 1990). In our study we did not found hepatic insufficiency in dopamine + noradrenaline group which is probably due to restoration of MAP, favouring the findings of Martin et. al.

Group IIIB shows that > 50% predicted preoperatively mortality was in 2 cases out of 3 (66%). Dopamine & Noradrenaline infusion for 3 days led to observe that > 50% predicted mortality was present only in one patient

(33.3%). So, decrease in >50% mortality by 32.7% is observed in this group, which is better than group I and group II but not group IIIA.

Amrinone, a selective phosphodiesterase III inhibitor is a positive inotrope as well as inodilator. It reduces preload and afterload in addition to increase cardiac output in septic shock patients. SVR is decreased. In low cardiac output septic shock (refractory to catecholamines), PDEs inhibitors have been shown to improve left ventricular function and cardiac output.⁴

Amrinone was given in a dosing of 0.75 mg/kg bolus (undiluted) and then 5-10 µg/kg/min diluted in dextrose free fluid.

Mortality was calculated on day basis using ODIN score. The following observations were noted.

Groups IIIC shows > 50% preoperative predicted mortality in all cases (100%). After infusion of dopamine & amrinone only 2 patients reflected > 50% mortality on 3rd postoperative day (i.e. 40%). So, this combination wonderfully decreased > 50% predicted mortality by 60% which is superior to group I, II & IIIB but not group IIIA.

Table-3 shows predicted mortality of different groups on different days as calculated by modified ODIN score. It indicates that mortality was in high range i.e., > 50% in preoperative period but it was reduced to lower range after giving inotropic and vasopressor support in postoperative period.

Conclusion

After evaluating the behaviour of septic shock patients during preoperative and post operative period we concluded that normo volumic status must be attained before initiating the vasopressor or inotropic support. The choice of vasopressor or inotropic agent will depend upon the clinical status of the patients. Early surgical intervention and inotropic support specially dobutamine or amrinone along with dopamine make the patients haemodynamic stable. Haemodynamic parameters of nor-adrenaline are also promising. This therapy also reduced the chances of landing haemodynamically compromised patients into multiple organs dysfunction syndrome and outcome is much better than predicted.

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