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Original Research Article

Comparison of central venous oxygen saturation and serum lactate clearance as predictors of outcome in septic shock patients: a prospective control trial

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ABSTRACT

Background: Sepsis is the leading causes of mortality and morbidity in ICU. Early recognition and intervention ensures speedy recovery and early discharge. It's possible only if good predicting parameters indicating optimum resuscitation are available. Lactate level reduction and ScvO2 level in the jugular vein can be utilized as predictors.
Methods: In this prospective study after applying exclusion inclusion criteria, 99 patients were selected and randomized into 2 groups. In one group reduction in lactate levels and in other ScVo2 levels were used as a predictor of resuscitation. Therapeutic interventions, Hospital stay, ICU Stay and 28-day mortality were compared in both groups. Statistical analysis was carried out by SPSS software.
Results: On comparison of demographic profile, morbidity, SOFA score and hemodynamic parameters, there was insignificant difference (P >0.05). No significant difference in the number of vasopressors, Average Hospital or ICU Stay (Group A is 10.68±21.46 while Group B is 9.49±17.22) and 28-day mortality rate (in Gp A 60% vs group B 57.1) was observed. Mean crystalloids administered in group A was 4.93±1.11 liters, significantly more than group B i. e. 4.19±1.17 liters. (P<0.05) which was statistically significant.
Conclusions: Although both parameters of resuscitation are used widely and sometimes simultaneously, in this study lactate and ScvO2 both used and compared in a similar set of patients, appeared to be equivocal in term of 28-day mortality, except the volume of crystalloids required was more in ScvO2 Group.

Keywords: Hypotension, Jugular vein saturation, Lactate levels, Mortality, Resuscitation, Sepsis

INTRODUCTION

Sepsis is a potentially fatal inflammatory response syndrome encompassing a spectrum of clinical conditions from SIRS, sepsis to severe sepsis (Refractory Shock).[1]

Septic shock as per Critical Care Medicine Consensus Conference is systemic inflammatory response as defined by two or more of the following ; temperature higher than 38.5°C or lower than 35°C, heart rate higher than 90 beats/min, respiratory rate higher than 20 breaths/min or partial pressure of arterial carbon dioxide ($PaCO_2$) less than 32 mmHg or need for mechanical ventilation, white blood cell count higher than 12.0×10^9/l or less than 4.0×10^9/l or containing more than 10% immature forms; evidence of a nidus of infection and systolic blood pressure less than 90 mmHg (for at least one hour) despite adequate fluid replacement and infusion of vasopressor associated with at least two signs of perfusion abnormality (lactic acidosis, oliguria, abrupt alteration in mental status.[2]

Pathophysiology of sepsis involves microcirculatory changes leading to insufficient oxygen delivered to the

cell. Monitoring of the sepsis patients includes hemodynamic parameters and indirect estimation of oxygen delivery to the tissues. Haemodynamic targets should include adequate cardiac preload (e.g. central venous pressure) and perfusion pressure (e.g., mean arterial pressure).[3]

An indirect estimation of the relationship between oxygen consumption and oxygen delivery in the tissues is the central venous (ScvO2) and mixed venous oxygen saturation (SvO2). SvO2 measured using PAC catheter located in the pulmonary and ScvO2 from a catheter located in superior vena cava. ScvO2 is usually higher than SvO2 as it is not mixed with the venous blood from the coronary sinus. Normal values of mixed venous oxygen saturation (SvO2) are 60 - 80%. Central venous oxygen saturation (ScvO2) values represent regional venous saturation with a normal value of ~70%. Although these values may differ, they follow each other.[4]

Measuring the ScvO2 offers an important tool in assessing oxygen delivery (DO2) and extraction at the cellular level a predictor of resuscitation. Although the sample is collected from Superior Vena Cava hence ScvO2 levels assess oxygen extraction from the brain and upper extremity only and SvO2 from the whole body despite this it can be used as a surrogate marker of mixed venous circulation (SvO2) as it trends in the same direction as SvO2. Therefore, it can be used in sepsis as a marker of resuscitation forms the basis of resuscitation in sepsis management.[5]

Lactate clearance is derived from calculating the change in blood lactate concentration at different times. It is an easily accessible method to assess tissue oxygen delivery. A lactate clearance of 10% or more predicts good resuscitation of Sepsis patient and improves survival from septic shock. Two normal lactate levels (<18 mg/dL [2 mmol/L]) at least 2 hours apart is taken as evidence of adequate tissue oxygenation.[6]

The aim of this study is to compare central venous oxygen saturation (SvO2) and serum lactate clearance as predictors of outcome and resuscitation in septic shock patients. To identify patients of sepsis with the working hypothesis that early resuscitation targeting lactate levels (serum lactate clearance at least 10%) as the marker of the adequacy of oxygen delivery was not inferior to the recommended ScvO2 (70%) by predicting 28-day mortality in two groups.

METHODS

A prospective randomized controlled trial was planned to assess the non-inferiority of serum lactate monitoring to the ScvO2 monitoring methods as a means to evaluate oxygen delivery to the tissues during resuscitation of patients in septic shock a tertiary care center. After ethical clearance from Hospital Ethical Committee around 100 patients were enrolled and randomized into two groups of 50 patients each using computer-generated numbers with the following specific management goals as shown in Figure 1.

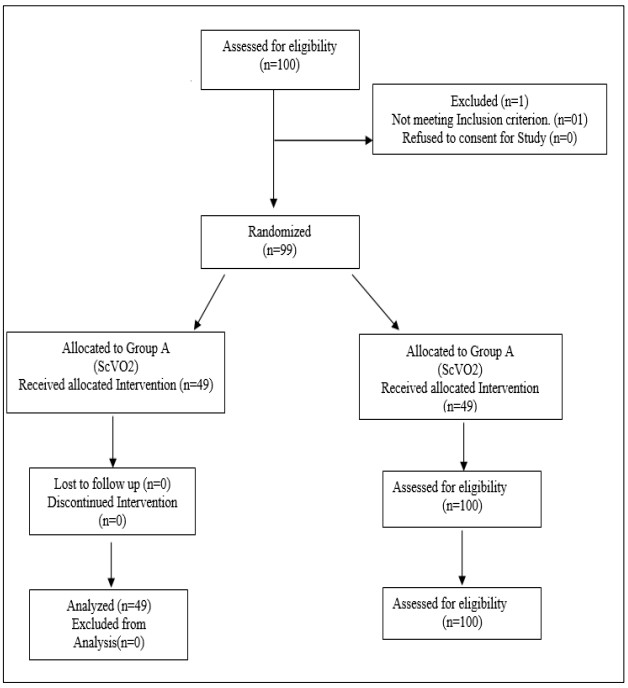

Figure 1: Consort formula.

The sample size was calculated using the formula below.

Sample size: N = 4 Z2 1-α/2 pq /d2

Where

Level of Confidence = 95%, Margin of error (d) = 10%, Z= Table Value of alpha error from Standard Normal Distribution table corresponding to area (area to the left of Z), p = Sensitivity, q= 1- p (1.00 - 0.81=0.19).

The sample size arrived at was 96 and rounded off to 100.

Patients admitted in septic shock with suspected/confirmed infection were screened so as to satisfy at least four of the clinical signs and symptoms of systemic inflammatory response criteria as part of inclusion criteria.

Inclusion Criteria were like Age group 18-70 yrs, and at least 4 signs of sepsis present at the time of admission to ICU enumerated as below in Table 1.

Patients excluded from the study due to lack of consent, pregnancy, any another type of shock viz cardiogenic, neurogenic and anaphylactic. Immediate surgery within 6 hours of diagnosis, any absolute contraindication to chest or neck central venous catheterization, cardiopulmonary resuscitation and transfer from another institution with a known case of sepsis.

Table 1: Criteria for sepsis.

S. No.	Criteria
1.	Fever (> 38.3°C)
2.	Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP
3.	decrease > 40 mm Hg in adults or less than two sd below normal for age)
4.	Heart rate > 90/min or more than two SD above the normal value for age
5.	Altered mental status
6.	Leukocytosis (WBC count > 12,000 /µL) or Leukopenia (WBC count < 4000 /µL) or Normal WBC count with greater than 10% immature forms
7.	Arterial hypoxemia (Pao2/Fio2 < 300)
8.	Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation) OR Creatinine increase > 0.5 mg/dL or 44.2 µmol/L
9.	Coagulation abnormalities (INR > 1.5 or aPTT > 60 s) or Thrombocytopenia (platelet count < 100,000 /µL)
10.	Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 µmol/L)
11.	Hyperlactatemia (> 2 mmol/L)

Patients admitted in ICU, after enrollment and randomization were resuscitated in a structured manner. ICU protocol was followed by monitoring temperature, pulse, blood pressure, SpO2, respiratory rate and investigations like Hb, total leucocytes, differential leucocyte counts, PT, PTTK, INR, serum lactate.

First, isotonic crystalloid was administered as boluses to attain a central venous pressure of 8 mm Hg or more. The mean arterial pressure goal was set at 65 mm Hg or higher. The blood pressure target if not achieved with fluid administration, it was achieved by initiating vasopressors (noradrenaline or dopamine).

Blood samples for culture and sensitivity pattern were withdrawn under aseptic precautions, before empirical antibiotics were initiated. Patients with a poor Pao2/Fio2 ratio or a GCS < 8 or both, were placed on mechanical ventilation. All physiological parameters were continuously monitored. Haemodynamics was monitored by means of an arterial catheter for blood pressure and a central venous catheter for assessing change in CVP when clinically indicated and feasible.

Patients randomized to Group A were resuscitated using ScvO2- 70% target as sequentially to achieve goals of CVP, MAP. If the ScvO2 was lower than 70% and the hematocrit was lower than 30%, packed red blood cells were transfused to achieve a hematocrit of at least 30%. If the ScvO2 remained lower than70% after the hematocrit was 30% or higher, dobutamine was titrated to achieve a ScvO2 of at least 70%.

In Patients randomized to the Group B i.e. Lactate group were managed with similar resuscitation target of CVP and MAP, however, clearance of lactate at least 10% was taken as the goal. Lactate clearance was defined by the formula (lactate initial –lactate later)/lactate initial x 100% where lactate initial was the concentration at the start of resuscitation and lactate later was at least two hours of resuscitative measures. If the lactate clearance was not at least 10% at the first measurement two hours later and the hematocrit was less than 30%, packed red blood cells were transfused to achieve a hematocrit of at least 30%. If the lactate clearance remained lower than 10% after the hematocrit was at least 30%, dobutamine was titrated to achieve a lactate clearance of at least 10%.

Statistical analysis

The data collected were analyzed accordingly. The data was entered and coded in MS Excel and statistical analysis was performed by SPSS software (SPSS Inc., Chicago, IL, USA) version 17.0. A P value <0.05 was considered as statistically significant.

RESULTS

A total of 100 patients were identified for the study. In two interventional groups, group A received monitoring through ScvO2 and group B was monitored by means of reduction in serum lactate. One patient was excluded from group B, as was operated upon within hours of admission. Standard protocol led sepsis management was carried out in both groups.

Table 2: Demographic representation in both groups.

Variable	Group A	Group B	Std. deviation	Std. error mean
Male	27	29	56	0.271
Female	23	20	43	0.603
Mean age	50.22	51.61	16.12	0.668
Mean weight	64.98	64.57	9.99	0.839

On demographic analysis as compared in Table 2, it was observed no significant variation in age, gender ratio, weight. The mean age of the patient of group A is 50.22±16.02 and of group B is 51.61±16.23.

On analyzing comorbidities present during admission, COPD is the most frequent associated comorbidity present in 43% of the patients followed by hypertension in 8%, asthma in 8% and 3% each with CAD and CKD in patients of group A. About 18% of the patients had no comorbidity. Whereas in Group B again COPD was the most frequent associated comorbidity present around 35%, followed by hypertension 13%, asthma 8%, Diabetes 6% and 2% each with CAD and CKD. Just like

Group A, 18% of the patients had no comorbidity as shown in Figure 2.

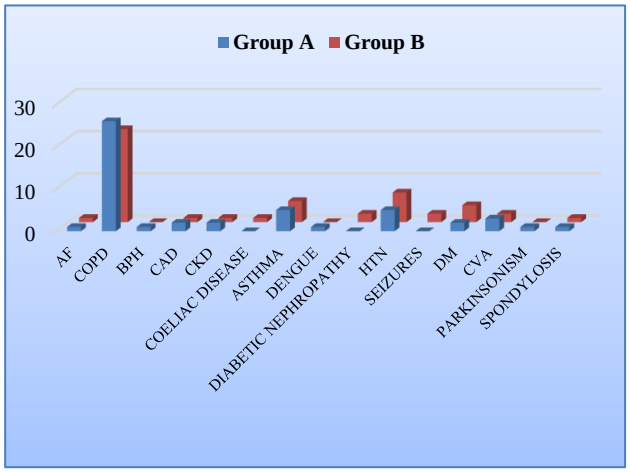

Figure 2: Associated co-morbidities present in group A and B.

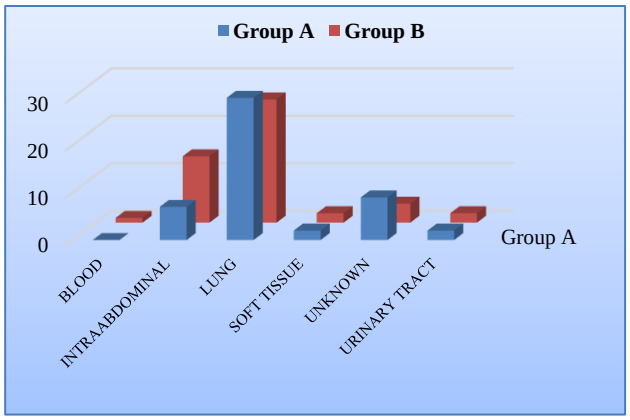

Figure 3: Site of infection present in group A and B.

In the patients of group A, the source of infection was the lung in 60%, unknown in 18%, intra-abdominal focus in 14 % and 4% each in the urinary tract and soft tissues. In comparison, group B, the source of infection was the lung in 53%, intra-abdominal focus in 29 %, unknown in 8%, and 4% each in the urinary tract and soft tissues as shown in Figure 3.

The mean heart rate of patients as shown in Table 3, group A is 99.08±17.09 and group B is 102.96±18.14. While the mean systolic and diastolic blood pressures on admission in group A is 80.76±5.58 and 46.5±5.14 respectively, that of group B is 81.27±4.83 and 48.04±5.68.

Thus, there is no statistically significant difference among study groups with regard to heart rate, systolic and diastolic blood pressures as measured on admission.

Regarding laboratory results, TLC counts at admission between groups A and B with mean 16,123.00+5379.28 and 17,563.00 3706.17 respectively. The mean SOFA score on the admission of group A is 11.68±3.36 while that of group B is 11.71+3.59. The comparison between the two groups is comparable and not significant.

Table 3: Comparision of haemodynamics and lab parameters in both group.

Variables	Group A	Group B	P Value
Heart Rate	99.08	102.96	0.285
SBP	80.76	81.27	0.631
DBP	46.5	48.04	0.16
TLC Count	16123.00	17563.00	0.125
Platelet count	221060.00	248860.00	0.198
Sr Urea	60.60	61.88	0.787
Sr creatinine	1.38	1.51	0.376
SOFA	11.68	11.71	0.961

Therapeutic interventions as enumerated in Table 4 like Noradrenaline was used in 84% (n=42) of patients in group A with mean dose of 0.06 mcg/kg/min while its usage in group B is 75.5% (n=37) with mean dose of 0.07 mcg/kg/min. Dopamine in group A was used in 6 patients with a mean dose of 0.15 mcg/kg/min while in group B it was used in 8 patients mean dose of 0.15 mcg/kg/min.

Table 4: Therapeutic intervention used in resuscitation in both groups.

Vasopressors used					
Therapeutic intervention	**GROUP**	**N**	**Mean**	**Std. deviation**	**Std. error mean**
Nor adr dose mcg/kg/min	Group A	42	0.0614	0.05551	0.401
	Group B	37	0.0708	0.04105	
Dopamine dose mcg/kg/min	Group A	6	0.1583	0.06646	0.589
	Group B	8	0.175	0.04629	
Crystalloids Used					
Groups	Group A	Group B	t value	p value	Result
Crystalloids	4.93	4.19	3.164279	0.002077	Significant p<0.05

Table 5: Hospital, ICU stay and mortality in both groups.

Variable	Group A	Group B	P value	Remarks
Hospital stay (days)	18.66	15.53	0.241668	Not significant
ICU stay (days)	10.68	9.49	0.38	Not significant
28 days mortality	30 (60%)	28 (57.14)	0.83	Not Significant

While group A had a mortality of 60% and that of group B was 57.14 %. The target of ScvO2 was achieved in all patients of group A. Table 5 depicts a mean lactate concentration of 5.4 mmol/l±1.95 in patients of group B. The target lactate clearance of 10% was achieved in all patients.

DISCUSSION

The word 'sepsis' is derived from the Greek word 'sepo' meant decay or putrefaction i.e decomposition of organic matter in a manner that resulted in decay and death.[7]

Angus et al in his study of a cohort of 192,680 cases, reported the incidence of sepsis and high mortality. This study offers the most reliable estimate of sepsis epidemiology.[8] In a multicentre, prospective, observational study by Todi S as in Table 6 reported 16.45% incidence of severe sepsis in hospital admissions and around 65.2% and 64.6% hospital mortality and 28-day mortality due to severe sepsis.[2,9,10]

Table 6: Definitions used to describe the condition of septic patients.

Bacteremia	Presence of bacteria in blood, as evidenced by positive blood cultures.
Septicemia	Presence of microbes or their toxins in the blood.
Systemic inflammatory response syndrome (SIRS)	Two or more of the following conditions: May have a non-infectious etiology • Fever (oral temperature >38°C) or hypothermia (<36°C). • Tachypnoea (>24 breaths/min). • Tachycardia (heart rate >90 Beats/min). • Leucocytosis (>12,000/L), Leucopenia (<4000/L), or >10% bands.
Sepsis	SIRS that has a proven or suspected microbial etiology.
Severe sepsis (similar to "sepsis syndrome")	Sepsis with one or more signs of organ dysfunction – for example • Cardiovascular: Arterial systolic blood pressure 90 mmHg or mean arterial pressure 70 mmHg that responds to administration of Intravenous fluids. • Renal: Urine output <0.5 ml/kg/hr for 1 hour despite adequate fluid resuscitation. • Respiratory: PaO2/FiO2 of 250 or, if the lung is the only dysfunctional organ, 200. • Hematologic: Platelet count <80,000/L or 50% decrease in platelet count from highest value recorded over previous three days. • Unexplained metabolic acidosis: A pH 7.30 or a base deficit 5.0mEq/L and a plasma lactate level >1.5 times upper limit of normal for reporting lab. • Adequate fluid resuscitation: Pulmonary artery wedge pressure 12 mmHg or central venous pressure 8 mmHg.
Septic shock	Sepsis with hypotension (arterial blood pressure <90 mmHg systolic, or 40mmHg less than patient's normal blood pressure) for at least 1 hr despite adequate fluid resuscitation; or Need for Vasopressor to maintain systolic blood pressure 90 mmHg or mean arterial pressure 70 mmHg.
Refractory septic shock	Septic shock that lasts for >1 hr and does not respond to fluid or vasopressor administration.
Multiple organ dysfunction syndrome	Dysfunction of more than one organ, requiring intervention to maintain homeostasis.

Early Goal Directed Therapy, a landmark study by Rivers et al was a single center, parallel- group, randomized, controlled trial in 263 patients with severe sepsis or septic shock. This trial aimed at managing sepsis targeted at specific sequential goals.

The benefits stemmed from the early identification of patients at high risk for cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and oxygen demand. ScvO2 was considered a vital index of tissue oxygenation.[8]

It has been observed that changes in cardiac output (CO) proportionately affect changes in ScvO2 i.e reduction in cardiac output decreases in ScvO2 and vice versa. Positive changes in ScvO2 reported in response to fluid

resuscitation and inotropic therapy, a valuable resuscitation end-point.[11]

Mixed-venous oxygenation (SvO2) represents the oxygen saturation of blood in the pulmonary artery which consists of blood returning from the SVC, IVC, and coronary sinuses. SvO2 is an admixture of the venous return from the whole body whereas central venous oxygenation (ScvO2) represents the oxygen saturation of blood in the SVC alone. Despite this, there is an accurate correlation in trends is observed between the two.[12]

Blood lactate concentration varies in proportion to the ongoing deficit in tissue oxygenation, and the ability of the patient to reduce the blood lactate concentration indicates restoration of oxygen delivery with resuscitation. A lactate clearance of 10% or more predicts survival from septic shock, providing the rationale for this goal. Additionally, two normal lactate levels (<18 mg/dL [2 mmol/L]) at least 2 hours apart is taken as evidence of ongoing adequate tissue oxygenation.[11,13]

In a retrospective study, Legrand M et al. observed a linear relationship between CVP and the risk of new or persistent acute kidney injury (AKI) in 137 ICU patients. The authors questioned the CVP endpoint in sepsis resuscitation and postulated that the association between elevated CVP and AKI suggests a role of venous congestion in the development of AKI.[14]

On the other hand, Jones et al conducted a multicenter randomized, non-inferiority trial involving 300 patients with severe sepsis and evidence of hypoperfusion or septic shock who were admitted to the emergency department. The patients were randomly assigned to one of two resuscitation protocols. The ScvO2 group was resuscitated to normalize central venous pressure, mean arterial pressure, and ScvO2 of at least 70%; and the lactate clearance group was resuscitated to normalize central venous pressure, mean arterial pressure, and lactate clearance of at least 10%. The study protocol was continued until all goals were achieved or for up to 6 hours.The authors concluded that treatment to normalize central venous and mean arterial pressure, additional management to normalize lactate clearance did not result in significantly different in-hospital mortality as compared with management to normalize ScvO2.[15]

The relationship between tissue hypoxia and lactate generation by a reduction in systemic oxygen delivery (hemoglobin level, oxygen saturation, and cardiac output) is well known. In such states of low perfusion or cellular hypoxia, pyruvate does not enter the mitochondria and is preferentially reduced to lactate, leading to an increase in arterial lactate concentrations. High serum lactate levels and poor lactate clearance is significantly associated with high morbidity, increased vasopressor requirements and mortality.[12,16]

Santana AR et al in a retrospective cohort study utilized lactate levels at admission as predictors of mortality in 195 patients with sepsis. The study concluded that higher lactate levels correlated with higher morbidity and mortality.[17] In another randomized trial on 348 patients in sepsis admitted to a tertiary level hospital, 171 patients were subjected to 'lactate clearance' of 20% as the treatment goal while in the remaining 177, though lactate levels were measured, these were neither utilized to treat nor were known to the treating team. All patients entering the trial had elevated lactate level at admission. The primary aim of the study was to test whether patients with elevated lactate benefit from serial monitoring of its levels. The analysis reported a statistically significant reduced mortality as well as morbidity in the lactate group. Similar results were obtained in a twenty patient trial by Permpikul C et al.[18.19]

Further research is needed before strong and definitive recommendations can be made regarding the effect of GDT on resuscitation of patients with sepsis. There is currently a number of studies were conducted and a lot of ongoing RCTs of GDT in patients with sepsis. The results of these ongoing trials should provide further guidance as to goals used for defining GDT for resuscitation of patients with sepsis.[20]

CONCLUSION

In this study, mortality at day 28 was 60% in Group A and 57.4 in Group B. The results were comparable between the two groups with a relative risk of 0.97, the 95% CI being 0.77-1.22 and an insignificant p-value (0.83). Thus, our initial presumption that S Lactate clearance being non-inferior to ScvO2 stands true. The lactate group portends a marginally better survival as compared to ScvO2 though the comparison may not be clinically significant. To conclude, monitoring serum lactate in the management of patients in septic shock is as good as scvo2 monitoring and can be used in conjunction with the established sepsis protocol.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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