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Dexmedetomidine administration is associated with reduced mortality in patients with sepsis-induced acute respiratory distress syndrome: a retrospective study

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Abstract

Background Although studies have revealed the benefits of using dexmedetomidine (DEX) in treating rodent models of acute lung injury (ALI) by improving their survival rates, clinical investigation on the effect of DEX on patients with acute respiratory distress syndrome (ARDS) remains scarce. Through this retrospective study, we aim to better understand the underlying mechanism of sepsis-induced ARDS and the effect of DEX on patients' standard treatment.

Methods A total of 208 patients with sepsis-induced ARDS, admitted to the intensive care unit (ICU) at Affiliated Hospital of Jiangsu University, China, from January 2017 to December 2019, were included. The patients were divided into the control group ($n=102$) and the DEX group ($n=106$). Both groups of patients received mechanical ventilation and standard care; however, the DEX group was additionally treated with DEX as a sedative. Demographic information, baseline characteristics, laboratory parameters, arterial blood gas (ABG) analyses, and inflammatory indicators were compared between the two groups to evaluate the therapeutic outcomes of different treatment approaches.

Results Age and male gender constituted risk factors for high ARDS incidence, and hypertension led in the list of patients' comorbidities. The baseline characteristics including primary diagnosis and ARDS causes, and prognostic values such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score and predicted mortality, were comparable between the two groups of patients. However, the multiple organ dysfunction syndrome (MODS) incidence and actual mortality rate were significantly lower in the DEX group compared to the control group. Additionally, the DEX group demonstrated improved ABG metrics, representing better acid-base balance and oxygenation, and enhanced inflammatory responses.

Conclusions Intravenous administration of DEX was associated with reduced in-hospital mortality, at least in part, by ameliorating ABG indices and inflammatory mediators.

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Keywords Sepsis, Acute respiratory distress syndrome, Dexmedetomidine, Blood oxygenation, Inflammatory response

Introduction

Acute lung injury (ALI) is clinically characterized by severe respiratory distress and progressive hypoxemia. Pathologically, it is marked by diffuse lung damage, alveolocapillary hyperpermeability, and pulmonary edema due to mass accumulation of protein-rich fluid in the alveolar cavity [1]. In developed countries like the United States, ALI remains a medical incidence as high as nearly 200,000 per year with an in-hospital mortality greater than 30% [2]. Triggered by many factors including lung infection and non-pulmonary sepsis, ALI can rapidly progress to ARDS, which is classified according to the Berlin definition into three levels of severity based on different degrees of oxygenations: mild (200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg), moderate (100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg) and severe (PaO_2/FiO_2 ≤ 100 mmHg) [3]. Following this definition, it was concluded that the patients with ARDS took up 10.4% of ICU admissions and 23.4% of those requiring mechanical ventilation, and the mortality rates were reported at 34.9%, 40.3%, and 46.1% for mild, moderate, and severe patients, comprising 30.0%, 46.6% and 23.4% of total ARDS hospitalizations, respectively [4].

Sepsis is the most common pathogenic factor that leads to ARDS [5]. It is defined as the life-threatening organ dysfunction caused by a dysregulated host response to infection, while the inflammatory cascade and septic shock complicate treatment and contribute to high mortality rates [6]. Compared to ARDS induced by non-sepsis-related causes, sepsis-induced ARDS including direct ALI due to pulmonary infections and indirect ALI arising from extrapulmonary sources, has a significantly higher mortality rate [7]. Given the heterogeneous nature of both sepsis and ARDS, although there has been lots of research in the past decades, the fundamental understanding of pathogenesis and the search for effective treatment of sepsis-induced ARDS in clinical settings are still of great need.

As a second-generation α2 adrenergic receptor (α2-AR) agonist with high selectivity, DEX has been widely used in clinical practice as a preoperative sedative and as an adjuvant to general or regional anesthesia, as well as for postoperative sedation and analgesia [8, 9]. Recently, DEX was found to suppress inflammatory responses effectively. It has demonstrated protective effects against oxidative damage due to ischemia reperfusion in various organs, including the brain, heart, and kidney, as observed in animal models [10–12] and clinical trials [13, 14]. Amid the coronavirus disease 2019 (COVID-19) pandemic, DEX has been actively applied in intensive care units (ICUs) to improve hypoxemia and reduce the need for intubation [15, 16].

In this retrospective study, the hospitalized patients with sepsis-induced ARDS received conventional antibiotic treatments and sedatives, with or without the intravenous administration of DEX. Their baseline characteristics were investigated, including demographic information, medical history, and clinical presentation. In addition, the ABG analyses and inflammatory responses were conducted both before and after their ICU stays, focusing on carbon dioxide levels, oxygenation indices, biochemical parameters, and cytokine concentrations. Treatments including mechanical ventilation and the use of antibiotics and sedatives, together with clinical outcomes, were evaluated to draw conclusions.

Methods

Study design

A flow chart depicting the patient screening and selection was shown in Fig. 1. Patients with sepsis admitted at Affiliated Hospital of Jiangsu University from January 2017 to December 2019 were first screened. Sepsis was diagnosed following the International Guidelines for Management of Sepsis and Septic Shock [17, 18]. Then ARDS diagnosis was following the formal guidelines published by the Chinese Society of Critical Care Medicine [19], consistent with Berlin definition [3]. A total of 208 patients were included and divided into the control group and the DEX group, having 102 and 106 patients, respectively. Demographic information, comorbidity, primary diagnoses prior to ICU transfer, and main causes for sepsis-induced ARDS were reported in Table 1, where the APACHE II scores and predicted mortality for all patients were also calculated and assessed. APACHE II scoring is a classification system that helps evaluate the severity of disease, when scores are determined by a list of physiological variables from the patients within 24 h upon their ICU admissions [20]. For MODS incidence, the scoring system for MODS assessment was applied [21], and the number of patients with MODS was further divided by the total number of patients in the group to yield MODS incidence.

Patient procedure

All patients with sepsis-induced ARDS following ICU admission were given invasive or non-invasive mechanical ventilation, and for invasive mechanical ventilation (intubation), the tidal volume was measured to 6–10 mL/kg based on predicted body weight to maintain the airway platform pressure < 30 cmH_2O. A continuous positive

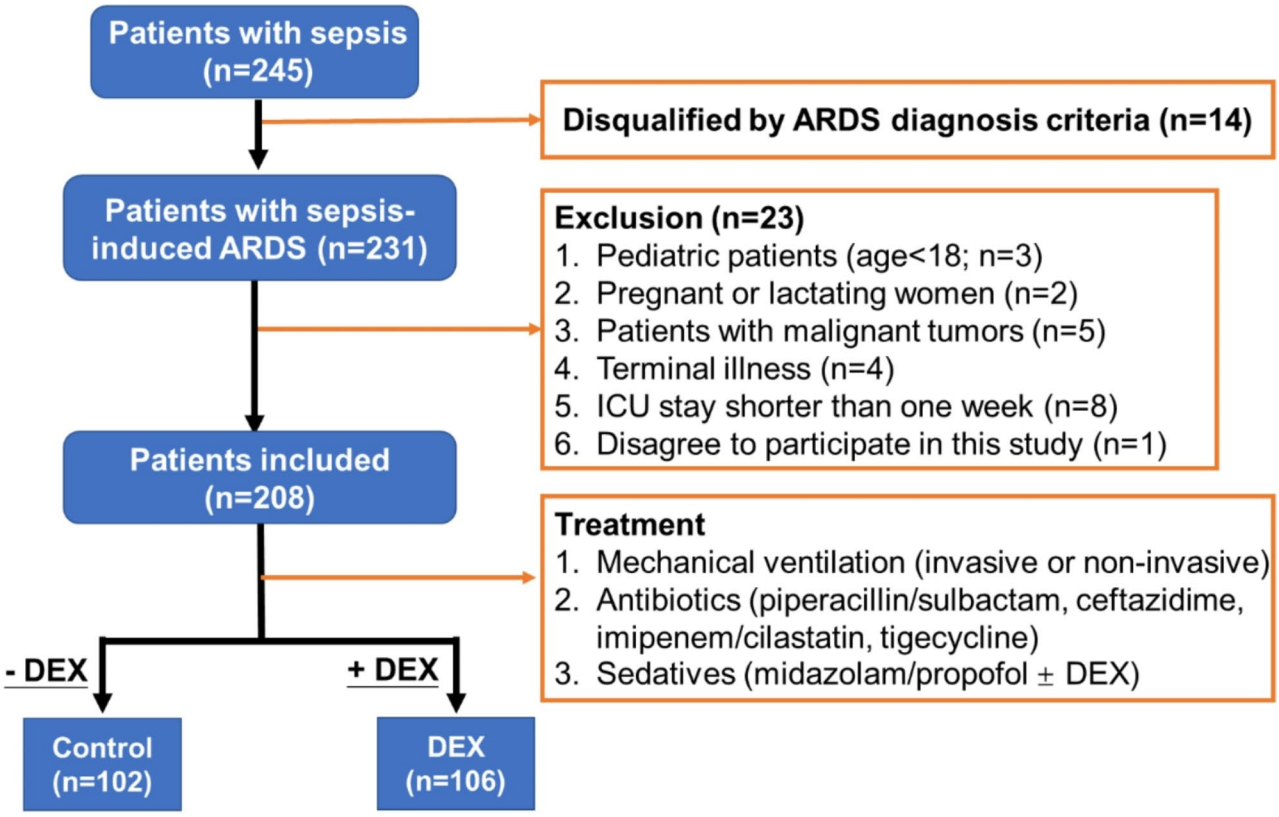

Fig. 1 The flow chart illustrates the patient screening, selection and enrollment in this study

Table 1 Demographic data, medical history, and baseline characteristics of patients with sepsis-induced ARDS. Data are presented as n (N%), where n stands for the patient number and N for the percentage in the group

	Control ($n=102$)	DEX ($n=106$)	*p*
Age (year)	69.0 (65.0–76.0)	69.0 (61.8–76.0)	0.507
Gender (male), n. (%)	79 (77.5%)	84 (79.2%)	0.753
ICU stay (day)	15.0 (11.8–19.3)	15.0 (12.0–19.0)	0.557
Smoking history, n. (%)	28 (27.5%)	44 (41.5%)	0.033
Comorbidity, n. (%)			
Hypertension	42 (41.2%)	42 (39.6%)	0.819
Diabetes	24 (23.5%)	19 (17.9%)	0.318
Coronary heart diseases	16 (15.7%)	13 (12.3%)	0.476
Bronchitis	13 (12.7%)	24 (22.6%)	0.062
Primary diagnosis, n. (%)			
Pneumonia (non-viral)	82 (80.4%)	76 (72.4%)	0.175
Respiratory failure	47 (46.1%)	36 (34.0%)	0.074
AECOPD	27 (26.5%)	23 (21.7%)	0.421
Multiple trauma	8 (7.8%)	18 (17.0%)	0.046
Intracerebral hemorrhage	2 (2.0%)	4 (3.8%)	0.714
Cause of ARDS, n. (%)			
Lung infection	57 (55.9%)	51 (48.1%)	0.262
Trauma	26 (25.5%)	25 (23.6%)	0.749
Surgery	15 (14.7%)	26 (24.5%)	0.075
Acute pancreatitis	11 (10.8%)	15 (14.2%)	0.463
Aspiration	9 (8.8%)	10 (9.4%)	0.879

end-expiratory pressure (PEEP) support was applied, while 8.0 cmH_2O support could be first performed depending on the respiratory status of the patient, and later adjusted according to the oxygenation state of the patient. All patients were given active treatment of their primary disease and strict control of blood sugar. For infection treatment, imipenem/cilastatin (Hangzhou Merck Sharp and Dohme Pharmaceuticals Ltd., China), ceftazidime (Pfizer Pharmaceuticals Ltd., China), or/and piperacillin/sulbactam sodium (China Resources Double Crane Pharmaceutical Company Ltd.), or tigecycline (Jiangsu Hansoh Pharmaceutical Group Co., Ltd., China) were given via injection based on the body weight of the patient. For improvement of wet cough, ambroxol hydrochloride was given via slow intravenous infusion to dilute and expel the phlegm. Upon mechanical ventilation, midazolam (Jiangsu Enhua Pharmaceuticals Ltd., China) or propofol (Xi'an Libang Pharmaceutics Ltd., China) was given via intravenous pumping. DEX (Jiangsu Hengrui Pharmaceuticals Ltd., China) (China National Medicine Approval No. H20090248) was administered to each patient in the DEX group for procedural sedation. In a typical case, 400 μg DEX was added into 50 mL 0.9% sodium chloride of injection grade and pumped into the veins of patients. The infusion rate of DEX was controlled at 0.2–0.7 μg/kg/h, with maximal total dosage no more than 1.2 mg DEX. For all sedative agents used in this study (i.e., midazolam, propofol, and DEX), minimal sedation is applied to patients with mechanical ventilation by following early Comfort using Analgesia, minimal Sedatives and maximal Humane care (eCASH) [22]. Patients using sedative agents were maintained in light sedation who were reassured to be kept in the calm, comfortable and cooperative states (the 3C rule), and could be awakened from time to time. Moderate or deep sedation was necessary for situations where the clinicians at bedside decided to manage severe respiratory failure by implementing these measures.

Data collection and analysis

Data were summarized as median and interquartile range (IQR) values for continuous variables, and frequencies for categorical variables. For comparisons between the two groups, the Mann-Whitney U test was used for continuous variables. Categorical variables were examined using the Chi-Square test to analyze the difference between the control group ($n = 102$) and the DEX group ($n = 106$). The selected variables according to their clinical relevance and statistical significance in univariate analysis ($p < 0.05$) were further assessed by multivariable logistic regression analyses, to explore the independent risk factors associated with different group pairings. All p values were two-sided, and p values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). As a result, the prognoses upon ICU admission and clinical outcome of all patients were compared.

For 95 patients with sepsis-induced ARDS in this study, where 45 were from the control group and 50 were from the DEX group, their blood samples were continuously gathered from the radial artery of the patient on day 0, 2, 4, and 6 upon ICU admission, and the ABG index was detected by a blood gas analyzer (Roche Cobas b123). Parameters in the arterial blood, including pH, actual bicarbonate concentration ($aHCO_3^-$), partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), oxygen saturation (SO_2), oxygenation index (PaO_2/FiO_2), alveolar-arterial oxygen pressure ($aADO_2$), total hemoglobin (tHb), and oxygenated hemoglobin (HbO_2) were recorded, together with plasma PCT and IL-1β levels. For those continuously monitored variables, data were presented as (average ± standard deviation), where the student t-test was used for the difference between the two groups and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients with sepsis-induced ARDS

As shown in Fig. 1, 208 patients with sepsis-induced ARDS were divided into two groups; that is, the control group ($n = 102$) and the DEX group ($n = 106$). While both groups of patients received standard care, the DEX group was additionally treated with DEX as a sedative. Upon ICU admission, the demographic data and medical history of patients in the two groups were summarized and compared in Table 1. Advanced age and male gender constituted risk factors for sepsis-induced ARDS, but the differences of median age and gender ratio between the two groups were insignificant. The ICU stays for both groups of patients were similar, while the proportion of patients with smoking history in the DEX group was significantly higher than that in the control group.

The leading comorbidity among all patients included hypertension, diabetes, coronary heart diseases, and bronchitis. There was no substantial difference between the two groups regarding the proportion of patients with each underlying disease. Among all patients, pneumonia remained the top primary diagnosis that led to ARDS, followed by respiratory failure, acute exacerbation of chronic obstructive pulmonary disease (AECOPD), multiple trauma, and intracerebral hemorrhage. The two groups showed no statistical difference in the primary diagnosis, except for multiple trauma where the DEX group had a higher proportion of patients. Furthermore, a diversity of causes that induce sepsis-induced ARDS spanned from direct lung infection (non-viral), trauma, surgery, acute pancreatitis to aspiration. But the

Table 2 Prognostic values, treatment routes and clinical outcomes of patients with sepsis-induced ARDS. Data are presented as n (N%), where n stands for the patient number and N for the percentage in the group

	Control ($n=102$)	DEX ($n=106$)	p
Prognosis			
APACHE II score	22.0 (18.0–25.0)	20.5 (17.8–25.0)	0.207
Predicted mortality	59.7 (50.3–68.7)	60.2 (48.8–69.5)	0.640
Mechanical ventilation, n. (%)			
Invasive	79 (77.5%)	73 (68.9%)	0.163
Non-invasive	25 (24.5%)	33 (31.1%)	0.287
Sedatives, n. (%)			
Midazolam	37 (36.3%)	27 (25.5%)	0.092
Propofol	66 (64.7%)	88 (83.0%)	0.003
DEX	0 (0%)	106 (100%)	< 0.001
Antibiotics, n. (%)			
Piperacillin/sulbactam	31 (30.4%)	20 (18.9%)	0.053
Ceftazidime	33 (32.4%)	35 (33.0%)	0.918
Imipenem/cilastatin	46 (45.1%)	64 (60.4%)	0.027
Tigecycline	5 (4.9%)	34 (32.1%)	< 0.001
Corticoids, n. (%)			
Methylprednisolone	18 (17.6%)	23 (21.7%)	0.464
Hydrocortisone	8 (7.8%)	7 (6.6%)	0.730
Outcome, n. (%)			
MODS incidence	72 (70.6%)	60 (56.6%)	0.036
Actual mortality	38 (37.3%)	24 (22.6%)	0.021

proportions of patients with each ARDS cause showed no noticeable difference between the two groups. Put together, baseline characteristics of patients between the control group and the DEX group were minimally different.

Prognosis and clinical outcome

Upon ICU admission, the APACHE II score and predicted mortality of patients with sepsis-induced ARDS were estimated based on their physiological variables to assess the disease severity (Table 2), whereas no statistical differences between the two groups were found. All patients in ICU were supported using mechanical ventilation, either invasively (intubation) or non-invasively (oxygen mask), where a few patients may require both in sequence. In the control group, midazolam and propofol were applied as sedative drugs during the mechanical ventilation. In contrast, the patients in the DEX group were all administered with DEX in addition to midazolam and propofol. Both groups of patients were administered with midazolam in a comparable manner, but the usage of propofol in the DEX group was higher than that in the control ($p<0.05$).

To treat infection and sepsis, antibiotics were administered as needed, including piperacillin/sulbactam, ceftazidime, imipenem/cilastatin, and tigecycline. The uses of tigecycline and imipenem/cilastatin in the DEX group were more frequent, while the uses of other antibiotics were similar between the two groups. Consequently, the MODS incidence and actual mortality rate were much lower in the DEX group. Variables with clinical relevance and significant difference ($p<0.05$) between the two groups were performed using multivariable regression analysis (Table 3). As a result, the imipenem/cilastatin usage and the MODS incidence were identified as independent risk factors for in-hospital mortality of patients with sepsis-induced ARDS. In sharp contrast, the DEX administration was a protective factor, having an odds ratio of 0.370 with 95% confidential interval of (0.170–0.802).

Table 3 Multivariable analysis of independent risk factors for in-hospital mortality of patients with sepsis-induced ARDS

Variable	Odds Ratio	95% Confidence Interval	p
Smoking history	1.079	0.522–2.228	0.837
Multiple trauma	1.232	0.429–3.541	0.698
Tigecycline	1.941	0.763–4.940	0.164
Propofol	1.106	0.519–2.356	0.794
DEX	0.370	0.170–0.802	0.012
Imipenem/cilastatin	2.618	1.274–5.381	0.009
MODS incidence	8.011	3.175–20.216	< 0.001

Clinical manifestation of patients with sepsis-induced ARDS upon ICU admission

Laboratory parameters in both groups of patients displayed substantial signs of sepsis, corroborated by abnormal cell counts in the peripheral blood, including leukocytosis, neutrophilia, lymphopenia, anemia, and thrombocytopenia (Table 4). In parallel, the deranged values of c-reactive protein (CRP), procalcitonin (PCT),

Table 4 Clinical presentation of patients with sepsis-induced ARDS upon their admission into ICU

	Control ($n=102$)	DEX ($n=106$)	p
Hematological parameters			
White blood cells, $\times10^9$/L	10.7 (7.3–15.4)	12.4 (8.1–18.4)	0.072
Neutrophils, $\times10^9$/L	8.9 (5.7–13.2)	10.5 (6.9–16.1)	0.032
Lymphocytes, $\times10^9$/L	1.0 (0.7–1.5)	1.1 (0.5–1.4)	0.617
Red blood cells, $\times10^{12}$/L	3.6 (3.1-4.0)	3.8 (3.3–4.3)	0.040
Hemoglobin, g/L	111.5 (96.8-125.5)	108.0 (95.8-127.5)	0.765
Platelets, $\times10^9$/L	157.0 (108.8-217.5)	162.5 (118.8-226.3)	0.670
CRP, mg/L	57.1 (21.1–93.1)	77.0 (20.3–138.0)	0.031
PCT, ng/mL	18.6 (10.2–22.7)	22.8 (18.6–27.4)	0.001
IL-1β, pg/mL	97.5 (58.3-108.3)	99.2 (89.4-106.9)	0.176
ABG profiles			
pH	7.27 (7.23–7.31)	7.30 (7.20–7.30)	0.001
Base excess, mmol/L	-3.5 (-7.5-1.9)	-5.6 (-8.2-1.7)	0.118
$aHCO_3^-$, mmol/L	20.8 (17.8–25.1)	20.9 (19.3–26.6)	0.147
$PaCO_2$, mmHg	50.3 (47.3–56.8)	51.5 (42.6–55.9)	0.237
PaO_2, mmHg	62.4 (57.4–67.6)	64.2 (60.8–70.1)	0.007
SO_2, %	92.0 (87.0–93.0)	93.0 (91.0–96.0)	0.001
PaO_2/FiO_2, mmHg	216.2 (199.1-241.6)	217.9 (205.1-235.9)	0.598
$aADO_2$, mmHg	107.3 (89.5-145.3)	92.0 (75.0-126.5)	0.002
tHb, g/dL	9.2 (8.4–10.2)	9.3 (8.7–10.3)	0.653
HbO_2, %	85.4 (80.7–87.9)	88.4 (85.9–90.4)	0.001
MetHb, mmHg	0.3 (0.3–0.5)	0.5 (0.3–0.6)	0.001

Abbreviations: Actual bicarbonate, [$aHCO_3^-$]; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; SO_2, oxygen saturation; PaO_2/FiO_2, oxygenation index; $aADO_2$, alveolar-arterial oxygen pressure; tHb, total hemoglobin; HbO_2, oxygenated hemoglobin; MetHb, methemoglobin

and interleukin-1β (IL-1β) were detected. The DEX group demonstrated more severe inflammation than the control group, evidenced by significantly higher levels of CRP and PCT ($p<0.05$).

The ABG metrics were also examined for all patients with sepsis-induced ARDS upon ICU admission (Table 4). Both groups of patients showed evident disorders of O_2-CO_2 exchange and acid-base balance in the arterial blood, explicated by plummeted values of pH and oxygenation-related parameters (e.g., PaO_2, SO_2, and HbO_2), where the DEX group exhibited even worsened conditions compared to the control group. Nonetheless, PaO_2/FiO_2, the diagnostic determinant of ARDS, showed similarity between the two groups, defining mild to moderate ARDS among most patients enrolled here.

Dynamic ABG analysis

The ICU-admitted patients were supported by an invasive or non-invasive mechanical ventilator when sedatives were given. For a part of 208 patients included in this study, i.e., a total of 95 patients (45 from the control group and 50 from the DEX group), midazolam and/or propofol were given for sedation. Additionally, DEX was given at a controlled dosage to maintain the light sedation in the DEX group. For each of these patients, the blood samples from the radial artery were continuously gathered and monitored on day 0, 2, 4, and 6 after ICU admission. Parameters in the arterial blood were recorded, together with PCT and IL-1β levels.

Key variables from ABG measurement were monitored for all patients and plotted versus (vs.) time (Fig. 2). Firstly, the acidity of the arterial blood was gradually improved over time, as the pH values were significantly increased from (7.26 ± 0.05) vs. (7.30 ± 0.05) on day 0 to (7.35 ± 0.07) vs. (7.39 ± 0.04) on day 6 for the control group vs. the DEX group, respectively (Fig. 2a). In parallel, from day 0 to day 6, [$aHCO_3^-$] (in mmol/L) was augmented from (20.3 ± 3.6) vs. (22.2 ± 5.2) to (23.7 ± 4.3) vs. (25.5 ± 1.6) (Fig. 2b), while $PaCO_2$ (in mmHg) declined from (52.6 ± 5.7) vs. (54.1 ± 8.4) to (45.1 ± 4.6) vs. (41.4 ± 5.3) for the control group vs. the DEX group, respectively (Fig. 2c). With treatment over a period of 6 days, acidity and dissolution of carbon dioxide in the arterial blood of patients were more significantly ameliorated in the DEX group compared to those in the control group.

Secondly, blood oxygenation was gradually enhanced. For PO_2, SaO_2, PaO_2/FiO_2, and $aADO_2$ as measured on day 6, it became 1.6, 1.1, 1.4 and 2.2 times of that on day 0 in the DEX group, and 1.1, 1.0, 1.2 and 1.2 times of that on day 0 in the control group (Fig. 2d-g). The blood oxygenation parameters in the DEX group were significantly higher than those in the control group, indicating a better therapeutic effect following DEX administration ($p<0.05$).

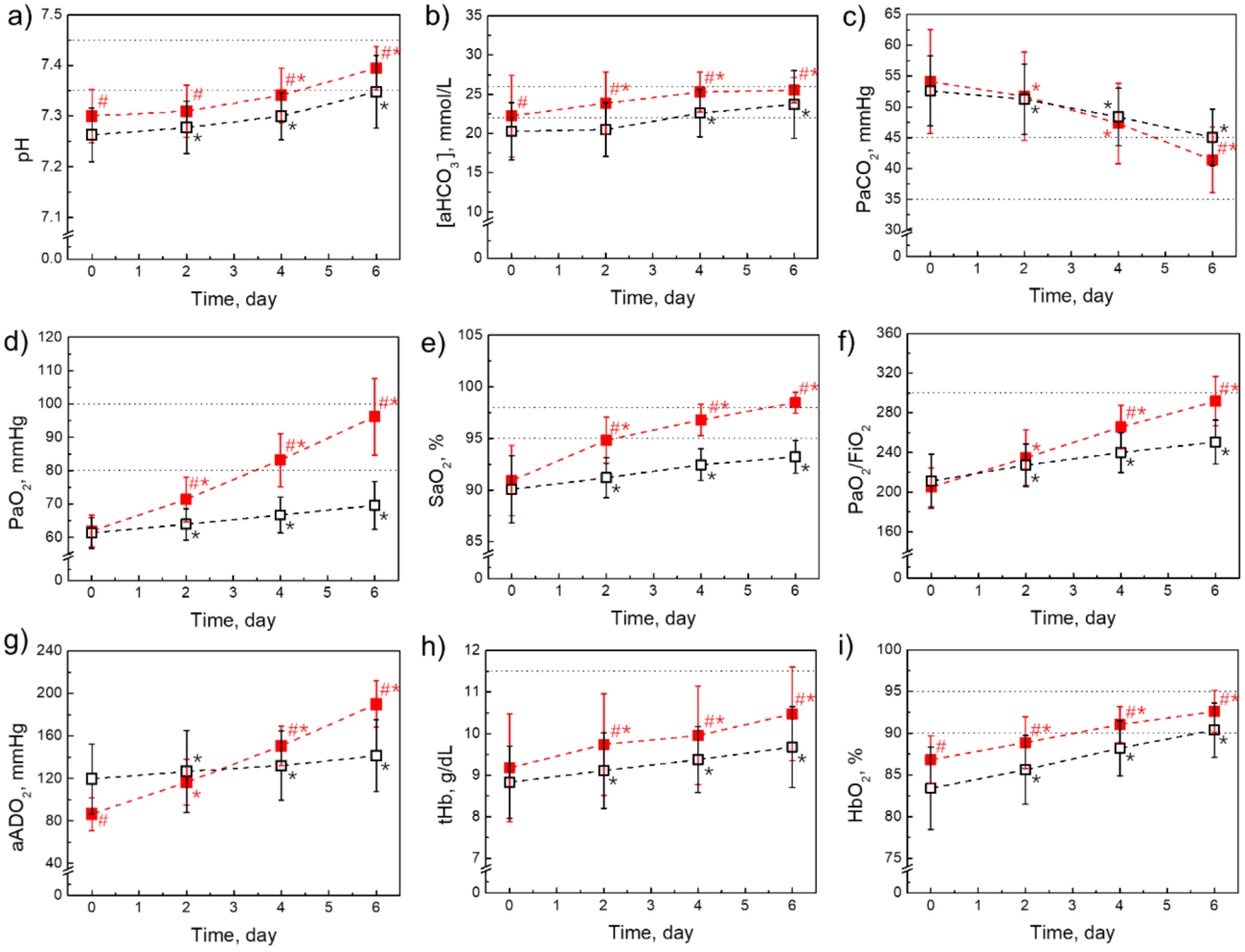

Fig. 2 Comparison of the blood gas parameters in the arterial blood of the patients between the control group (black empty squares) and the DEX group (red solid squares). Day 0 corresponds to the day of ICU admission when the treatment is initiated. Asterisk (*) indicates $p < 0.05$ when the parameter is compared to that on day 0 within the same group; pound sign (#) indicates $p < 0.05$ when the parameter is compared between the two groups at the same time. The dotted line in each graph indicates a reference value or a normal range. (**a**) Acidity in the blood samples with reference range of 7.35–7.45; (**b**) [$aHCO_3^-$] with a normal value of 22–26 mmol/L; (**c**) $PaCO_2$ with a normal range of 35–45 mmHg; (**d**) PaO_2 with a normal range of 80–100 mmHg; (**e**) SO_2 in the arterial blood with a normal range of 95–98%; (**f**) PaO_2/FiO_2 with a critical value of 300 mmHg; (**g**) $aADO_2$ in mmHg; (**h**) tHb in the blood with a normal range of 11.5–17.4 g/dL; (**i**) HbO_2 shown as the percentage of tHb, with a normal range of 90–95%

Thirdly, tHb and HbO_2 were continuously monitored over the 6-day treatment (Fig. 2h and i). In the control group, tHb (in g/dL) and HbO_2 (in %) were increased from (8.8 ± 0.9) and (83.4 ± 4.9) to (9.7 ± 1.0) and (90.4 ± 3.2) with significance; in the DEX group, tHb and HbO_2 climbed from (9.2 ± 1.3) and (86.8 ± 2.9) to (10.5 ± 1.1) and (92.6 ± 2.5) with significance, respectively. Following a 6-day monitoring, patients in the DEX group attained much higher levels of tHb and HbO_2 than those in the control group ($p < 0.05$).

PCT and IL-1β as potential biomarkers for sepsis-induced ARDS

In both groups the dynamic changes of PCT and IL-1β levels at diverse time points during treatment were explored (Fig. 3). For PCT, the patients in the DEX group began with a slightly higher concentration in their blood samples than those in the control group (Fig. 3a). Through the 6-day treatment, the PCT level continuously decreased to 58.3% vs. 45.5% on day 2, 48.4% vs. 30.6% on day 4, and 39.4% vs. 14.7% on day 6 in the control group vs. the DEX group, respectively.

For IL-1β levels, there was no statistically significant difference between the two groups before treatment. During the 6-day ICU stay, the alterations in IL-1β levels resembled those in PCT concentrations (Fig. 3b). In the control group, IL-1β concentration declined to 86.8%, 71.0%, and 51.8% on day 2, 4, and 6, respectively. Simultaneously, IL-1β concentration in the DEX group dropped to 75.2%, 57.9%, and 39.0% on day 2, 4, and 6, respectively, each value significantly lower than that in the control group during the same treatment time ($p < 0.05$).

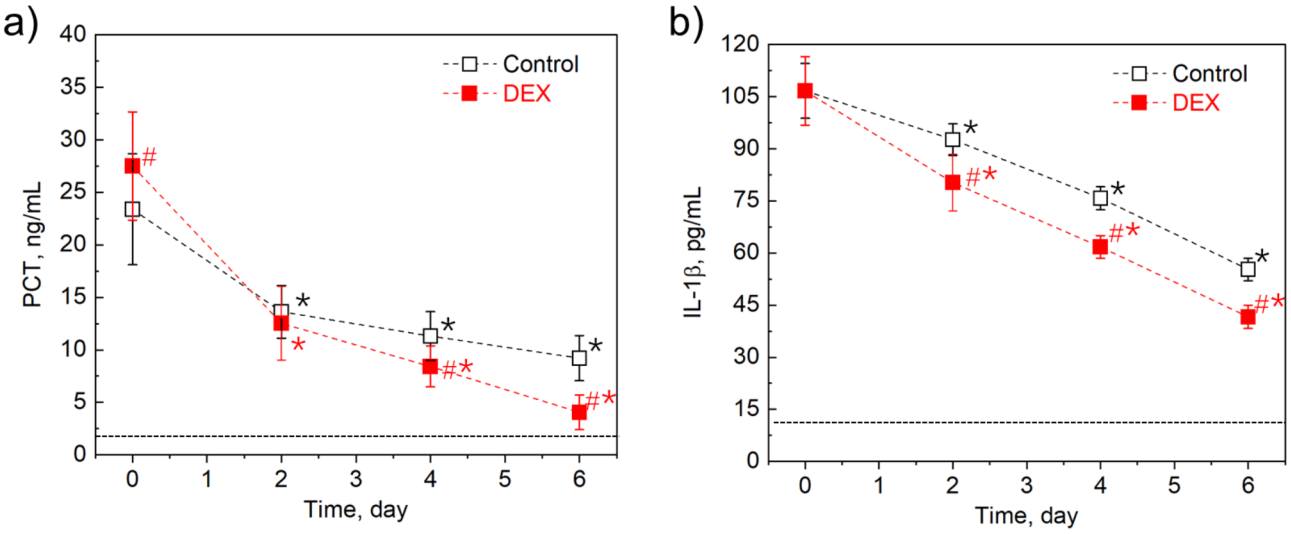

Fig. 3 Changes of PCT and IL-1β concentrations in patients with sepsis-induced ARDS during treatment after ICU admission. Data in the control group (shown in black empty squares) were compared to data in the DEX group (shown in red solid squares) over a period of 6 days. Pound sign (#) indicates $p < 0.05$ when the parameter in the DEX group is compared to that in the control group at the same time. Asterisk (*) indicates $p < 0.05$ when the parameter is compared to that on day 0 within the same group. The dotted line in each graph indicates a mild or non-severe value of cytokine, which equals to **a**) 2 ng/mL PCT and **b**) 12 pg/mL IL-1β

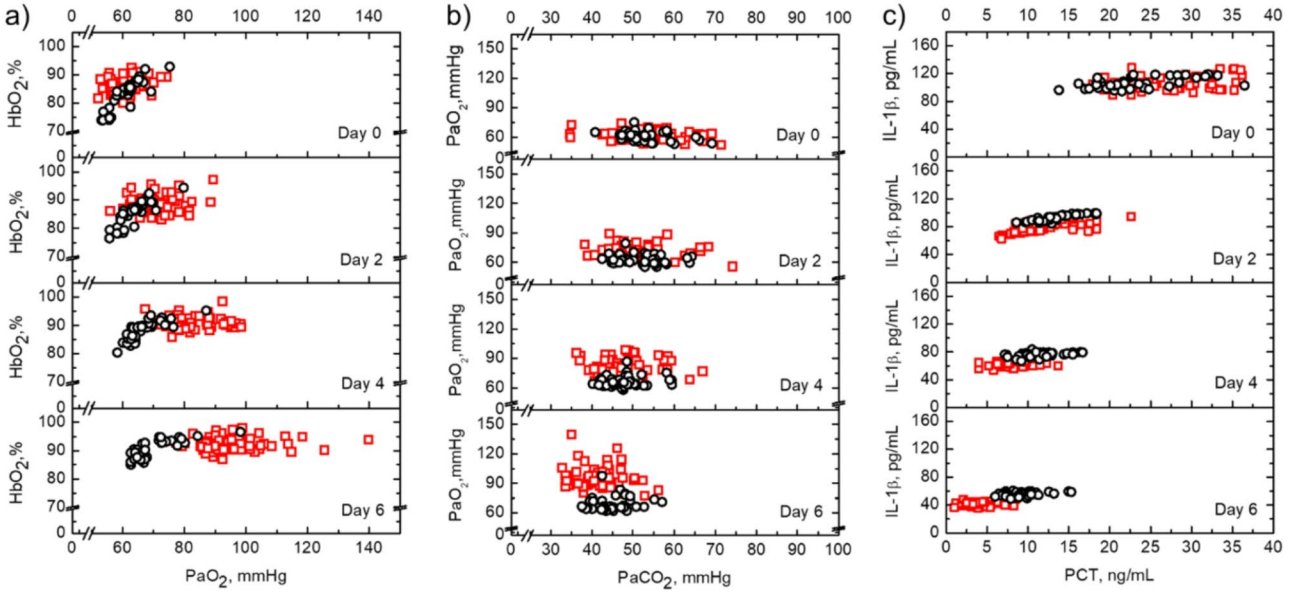

Fig. 4 The effect of DEX administration on gas exchanges and cytokine productions. (**a**) PaO_2 vs. HbO_2; (**b**) $PaCO_2$ vs. PaO_2; and (**c**) PCT vs. IL-1β. Data from patients in the control group (in black empty cycles) were plotted with those in the DEX group (in red empty squares) at different time points during treatment

To understand the effect of DEX administration on gas exchanges and cytokine productions, we next plotted PaO_2 vs. HbO_2, $PaCO_2$ vs. PaO_2, and PCT vs. IL-1β for both groups of patients at different time points after treatment (Fig. 4). In Fig. 4a, the affinity of oxygen and hemoglobin in patients was examined as a function of PaO_2, showing that with the DEX treatment over time the patients' oxygen-hemoglobin affinity tended to be stable, while PaO_2 in the blood increased much faster than that in the control group. In Fig. 4b, PaO_2 was probed as a function of $PaCO_2$ in the arterial blood, revealing a more robust O_2-CO_2 exchange in the alveoli following the DEX treatment over time than that in the control group. In parallel, as shown in Fig. 4c, both PCT and IL-1β were concurrently reduced, while DEX administration in a 6-day course distinguished this patient group by significantly lower cytokine profiles compared to those in the control group. Thus, DEX treatment alleviated the gas

exchange in the arterial blood of patients with sepsis-induced ARDS and quenched the cytokine release in a distinctive manner.

Discussion

In this retrospective study, we analyzed clinical data from patients with sepsis-induced ARDS to compare their demographic information, medical history, baseline characteristics, and laboratory parameters in the presence and absence of DEX treatment. Our findings suggest that administering DEX is associated with a significantly lower in-hospital mortality rate of patients with sepsis-induced ARDS, possibly through a mechanism where DEX might enhance the arterial gas exchange and inhibit the inflammatory responses in these patients.

Here we found out that advanced age and male gender predisposed to a higher ARDS incidence. It has been noted that age is related to both acute and chronic lung diseases owing to the changing pulmonary physiology and function in older adults and their weakened responsiveness to pathogenic challenges [23]. Moreover, gender difference in susceptibility of developing ARDS has been attributed to the fact that sex hormones might mediate the ARDS pathogenesis by interplaying with pro-inflammatory cytokines [24, 25]. However, other studies also pointed out that pre-hospital history (e.g., smoking, alcohol abuse) and in-hospital healthcare may have a substantial impact on such disparity as race and gender [26]. Our findings support the idea that the male gender or a history of smoking has a substantial impact on pathogenesis of ARDS. Nonetheless, the reasons behind the susceptibility of male gender to ARDS remain unclear and require further investigation.

Due to the complex pathogenesis of ARDS, the search for specific biomarkers for its diagnosis and therapy in clinical practice is still under the way. However, several molecules marking biochemical events in ARDS have been utilized to assess and predict the disease severity, such as pro-inflammatory cytokines (e.g., TNF-α, IL-1β, or IL-6) and alveolar damage indicators (e.g., surfactant D) in plasma or bronchoalveolar lavage [27, 28]. In addition, PCT, a chemokine that modulates the pro-inflammatory cytokines, has also been used to predict ARDS severity [29, 30]. In our study here the decreased levels of IL-1β and PCT correlated with the timing of ARDS treatment and the administration of DEX, supporting their potential as biomarkers for ARDS.

Currently, there is no effective therapy for ARDS. The clinical treatment of ARDS includes respiratory support, antibiotics for treating infection, fluid management, nutrition supplementation, and medications targeting for primary diseases. This therapeutic approach presents a dilemma similar to the clinical management of sepsis [28, 31]. During ARDS treatment, sedatives play a crucial role in comforting patients by alleviating stress, facilitating treatment procedures, and minimizing movement, which in turn helps reduce oxygen consumption during hypoxemia. DEX is approved for sedation as it has minimal effects on respiration and delirium incidence. DEX primarily binds to α2-AR on the locus coeruleus in brainstem and stops neurotransmission responsible for arousal in a concentration-dependent manner [32]. It is metabolized in the liver with an elimination half-life of 2–3 h [32]. Intriguingly, the DEX administration in animal models of ALI has been reported to substantially suppress the pro-inflammatory cytokines by inhibiting several signaling pathways in immune cells, particularly PI3K/Akt, MAPK and NF-κB phosphorylation pathways [33–35].

Our study here revealed that administering DEX to patients with sepsis-induced ARDS could effectively mitigate the detrimental effect of excessive CO_2 in the blood, and significantly heighten values of PaO_2, SaO_2, PaO_2/FiO_2 and $aADO_2$, as well as the amount of tHb and HbO_2 as oxygen carriers, so enhancing oxygenation in both alveolar and arterial blood. Simultaneously, the levels of PCT and IL-1β after DEX treatment were notably reduced, compared to those without DEX administration. This portrayed that DEX could effectually suppress inflammatory responses by inhibiting production of pro-inflammatory cytokines, besides its established sedative property. Our clinical findings were supported by results from experimental medicine studies in rodent models of sepsis-induced ARDS, which indicated the suppressive role of DEX in effectively reducing inflammatory levels, so restoring the endothelial barrier integrity in the damaged lungs [36, 37]. Of note, although most patients in our study met the diagnosis criteria of mild ARDS based on the oxygenation index and ARDS definition, this mediating effect of DEX may be also applied to patients with moderate and severe ARDS. Further investigations are needed to explore this potential.

This study has some limitations. Mainly, the retrospective and single-center nature of this study enrolled a relatively small number of patients, and their data availability was restricted. Many hematological parameters of patients receiving critical care were missing, such as coagulation factors and immune features. Continuous monitoring of ABG exchange and inflammation mediation upon ICU admission was only recorded up to a duration of 6 days, as the records covering the entire period of ICU stay would otherwise render more factorial evidence that contributes to a better understanding of effective treatment on sepsis-induced ARDS.

Conclusion

In the ICU setting, the administration of the sedative DEX was linked to reduced mortality in patients with sepsis-induced ARDS. This reduction in mortality may be due to improvement in key physiological variables related to inflammation and ABG exchange. In the real-world scenario, there is a dearth of clinical research on how DEX affects critically ill patients with sepsis or ARDS. Our ongoing research aims to investigate this further.

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Author contributions
JZ and ZT conceived the idea and designed the study. JZ, ZJ, YZ, and ZT contributed to data processing and table/figure preparation. ZJ, YZ, and ZT contributed to the statistical analysis. All authors contributed to the manuscript writing and approved the manuscript submission.

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Data availability
The datasets used and/or analyzed during the current study are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Affiliated Hospital of Jiangsu University. The informed consents of patients were waived by the Research Ethics Committee of Affiliated Hospital of Jiangsu University due to the retrospective nature of this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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