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ORIGINAL ARTICLE

Feasibility of Targeting Lactate Clearance versus Central Venous Oxygen Saturation during Early Resuscitation of Septic Patients

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ABSTRACT

Background: Early and appropriate management of patients with sepsis and septic shock markedly improves the clinical outcomes and decreases the mortality rate.

Methods: It was a prospective randomized study in which 62 adult septic patients of both sexes were randomly assigned to either $ScvO_2$ group or lactate clearance group. All patients were resuscitated to optimize central venous pressure and mean arterial pressure then targeting either $ScvO_2$ of at least 70% or lactate clearance of at least 20%. The study protocol was continued until all goals were achieved or up to 6 hours. Mortality at 28 days was measured for all patients. All the obtained data showed no significant differences between the two main groups except for the duration of the vasopressor free days. Thereby, two subgroups were created from the same acquired data as a $ScvO_2$ only subgroup (n=12) and Lactate clearance only subgroup (n=10).

Results: The overall mortality was 51.6%. Main group analysis revealed comparable results except for the duration of vasopressor free days which was longer in lactate clearance group. Subgroup results: the mortality rate was significantly lower in lactate clearance only subgroup [20% (2/10)] versus [75% (9/12)] in $ScvO_2$ only subgroup. Moreover, the durations of vasopressors and organ failure free days were longer in lactate clearance only subgroup.

Conclusion: Achievement of lactate clearance of $\geq 20\%$ goal only was associated with lower rate of mortality and better clinical outcomes than achievement of $ScvO_2 \geq 70\%$ goal only during early resuscitation of septic patients.

Key words: sepsis - septic shock - lactate clearance – central venous oxygen saturation.

INTRODUCTION

Sepsis is one of the oldest and most serious diseases in medicine. Despite the promising results of the recent researches, sepsis is still a major cause of death all over the world **(1)**. Formerly sepsis was defined as the state of systemic inflammatory response syndrome (SIRS) that occurs secondary to infection and when it is complicated by organ dysfunction it was termed severe sepsis while septic shock was defined as sepsis-induced hypotension that persists despite adequate fluid resuscitation. Recently the term of severe sepsis was abolished and sepsis is defined now as life-threatening organ dysfunction caused by a dysregulated host response to infection while septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality **(2)**.

Hemodynamic assessment which is totally dependent on clinical signs and symptoms may fail to early detect septic shock

while markers of global tissue hypoxia such as serum lactate and central venous oxygen saturation (**$ScvO_2$**) can help to timely detect and treat sepsis and potentially prevent organ dysfunction **(3). This study aimed to determine which is a better target for resuscitation of septic patients either $ScvO_2$ or lactate clearance.**

PATIENT AND METHOD

Study design

This study was performed as prospective interventional **randomized study** in trauma and surgical intensive care units of Zagazig University Hospitals over a period of 6 months after obtaining an approval from institutional review board (IRB) and a written informed consent from the patient or his relatives according to patient condition. **The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

The study was conducted upon **62 adult patients of both sexes** with septic shock who were **randomized** in two groups, 31 patients for each, **$ScvO_2$ Group** was targeted to achieve a $ScvO_2$ of ≥70 % and **lactate clearance Group was** targeted to achieve a lactate clearance of ≥20%. **Patients were assigned by simple randomization method using shuffled deck of cards placed in sealed opaque envelopes with even numbers for $ScvO_2$ Group and odd numbers for Lactate Clearance group.**

Participants

Patients presented with septic shock were assessed for presence of inclusion criteria, which required that patient's age **more than** 18 years, a clinical evidence of infection as in **the** form of positive microbiological cultures, radiological finding as pulmonary consolidation in case of pneumonia or direct visualization of pus in biological fluid or surgical wounds, and ≥ 2 of SIRS criteria: temperature < 36.0°C or >38.0°C, HR > 90 beat/m, need of mechanical ventilation, RR > 20/m or $PaCO_2$ < 32 mmHg, and leukocytosis >12,000/µL or leucopenia < 4,000/µL in association with hypoperfusion and septic shock in the form of either serum lactate > 4 mmol/L or sustained systemic hypotension (systolic arterial pressure < 90 mmHg or MAP < 65 mmHg) after a fluid challenge of 30 ml/kg.

Exclusion criteria included age less than 18 years, pregnancy, patients who are suffering from hemorrhagic shock, pulmonary edema, cardiac arrhythmia, valvular heart disease, acute coronary syndrome, or liver dysfunction, presence of a contraindication or failed trial to insert a central venous catheter (CVC), possibility of a requirement for immediate surgery within 6 hours of diagnosis or after receiving cardiopulmonary resuscitation.

Patient management

The patient resuscitation was started from time zero which was the time of the first diagnosis of the septic shock which was based on the presence of evidence of sepsis and sustained hypotension after the fluid challenge.

During the first 3 hours:

Appropriate specimens were taken for cultures as blood, sputum, urine and pus cultures. Two sets of blood cultures were collected each one by aspiration of 20 ml of blood under complete aseptic condition either from venous puncture or CVC after aspiration of 10 ml of blood. Broad spectrum antibiotics were administered in the first hour of diagnosis according to the suspected source of sepsis and institutional antibiogram. Blood pressure was monitored either noninvasively by automated cuff sphygmomanometer or invasively after insertion of an arterial catheter according to the patient's condition and the available facilities. All patients received CVC that were inserted through subclavian or internal jugular approaches.

All over the 1st 6 hours

In conjunction with insertion of CVC, aspiration of blood samples for culturing, administration of antibiotics and blood pressure monitoring intravenous administration of isotonic crystalloids was started from zero hour to achieve a central venous pressure (CVP) of

8-12 mm Hg or higher, after that the patient was assessed for the achievement of the second goal which was a mean arterial pressure (MAP) of 65 mm Hg or higher. If this value was not achieved by fluid administration, vasopressors (norepinephrine) infusion was started at a dose of 0.05ug/kg/min which was then titrated to achieve this desired MAP level.

After stabilization of patient volume status and MAP:

1- In $ScvO_2$ group; $ScvO_2$ of ≥ 70% was the resuscitation end goal. $ScvO_2$ was measured by a venous blood sample of 1 ml taken from the CVC after aspiration of 10 ml of venous blood then this sample was injected in the blood gas analyzer to measure $ScvO_2$. If the $ScvO_2$ was < 70%, hematocrit value was measured. If hematocrit value was <30%, packed red blood cells (RBCs) were transfused to achieve a value of ≥ 30%. If the $ScvO_2$ remained < 70% after optimization of hematocrit value to 30% or higher, dobutamine infusion was started at a dose of 3µg/kg/min and then titrated to obtain a $ScvO_2$ value of at least 70% within 6 hours.

2- In Lactate clearance group; lactate clearance of ≥ 20% was the resuscitation end goal. Lactate was measured by venous blood sample of 1 ml taken from the CVC after aspiration of 10 ml of venous blood then this sample was sent to clinical laboratory unit within less than 20 minutes from its aspiration to be measured. When treatment protocol was continued because the lactate clearance was less than 20%, subsequent lactate measurements were performed at a minimum of 2-hour intervals and repeated lactate clearance was calculated. Lactate clearance was calculated according to **Jones et al. (4)** as **[(lactate initial –lactate delayed) / lactate initial] x 100%, lactate initial** was the measurement before starting the resuscitation and **lactate delayed** was another measurement every 2-hour period after resuscitation was initiated**.** If the value of lactate clearance didn't reach 20% or more after 2 hours from initiation of resuscitation, hematocrit value was measured. If hematocrit value was < 30%, packed RBCs were transfused to achieve a value of ≥ 30%. If the lactate clearance remained < 20% dobutamine infusion was started at a dose of 3µg/kg/min and then titrated to obtain a lactate clearance value of ≥ 20% within 6 hours.

Data collection:

From all patients the following data were collected:

- **Upon admission:** Name, Age, Sex, Hospital diagnosis, Medical and Past history, SOFA and APACHI II scores and Basal serum lactate and $ScvO_2$.
- **During the study:** Serial measurement of $ScvO_2$ for all patients of $Scvo_2$ group until achieving a target of $ScvO_2$ ≥ 70% or a maximum time of 6 hours. In lactate clearance group serum lactate was measured every 2 h. during 1st 6 h until achieving a target of lactate clearance ≥ 20% or a maximum time of 6 hours. Serum lactate and $Scvo_2$ were measured at end of resuscitation for all patients. Volume of fluid administrated from 0 h to 6 h and from 0 h to 72 h, Fluid Balance (measured every day for the first 3 days), Ventilator-free days (from 1 to 28), Vasopressor-free days (from 1 to 28), Organ failure-free days [(CNS, renal, hepatic) from 1 to 28], Coagulation abnormalities, ICU length of stay (days), and SOFA and APACHI II scores measurement every day for the first 3 days and Mortality at 28 days.

Subgroup analysis

The total number of our population study was 62 patients, by the end of resuscitation protocol it was found that there were 27 patients achieved both goals of $ScvO_2$ ≥ 70%

and lactate clearance ≥ 20%, 3 patients didn't achieve neither $ScvO_2$ ≥ 70% nor lactate clearance ≥ 20% and 22 patients achieved either one of the two goals. These 22 patients were subjected to subgroup analysis; 12 patients in whom $ScvO_2$ ≥ 70% was achieved but lactate clearance ≥ 20% wasn't achieved scheduled in a subgroup called **$ScvO_2$ only subgroup** and 10 patients in whom lactate clearance ≥ 20% was achieved but $ScvO_2$ ≥ 70% wasn't achieved scheduled in a subgroup called **Lactate clearance only subgroup.**

Sample size

According to study of **Puskarich et al. (5)** achievement of the $ScvO_2$ goal only was associated with a mortality rate of 41% while achievement of the lactate clearance goal only was associated with a mortality rate of 8% so at power 80% and 95% CI (confidence interval), the estimated sample was 31 subjects in each group (using Epi – Info version 6) with a total number of 62 patients.

Statistical analysis

Patients' basal characteristic data and clinical outcomes were compared by use of descriptive analysis. Continuous data were presented in **the** form means and SD, or medians and inter-quartile ranges (IQR). Categorical data were described as proportions. Results were compared by use of independent t-tests or Mann-Whitney tests for continuous data, and chi square tests for categorical data, as appropriate. The applied statistical tests were two-sided with $P < 0.05$ was considered to be significant. To test whether failure to achieve one of these targets has clinical significance or not, a subgroup analysis was done to evaluate outcome of patients who achieved the $ScvO_2$ goal only, in comparison to patients who achieved the lactate clearance goal only.

RESULTS

A- Main group results:

All patients completed the study and there were no significant differences as regard age and sex distribution, co-morbidities, sources of infection and basal physiological measurements between the two main groups **(Table 1).**

There were no significant differences between the two main groups as regard the basal and the next three days values of both SOFA and APACHE II scores. The difference between the values of $ScvO_2$ and lactate at the start and end of resuscitation was statistically insignificant **(Table 2).** The differences between the two main groups regarding the total volume of the administrated fluid and the fluid balance all over the first three days were also statistically insignificant.

There were no significant differences between the two main groups as regard the durations of mechanical ventilation free days ($P = 0.686$), organ failure free days ($P = 0.082$) and ICU stay ($P = 0.437$) and the incidence of coagulation abnormalities ($P = 0.43$) but the period of vasopressor free days was significantly longer in lactate clearance Group ($P = 0.032$). Eighteen patients (58.1%) died in group who received $ScvO_2$ guided therapy versus fourteen patients (45.2%) in group who received lactate clearance guided therapy but this difference was statistically insignificant ($P = 0.309$) **(Table 3).**

B- Subgroup results

There were no significant differences between the two subgroups as regard age and sex distribution, co-morbidities, sources of infection and basal physiological measurements **(Table 4).** The differences between the two subgroups as regard the total volume of the administrated fluid and the fluid balance all over the first three days were also statistically insignificant.

There were no significant differences between the two subgroups as regard basal values of SOFA and APACHE II score and $ScvO_2$ and lactate levels. At the end of resuscitation (after 6 h) the lactate level was significantly lower in Lactate clearance only subgroup ($P = 0.002$) while $ScvO_2$ level was highly significantly higher in $ScvO_2$ only subgroup (P value < 0.001). Also, on the next three days there were significant differences in

the values of both SOFA and APACHE II scores between the two subgroups, the values were significantly lower in Lactate clearance only subgroup **(Table 5).**

There were no significant differences between the two subgroups as regard the durations of mechanical ventilation free days (P = 0.159), and ICU length of stay (P = 0.849) and the incidence of coagulation abnormalities (P = 0.225) but the periods of vasopressor free days and organ failure free days were significantly longer in Lactate clearance only subgroup compared to $ScvO_2$ only subgroup (P = 0.013 and 0.007 respectively) (**Table 6)**.

There was statistically significant difference between the two subgroups as regard the 28 days mortality, 75% of patients (9 of 12) died in $ScvO_2$ only subgroup while 20% of patients (2 of 10) died in Lactate clearance only subgroup (P = 0.01) (**Figure 1**). **Regarding the 3 patients who didn't achieve neither $ScvO_2$ nor lactate clearance goals, all of them died.**

Table 1: Basal clinical data and physiological parameters of the two main groups

Variable		$ScvO_2$ Group N = 31		Lactate clearance Group N = 31		P value
Age (**years**)		60.45±11.14		62.90±9.96		0.365
Sex	Male	15	48.4%	16	51.6%	0.799
	Female	16	51.6%	15	48.4%	
Comorbidities	HPN	12	38.7%	**8**	25.8%	0.277
	DM	14	45.2%	**11**	35.5%	0.407
	HCV	9	29.0%	**8**	25.8%	0.776
	CLD	5	16.1%	**3**	9.7%	0.449
	malignancy	3	9.7%	**4**	12.9%	0.688
	stroke	3	9.7%	**4**	12.9%	0.688
	NHMD	5	16.1%	**6**	19.4%	0.740
	Nursing home resident	1	3.2%	**2**	6.5%	0.554
Source of infection	Intra-abdominal	10	32.3%	**11**	35.5%	0.985
	pulmonary	7	22.6%	**9**	29.0%	
	Skin and soft tissue	5	16.1%	**4**	12.9%	
	Urinary tract	4	12.9%	**3**	9.7%	
	More than one source	3	9.7%	**3**	9.7%	
	Unknown source	2	6.5%	**1**	3.2%	
MAP **mmHg**		53.19 ± 6.77		54.81 ± 7.6		0.381
HR **beat/min**		106.94 ± 15.04		108.23 ± 15.26		0.739
RR **breath/min**		38.27 ± 0.93		38.43 ± 1.04		0.623
Temperature **°C**		27 (18 - 61)		25 (16 -72)		0.139
CVP **mmHg**		7 (0 -18)		5 (0 -16)		0.631

Hypertension (HPN), Diabetes Mellitus (DM), Hepatitis C Virus infection (HCV), Chronic lung disease (CLD), No history of medical disease (NHMD), Mean arterial blood pressure (MAP), Hear rate (HR), Respiratory rate (RR), Central venous pressure (CVP), Central venous oxygen saturation (**$ScvO_2$**).
Independent t, Man Whitney and chi square tests were applied when appropriate.
P value was considered to be significant if < 0.05 and highly significant if <0.001.
Data were represented in the form of mean ± SD, median and range or number and percentage.

Table 2: Severity of illness of the two main groups

Variable		$ScvO_2$ Group N = 31	Lactate clearance Group N = 31	P value
SOFA	On admission	9 (4 -13)	9 (4 -13)	0.782
	at 24 hours	9 (3 -14)	9 (3 -12)	0.304
	at 48 hours	8 (2 -13)	6 (2 -15)	0.223
	at 72 hours	6 (3 - 13)	5 (2 -13)	0.182
APACHE II	On admission	17 (11- 26)	18 (11 -25)	0.444
	at 24 hours	14 (10 -23)	15 (8 -23)	0.876
	at 48 hours	11 (8 - 20)	10 (5 -23)	0.291
	at 72 hours	9 (5 - 19)	8 (4 -21)	0.104
Basal $ScvO_2$		58.0 (42 - 83)	63 (46 -86)	0.223
$ScvO_2$ at end of resuscitation		73.94 ± 7.65	72.16 ± 6.50	0.329
Basal lactate		7.8 (3.2-12.8)	8.7 (3.2 -13.6)	0.596
Lactate at end of resuscitation		5.6 (1.8-12.6)	5.6 (1.8 -10.5)	0.513

Sequential Organ Failure Assessment (SOFA), Acute physiology and chronic health evaluation (APACHE II), Central venous oxygen saturation ($ScvO_2$),
Independent t test and Man Whitney test were applied when appropriate.
P value was considered to be significant if < 0.05 and highly significant if <0.001.
Data were represented in the form of median and range or mean ± SD.

Table 3: Measured outcomes of the two main groups within the 28 days of the study and ICU length of stay

Variable	$ScvO_2$ Group N = 31	Lactate clearance Group N = 31	P value
Mechanical ventilation free days	3 (0 -25)	10 (0 -23)	0.686
Vasopressor free days	3 (0 -26)	15 (0 -26) *	0.032
Organ failure free days	5 (0 -28)	19 (0 -28)	0.082
Coagulation abnormalities	21 (67.7%)	18 (58.1%)	0.430
ICU length of Stay	10 (4-23)	11 (4-22)	0.437
28 days mortality	18 (58.1%)	14 (45.2%)	0.309

Intensive care Unit (ICU). Central venous oxygen saturation ($ScvO_2$),
Man Whitney test and chi square test were applied when appropriate.
P value was considered to be significant if < 0.05 and highly significant if <0.001.
Data were represented in the form of **median and range** or number and percentage.
(*) statistically significant longer duration as compared to the other group.

Table 4: Basal clinical data and physiological parameters of the two subgroups

Variable		$ScvO_2$ only subgroup N = 12		Lactate clearance only subgroup N = 10		P value
Age (**years**)		59.25 ± 7.84		62.40 ± 8.62		0.380
Sex	Male	5	41.7%	6	60.0%	0.392
	Female	7	58.3%	4	40.0%	
Comorbidities	HPN	4	33.3%	3	30.0%	0.867
	DM	6	50.0%	4	44.4%	0.801
	HCV	3	25.0%	4	40.0%	0.652
	CLD	2	16.7%	1	10.0%	0.650
	stroke	1	8.3%	2	20.0%	0.571
	malignancy	2	16.7%	2	20.0%	0.840
	NHMD	2	16.7%	1	10.0%	0.650
Source of infection	Intra-abdominal	4	33.3%	4	40.0%	1.00
	pulmonary	2	16.7%	3	30.0%	
	Skin and soft tissue	1	8.3%	1	10.0%	
	Urinary tract	2	16.7%	1	10.0%	
	More than one source	2	16.7%	1	10.0%	
	Unknown source	1	8.3%	0	0.0%	
MAP/**mmHg**		54.42 ± 7.66		58 ± 5.35		0.227
HR **beat/ min**		102.08 ± 12.65		110.50 ± 12.89		0.139
Temperature **°C**		38.18 ± 0.87		38.43 ± 0.95		0.696
RR **breath/min**		28.17 ± 6.07		24.80 ± 6.11		0.211
CVP **mmHg**		9 (2-16)		3.5 (0-13)		0.143

Hypertension (HPN), Diabetes Mellitus (DM), Hepatitis C Virus infection (HCV), Chronic lung disease (CLD), No history of medical disease (NHMD), Mean arterial blood pressure (MAP), Hear rate (HR), Respiratory rate (RR), Central venous pressure (CVP), Central venous oxygen saturation ($ScvO_2$),

Independent t, Man Whitney and chi square tests were applied when appropriate. P value was considered to be significant if < 0.05 and highly significant if <0.001. Data were represented in the form of mean ± SD, median and range or number and percentage.

Table 5: Severity of illness of the two subgroups

Variable		$ScvO_2$ only subgroup N = 12	Lactate clearance only subgroup N = 10	P value
SOFA	On admission	9.67 ± 2.64	8.10 ± 2.28	0.157
	at 24 hours	9.00 ± 3.98	5.80 ± 2.39*	0.038
	at 48 hours	7.92 ± 3.03	5.20 ± 2.20*	0.029
	at 72 hours	7.33 ± 3.28	4.20 ± 1.99*	0.016
APACHE II	On admission	18.25 ± 2.8	16.90 ± 2.85	0.277
	at 24 hours	17.75 ± 3.65	14.00 ± 3.74*	0.028
	at 48 hours	14.83 ± 3.95	11.40 ± 2.76*	0.03
	at 72 hours	12.67 ± 4.10	7.90 ± 3.00*	0.006
Basal $ScvO_2$		65.25 ± 11.25	58.80 ± 7.73	0.141
$ScvO_2$ at end of resuscitation		79.83 ± 4.20	63.5 ±3.87**	<0.001
Basal lactate		8.22 ± 2.54	6.65 ± 2.08	0.135
Lactate at end of resuscitation		7.59 ± 2.62	4.14 ±1.72*	0.002

Sequential Organ Failure Assessment (SOFA), Acute physiology and chronic health evaluation (APACHE II), Central venous oxygen saturation ($ScvO_2$),
Independent t test was applied when appropriate.
P value was considered to be significant if < 0.05 and highly significant if <0.001.
Data were represented as mean ± SD.
(*) statistically significant lower difference as compared to the other group.
(**) highly significant lower difference as compared to the other group.

Table 6: Measured outcomes of the two subgroups within the 28 days of the study and ICU length of stay

Variable	$ScvO_2$ goal only subgroup N = 12	Lactate clearance goal only subgroup N = 10	P value
Mechanical ventilation free days	5 (0 - 24)	16.5 (0 - 23)	0.159
Vasopressor free days	2.5 (0 - 26)	17 (4 - 23) *	0.013
Organ failure free days	4.5 (0 -25)	22.5 (5 - 28) *	0.007
Coagulation abnormalities	9 (75.0%)	5 (50%)	0.225
ICU length of Stay	10.42 ± 5.92	10.8 ± 2.2	0.849
28 days mortality	9 (75%)	2 (20%)*	0.010

Intensive care Unit (ICU)
Independent t, Man Whitney and chi square tests were applied when appropriate.
P value was considered to be significant if < 0.05 and highly significant if <0.001.
Data were represented in the form of mean ± SD, **median and range** or number and percentage.
(*) statistically significant longer duration and lower difference as compared to the other group.

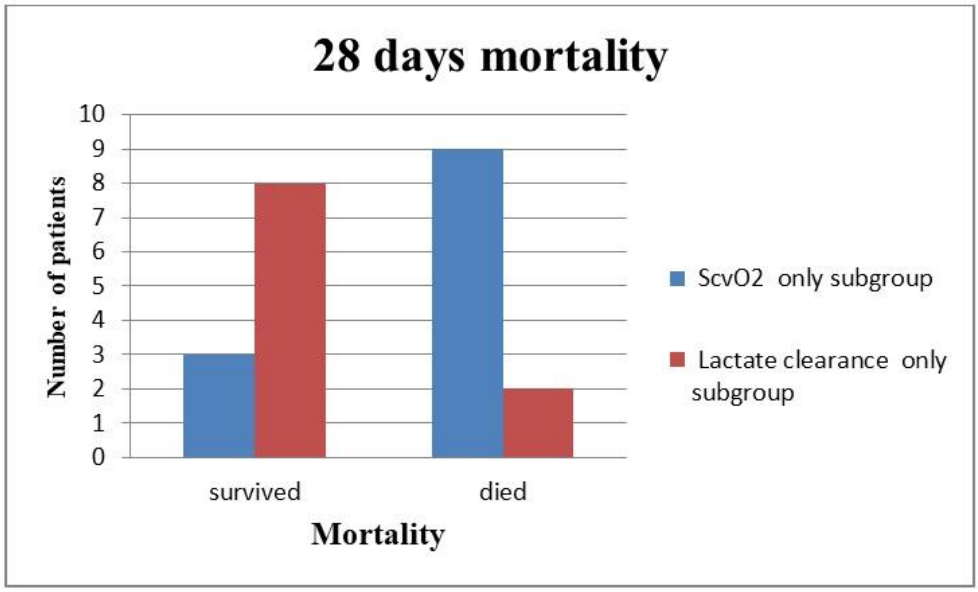

Figure 1: The difference between the two subgroups regarding 28 days mortality.

DISCUSSION

The results of the current study revealed that septic shock patients who achieved a lactate clearance of ≥ 20% without achieving $ScvO_2$ of ≥ 70% had a statistically significant lower rate of 28 days mortality than those who achieved a $ScvO_2$ of ≥ 70% without achieving lactate clearance of ≥ 20%.

The protocolized quantitative resuscitation of septic shock patients was first described by **Rivers et al. (6)** in **the** form of early goal directed therapy (EGDT) that aimed **at** achievement of certain hemodynamic parameters (CVP from 8-12 mmHg and MAP ≥ 65mmHg) by fluids administration, vasopressors and dobutamine infusion and RBCs transfusion to optimize $ScvO_2$ at a value of ≥ 70% as an endpoint of resuscitation. They reported that all of in- hospital, 28 days and 60 days mortality were significantly higher in the standard therapy group. These results were supported by another clinical trial performed by **Wang et al**. **(7)** who reported that rate of mortality was significantly lower in goal directed therapy group in comparison to patients' group who received conventional therapy.

The choice of $ScvO_2$ as an indicator of adequacy of tissue perfusion was based on its ability to measure the balance between oxygen delivery (DO_2) and oxygen consumption (VO_2) which in turn indicates the ability of cardiac output to meet the tissues oxygen and metabolic needs **(3).**

Textoris and colleagues (8) claimed that high $ScvO_2$ is associated with higher rate of mortality and they explained that finding by the possibility of impaired ability of the tissues to extract or utilize oxygen at the late stages of septic shock. However, that study had some limitations including that it was a single-center retrospective study and this might carry some risk of selection bias. Moreover, $ScvO_2$ wasn't continuously measured so several events might **have** been missed. Lastly, VO_2 wasn't measured and this might affect the interpretation of the results.

Lactate clearance has been used as an end-point of EGDT (4,5) and as a tool for prediction of mortality in critical ill patients with sepsis **(9). Nguyen et al. (10)** found that the group of patients who achieved lactate clearance of ≥ 10% had a significant lower rate of in-hospital, 30-day and 60-day mortality than those who didn't achieve lactate clearance of ≥ 10%**.**

A large multicenter randomized controlled study was performed on critically ill

patients in ICU and demonstrated that reducing lactate levels by at least 20% every 2 hours, significantly reduced ICU length of stay and also ICU and hospital mortality when adjusting for predefined and commonly accepted risk factors **(11).**

The results of the current study emphasize the clinical concept which has been established by **Jones et al. (4)** that lactate clearance is absolutely not inferior to $ScvO_2$ to evaluate the resolution of global tissue hypoxia during the early sepsis resuscitation. Furthermore, the present study and **Puskarich et al. (5)** work pointed out that early lactate clearance during the first 6 hours of resuscitation is a strong independent predictor of survival even in case of failure to achieve $ScvO_2 \geq 70\%$**.**

Lee and colleagues (12) applied EGDT on patients admitted with severe sepsis and septic shock, in a design similar to that was described by **Rivers et al. (5)** with measurement of $ScvO_2$ and lactate for all patients at 0 and 6 h but without lactate guidance. They found that patients with lactate normalization showed significantly lower 28-days mortality compared to patients without lactate normalization (3% vs. 28%, $P<0.01$).These results and the results of the current study somewhat coincide with the most recent recommendations of the surviving sepsis campaign **(13)**.

Although there is an accordance between the results of the current study and these of the studies that compared the clinical utility of targeting $ScvO_2$ and lactate during resuscitation of sepsis as regarding the better outcomes related to the lactate clearance group, however, the current study was associated with higher mortality rates than those studies and this might be attributed to the more clinical severity of patients' illness at time of presentation. The population of the current study had a higher level of lactate and higher values of SOFA and APACHE II scores at time of initiation of resuscitation.

The results obtained in the current study supports the recommendations made by **Jones (14)** who called for substitution of $ScvO_2$ by lactate clearance as a goal during early resuscitation of septic shock patients for many reasons. First, the published studies supporting the use of $ScvO_2$ as a resuscitative goal were derived from single center randomized trials whereas those supporting the use of lactate were derived from large multicenter randomized trials. Second, $ScvO_2$ is considered a rudimentary indicator of only the balance between oxygen supply and demand while elevated blood lactate provides more data about energy metabolism in septic patient including both anaerobic metabolism that results from tissue hypoxia and some other aerobic metabolic processes that affects energy transfer and contribute to lactate production. Third, $ScvO_2$ may be normal or high even in the presence of severe organ hypoperfusion due to inability of the tissues to extract or utilize oxygen**.**

On the other hand, **Rivers et al. (15)** criticized the suggestion of entirely depending upon lactate clearance usage instead of $ScvO_2$ as a sepsis resuscitation goal. They mentioned that $ScvO_2$ is more sensitive as an early-warning indicator in sepsis than lactate which may be of normal value at time of presentation in spite of presence of tissue hypoperfusion and organ dysfunction. They also commented that the interpretation of lactate clearance percent is oversimplified. Although the percentage of lactate reduction from 10 to 9 is the same as that from 4 to 3.6 (both are of 10% clearance) but they have significantly different clinical and outcome implications.

Hernandez et al. **(16)** also resisted the use of lactate clearance in sepsis as it has some pitfalls. They justified that lactate kinetics is so complex and there are other factors that induce hyperlactemia rather than anaerobic metabolism that occurs during periods of hypoperfusion as stress-related adrenergic-induced aerobic glycolysis, impaired hepatic lactate clearance, mitochondrial dysfunction limiting pyruvate metabolism and intravenous infusion of large volumes of Ringer's solutions.

The present study has a point of strength which is presented in the ability of the research team to be flexible and open minded as when they found that there weren't significant differences between the two main groups they tried to obtain more comprehensive results by performing subgroup analysis by usage of the same collected data, the way that eventually resulted in getting more significant results.

LIMITATIONS AND RECOMMENDATIONS

The current study has some points of limitations; It was performed as a single center trial on small sample size of populations**.** The research team weren't blinded for the patients group which might carry the risk of intention-to-treat**.** The study included patients suffering from malignancy which is an element that might **affect** the mortality**.** There was a blind time zone during which the patients data weren't collected nor analyzed in the period from the fourth day of admission until patients death or discharge from the hospital, a matter that **makes** it is uncertain whether patients received the appropriate management or not during this period**.** The study didn't provide data about hospital length of stay, in-hospital mortality, cost effectiveness and the long term mortality.

Although three large randomized clinical trials; Australasian Resuscitation in Sepsis Evaluation (**ARISE**) **(17)**, Protocolized Care for Early Septic Shock (**ProCESS) (18)** and Protocolised Management in Sepsis (**ProMISe**) **(19)** showed no benefit of usage EGDT over usual care which is based on physician clinical judgment for treatment of septic shock but these trials studied the goal therapy targeting $ScvO_2$ and not lactate clearance so we are looking for future researches that will compare between the usual care and goal therapy targeting lactate normalization or clearance for management of sepsis. We also recommend that further studies are to be conducted as multicentre studies.

CONCLUSION

In septic shock patients treated with an early quantitative resuscitation protocol, it was found that achievement of lactate clearance of 20% or more without achieving central venous oxygen saturation of 70% or more is significantly associated with lower mortality rate than achieving central venous oxygen saturation of 70% or more with failure to achieve a lactate clearance of 20%, a matter that **denotes** lactate clearance to be of a higher prognostic utility.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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