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MOTTLING SCORE AND CENTRAL VENOUS OXYGEN SATURATIONIN SEPTİC SHOCK PATIENTS

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ABSTRACT

Background: Mottling score and central venous oxygen saturation are described as a clinical evaluation of microcirculation impairment having a crucial role in the physiopathology of the sepsic shock. This study describes mottling incidence and mottling score in septic shock patients according to central venous oxygen saturation. **Methods:** We prospectively analyzed the data of patients admitted to ICU between October 2022 to December 2022 in a tertiary teaching hospital. All septic patients in whom the ScvO2 was measured and mottling scores were evaluated were included. Data collection was realized at ICU admission (H0) and after six hours (H6); after initial resusciation. Hemodynanamic parameters, the mottling score (from 0 to 5), based on mottling area widening from the knees to the periphery and ScvO2 measured from a central intravenous catheter. **Results:** A total of 62 patients were included. Among patients with ScvO2 <70 at H0, SOFA score, lactate level, mean arterial pressure, and norepinephrine dose were lower than ScvO2 ≥70 (p-value <0. 001; p= 0.016; p-value <0. 001; p-value <0.001, respectively). However, there was no statistical difference in mottling in these patients. Similarly, at H6, patients with ScvO2 <, 70 had a lower SOFA score and lactate level (p-value <0.001; p-value <0.001, respectively). However, at H6, patients with ScvO2 ≥70 presented higher mottling scores than patients with ScvO2 <70 (p=0.012). **Conclusion:** A high level of ScvO2 in septic shock patients may be associated with higher mottling scores. However, mortality was not influenced by central venous oxygen saturation.

KEYWORDS: Central oxygen saturation, microcirculation, mottling score, septic shock.

INTRODUCTION

The microcirculatory perfusion abnormalities are the primarily critical dysfunction in the pathogenesis of septic shock causing suboptimal tissue oxygenation.[1] Increasingly, evidence has recently been shown that inconsistancy between microcirculatory alterations and systemic hemodynamic parameters is more considerable during shock. [2] Clinically, many assessment methods for microcirculation including peripheral tissue perfusion and oxygenation have been studied such as visual assessment, laboratory biomarkers, and direct visualization of the microcirculation. [2,3] In the event of none of these methods has shown superiority over the other, the evaluation of the microcirculation is the main subject at the bedside in intensive care units (ICU), especially in resource-limited settings.

A thorough examination of the skin can provide important clinical information regarding microcirculation at the bedside. Skin mottling provides quick and useful information, especially in cases where laboratory values (such as lactate) have not measured. Skin mottling is defined as a bluish, patchy skin discoloration most commonly assessed peripherally at the knees. It is a clinical sign of shock and reflects microcirculatory alterations in the skin.[4,5] The mottled areas of the skin have been shown to have reduced blood flow and low muscle oxygen saturation.[6,7] The proposed mechanisms are the activation of the coagulation cascade, vasoconstriction due to high sympathetic tone, and endothelial dysfunction.[8,9,10] The skin mottling score is a scale from 0 (no mottling) to 5 (grave mottling) used for semiquantitative assessment of the skin. This scale correlates with blood lactate concentrations, urine output, degree of organ dysfunction, and negative outcomes in patients with sepsis or septic shock.[11]

Central venous oxygen saturation (ScvO2) is a serum marker reflecting the global metabolism of oxygen. Low levels reflect a decreased cardiac output with an excessive extraction of oxygen; a low hemoglobin

concentration; a low level of arterial oxygen pressure (PaO2). A high level of ScvO2 conversely reflects an increased oxygen delivery above tissue requirements; decreased cellular consumption of oxygen (such as mitochondrial dysfunction in sepsis).

We hypothesized primarily that, there was a difference in mottling incidence and mottling score according to ScvO2 level during a septic shock. We supposed the extent of mottling in the knee area related to abnormal microcirculatory perfusion should be correlated with increased ScvO2 (above 70%) in patients in septic shock hospitalized in the intensive care unit. Second, there was a relationship between mottling and severity scores at admission, vasopressor level, hemodynamic parameters, and ICU mortality.

MATERIAL AND METHODS

This study was a prospective observational study and was conducted after the approval of the Ethics Committee (Decision no: 05/12). This study was a single-center trial. From October 2022 to December 2022, all patients admitted to the ICU of our institution (Mengücek Gazi Training and Education Hospital, Erzincan, Turkey) were prospectively screened. All of the patients were intubated, so oral information was given to all patients' relatives. Written informed consent was also taken from patients' relatives. This study was carried out under the principles of the Helsinki Declaration. This trial was also registered (NCT05681052) at http://www.clinicaltrials.gov.

We enrolled patients aged ≥ 18 years in septic shock. Those excluded include peripheral arterial disease, black skin, cutaneous infection of the lower limbs, pregnancy, and relative refusal. The characteristics of patients were recorded at admission (H0), including demographics (age, sex, body mass index (BMI), admission the Acute Physiology and Chronic Health Evaluation (APACHE II) score, Glasgow Coma Scale (GCS) and sequential organ failure assessment (SOFA) score. Variables such as plasma lactate level, daily urine output, plasma creatinine level, the ratio of arterial oxygen pressure related to inspired oxygen fraction (PaO2/FiO2), hemoglobin level, heart rate, mean arterial pressure, pulsatile saturation in oxygen (SpO2) and body temperature were recorded also at H0 and 6 hours after initial resuscitation (H6).

Septic shock is defined as sepsis associated with lactate ≥ 2 mmol/L and the vasopressor requirement to maintain mean arterial pressure (MAP) ≥ 65 mmHg (1). The patients in septic shock were managed according to the Surviving Sepsis Campaign Guidelines (2). At admission, patients were resuscitation with intravenous crystalloids. Norepinephrine was used as a first-line vasopressor, when needed, epinephrine and positive inotropes were added to achieve a mean arterial pressure of 65 mmHg and urine output >0,5 mL/kg/hour. Continuous and invasive arterial pressure, central venous catheter, and mechanical ventilation were provided when needed. As hemodynamic monitoring, we used transthoracic echocardiography. According to local protocol, sedation and analgesia were performed with midazolam and fentanyl, respectively.

ScvO2 samples were obtained at H0 and H6. The central venous catheter was in the superior vena cava. The position of the tip of the catheter was checked with chest radiography. The mean of the two measured values was recorded as other parameters were measured.

Mottling score (from 0 to 5) of the anterior aspect of the knee was assessed visually on both legs concurrently. Patients have placed their spine with legs straight. When mottling was present, then the leg with the more prominent mottling was chosen for scoring. The assessment was done simultaneously with the ScvO2 assessment (Table 1).

Table 2: Skin mottling score after initial fluid resuscitation.

Score		Description
0	No	No mottling
1	Modest	Coin size, localized to the centre of the knee
2	Moderate	Mottling does not exceed the superior edge of the kneecap
3	Mild	Mottling does not exceed the middle thigh
4	Severe	Mottling does not exceed beyond the fold of the groin
5	Grave	Mottling exceeds beyond the fold of the groin

We compared the characteristics of patients, mottling incidences, mottling scores, ICU mortality rate at day 14, and length of stay between groups ScvO2≥ 70 and ScvO2≤ 70.

Statistical Analysis

Data are presented as number (%), mean ± SD (standard deviation) for normally distributed values, and median (minimum and maximum) for non-normally distributed values. The Shapiro-Wilk test was used for normality. Comparisons of the percentages were performed with the Chi-square test. Differences in the variables between groups were examined using Student's t-test, the Mann-Whitney U test, and Fisher's exact test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS (version 20.0) package program.

RESULTS

Sixty-two patients were prospectively included for septic shock fulfilling the inclusion criteria during three months in the ICU. The general characteristics of the patients were compared in Table 2. Thirty-one patients (50%) were male. The mean age was 75.81 ± 5.65 years.

Tablo 2: General characteristics of the patients. Values are expressed as absolute values (n), mean (±SD) or median (min-max).

	All patients n =62	SvO_2 < 70 n=31	SvO_2 ≥ 70 n=31	P value
Demographics				
Age (years)				0.195
(mean±SS)	75.81 ± 5.65	76.74 ± 5.77	74.87 ± 5.47	
(median, min-max)	77 (56-86)	78 (56-86)	75 (65-84)	
Male, n (%)	31 (50)	15 (48.4)	16 (51.6)	0.098
BMI (kg/m^2)	28.05 ± 2.84	28.05 ± 3.40	28.05 ± 2.21	0.993
APACHE II	65.05 ± 13.88	58.37 ± 13.71	71.72 ± 10.56	<0.001
GlasgowComa Scale	7 (4-14)	6 (4-8)	9 (5-14)	<0.001
Clinical parameters				
Hemoglobin (g/dl)	10.0 (8.60-12.80)	9.9 (8.60-11.40)	7.3 (7.20-7.43)	0.530
Creatinine	1.10 (0.60-2.2)	1.10 (0.60-2.20)	1.10 (0.6-2.2)	0.955
Urinary output (ml/24 hour)	1175 (900-1400)	1150 (950-1400)	1200 (900-1400)	0.681
pH (arterial)	7.32 (7.00-7.44)	7.32 (7.00-7.44)	7.31 (7.20-7.43)	0.146
PaO2/FiO2, mmHg	250 (150-310)	260 (185-310)	240 (150-310)	0.004
SvO_2	73.10 ± 0.06	65.97 ± 2.38	80.23 ± 2.57	<0.001
ICU length-of-stay (days)	7 (4-16)	7 (4-15)	6 (4-16)	0.920
14- day mortality, n (%)	46 (74.2)	24 (77.4)	22 (71.0)	0.562

At admission, the APACHE and Glasgow Coma Scale were significantly higher in the patients with ScvO2 ≥70 than in the patients with ScvO2 <70 (p-value <0.001; p-value <0. 001; p value= 0.001, respectively). PaO2/FiO2 ratio also decreased in the patients with ScvO2 ≥70 (p= 0.004) (Table 2).

All the patients received sedation (Ramsey score between 3 and 5) and were mechanically ventilated in the same protocol. Norepinephrine was used in all patients. Fifteen patients (24.19 %) were discharged from the hospital. The mean length of stay in the ICU was 7 days (Table 2). Overall ICU mortality reached 74.19% on day 14. Septic shock was mainly associated with respiratory (66.12 %) and gastrointestinal (16.12 %) infection (Table 3).

Table 3: Origin of sepsis of patients with septic shock.

Source of infection	n (%)
Respiratory	41 (66.12)
Gastrointestinal	10 (16.12)
Urinary	5 (8.06)
Cutaneous	1 (1.61)
Undefined	5 (8.06)

We compared the clinical parameters and mottling at ICU admission (H0) between patients with ScvO2 <70 and those with ScvO2 ≥70. Results are presented in Table 3 for H0 (ICU admission) and in Table 4 for H6. Among patients with ScvO2 <70 at H0, SOFA score, lactate level, mean arterial pressure, and norepinephrine dose were lower than ScvO2 ≥70 (p-value <0. 001; p= 0.016; p-value <0. 001; p-value <0.001, respectively). However, there was no statistical difference in mottling in these patients. Similarly, at H6, patients with ScvO2 <, 70 had a lower SOFA score and lactate level (p-value <0.001; p-value <0.001, respectively). However, at H6, patients with ScvO2 ≥70 presented higher mottling scores than patients with ScvO2 <70 (p=0.012) (Table 5).

Table 4: Clinical parameters and mottling score at ICU admission (H0) according to central venous oxygen saturation. Values are expressed as absulate values (n), %, mean (± SD) or median (min- max).

H0 (admission)	SvO_2 <70 n= 31	$SvO_2 \geq 70$ n= 31	p value
SOFA score	6 (4-9)	9 (6-13)	<0.001
Lactate (mml/L)	2.91 ±0.80	3.51 ±1.19	0.016
	2.70 (2.00-5.80)	3.10 (2.00-6.40)	
Mean arterial pressure (mmHg)	75.29 ± 8.04	61.81 ± 8.22	<0.001
Heart rate (minute)	95 (79-143)	98 (88-120)	0.150
Norepinephrine	0.10 (0.04-0.20)	0.13(0.06-0.42)	<0.001
doses (mcg/kg(min)			
Mottling score (%)			
0	12.90	16.12	
1	0	0	
2	22.58	3.22	
3	38.70	45.16	
4	25.80	29.03	
5	0	6.45	0.245

Table 5: Clinical parameters and mottling score at 6 hours after initial resuscitation (H6) according to central venous oxygen saturation. Values are expressed as absulate values (n), %, mean (± SD) or median (min- max).

H6	SvO_2 <70 n= 31	$SvO_2 \geq 70$ n= 31	p value
SOFA score	8 (5-9)	10 (7-13)	<0.001
Lactate (mml/L)	2.96 ± 0.66	4.01 ± 0.89	<0.001
	3.0 (2.10-4.30)	3.7 (2.70-6.30)	
Mean arterial pressure (mmHg)	67.38 ± 2.89	66.03 ± 3.90	0.53
Heart rate (minute)	95 (86-120)	98 (78-118)	0.393
Norepinephrine	0.12 (0.04-0.24)	0.16- (0.06-0.50)	0.050
doses (mcg/kg/min)			
Mottling score (%)			
0	0	0	
1	0	0	
2	19.35	3.22	
3	51.61	35.48	
4	29.03	54.83	0.012
5	0	6.45	

DISCUSSION

Our study found that in patients with septic shock, mottling distribution was different measured at 6 h after initial resuscitation according to central venous oxygen saturation. Patients with ScvO2 ≥ 70 had higher mottling scores. Furthermore, in this study SOFA score and lactate level were higher both at H0 and at H6 among patients with ScvO2 ≥70 similarly. However, the ICU mortality rate at day 14 and length of stay was not associated with increased central venous oxygen saturation.

In septic shock, persistent hypotension requiring vasopressors to maintain a mean arterial pressure and a higher lactate level are two cornerstone issues in ICU for physicians. This relative and absolute hypotension are compensated by vasoconstriction to maintain optimal blood pressure (macrocirculation) and organ perfusion (microcirculation). Both components are crucial to the initial resuscitation of patients with sepsis. However, neither MAP nor cardiac output, common indicators of macrocirculation, assess tissue hypoperfusion at the microvascular level, which is the main driver of organ dysfunction in sepsis.[12,13] Sepsis causes dysfunction of microcirculatory autoregulation, which results in heterogeneous abnormalities in blood flow and subsequent tissue malperfusion.[12,14,15,16] Not only sepsis but also many other critical pathologies may cause microcirculatory alterations such as trauma and cardiogenic shock.[17,18] In our study, we focus on the septic shock to consist of a homogenous cohort with the physiopathology of sepsis to avoid bias.

Monitoring of the microcirculation status was shown to have a strong prognosis value in septic shock.[19,20] Therefore exploration of the microcirculation using clinical and biological parameters is crucial. Many microcirculation assessment methods were published. Some devices are developed as videomicroscopy, side streams dark field imaging to direct visualization of microcirculation, or spectral orthogonal polarization.[21] However, these methods are not daily practice and are

difficult to obtain in resource-limited settings. Other clinical assessments can be readily done at the bedside or with rapid laboratory testing including a proportion of perfused vessels, lactate, skin mottling and capillary refill time, central venous oxygen saturation, and peripheral perfusion index.[11,22] In the literature, there is no gold standard method, so, we focus on the mottling score which is an easy and simple assessment. High central venous oxygen saturation, another microcirculatory biological marker, is associated with increased mortality in septic shock patients and one of the objectives of septic shock resuscitation is to raise the ScvO2 level above 70%.[23] We also focus on this marker which is with the necessity of inserting a central catheter to evaluate. We think this issue is important, especially in patients who cannot insert a central venous catheter or that will take time to insert, to make an objective evaluation.

In this study, H0 and H6 time points were determined similarly to previous studies in the literature.[7,11, 24] At H0 we expect the worst microcirculation situation especially in patients ScvO2 ≥70 and at H6 after initial resuscitation, we also expect a stabilization of mottling, still higher in patients ScvO2 ≥70. Ferraris at all. revealed a prospective cohort of 46 patients in septic shock and established a relation between mottling score and lactate level at H6. However, no correlation was found between 28- day ICU mortality.[24] This current work is the first study to analyze mottling scores according to central venous oxygen saturation cut-off of 70% in septic shock. This study confirms a relationship between central venous oxygen saturation and microcirculatory disorders, such as mottling. At HO, mean arterial pressure was lower in patients with ScvO2 ≥70 needing higher doses of inotrope with higher lactate levels without a difference in mottling. At H6, after resuscitation, while mean arterial pressure was higher than 65 mmHg in both groups (macrocirculation), the lactate level and mottling score (microcirculation) were higher in patients with ScvO2 ≥70. This clinical finding supports the hypothesis of a decreased use of oxygen in sepsis even if the blood pressure is normal. A defect in oxidative phosphorylation in the cells causes impairment of oxygen for adenosine triphosphate production. This misuse of oxygen, so-called, cytopathic dysoxia, may cause high levels of ScvO2.

Nevertheless, no correlation was found 14- between day ICU mortality and length of stay in the ICU between central venous oxygen saturation groups. In the literature, there are different cut-off points optionally [23]. The difference in mortality in such groups may depend on this dissimilarity. In addition, we did not measure ScvO2 continuously, thus we might have missed some events. We paid attention to making the variables similar such as oxygenation, and hemoglobin content including ScvO2 between groups. However, we did not measure the oxygen consumption and cardiac output continuously, which may be important for the interpretation of the study findings. This result may not be generalizable to all septic patients because of the limited cohort of the study. We conducted a single-center study and the number of patients was limited without previous calculation of the number of subjects required. Other studies need to be conducted to confirm these data with a larger cohort using the other microcirculatory parameters.

In conclusion, a level of ScvO2 ≥70 in septic shock patients may be associated with higher mottling scores. Future studies relating mottling and ScvO2 assessment should be realized with the other microcirculation methods in a larger cohort.

Conflict of interest statement: No conflict of interest.

Author contributions: Kutluer Karaca N. participated in research design, in the writing of the paper and in the performance of the research. Eren N. and Tülay Ceren Ölmeztürk Karakurt T. C participated in the performance of the research. Hayme S. contributed new reagents or analytic tools and participated in data analysis.

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