

## Original Article

# A clinical study on the effects of dexmedetomidine on off-line extubation of invasive mechanical ventilation

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**Abstract:** Objective: To analyze the clinical efficacy of dexmedetomidine (DEX) on off-line extubation of invasive mechanical ventilation (IMV). Methods: A total of 84 intensive care unit (ICU) patients receiving IMV were selected as the objects of study. They were randomly divided into test group (n=42) and control group (n=42) based on the sequence of the patients' admission into ICU. The patients in the test group took DEX for sedation at 4 h before off-line extubation, which lasted until the offline and extubation, while those in the control group used midazolam (MID) for sedation at 4 h before off-line extubation, which lasted until 1 h before off-line extubation. The effects of sedative treatment were evaluated using richmond agitation sedation scale (RASS) scoring. The changes in RASS score, heart rate (HR), mean arterial pressure (MAP) and respiratory rate (RR) before drug administration, 10 min, 1 h and 3 h after drug administration, during extubation and at 10 min after extubation were compared between the two groups of patients. The incidence of adverse reactions, ICU retention time and hospitalization cost were recorded. Results: The proportions of patients in the test group reaching the target of sedation 10 min, 1 h and 3 h after drug administration, during extubation and 10 min after extubation were significantly higher than those in the control group. The differences were statistically significant (P=0.03, P=0.02, P=0.03, P=0.04, P=0.02, respectively). The differences in HR, MAP and RR before drug administration, at different time points after drug administration, during extubation and 10 min after extubation in the test group were not statistically significant (P>0.05). In the control group, HR and MAP during extubation were obviously higher than those at other time points. The values of R 10 min, 1 h and 3 h after drug administration were significantly higher than those at other time points. The differences had statistical significance (P<0.05). ICU hospitalization time, cost of the patients and the incidence of respiratory depression in the test group were lower than those of the patients in the control group, whose differences were statistically significant (P=0.02, P=0.03, P=0.01). There was no significant difference in the incidence of circulatory depression between the two groups (P=0.33). Conclusion: DEX has good sedative effects on ICU patients with IMV, maintain the stability of hemodynamics and respiratory function during off-line extubation, and have a positive effect on the successful completion of off-line extubation.

**Keywords:** Invasive mechanical ventilation, extubation, dexmedetomidine, midazolam

## Introduction

It is well-known that patients admitted to the intensive care unit (ICU) are prone to experience respiratory failure. Using invasive mechanical ventilation (IMV) to restore and maintain the patient's respiratory function has important clinical significance. Stress response in ICU patients with IMV is further aggravated due to the stimulation of tracheal intubation on the respiratory tract, limited limb activity, relatively great psychological burden, etc., leading to respiratory disorders and large circulation fluctuations, which increase the risk of complica-

tions [1]. Studies have shown that the risks of complications such as ventilator-associated pneumonia and pulmonary barotrauma increase with the extension of the time of IMV which is an invasive operation [2]. Therefore, good sedation, analgesia, and timely offline and extubation are extremely essential to improve the prognosis of ICU patients with IMV. Midazolam (MID) is a sedative commonly used in clinic. It has the effects of sedation, resisting anxiety and anterograde amnesia, but can also cause mild respiratory depression [2]. There is a high incidence of delirium after surgery [3]. Dexmedetomidine (DEX) hydrochloride is a new highly-

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selective  $\alpha_2$  receptor agonist. It has the effects of sedation, hypnosis, analgesia and inhibiting sympathetic nerve, and can also reduce various harmful stimuli during surgery such as immediate hemodynamic responses in the intubation period, in the recovery period and during extubation [4]. It is of great importance to withdraw the machine and remove the tube in time when the condition allows, thus mechanical ventilation can be used more reasonably and effectively, and spontaneous breathing of the patient can be recovered as early as possible. In this paper, the clinical efficacy of DEX on offline and extubation of IMV is discussed through the use of DEX in patients with the need of mechanical ventilation for breathing support.

### Materials and methods

#### *General data*

A total of 84 ICU patients with IMV treated in Affiliated Hospital of Jining Medical University from March 2015 to March 2016 were selected as the objects of study. The patients included 46 males and 38 females aged 23-71 years old with an average age of  $58.3 \pm 5.69$  years old.

**Inclusion criteria:** Patients aged 18-75 years old; patients for whom off-line extubation of IMV was expected to be conducted within 4 h, the function of important organs had no obvious anomaly, the vital signs were stable before sedative treatment, and circumstances such as hypotension, respiratory dysfunction and bradycardia were not observed; patients who did not use other types of sedative drugs or stopped drug use for more than 6 h before the sedative treatment with DEX or MID.

**Exclusion criteria:** Patients with unstable hemodynamics or respiratory function; patients complicated with dysfunctions in vital organs such as heart, liver and kidney; patients with severe disturbance of consciousness; patients who once suffered from mental illness previously.

#### *Study methods*

The aforementioned 84 ICU patients with IMV were randomly divided into the control group (n=42) and the test group (n=42) based on the sequence of admission into ICU. The two groups of patients received fentanyl at a dose of 1-2  $\mu\text{g}/(\text{kg}\cdot\text{h})$  for analgesia and MID for sedation. The patients in the test group received DEX for

sedation at 4 h before off-line extubation, which lasted until the offline and extubation. The loading dose of DEX was 1  $\mu\text{g}/\text{kg}$  which was injected using micro-injection pump. When richmond agitation sedation scale (RASS) score was within +1 to -2 points 10 min after drug administration, the use of loading dose of DEX was stopped, and a maintenance dose (0.25-0.75  $\mu\text{g}/(\text{kg}\cdot\text{h})$ ) was given instead. After 4-hour continuous sedative treatment, off-line extubation of IMV was conducted, and the use of DEX was stopped. The patients in the control group received MID for sedation at 4 h before off-line extubation, which lasted until 1 h before off-line extubation. MID (0.1 mg/kg) was given by intravenous bolus at an interval of about 4 min. When RASS score was within +1 to -2 points, a maintenance dose (0.1 mg/(kg·h)) was given, and the dose of MID was adjusted timely based on RASS scores.

#### *Evaluation of off-line extubation of IMV*

Determination of whether the patients met the criteria for machine withdrawal from IMV: The causes of IMV have been dispelled, the oxygenated function was good, the haemodynamics was stable, and spontaneous breathing capacity was available.

**Extubation signs:** Extubation could be considered in combination with the following indexes after successful machine withdrawal. The specific indexes were as follows: it was observed that the oxygenation and blood gas analysis were normal after successful machine withdrawal. Cough reflex was good, and sputum excretion could be conducted spontaneously under effective coughing. The amount of respiratory secretions was decreased, and the infectious disease was controlled. Spontaneous respiratory function continued to improve. The mandibular activity was good, the upper respiratory tract was smooth, and the amount of residue in the stomach was relatively small [4, 5].

#### *Observation indexes*

The effects of sedative treatment were evaluated according to RASS scores. The changes in RASS scores, heart rate (HR), mean arterial pressure (MAP) and respiratory rate (RR) before drug administration, 10 min, 1 h and 3 h after drug administration, during extubation and 10 min after extubation were compared between the two groups of patients. RASS scoring meth-

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**Table 1.** Comparison of general data between the two groups of patients

Group	Age (years)	Gender (male/female)	Body mass (kg/m <sup>2</sup> )	APACH-II score	GCS score
Test group (n=42)	56.8±5.12	21/21	23.8±2.17	18.5±2.7	10.1±2.9
Control group (n=42)	59.8±6.08	25/17	24.1±2.35	17.8±2.2	10.9±3.1
t/χ <sup>2</sup>	1.38	3.07	2.15	2.34	1.54
P	0.38	0.26	0.19	0.17	0.23

Note: APACH-II, acute physiology and chronic health evaluation II; GCS, Glasgowcoma scale.

re not statistically significant ( $P>0.05$ ). These data were comparable (**Table 1**).

*Comparison of RASS scores between the two groups of patients before and after extubation*

**Table 2.** Comparison of the proportion of patients with a RASS score within the normal range between the two groups of patients before and after extubation (%)

Group	Test group	Control group	t/χ <sup>2</sup>	P
10 min after drug administration	85.70	76.20	5.39	0.03
1 h after drug administration	90.50	78.60	6.18	0.02
3 h after drug administration	92.90	81.00	5.61	0.03
During extubation	97.60	85.70	4.97	0.04
10 min after extubation	95.20	83.30	6.27	0.02

Note: RASS, richmond agitation sedation scale.

The proportions of patients in the test group reaching the target of sedation 10 min, 1 h and 3 h after drug administration, during extubation and 10 min after extubation were significantly higher than those in the control group. The differences were statistically significant ( $P=0.03$ ,  $P=0.02$ ,  $P=0.03$ ,  $P=0.04$ ,  $P=0.02$ , respectively). See **Table 2**.

*Comparisons of HR, MAP and RR between the two groups of patients before and after extubation*

od: aggressive (+4 points), very restless (+3 points), restless anxiety (+2 points), restless anxiety (+1 point), alertness but quietness (0 point), drowsiness (-1 point), mild sedation (-2 points), moderate sedation (-3 points), severe sedation (-4 points), and coma (-5 points), of which the RASS score within +1 to -2 points suggested that the effects of the sedative treatment are satisfactory [6]. The incidence of adverse reactions, ICU retention time and hospitalization time were recorded.

### Data processing

SPSS13.0 software was used for processing research data. The measurement data were expressed as mean ± standard deviation. One-way analysis of variance was adopted for inter-group comparison, and paired t test was adopted for within-group comparison. The enumeration data were expressed as percentage. χ<sup>2</sup> test was used for comparison among groups.  $P<0.05$  suggested that the difference was statistically significant.

### Results

#### *Comparison of general data between the two groups of patients*

The differences in age, gender, body mass, acute physiology and chronic health evaluation II (APACH II) scores and Glasgow coma scale (GCS) between the two groups of patients we-

The differences in HR, MAP and RR before drug administration, at different time points after drug administration, during extubation and 10 min after extubation in the test group were not statistically significant ( $P>0.05$ ). In the control group, HR and MAP during extubation were obviously higher than those at other time points. The values of RR at 10 min, 1 h and 3 h after drug administration were higher than those at other time points. The differences were statistically significant ( $P<0.05$ ). In comparison with those in the control group, the values of RR in the test group were higher at 10 min, 1 h and 3 h after drug administration, and HR and MAP in the test group were lower during extubation. The differences were statistically significant ( $P<0.05$ ). See **Table 3**.

#### *Comparisons of hospitalization time and cost between the two groups*

ICU hospitalization time and cost of the patients in the test group were lower than those of the patients in the control group. The differences were statistically significant ( $P=0.02$ ,  $P=0.03$ , respectively). See **Table 4**.

#### *Comparisons of adverse reactions between the two groups of patients*

The incidence of respiratory depression in the test group was lower than that in the control group. The difference was statistically signifi-

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**Table 3.** Comparisons of HR, MAP and RR between the two groups of patients before and after extubation

Group	Test group			Control group		
	HR	MAP	RR	HR	MAP	RR
Before drug administration	95.8±13.7	93.2±12.5	17.4±6.5	96.4±12.8	92.4±12.2	17.3±6.7
10 min after drug administration	86.7±12.3	84.5±11.3	16.3±5.4	90.6±11.8	86.2±12.3	7.4±3.5* <sup>#</sup>
1 h after drug administration	86.9±12.1	81.7±11.3	15.6±7.4	92.1±11.7	85.3±10.2	7.6±4.5* <sup>#</sup>
3 h after drug administration	85.9±10.2	84.7±9.3	16.6±4.1	90.1±10.3	84.9±9.7	8.1±3.9* <sup>#</sup>
During extubation	92.1±9.3	86.9±11.2	16.3±4.9	121.2±9.2* <sup>#</sup>	116.4±14.5* <sup>#</sup>	16.8±4.7
10 min after extubation	89.2±11.2	83.3±9.1	16.2±6.7	94.7±10.8	89.6±10.5	16.3±7.4

Notes: Compared with other time points, \*P<0.05; compared among groups, <sup>#</sup>P<0.01. HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate.

**Table 4.** Comparisons of ICU hospitalization time and cost between the two groups of patients

Group	ICU hospitalization time (d)	ICU cost (ten thousand yuan)
Test group	5.1±1.3	3.8±0.7
Control group	7.8±1.6	5.5±1.0
t	9.04	8.45
P	0.02	0.03

Note: ICU, intensive care unit.

**Table 5.** Comparisons of adverse reactions between the two groups of patients (n, %)

Group	Respiratory depression	Circulatory depression	Other complications
Test group (n=42)	6 (14.3)	18 (42.9)	3 (7.1)
Control group (n=42)	23 (54.8)	19 (45.2)	4 (9.5)
χ <sup>2</sup>	15.80	0.00	0.23
P	0.01	0.33	0.29

cant (P=0.01). There was no significant difference in the incidence of circulatory depression between the two groups (P=0.33). Other complications in the test group included nausea and dry mouth, and those in the control group included nausea, vomiting, dizziness and headache. The differences in other complications between the two groups had no statistical significance (P=0.29). See **Table 5**.

### Discussion

Of the patients who leave the ICU, many patients retain poor memory of their pain experienced in the ICU with anxiety and agitation. Among them, tracheal intubation is the most intense noxious stimulation. Restlessness can lead to man-machine counteraction during mechanical ventilation, increase patients' oxy-

gen consumption, elevate the incidence and mortality of complications, prolong hospitalization time and mechanical ventilation time, and increase the incidence of self-extubation by the patients. Therefore, attention should be paid to observe and timely handle various reactions such as irritability and anxiety in patients with mechanical ventilation. Currently, analgesia and sedation have been routine treatments for ICU patients.

In this study, patients in the test group used a loading dose of DEX. Ten minutes after drug administration, the proportion of the patients in the test group achieving the targeted RASS score was significantly higher than that of the patients in the control group, indicating that DEX has a good sedative effect in the early phase. Based on the aforementioned results, the patients in the test group continued to use a maintenance dose of DEX, and RASS score was monitored. When RASS score was maintained within +1 to -2 points, a good sedative effect could be maintained in ICU patients with IMV. A study of Waleed et al. showed that obvious sedation could be observed in the patients after continuous 10-minute intravenous injection of a loading dose (0.5 µg/kg) of DEX [7]. Other studies indicated that during the sedative treatment with DEX, the difference in the sedative effect generated by the use of a small dose (0.25 µg/(kg·h)) and a high dose (0.75 µg/(kg·h)) for continuous 60 min is not statistically significant when the sedative effect is satisfactory [8]. Meanwhile, in this study, the effects of sedative treatment with DEX showed obviously individu-

al variation among different ICU patients with IMV. In this regard, the maintenance dose of DEX should be adjusted timely but controlled within 0.25-0.75  $\mu\text{g}/(\text{kg}\cdot\text{h})$  to maintain the RASS score within +1 to -2 points and keep good and stable effects of sedative treatment. Many studies in China and foreign countries showed that both MID and DEX had the effects of making the patients stay in a good sedative state, meeting the sedative requirements for off-line extubation of IMV and maintaining RASS scores within +1 to -2 points [9-11]. As MID has a significant inhibition effect on the respiratory center, the use of MID should be stopped 1 h before off-line extubation, causing increased irritability in a considerable number of patients in the short period of time after drug withdrawal. The results of this study showed that the proportion of patients achieving the goal of sedation 10 min after extubation was lower than that during extubation. DEX had no respiratory depression compared with MID during the sedative treatment with off-line extubation of IMV, and the use of DEX did not need to be stopped before off-line extubation. The results of this study showed that the effects of sedative treatment in patients in the test group were good 10 min after extubation, which could effectively avoid the failure of extubation or other adverse reactions due to increased irritability.

In addition, during the sedative treatment with a loading dose of DEX and MID, both HR and MAP after drug administration were lower than those before drug administration. They showed a decrease tendency, but the differences had no statistical significance. Most of patients did not need special treatment. Even a small number of patients needed symptomatic treatment, the prognosis was good. In this study, the differences in HR, MAP and RR in the test group before drug administration, at different time points after drug administration, during extubation and 10 min after extubation had no statistical significance ( $P>0.05$ ), which also further proves the above viewpoints. The phenomenon that HR and MAP are decreased under a sedative state may be related to the decreased sympathetic excitability due to the effect of sedative drugs. As an  $\alpha_2$  adrenergic receptor agonist with strong targeting ability, DEX can block the sympathetic nerve and has pharmacological effects of sedation and hypnosis,

which preserve awake system function while producing natural non-eye movement sleep [12, 13]. A study of Zhang et al. showed that DEX can help the patients fall asleep quickly, but the patients are easy to be aroused [14]. However, a study of Chen et al. indicated that DEX has a relatively great influence on circulation [15]. A study of Tan et al. showed that DEX has a satisfactory sedative effect, and will not result in an obvious change in circulation [16]. In this study, If RASS score was within +1 to -2 points after 10-min use of a loading dose (1  $\mu\text{g}/\text{kg}$ ) of DEX by micro-injection pump injection, satisfactory effects of sedative treatment were achieved, and a maintenance dose (0.25-0.75  $\mu\text{g}/(\text{kg}\cdot\text{h})$ ) was given instead. However, HR, MAP and RR were not affected obviously, and a transient increase in blood pressure was not observed, which are consistent with the results of previous studies, indicating that it is safe to use a small dose of DEX in off-line extubation of IMV [17, 18]. This study also indicated that in comparison with MID, DEX had a higher selectivity, less adverse reactions and did not induce respiratory compression with clinical significance in the treatment scope. The patients in the control group received a sedative treatment with MID. As MID has the effect of respiratory depression, it should be withdrawn at 1 h before off-line extubation, which is the reason why both HR and MAP in the control group during extubation were significantly higher than those at other time points, and why the values of RR at 10 min, 1 h and 3 h after drug administration were obviously higher than those at other time points. The burden of the heart may be increased, and wound bleeding may even be caused. Moreover, the patients in the test group did not need to stop the use of drug before extubation. The effects of sedative treatment were maintained to off-line extubation so as to make the stimulation of off-line extubation have no obvious effect on HR, MAP and RR, keep the hemodynamics and respiratory function stable, and greatly reduce the occurrence of off-line extubation. Studies have proved that the continuous pumping of DEX (0.5  $\mu\text{g}/\text{kg}$ ) 5 min before off-line extubation can reduce airway and circulatory responses, but it will not affect the recovery of the disease [19]. This study proved that ICU retention time and hospitalization time of the patients in DEX group were shorter than those of the patients in the control group. The differences were statistically

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significant ( $P < 0.05$ ). The results are identical with that obtained in other studies [20].

The shortcomings of this study were: (1) it is a single-center study; (2) the methodology (blind method) had defects; (3) the number of patients included in this study was relatively small and multi-center randomized and double-blind trial should be conducted further.

In conclusion, DEX can keep a good sedative effect in ICU patients with IMV, maintain the stability of hemodynamics and respiratory function during off-line extubation, and have a positive effect on the successful completion of off-line extubation.

### Disclosure of conflict of interest

None.

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