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Original article

Clinical study of midazolam sequential with dexmedetomidine for agitated patients undergoing weaning to implement light sedation in intensive care unit

Xing Lu¹, Jun Li¹, Tong Li, Jie Zhang, Zhi-Bo Li, Xin-Jing Gao, Lei Xu*

Department of Intensive Care, Tianjin Third Central Hospital, Tianjin 300170, China

ARTICLE INFO

Article history:

Received 10 March 2015

Received in revised form

8 August 2015

Accepted 13 September 2015

Available online 28 January 2016

Keywords:

Dexmedetomidine

Midazolam

Light sedation

Mechanical ventilation

ABSTRACT

Purpose: To evaluate midazolam sequential with dexmedetomidine for agitated patients undergoing weaning to implement light sedation in ICU.

Methods: This randomized, prospective study was conducted in Tianjin Third Central Hospital, China. Using a sealed-envelope method, the patients were randomly divided into 2 groups (40 patients per group). Each patient of group A received an initial loading dose of midazolam at 0.3–3 mg/kg·h 24 h before extubation, followed by an infusion of dexmedetomidine at a rate of 0.2–1 µg/kg·h until extubation. Each patient of group B received midazolam at a dose of 0.3–3 mg/kg·h until extubation. The dose of sedation was regulated according to RASS sedative scores maintaining in the range of -2–1. All patients were continuously monitored for 60 min after extubation. During the course, heart rate (HR), mean artery pressure (MAP), extubation time, adverse reactions, ICU stay, and hospital stay were observed and recorded continuously at the following time points: 24 h before extubation (T1), 12 h before extubation (T2), extubation (T3), 30 min after extubation (T4), 60 min after extubation (T5).

Results: Both groups reached the goal of sedation needed for ICU patients. Dexmedetomidine was associated with a significant increase in extubation quality compared with midazolam, reflected in the prevalence of delirium after extubation (20% (8/40) vs 45% (18/40)), respectively ($p = 0.017$). There were no clinically significant decreases in HR and MAP after infusing dexmedetomidine or midazolam. In the group A, HR was not significantly increased after extubation; however, in the group B, HR was significantly increased compared with the preextubation values ($p < 0.05$). HR was significantly higher in the group B compared with the group A at 30 and 60 min after extubation (both, $p < 0.05$). Compared with preextubation values, MAP was significantly increased at extubation in the group B ($p < 0.05$) and MAP was significantly higher at T3, T4, T5 in the group B than group A ($p < 0.05$). There was a significant difference in extubation time ((3.0 ± 1.5) d vs (4.3 ± 2.2) d, $p < 0.05$), ICU stay ((5.4 ± 2.1) d vs (8.0 ± 1.4) d, $p < 0.05$), hospital stay ((10.1 ± 3.0) d vs (15.3 ± 2.6) d, $p < 0.05$) between group A and B.

Conclusion: Midazolam sequential with dexmedetomidine can reach the goal of sedation for ICU agitated patients, meanwhile it can maintain the respiratory and circulation parameters and reduce adverse reactions.

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Introduction

Tracheal intubation and extubation may be associated with hypertension and tachycardia. Dexmedetomidine, a highly

selective α_2 -adrenoreceptor agonist, is used for sedation management in various clinical settings and shows an anesthetic-sparing effect.^{1,2} Dexmedetomidine provides excellent sedation with minimal cardiovascular instability or respiratory depression and may be a useful adjunct to facilitate smooth tracheal extubation. It has also been reported to decrease the plasma catecholamine responses to intubation and extubation.^{3,4} The aim of this study was to compare the effects of dexmedetomidine and midazolam on recovery and hemodynamic responses to tracheal extubation in patients. It was a prospective analysis in 80 patients involved in a randomized, double-blind trial.

* Corresponding author.

E-mail address: nokia007008@163.com (L. Xu).

Peer review under responsibility of Daping Hospital and the Research Institute of Surgery of the Third Military Medical University.

¹ Those authors contributed equally to this study.

Methods

Patients and study design

This study was carried out in 80 patients (40 in each group) at the age range of 38–76 years. Table 1 shows the study group's main demographics. Using a computer-generated randomization scheme, the patients were randomly divided into 2 groups (40 patients per group). Patients with cardiovascular disorders, diabetes, hypertension, morbidly obese patients, difficult airway, medications that affect heart rate (HR) or blood pressure (BP), pregnancy, currently breast feeding, history of sleep apnea and those for emergency procedures were excluded. Patient exclusion criteria were as follows: (1) patient age <18 years or >80 years, (2) mean arterial pressure (MAP) <55 mmHg, (3) HR <55 beats/min, (4) dysrhythmia, (5) those with a history of psychiatric/neurological illness, (6) patients with known allergic reaction to any medication used in this study and (7) patients on recent use of sedatives or analgesics.

This double-blind, randomized study was conducted in Tianjin Third Central Hospital, Tianjin, China. A total of 80 agitated patients with tracheal intubation in ICU were divided into two groups as midazolam sequential with dexmedetomidine group (group A), midazolam group (group B). Each patient of group A received an initial loading dose of midazolam at 0.3–3 mg/kg·h 24 h before extubation, followed by an infusion of dexmedetomidine at a rate of 0.2–1 mg/kg·h until extubation. Each patient of group B received midazolam at a dose of 0.3–3 mg/kg·h until extubation. The dose of sedation was regulated according to RASS sedative scores maintaining in the range of -2-1. All patients were continuously monitored for 60 min after extubation. During the course, HR, MAP, extubation time, adverse reactions, ICU stay, and hospital stay were observed and recorded continuously at the following time points: 24 h before extubation (T1), 12 h before extubation (T2), extubation (T3), 30 min after extubation (T4), 60 min after extubation (T5).

RASS and extubation index

The Richmond agitation-sedation scale (RASS) is demonstrated in Table 1.

Extubation index

Resolution of the underlying cause of acute respiratory failure; hemodynamic stability, defined as no need for vasoactive/inotropic drugs; preferably absence of fever (defined as temperature <38 °C);

Table 1
Richmond agitation-sedation scale.

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive
+2	Agitated	Frequent unpurposed movement, intolerant for ventilator
+1	Restless	Anxious but movement not aggressive or vigorous
0	Alert and calm	Awake and quiet
-1	Drowsy	Not fully alert, but having sustained awakening (eye opening/eye contact) to voice (>10 s)
-2	Light sedation	Being briefly awake, with eye contact to voice (<10 s)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

adequate gas exchange, as indicated by a partial pressure of oxygen (fraction of inspired oxygen ratio >200 with a positive end-expiratory pressure of 5 cm H₂O); partial pressure of carbon dioxide adjusted to bring blood pH value into the normal range.

Statistical analysis

Data were analyzed with SPSS 18 (SPSS Inc, Chicago, IL). Demographic and clinical data were compared using the Mann–Whitney U test for continuous variables and χ^2 or Fisher's exact test, where appropriate, for categorical variables. $p < 0.05$ was considered significantly different.

Results

Baseline characteristics

The demographic data are shown in Table 2. There were no significant differences between two groups.

There were no clinically significant decreases in HR and MAP after infusing dexmedetomidine or midazolam. In the group A, HR was not significantly increased after extubation; however, in the group B, HR was significantly increased compared with the pre-extubation values ($p < 0.05$). HR was significantly higher in the group B compared with the group A at 30, 60 min after extubation (both, $p < 0.05$, Fig. 1). Compared with preextubation values, MAP was significantly increased at extubation in the group B ($p < 0.05$) and MAP was significantly higher at T3, T4, T5 in the group B than group A ($p < 0.05$, Fig. 2).

Dexmedetomidine was associated with a significant increase in extubation quality compared with midazolam, reflected in the prevalence of delirium after extubation (20% (8/40) vs 45% (18/40)), respectively ($p = 0.017$). There was a significant difference in extubation time (3.0 ± 1.5 vs 4.3 ± 2.2 , $p < 0.05$), ICU stay (5.4 ± 2.1 vs 8.0 ± 1.4 , $p < 0.05$), hospital stay (10.1 ± 3.0 vs 15.3 ± 2.6 , $p < 0.05$) between group A and B (Table 3).

Table 2
Clinical characteristics of the study patients.

Characteristic	Group A	Group B
Sex (male: female)	18:22	21:19*
Age (years)	64.2 ± 9.9	62.5 ± 9.6*
APACHEII score	20.2 ± 5.0	19.8 ± 6.2*
Weight (kg)	71.5 ± 10.5	70.2 ± 11.2*
Height (cm)	172.8 ± 11.6	175.1 ± 12.5*
COPD (n)	25	24*
ARDS (n)	11	11*
Severe asthma (n)	2	2*
Others (n)	2	3*

Note: * $p > 0.05$, compared with group A; COPD = chronic obstructive pulmonary disease; ARDS = acute respiratory distress syndrome.

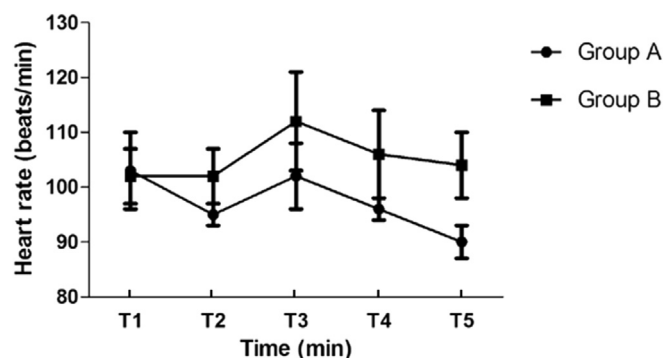


Fig. 1. Trend of heart rate in two groups.

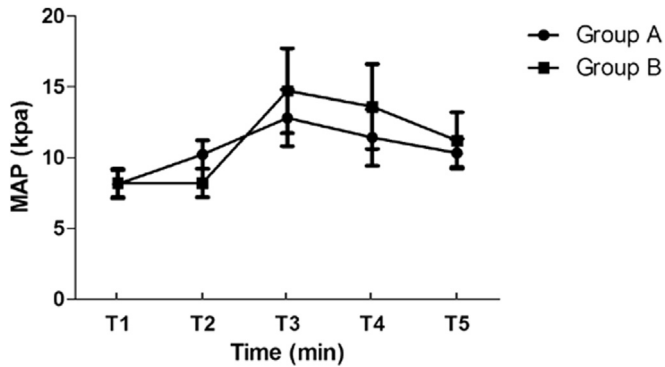


Fig. 2. Trend of mean arterial pressure in two groups.

Table 3
Recovery parameters.

Variable	Group A	Group B	p value
Duration of mechanical ventilation (d)	3.0 ± 1.5	4.3 ± 2.2	<0.05
ICU stay (d)	5.4 ± 2.1	8.0 ± 1.4	<0.05
Length of hospital stay (d)	10.1 ± 3.0	15.3 ± 2.6	<0.05
Cases of delirium	8	18	0.017

Discussion

The presence of delirium in the ICU has been shown to increase the period of mechanical ventilation, ICU and hospital stay, and overall hospitalization cost.^{5–8} Several studies reported that prolonged periods of intubation increased the risk of delirium by 1.10–7.90 times as compared to short periods of intubation.⁹ Consequently, choices of sedatives may be critical for preventing delirium. This study, together with previous work,¹⁰ proved dexmedetomidine to be an effective and safe agent for sedation in the ICU. Unlike previous studies, this one sought to compare midazolam sequential with dexmedetomidine with midazolam alone.

Dexmedetomidine has recently attracted considerable attention due to its ability to provide adequate sedation and analgesia without producing excessive hypotension. Unlike conventional sedatives such as midazolam, dexmedetomidine can produce anxiolysis and sedation without provoking significant respiratory depression. Koroglu et al¹⁰ found that dexmedetomidine had better quality of sedation and less need for rescue sedation compared with midazolam, without significant adverse effect on hemodynamic or respiratory function. These findings were consistent with our study results, which indicated a significant decrease in HR and MAP. The increases in HR and MAP after extubation were significantly lower with midazolam sequential with dexmedetomidine compared with midazolam used alone ($p < 0.05$). Thus, because of its sympatholytic activity, dexmedetomidine attenuates various stress responses during extubation and maintains hemodynamic stability.

Several important differences were noted in this study. Midazolam sequential with dexmedetomidine could reduce the length of ICU stay and hospital stay and duration of mechanical ventilation and incidence of delirium. Riker et al¹¹ found that extubation time was significantly shortened in patients sedated with dexmedetomidine compared with those receiving midazolam. In some studies,

no intraoperative or post-operative adverse effects were reported in dexmedetomidine group.^{12,13} In contrast, few patients in the midazolam group had oxygen desaturation, nausea and vomiting. The patients treated with dexmedetomidine could be aroused easier with adequate sedation and presented less significant respiratory depression.¹⁴ Consequently, the patients had a shorter overall ventilation time and an decreased risk of prolonged hospitalization, which may explain the improved outcomes.

There were some limitations in our study: (1) it was conducted in a single medical center; (2) the timing, dosage and target group of dexmedetomidine needed to be validated by future extensive randomized studies to confirm the benefit; (3) the sample size was too small for broad generalization.

In conclusion, midazolam sequential with dexmedetomidine can reach the goal of sedation for ICU agitated patients, meanwhile it can maintain the respiratory and circulation parameters and reduce adverse reactions.

Fund

This research was supported by a grant from Chinese Medical Association (No. 13010090394) and Tianjin Medical Major Project (12KG106, 14KG111).

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