

Effects of different doses of dexmedetomidine on heart rate and blood pressure in intensive care unit patients

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Abstract. The aim of the present study was to observe and compare the sedative effect of different doses of DEX on heart rate (HR) and blood pressure (BP) in critically ill patients admitted to intensive care units (ICUs). The study included patients that were retained in ICUs and required sedation between January and March 2014. Patients were excluded if they had a BP of >200 mmHg, a HR of <60 bpm or were in a state of shock. The included patients were randomized into three groups: Group A, 1.0 $\mu\text{g/kg/10 min}$ DEX; group B, 0.5 $\mu\text{g/kg/10 min}$ DEX; and group C, 0.4 $\mu\text{g/kg/h}$ DEX. After receiving these initial designated doses of DEX via an intravenous (IV) infusion pump for 10 min, the patients were maintained continuously at an identical dose of 0.4 $\mu\text{g/kg/h}$ DEX. Ramsay score, HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), breathing rate (BR) and peripheral capillary oxygen saturation (SpO_2) were recorded prior to the IV pump infusion and at 2, 4, 6, 8, 10, 60, 120, 180 and 240 min following infusion. Patients in groups A and B achieved sedation more rapidly compared with those in group C ($P<0.05$). HR decreased more significantly at 8 and 60 min after the initial IV pump infusion with DEX in groups A and B compared with group C ($P<0.05$). SBP decreased significantly at 10 min after IV pump infusion in group A compared with groups B and C ($P<0.05$). No significant difference existed in the SBP reduction trend between the three groups during the maintenance period. Therefore, the routine dose of DEX (0.4 $\mu\text{g/kg/h}$) provides an ideal sedative effect in ICU patients. The recommended loading dose for a more rapid sedation is 0.5 $\mu\text{g/kg/h}$. High loading doses of DEX via IV pump infusion should be avoided in elderly individuals, patients with acute exacerbation of chronic obstructive pulmonary disease and anemic patients, in whom combination medication, such as midazolam or propofol, may be considered when necessary.

Introduction

Ideal sedatives for use in intensive care units (ICUs) should have following properties: Rapid action, easy control of the depth of sedation, minor impact on respiratory function, no accumulation of metabolites, no obvious interference with other medicine and multiple *in vivo* metabolic pathways, eliminating without relying on liver, kidney or pulmonary function, low cost and minimal side effects (1). At present, no medicine exhibits all of the aforementioned conditions, and benzodiazepines, opioid agonist, propofol and α_2 -epinephrine agonists are commonly used in ICUs. However, it has been demonstrated that high speed injection and high dose of midazolam may result in respiratory depression and reduced blood pressure, particularly in those elderly, hypovolemic patients or patients with respiratory failure (2). Furthermore, high-dose infusion of propofol for an extended period may cause propofol infusion syndrome, which may involve serious lactic acidosis, hyperlipemia, liver fatty infiltration, rhabdomyolysis and mortality (3). Therefore, these is a requirement for alternative sedative agents for use in ICUs

Dexmedetomidine (DEX) is a highly selective α_2 -adrenoceptor agonist with sedative, analgesic, anti-anxiety and sympathetic nerve inhibitory activities. Patients receiving DEX may be awakened easily without producing respiratory arrest. Therefore, DEX has been considered to be an ideal sedative and analgesic agent for use in intensive care unit (ICU) patients (4,5). DEX is the dextro-isomer of medetomidine, which exerts sedative and analgesic effects. In addition, DEX has been shown to exert neuroprotective effects (6) by agitating α_2 receptor mediated the receptor tyrosine kinase phosphorylation. Furthermore, DEX promotes the release of various growth factors by agitating astrocytes to participate in neural protection (7). DEX is able to activate survival promoting enzymes by activating α_2 adrenoceptor may exert cardioprotective effects by adjusting the protein kinase, protein kinase B and endothelial nitric oxide synthase pathways extracellularly (8).

Currently, the infusion speed of DEX in mechanical ventilation patients ranges between 0.2 and 0.7 $\mu\text{g/kg/h}$. Previous studies have shown that DEX is safe for use in healthy patients at 10-15 times the normal dosage, producing no obvious side effects or loss of blood pressure and heart rate (9-11). However, a previous study indicated that DEX may reduce blood pressure and heart rate in critical patients, potentially necessitating drug discontinuation (12).

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It was observed in our clinical practice that certain patients receiving the recommended loading dose ($1.0 \mu\text{g/kg}/10 \text{ min}$) plus the maintenance dose ($0.2\text{--}0.7 \mu\text{g/kg/h}$) of DEX for sedation developed hypotension and bradycardia (13). In specific patients, DEX administration had to be suspended, even in certain serious cases. These observations are consistent with the most commonly known adverse reactions of DEX, which include hypotension, nausea, bradycardia and dry mouth (14). However, critically ill patients in ICUs are physiopathologically different from patients undergoing selective surgery, since they frequently exhibit multi-organ dysfunctions involving the heart, liver and kidney (15); therefore, the *in vivo* metabolic process of DEX in ICU patients may also be different.

The aim of the present study was to determine the optimal dose of DEX for use in ICU patients by observing and comparing the sedative effect of different doses of DEX on the circulatory system of critically ill patients, in an attempt to provide experimental references for the safe and effective clinical use of DEX.

Materials and methods

General patient data. This study initially considered a total of 82 patients who were retained in the ICU at the First People's Hospital Affiliated to Shanghai Jiao Tong University (Shanghai, China) and required sedation between January and March 2014. Patients were excluded if they presented blood pressure (BP) of $>200 \text{ mmHg}$ and heart rate (HR) of $<60 \text{ bpm}$, or if they exhibited circulatory shock. A total of 24 patients were excluded for these reasons. The remaining 58 patients were randomized into three groups: Group A, high-dose group ($1.0 \mu\text{g/kg}/10 \text{ min}$ DEX; $n=18$); group B, mid-dose group ($0.5 \mu\text{g/kg}/10 \text{ min}$ DEX; $n=24$); and group C, routine-dose control group ($0.4 \mu\text{g/kg/h}$ DEX; $n=16$). The patients in the three groups initially received the designated doses of DEX via an intravenous (IV) infusion pump for 10 min, and were subsequently maintained continuously at the same dose of $0.4 \mu\text{g/kg/h}$ DEX (Fig. 1).

The study complied with the Declaration of Helsinki. The data collection protocol was approved by the Shanghai First People's Hospital Institutional Review Board. All participants signed informed consent statements that allowed access to their medical records.

Drug administration. DEX (2 ml; Sichuan Guorui Pharmaceutical Co., Ltd., Sichuan, China) was first diluted with 0.9% sodium chloride solution to a total volume of 4 ml. Patients in the three groups received the designated doses of DEX via an IV infusion pump for 10 min, and were then administered continuously with the same dose of $0.4 \mu\text{g/kg/h}$ DEX in order to maintain an ideal state of sedation, if no significant adverse reaction occurred. DEX IV infusion was controlled at a rate of $0.2\text{--}1.4 \mu\text{g/kg/h}$. Propofol (Fresenius Kabi Deutschland GmbH, Langenhagen, Germany) or midazolam (Jiangsu Enhua Herun Medicine Co., Ltd., Xuzhou, China) was added to achieve appropriate depth of sedation if necessary. If adequate sedation was not achieved using DEX, fentanyl (Yichang Renfu Pharmaceutical Co., Ltd., Yichang, China) was administered in a single dose of $1\text{--}4 \mu\text{g/kg}$. IV pump infusion was suspended in patients with an HR of $<50 \text{ bpm}$ or HR that had reduced by $>30\%$, and a systolic blood pressure (SBP) of $<90 \text{ mmHg}$.

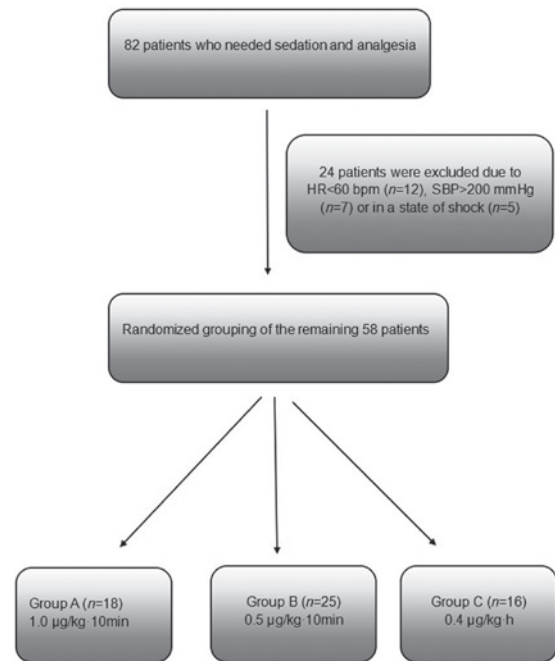


Figure 1. Randomization of the patients into three groups.

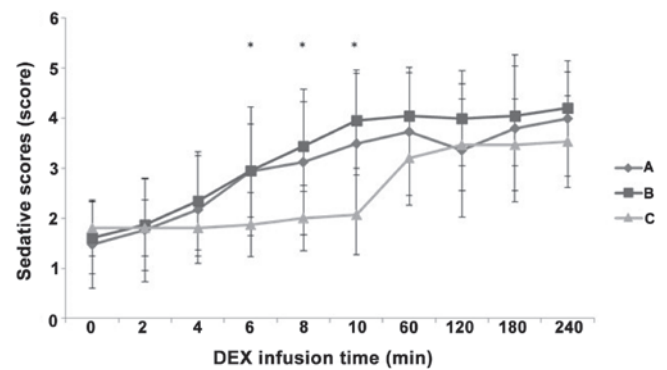


Figure 2. Comparison of sedative scores between the three groups. Group A, $1.0 \mu\text{g/kg}/10 \text{ min}$; group B, $0.5 \mu\text{g/kg}/10 \text{ min}$; and group C, $0.4 \mu\text{g/kg/h}$.

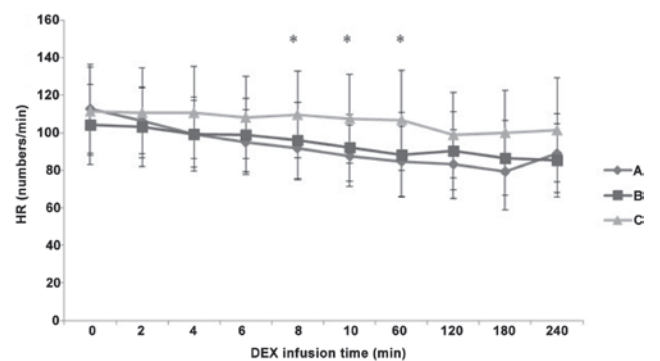


Figure 3. Comparison of HR between the three groups. Group A, $1.0 \mu\text{g/kg}/10 \text{ min}$; group B, $0.5 \mu\text{g/kg}/10 \text{ min}$; and group C, $0.4 \mu\text{g/kg/h}$. * $P < 0.05$ vs. group C. HR, heart rate.

Observation parameters. Ramsay score, HR, SBP, diastolic blood pressure (DBP), breathing rate (BR) and peripheral capillary oxygen saturation (SpO_2) were recorded prior to the IV pump infusion (0 min) and at 2, 4, 6, 8, 10, 60, 120,

Table I. General data comparison between the three groups.

Parameter	Group A (n=18)	Group B (n=24)	Group C (n=16)
Gender (male/female)	6/12	19/5	11/5
Age (years) ^a	57.72±16.50	50.83±20.53	50.25±21.43
APACHE II score ^a	12.78±5.31	8.54±4.84	10.44±7.07
Primary diagnosis (n)			
AECOPD	2	2	1
Severe pneumonia	1	0	1
Pneumothorax	0	1	0
Cholecystitis	2	1	0
Pancreatitis	0	1	0
Digestive tract perforation	1	0	1
Cirrhosis	0	1	0
Upper digestive tract hemorrhage	0	2	0
Intestinal obstruction	1	0	1
Sepsis	1	1	0
Multiple trauma	3	7	8
Post-operation	3	4	2
Encephalitis	0	2	0
Cerebral infarction	1	1	2
Poisoning	1	0	0
HELLP syndrome	0	1	0
Post CPR	1	0	0
Multiple myeloma	1	0	0
Organ dysfunction (n)			
Respiratory failure	1	2	3
Cardiac dysfunction	2	0	0
Renal failure	0	0	1
Concomitant use of sedatives (n)			
Midazolam	1	1	0
Propofol	0	5	0
Midazolam + propofol	0	0	3
Concomitant use of vasoactive agents (n)			
Norepinephrine	1	1	0
Dopamine	1	1	1
Norepinephrine + dopamine	2	0	0
Use of mechanical ventilation (n)	11	8	8
Drug discontinuation (n)	4	4	0

^aData presented as mean ± standard deviation. APACHE II, Acute Physiology and Chronic Health Evaluation II; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HELLP, hemolysis, elevated liver enzymes, low platelet count; CPR, cardiopulmonary resuscitation.

180 and 240 min following infusion. Blood routine, electrolyte, liver/kidney function and blood gas measurements were obtained prior to IV pump infusion. Ramsay Score was evaluated by a physician according to the Ramsay rating scale. HR and SBP were determined using an MP50 electrocardiogram monitor (Philips Healthcare, DA Best, The Netherlands). Blood routine, electrolyte, liver/kidney function, blood gas measurements were obtained using a Beckman Power Processor Sample-Handling System (Beckman Coulter, Inc., Brea, CA, USA). Acute Physiology

and Chronic Health Evaluation II (APACHE II) score was calculated (16).

Statistical treatment. Data analysis was performed using SPSS software, version 16.0 (SPSS, Inc., Chicago, IL, USA). The results are expressed as the mean ± standard deviation. The Shapiro-Wilk test was used in combination with a histogram to determine whether data were normally distributed. Data of normal distribution were analyzed by analysis of variance, and data of non-normal distribution were compared for inter-group

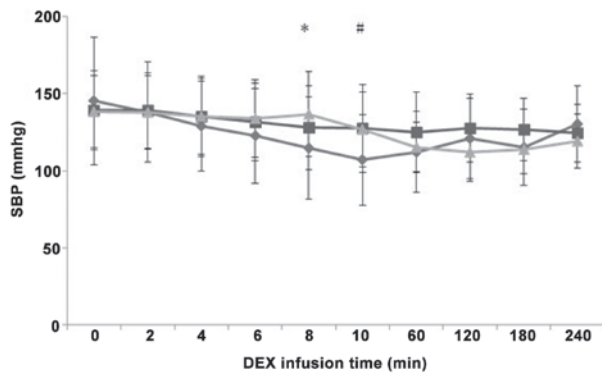


Figure 4. SBP values in the three groups at various time-points after IV pump infusion of DEX. *C comparison between group A and C, $P<0.05$. *BC comparison between group A and group BC, $P<0.05$. Group A, 1.0 $\mu\text{g}/\text{kg}/10$ min DEX; group B, 0.5 $\mu\text{g}/\text{kg}/10$ min DEX; and group C, 0.4 $\mu\text{g}/\text{kg}/\text{h}$ DEX; SBP, systolic blood pressure; DEX, dexmedetomidine.

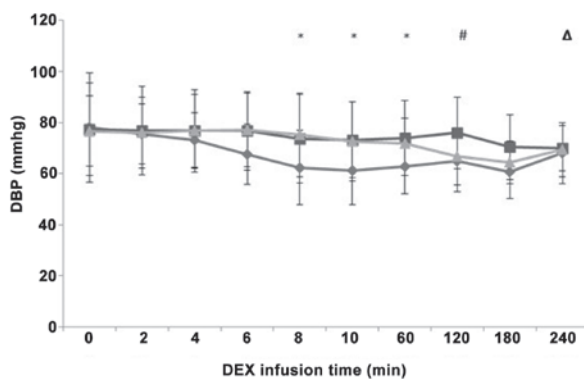


Figure 5. DBP values in the three groups at various time-points after IV pump infusion of DEX. *BC comparison between group A and group BC, $P<0.05$. *AC comparison between group B and group AC, $P<0.05$. *B comparison between group A and B, $P<0.05$. Group A, 1.0 $\mu\text{g}/\text{kg}/10$ min DEX; group B, 0.5 $\mu\text{g}/\text{kg}/10$ min DEX; and group C, 0.4 $\mu\text{g}/\text{kg}/\text{h}$ DEX; DBP, diastolic blood pressure; DEX, dexmedetomidine.

difference using the Mann-Whitney U nonparametric test. Categorical data were tested using the χ^2 test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

General data comparison. General patient characteristics in the three groups are listed in Table I. No statistically significant difference was observed in the APACHE II score, gender, age and primary diagnosis between the three groups ($P>0.05$).

Achievement of the sedative state. Patients in all three groups achieved an ideal state of sedation at 1 h after IV pump infusion of DEX, with a Ramsay score of 3-4 ($P>0.05$). Groups A and B achieved an ideal state of sedation at 6 min, which was more rapid compared with group C ($P<0.05$; Fig. 2).

Differences in HR, SBP and DBP following IV pump infusion of DEX. A decreasing tendency was observed in the HR, SBP and DBP values following the initial IV pump infusion of DEX in all three groups (Figs. 3-5). HR decreased more notably in groups A and B compared with group C at 8 min and

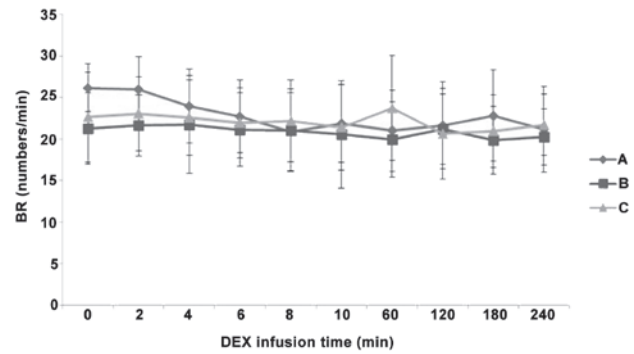


Figure 6. BR values in the three groups at various time-points after IV pump infusion of DEX. Group A, 1.0 $\mu\text{g}/\text{kg}/10$ min DEX; group B, 0.5 $\mu\text{g}/\text{kg}/10$ min DEX; and group C, 0.4 $\mu\text{g}/\text{kg}/\text{h}$ DEX; BR, breathing rate; DEX, dexmedetomidine.

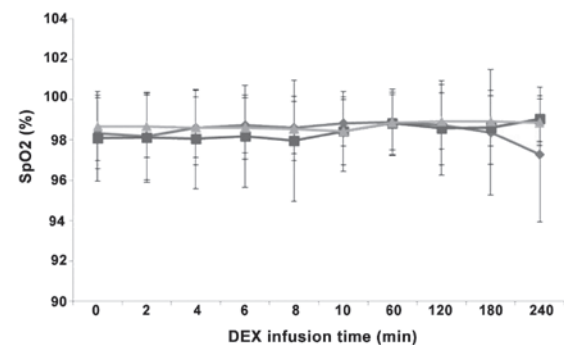


Figure 7. SpO₂ values in the three groups at various time-points after IV pump infusion of DEX. Group A, 1.0 $\mu\text{g}/\text{kg}/10$ min DEX; group B, 0.5 $\mu\text{g}/\text{kg}/10$ min DEX; and group C, 0.4 $\mu\text{g}/\text{kg}/\text{h}$ DEX; SpO₂, peripheral capillary oxygen saturation; DEX, dexmedetomidine.

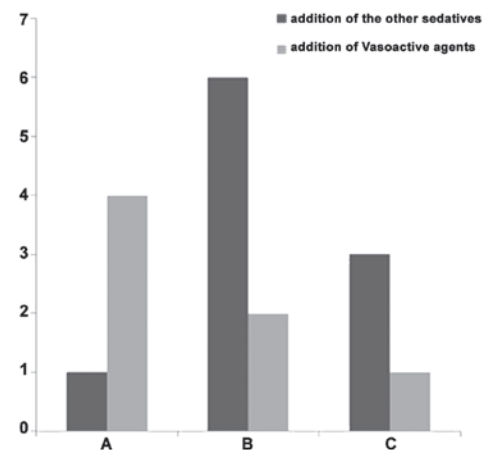


Figure 8. Concomitant use of medications in the three groups. Group A, 1.0 $\mu\text{g}/\text{kg}/10$ min DEX; group B, 0.5 $\mu\text{g}/\text{kg}/10$ min DEX; and group C, 0.4 $\mu\text{g}/\text{kg}/\text{h}$ DEX; DEX, dexmedetomidine.

60 min after IV pump infusion of DEX ($P<0.05$), while there was no significant difference in HR between groups A and B ($P>0.05$; Fig. 3). At 8 min after IV pump infusion of DEX, SBP decreased more evidently in group A compared with the value in group C ($P<0.05$; Fig. 4). In addition, at 10 min after IV pump infusion, SBP decreased more evidently in group A compared with the value in both groups B and C ($P<0.05$).

Table II. Details of patients that underwent drug withdrawal in the three groups.

Patient	Time of drug suspension after medication	Age (years)	Gender	APACHE II score	Primary diagnosis	Abnormal laboratory results		
						Mechanical ventilation	Complete blood count (Hb; g/l)	Blood gas (PaCO ₂ ; mmHg)
A1	3 h	88	Female	9	AECOPD, pleural effusion, pericardial effusion	BIPAP	63.3	57.4
A2	2 h	55	Male	8	Total hip replacement	IPPV	Normal	Normal
A3	1 h	59	Female	16	Multiple myeloma	IPPV	Normal	68
A4	3 h	74	Female	3	Postoperatively - left femoral intertrochanteric fracture	No	Normal	Normal
B1	4 h	70	Male	16	Upper digestive tract hemorrhage, postoperation - gastric cancer	No	37.6	Normal
B2	3 h	49	Male	8	Cerebral infarction	No	73.3	Normal
B3	10 min	77	Male	20	AECOPD, pleural effusion	BIPAP	Normal	66.7
B4	1 h	83	Male	6	AECOPD, pulmonary encephalopathy	BIPAP	Normal	77.3

All patients exhibited normal blood biochemistry. APACHE II, Acute Physiology and Chronic Health Evaluation II; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BIPAP, bilevel positive airway pressure; IPPV, intermittent positive-pressure ventilation.

However, no statistically significant differences were detected in SBP reduction among the three groups during the maintenance period ($P>0.05$). DBP was significantly decreased in group A compared with groups B and C at 8 min and 60 min after IV pump infusion ($P<0.05$; Fig. 5). DBP in group B was increased compared with groups A and C at 120 min after IV pump infusion ($P<0.05$), while it decreased more significantly in group A compared with group B at 240 min after IV pump infusion ($P<0.05$).

Differences in BR and SpO₂ following IV pump infusion of DEX. There were no indications of respiratory arrest in any of the three groups, as well as no significant differences in BR and SpO₂ values between the three groups ($P>0.05$). In addition, SpO₂ was $>97\%$ at all time points in all three groups (Figs. 6 and 7), indicating no indirect inhibition of respiration.

Concomitant use of medications. There was no significant difference between the three groups following addition of other sedatives ($P>0.05$). Vasoactive agents were administered to 4 patients in group A, 2 patients in group B and 1 patient in group C, and the difference was not statistically significant ($P>0.05$; Table I; Fig. 8).

Drug withdrawal. DEX administration was suspended in 4 patients in group A, 4 patients in group B and no patients in group C. Drug withdrawal in group A was due to HR reduction of $>30\%$ in 2 patients and an SBP value of <90 mmHg in the other 2 patients. Drug suspension in the 4 patients of group B was due to HR reduction of $>30\%$ in 1 patient and an SBP value of <90 mmHg in the other 3 patients. HR and BP values gradually returned to the normal ranges following drug discontinuation, with no severe consequences in any of the 8 patients (Table II).

Discussion

Critically ill patients in ICUs frequently require various supportive therapies, including mechanical ventilation, vital sign monitoring, critical nursing care and constant illumination to maintain the patients in a long-term sleep-deprived state (17,18). Therefore, appropriate sedative treatment is often required for ICU patients, as well as for postoperative patients and patients with severe multiple injuries. Midazolam, propofol and DEX are among the primary sedatives used in ICUs. DEX is a highly selective α_2 -adrenoceptor agonist that exerts its sedative and anti-anxiety effects by agonizing the brainstem locus ceruleus, which is the most concentrated area of α_2 receptor in the central nervous system (19-21). DEX exerts an analgesic effect and ameliorates stress response; however, DEX simultaneously inhibits respiration by acting on α_2 receptors in the presynaptic membrane of the spinal dorsal horn and postsynaptic membrane of interneurons (22,23). DEX may be the preferred option for inducing sedation in ICU patients as it is able to reduce the occurrence of delirium and minimize the period of mechanical ventilation required (24,25).

The results of the present study showed that continuous IV pump infusion of DEX was able to induce an ideal state of sedation (Ramsay score, 3-4) in all three groups of patients. The target level of sedation was achieved at ~6 min

after DEX infusion in groups A (1.0 $\mu\text{g/kg/10 min}$) and B (0.5 $\mu\text{g/kg/10 min}$). This is particularly crucial for the sedation of ICU patients, as antagonism between spontaneous breathing and mechanical ventilation may occur in patients if adequate sedation cannot be achieved rapidly, which may affect the target tidal volume, or even aggravate the existing pulmonary injury. Therefore, a key aim of using DEX is to enable the patient to enter an ideal state of sedation (24,26). In addition, continuous IV pump infusion of DEX is able to maintain a Ramsay score of 3-4, at which the patient is in an arousable 'dormant' state, which may attenuate the injury from severe pathological factors while allowing the patient to be awakened if necessary in order to perform actions for the convenience of observing the condition and assessing neurological functions.

A previous study demonstrated that DEX has the function of bidirectional regulation of the cardiovascular system (27). DEX initially agonizes the α_{2B} receptor of the postsynaptic membrane of the vascular smooth muscle to induce tachycardia and hypertension via vascular constriction. Subsequently, hypotension is induced via vascular dilation under the central sympatholytic effect produced by the continuous infusion of DEX. Therefore, DEX exerts a predictable effect on hemodynamics (28). In the present patients, HR, SBP and DBP tended to decrease following IV pump infusion with DEX; however, all the mean values of these parameters were within the normal ranges at all time points (HR, >60 bpm; SBP, >115 mmHg; and DBP, >60 mmHg). DEX administration was suspended in 8 patients in the present study due to unstable hemodynamics. The HR and BP values of these patients were restored gradually to within normal ranges following the withdrawal of DEX, with no severe consequences.

Analysis of 8 patients (4 with hypercapnia, 3 with anemia and 1 with hypercapnia and anemia) who were withdrawn from DEX indicates that hypercapnia and anemia are two high-risk factors contributing to unstable hemodynamics. The primary causes underlying these results may be explained as follows: i) Patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) are the primary group of patients in ICUs that typically require mechanical ventilation due to unconsciousness and severe hypercapnia. A previous study demonstrated that COPD may excite the sympathetic nerve system and induce the reflexory release of norepinephrine from the heart, causing hypertension and increasing the HR (29). In COPD patients with hypercapnia, the sympathetic system may be in a state of persistent excitement even under normal blood gas conditions (30,31). ii) Peripheral vascular dilation, decline in BP, excitement of the sympathetic system, increase in HR and cardiac output and subsequent renal vascular restriction, water-sodium retention and increased BP are the primary physiopathological changes observed in anemic patients. iii) The α_{2A} receptor subtype serves a crucial role in the pharmacology of DEX. This receptor exists in pre- and postsynapses, primarily serving the function of inhibiting norepinephrine release and neural excitement. DEX inhibits norepinephrine release by agonizing the presynaptic membrane α_2 receptor, thus terminating transmission of the pain signal. In addition, DEX inhibits the sympathetic activity by agonizing the postsynaptic membrane α_2 receptor. When the *in vivo* blood concentration of DEX is sufficient to inhibit sympathetic activity, the effect of sympathetic excitement induced by AECOPD and anemia is also inhibited. This

mechanism may underlie the observed reduction in cardiovascular function and the more marked differences in HR and BP in patients with AECOPD and anemia (32-34). This mechanism is consistent with the results of the present study, which identified that the majority of patients that were withdrawn from DEX suffered from hypercapnia and anemia.

An ideal state of sedation may be achieved using the maintenance dose of DEX (0.4 $\mu\text{g/kg/h}$); however, this effect is induced slowly. In order to achieve a more rapid sedative effect, we suggest the use of a loading dose of 0.5 $\mu\text{g/kg/10 min}$. In patients with AECOPD and anemia, high loading doses at a rapid rate of IV pump infusion should be avoided. Combination medication may be considered if necessary. As the sample size of the present study is relatively small, the results obtained may not fully reflect the effect of DEX on the circulatory system. Multi-center randomized controlled trials in larger samples are required to verify the present conclusions.

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