Taylor & Francis
Taylor & Francis Group

Effect of dexmedetomidine vs midazolam on the microcirculation of septic patients who are mechanically ventilated

Mostafa Mohamed Atef Refaat, Laila Ali Elkafrawy, Reem Hamdy Elkabarity and Amr Fouad Hafez

Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Ain-Shams University, Cairo, Egypt

ABSTRACT

Background: Sepsis has been associated with microvascular alterations. Studies have shown dexmedetomidine to have a beneficial effect on the microcirculation in patients with sepsis. In search for better sedation modality, we compared between dexmedetomidine and midazolam in terms of tissue perfusion in patients suffering from sepsis.

Methods: A total of 128 patients with sepsis requiring sedation and mechanical ventilation were randomized into 2 groups. Each group comprised 64 patients: Group A (sedated by dexmedetomidine) and Group B (sedated by midazolam); assessment of microcirculation during sedation infusion was performed directly through the peripheral perfusion index (PPI) and indirectly by using global markers of perfusion (ScvO2, P(v-a)Co2).

Results: Sixty-four patients were analyzed in each group. Base line characteristics were similar in both groups. We found no significant differences ($p > 0.05$) between microcirculatory parameters, PPI, Scvo2, and P(v-a)CO2 when comparing between both sedated groups. The 28-day mortality rate was significantly lower ($p = 0.042$) in dexmedetomidine patients (26.6%) as compared to midazolam patients (43.8%). In addition, there was no difference in ICU stay between the two groups ($p = 0.061$).

Conclusion: Using dexmedetomidine as a sedation option did not provide better peripheral perfusion in patients with sepsis.

1. Background

Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection [1]. Sepsis affects all elements of the microcirculation where it causes a decrease in capillary density and an increase in heterogeneity of perfusion, leading to decreased oxygen delivery, tissue hypoxia, and organ dysfunction [2].

The assessment and follow-up of the microcirculation during sepsis can be used as a measure of prognosis and a guide for treatment, as studies showed that an early increase in microcirculatory perfusion is associated with reduced multi-organ failure [3].

Many techniques are used in evaluating the microcirculation; clinical assessment methods include the peripheral perfusion index (PPI). Indirect measures reflect tissue oxygenation as a surrogate for microcirculatory function as with Central venous oxygen saturation (ScvO2), mixed venous oxygen saturation (SvO2), or cellular anaerobic metabolism as with lactate [4].

PPI is measured by pulse oximetry, and it represents a simple non-invasive direct method for assessment of the peripheral microcirculation. PPI values of less than or equal to 1.4 have been related to the presence of tissue hypoperfusion; it was also shown to be a predictor of mortality with a cut-off ≤0.2 in septic patients in ICU [5–7].

P(v-a)CO2(Co2 Gap) is a marker of perfusion and a predictor of the microvascular blood flow maldistribution where values <6 mmHg indicate adequate tissue perfusion [8].

Studies proposed different mechanisms for possible beneficial impact of dexmedetomidine on the septic microcirculation [9–12]. In search of a better sedative for intensive care patients suffering from sepsis, the study aimed to compare between dexmedetomidine and midazolam effects on the microcirculation in septic patients who are mechanically ventilated and require sedation through the Peripheral Perfusion Index (PPI), Co2 Gap, and ScvO2. It secondarily set out to correlate between the different markers used for microcirculatory assessment in the study.

1.1. Methods and measurements

The current study is a prospective randomized controlled single blinded clinical trial, which was performed in the surgical intensive care unit of Ain Shams University, which is a medical-surgical ICU from 1 April 2021 to 28 February 2022.

The study was performed after the approval of the ethical committee in faculty of Medicine-Ain Shams University, number FMASU MD 51/2020. All procedures

in the study were performed in accordance with the ethical standards of the institutional research committee, as well as with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The study was registered at the Pan African Clinical Trial Registry, and the number of the registry is PACTR202112845314910. After clearly explaining the procedure, and any potential complication, written informed consent from all participants or their legal guardians was obtained.

1.1.1. The inclusion criteria

Patients are above the age of 21 years, in sepsis, defined as suspected or documented infection with an acute increase of ≥ 2 points of Sequential Organ Failure Assessment score (SOFA score), requiring sedation for mechanical ventilation.

1.1.2. The exclusion criteria

Patients less than 21 years old, pregnant or breast-feeding females, history of allergy to any of the drugs used in the study, second- or third-degree heart block, systolic blood pressure < 90 mmHg, ejection fraction < 30%, bradycardia with a heart rate <50 bpm, child B or C cirrhotic liver disease, documented acute coronary syndromes, intubation and mechanical ventilation ≥24 h before enrolment, and vasopressor infusion were excluded.

1.2. Sample size

G. power program is used for sample size calculation, as there is no adequate information regarding the difference between the two groups. The present study will target a medium effect size of 0.5 and a sample size of 128 patients (64 per group) achieving 80% power to detect statistically significant difference between two groups, regarding quantitative outcomes measures using a two-sided t-test with ∝-error = 0.05.

1.3. Randomization and patient allocation

The study population was sampled randomly; Permuted blocked randomization was performed online to generate the randomization list. Categorization of study groups was reserved in closed non-transparent envelopes that were unsealed after enrolment of patients. The ICU doctors and nurses were not blinded to the study assignment. Participants or their guardians, the data collector, and the statistician were all blinded to the study assignment.

The patients were randomly allocated into two groups: Group A: received dexmedetomidine infusion and Group B: received midazolam infusion.

1.4. Patients' interventions and management

On admission to ICU, detailed baseline data, including demographics and comorbidities, were recorded. Patients were assessed using the SOFA score, and standard monitors were applied; ECG, pulse oximeter, non-invasive arterial blood pressure monitor, axillary temperature probe, and a central venous catheter were inserted under complete aseptic conditions, guided by ultrasound (Mindray M5, UMT200/China).

The surviving sepsis campaign recommendations were followed, including appropriate broad-spectrum antibiotics according to the protocol of our institute [13]. Daily laboratory investigations were allowed according to the ICU protocol.

Patients were mechanically ventilated (Newport™ e360 Ventilator; Newport Medical Instrument, CA) by Synchronised intermittent mandatory ventilation – volume control mode (SIMV -VC), with lung protective ventilation as per ARDS network guidelines [14]. Changes in ventilatory settings were left for the attending physician according to patient's condition.

1.5. Study procedures

Data collection and assessment parameters for the study were obtained during 24 hrs, where 0 hr (t 0) is just before the start of infusion.

Sequential Organ Failure Assessment Score (SOFA score) was calculated just before starting (t 0) and after 24 hours (t 24).

PPI was measured using a Massimo Radical-7® Pulse CO-Oximeter (Masimo Corp., Irvine, CA). Each patient wore an adhesive oximeter probe attached on a finger and connected to a Masimo Radical-7 Pulse Co-oximeter. PPI was measured from the middle finger in the contralateral hand to that containing the non-invasive blood pressure cuff, and it was wrapped by a towel to decrease heat loss and interference by ambient light. The ambient temperature of the room was consistent at approximately 23 to 25°C (climate-controlled).

The CO_2 gap was measured by obtaining an arterial and venous sample at the same time and subtracting the venous pCo2, which is obtained from the central venous line from the arterial pCo2 sample that is obtained from an Arterial Blood Gas (ABG) sample.

PPI readings measurements were taken just before starting infusion (t 0) and after two hours (t 2), four hours (t 4), six hours (t 6), and twenty four hours (t 24).

CO_2 gap, $ScvO_2$, and Mean Arterial blood pressure (MAP) readings were taken at starting infusion (t 0), twelve hours (t 12), and twenty four hours (t 24).

Group A received dexmedetomidine infusion with a dose range of 0.2 to 0.7 mcg/kg/hr [15]. In Group B, the used dose for midazolam infusion was 0.05 to 0.15 mg/kg/hr [16].

The used sedative was infused through an intravenous route through a dedicated central or peripheral line and a 50 ml syringe. The used doses were adjusted as required according to the hemodynamics of the patients and sedation needs. The patients were maintained at a Richmond Agitation-Sedation Scale (RASS) of (−1 to −4)[17].

1.6. Measured outcomes

1.6.1. Primary outcome
Effect of sedation modality on PPI.

1.6.2. Secondary outcome
1. 28-Day mortality rate in both groups.
   2. Length of ICU stay (days) in both groups.
   3. Efficacy of PPI measurement in comparison with global markers of perfusion (ScvO2, P(v-a)Co2) in assessment of the microcirculation.

2. Statistical methods

Recorded data were analysed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

2.1. The following tests were performed:

Mann–Whitney U test: for two-group comparisons in non-parametric data

Spearman's rank correlation coefficient (rs) was used to assess the degree of association between two sets of variables if one or both of them was skewed.

The chi-square (χ^2) test of significance was used in order to compare proportions between qualitative parameters.

The confidence interval was set to 95%, and the margin of error accepted was set to 5%. Thus, the p-value was considered significant as follows:
   Probability (P-value)
   – P-value <0.05 was considered significant.
   – P-value <0.001 was considered as highly significant.
   – P-value >0.05 was considered insignificant.

Table 1. Comparison between groups according to demographic data.

Demographic data	Dexmedetomidine (n = 64)	Midazolam (n = 64)	Test value	p-value
Age (years)				
Range	22–68	23–71	t = 1.446	0.151
Mean ± SD	48.15 ± 8.19	50.29 ± 8.55		
Sex				
Male	38 (59.4%)	35 (54.7%)	$\chi^2 = 0.128$	0.721
Female	26 (40.6%)	29 (45.3%)		

Data are shown as mean ± SD
Using t-Independent Sample t-test χ^2: Chi-square test
P-value >0.05 NS

3. Results

A total of 140 patients were assessed for eligibility, two refused to participate, leaving 138 patients for original enrolment in the study. Nine patients were dropped due to their need for vasopressor support; five patients from the dexmedetomidine group, four patients from the midazolam group, and another patient from the midazolam group were dropped as sedation was replaced by fentanyl infusion when suspected to suffer an acute coronary syndrome. These patients were not included in the study population, and thus, the study was completed on 128 patients (64 per group) as shown in (Figure 1); there was no statistically significant difference between both groups in terms of demographic data (Table 1), baseline characteristics, and baseline SOFA score at inclusion (Table 2).

PPI readings in both groups were higher after starting sedation infusion, but differences between both groups were non-significant (Table 3). There were generally higher PPI readings observed in the dexmedetomidine group. There were higher change % of mean from (t 0) to (t 24); (124.4%) in Group A, and (75.82%) in Group B.

Dexmedetomidine was associated with modest lower 28-day mortality rate (P- value 0.042) (Table 4).

There was no statistically significant difference between both groups in length of ICU stay (p-value 0.061) (Table 5).

In both groups, when evaluating PPI against standard measurements of tissue perfusion (PCo2 Gap and ScvO2), we found a statistically significant positive correlation between PPI and ScvO2 (p-value<0.05) and there was a significant negative correlation between PPI and PCo2 Gap (p-value<0.05).

4. Discussion

The present study targeted the microcirculation in mechanically ventilated patients with sepsis sedated with either dexmedetomidine or midazolam. The microcirculation was assessed directly by using PPI and indirectly by using global markers: Scvo2, which is a marker for tissue oxygenation, and CO2 Gap, which is a marker for tissue perfusion. The study was carried out over 24 hr.

It is worth mentioning that those patients who required vasopressors during the 24-hr period were excluded from the study as that would have presented a major confounding factor on peripheral perfusion index readings.

The rising interest in using dexmedetomidine in sepsis came from several studies that proposed different actions and immunomodulatory roles of dexmedetomidine with favourable outcomes in septic patients, the clinical implications of which, if proved, would be choosing dexmedetomidine over other drugs to sedate patients in sepsis.
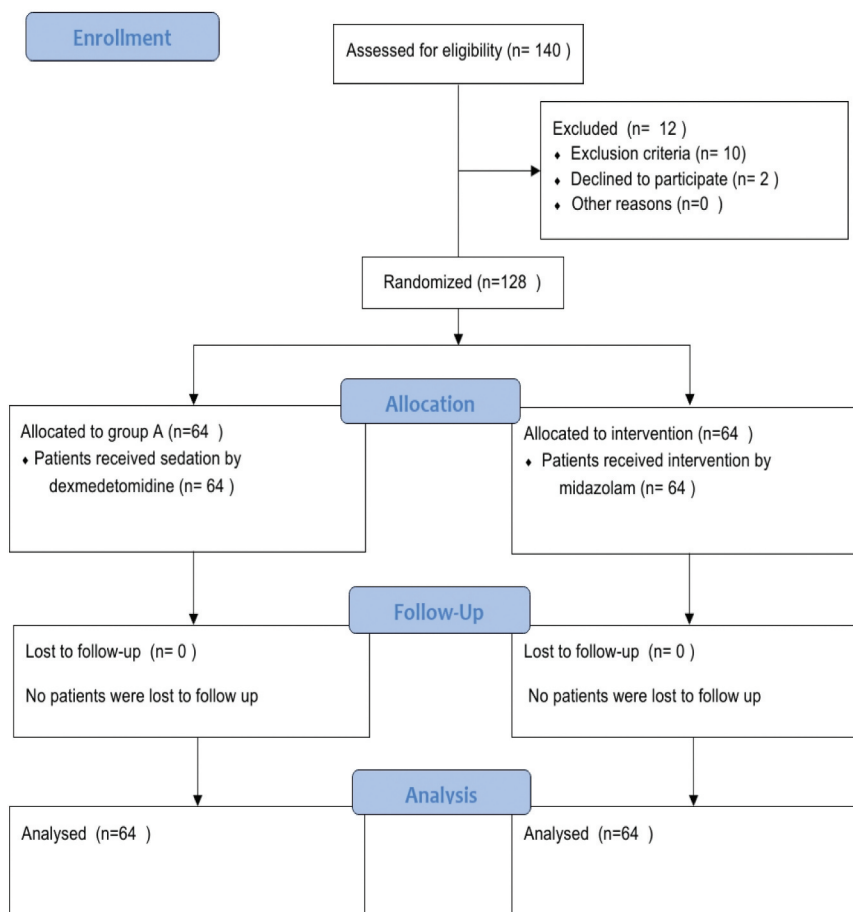
Figure 1. CONSORT diagram.

Table 2. Comparison between groups according to SOFA score.

SOFA score	Dexmedetomidine (n = 64)	Midazolam (n = 64)	z-value	p-value
0 hr.				
Range	3–17	4–17	1.130	0.443
Median (IQR)	7 (5–14)	8 (4–15)		
24 hrs.				
Range	4–16	4–17	1.720	0.254
Median (IQR)	6 (3–14)	8 (4–14)		

Data are shown as median (range).
Using z-Mann-Whitney test; P-value >0.05 NS
SOFA score: Sequential Organ Failure Assessment score

By using dexmedetomidine in septic rats, Marcos et al. documented positive microcirculatory effects in endo-toxemic rats for dexmedetomidine by attenuation of capillary perfusion defects [9]. Furthermore, She et al. demonstrated improvement of mitochondrial function of vascular endothelial cells, which led to improvement of vascular leakage and endothelial barrier dysfunction [10].

Clinically, by examining patients with sepsis in ICU, Moeen et al. concluded that dexmedetomidine attenuated the inflammatory response in contrast to both propofol and midazolam, by significantly reducing (IL-1β, IL-6) and declining the capillary leak index through 48 hours [11].

Table 3. Comparison between groups according to PPI.

PPI	Dexmedetomidine (n = 64)	Midazolam (n = 64)	z-value	p-value
0 hr				
Range	0.15–7.4	0.08–6.6	0.780	0.677
Mean ± SD	0.86 ± 0.36	0.91 ± 0.43		
2 hrs				
Range	0.12–7.7	0.1–7.1	1.130	0.481
Mean ± SD	1.12 ± 0.48	0.84 ± 0.40		
4 hrs				
Range	0.10–8.3	0.1–7.5	1.040	0.489
Mean ± SD	0.78 ± 0.34	0.75 ± 0.39		
6 hrs				
Range	0.09–7.4	0.12–6.9	1.190	0.422
Mean ± SD	1.44 ± 0.59	1.02 ± 0.46		
24 hrs				
Range	0.09–7.6	0.09–7.3	1.510	0.296
Mean ± SD	1.93 ± 0.83	1.60 ± 0.83		

Using z-Mann-Whitney test; P-value >0.05 NS.

Management of sepsis was carried while following the surviving sepsis update recommendations [13]. Our results presented clinical improvement during the ICU management of patients over the 24-hr period of management of patients in both groups, which was detected successfully by the used markers, as there were improvements in mean ScvO2 values at 12 hrs and at 24 hrs when compared to 0 hr when examining both groups individually and there was gradual improvement in PCo2Gap values in both groups,

Table 4. Comparison between groups according to the 28-day mortality rate.

	Dexmedetomidine (n = 64)	Midazolam (n = 64)	x^2	p-value
28-Day mortality rate	17 (26.6%)	28 (43.8%)	4.118	0.042*

Using Chi-square test; P-value >0.05 NS

Table 5. Comparison between groups according to the ICU length (day).

ICU length (day)	Dexmedetomidine (n = 64)	Midazolam (n = 64)	z-value	p-value
Range (day)	2–14	1–11	1.891	0.061
Mean ± SD	11.20 ± 4.69	9.85 ± 3.26		

Using z-Mann-Whitney test; P-value >0.05 NS

where after 24 hrs each of the two groups showed a mean PCO2 gap <6 mmHg, indicating adequate tissue perfusion (Supplementary figure 3).

The results, however, indicated no significant difference in the microcirculation between both sedation modalities by failing to demonstrate statistically significant differences when comparing the values of the dexmedetomidine group with those of the midazolam group, with p value >0.05 when comparing Scvo2 at 12 hrs and at 24 hrs and p value >0.05 when comparing the Co2 gap at 12 hrs and 24 hrs, and we advice adding laboratory markers of inflammation and a longer duration of observation for future studies.

While differences between the groups A and B were also statistically insignificant, we observed modest higher PPI readings in the dexmedetomidine group, and we think that limitations contributed to that outcome. Moreover, a longer duration of the study in a bigger sample was needed to give a clearer view of a possible significant difference. When comparing the PPI readings in the end at 24 hrs in comparison with the beginning at 0 hrs, we find improved readings in both groups and a greater change % of PPI readings at the end of 24 hrs in the dexmedetomidine group (124.4%), when compared with midazolam (75.82%).

PPI was shown to be a reliable tool in evaluating microcirculation by having a statistically significant correlation with other global markers of perfusion (PCo2 Gap and ScvO2), where there were positive correlation between PPI and ScvO2 and negative correlation between PCo2 Gap with PPI and ScvO2.

These findings are consistent with the correlation showed by He et al. who presented significant correlation between PPI, lactate, P(v-a)CO2, and ScvO2 [18]. This correlation points to the value of using the previous markers when assessing the prognosis during managing sepsis.

Regarding the hemodynamics, our findings showed no statistically significant difference in mean arterial blood pressure readings in both groups despite showing modest lower readings with the dexmedetomidine group. Similarly, Cioccari et al. also showed non-significant haemodynamic changes in those who received dexmedetomidine when compared with those who did not in the first 48 hours with dexmedetomidine versus non-dexmedetomidine sedation by examining mechanically ventilated sedated patients in sepsis [19]. On the other hand, Sigler et al. observed higher use of vasopressors by dexmedetomidine in mechanically ventilated septic patients; however, his comparison was made with propofol [20].

Dexmedetomidine was associated with statistically better survival compared to midazolam , which goes with the meta-analysis by Chen et al. who similarly presented that dexmedetomidine reduced 28-day mortality as with our study [21]. Regarding the length of ICU stay, no statistically significant difference was found between both groups , similar to what Jakob et al. showed [22].

The improved mortality along with higher readings and larger change % of PPI with dexmedetomidine may suggest that dexmedetomidine could have a positive effect on the microcirculation of septic patients, despite the fact that our results showed no significant difference in the microcirculatory parameters between both sedation modalities.

Interestingly, COVID-19 infection, which is a cause of sepsis, is treated by drugs with anti-interleukin effects in practice, due to the presence of high expression of inflammatory chemokines and cytokines, where markedly elevated levels of IL-1 and IL-6 are shown with serious COVID-19 infections [23].

The possible benefit of dexmedetomidine in sepsis on the microcirculation due to its anti-IL-1 and anti-IL-6 effects raises an important practical implication by favouring dexmedetomidine over other sedatives now with COVID-19 patients.

5. Conclusions

Using dexmedetomidine as a sedation option did not provide better peripheral perfusion in patients with sepsis. The dexmedetomidine group showed statistically significant better 28-day survival, but without difference in ICU stay. Additionally, peripheral perfusion index efficiently correlated with the global markers of microcirculatory assessment (Scvo2 and P(v-a) CO2).

6. Limitations

Some limitations of our study need to be acknowledged;

- The time of this study is short as the study was carried out over 24 hrs; the microcirculation could be assessed over a longer period during ICU stay.

- Although efforts were made to decrease heat loss and keep ambient temperature consistent, patients peripheral temperature was not constant and temperature changes of the fingers might impact the readings of the peripheral perfusion index, rendering them less accurate.
- More research can be performed in the future by employing more direct and indirect methods for microcirculatory assessment and correlating with laboratory markers for inflammation.
- More frequent blood pressure readings are needed for better presentation of the effect on haemodynamics of both drugs.
- A bigger sample size would give more significant results.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research received no external funding.

Author contributions

MR designed the study, revised the literature, followed up the patients, took and recorded the measurements, analysed the data, and wrote the manuscript. LA revised the literature and critically reviewed the manuscript. RH revised the literature, analysed the data, and critically reviewed the manuscript. AF revised the literature, analysed the data, and critically reviewed the manuscript. All the authors contributed to editorial changes in the manuscript. All the authors read and approved the final manuscript.

Availability of data and material

The data sets used and/or analysed during the current study are available from the corresponding authors on reasonable requests.

References

[1] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama. 2016;315(8):801–810.

[2] De Backer D, Donadello K, Sakr Y, et al. Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. Crit Care Med. 2013;41(3):791–799.

[3] Trzeciak S, McCoy JV, Phillip Dellinger R, et al. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med. 2008;34 (12):2210–2217.

[4] Charlton M, Sims M, Coats T, et al. The microcirculation and its measurement in sepsis. J Intensive Care Soc. 2017;18(3):221–227.

[5] Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. Crit Care Med. 2002;30(6):1210–1213.

[6] He HW, Liu DW, Long Y, et al. The peripheral perfusion index and transcutaneous oxygen challenge test are predictive of mortality in septic patients after resuscitation. Crit Care. 2013;17(3):R116.

[7] Bakker J. Biochemical markers for clinical monitoring of tissue perfusion. Curr Opin Crit Care. 2021;27(3):269–273.

[8] Ospina-Tascón GA, Umaña M, Bermúdez WF, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med. 2016;42 (2):211–221.

[9] Miranda ML, Balarini MM, Bouskela E. Eliete bouskela dexmedetomidine attenuates the microcirculatory derangements evoked by experimental sepsis. Anesthesiology. 2015;122(3):619–630.

[10] Ma Y, Yu XY, Wang Y. Dose-related effects of dexmedetomidine on immunomodulation and mortality to septic shock in rats. World J Emerg Med. 2018;9 (1):56–63.

[11] She H, Zhu Y, Deng H, et al. Protective effects of dexmedetomidine on the vascular endothelial barrier function by inhibiting mitochondrial fission via ER/ Mitochondria contact. Front Cell Dev Biol. 2021;9:636327.

[12] Moeen SM, Abdelhakeem EE, Abdalla EM, et al. Dexmedetomidine versus propofol or midazolam in patients with abdominal sepsis regarding inflammatory response and capillary leak. Egypt J Anaesth. 2022;38(1):23–32.

[13] Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063–e1143.

[14] Papazian L, Aubron C, Brochard LCJ-D, et al. Dreyfuss D, et al.Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care. 2019;9(1):69.

[15] Yu SB. Dexmedetomidine sedation in ICU. Korean J Anesthesiol. 2012;62(5):405–411.

[16] Reves JG, Fragen RJ, Vinik HR, et al. Midazolam: pharmacology and uses. Anesthesiology. 1985 Mar;62 (3):310–324.

[17] Sessler CN, Gosnell MS, Grap MJ, et al. The richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–1344.

[18] He H, Long Y, Liu D, et al. Clinical classification of tissue perfusion based on the central venous oxygen saturation and the peripheral perfusion index. Crit Care. 2015;19(1):330.

[19] Cioccari L, Luethi N, Bailey M, et al. The effect of dexmedetomidine on vasopressor requirements in patients with septic shock: a subgroup analysis of the Sedation Practice in Intensive Care Evaluation [SPICE III] trial. Crit Care. 2020;24(1):441.

[20] Sigler M, Islam E, Nugent K. Comparison of dexmedetomidine and propofol in mechanically ventilated patients with sepsis: a pilot study. Southwest Respir Crit Care Chron. 2018;6(22):10–15.

[21] Chen P, Jiang J, Zhang Y, et al. Effect of dexmedetomidine on duration of mechanical ventilation in septic patients: a systematic review and meta-analysis. BMC Pulm Med. 2020;20(1):42.

[22] Jakob SM, et al. Dexmedetomidine vs Midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307(11):1151–1160.

[23] Chen LYC, Hoiland RL, Stukas S, et al. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. Eur Respir J. 2020;56 (4):2003006.