## Original Research Article

# Therapeutic effect of cisatracurium in patients with acute respiratory distress syndrome

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## Abstract

**Purpose:** To investigate the therapeutic effect of cisatracurium, (a neuromuscular blocking agent) in the treatment of acute respiratory distress syndrome (ARDS).

**Methods:** A total of 94 ARDS patients admitted to The Third People's Hospital of Honghe Hani and Yi Autonomous Prefecture ICU from March 2020 to December 2021 were randomly assigned to study and control groups (47 patients each). Both groups received mechanical ventilation, but the study group also received continuous intravenous cisatracurium for 48 h. Health parameters, such as blood gas levels, respiratory mechanics, duration of stay in intensive care unit ICU), mortality rate, and the occurrence of complications, were monitored at 3, 6, and 12 months after treatment.

**Results:** The study group showed significant improvements compared to control group. Study group also had reduced duration of mechanical ventilation, duration of ICU stay, ICU mortality rate, and incidence of complications (p < 0.05). There were no significant differences in pre-treatment health parameters, but post-treatment, study group had significantly higher levels of blood gas levels and improved lung function (p < 0.05). Study group also had lower scores of illness severity and reduced total mortality rate at 3, 6, and 12 months (p < 0.05).

**Conclusion:** Administering cisatracurium reduces mechanical ventilation, duration of ICU stay and mortality rate, as well as improves lung function in ARDS patients. Future research involving larger sample size, and takes into consideration regional/environmental differences, is required to validate these findings for reliability.

**Keywords:** Acute respiratory distress syndrome, Neuromuscular blockade, Cisatracurium, Drug delivery, Treatment, Impact

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) is an acute respiratory disease that occurs within one week and is characterized by an acute inflammatory response in the lungs and an increase in pulmonary vascular permeability [1]. The prognosis for patients with ARDS is poor, and ARDS survivors present with long-term and potential cognitive, psychological, and permanent neuromuscular problems due to long-term bed rest, mechanical ventilation, and use of paralytic

and steroidal drugs, which dramatically affects their quality of life [2]. Therefore, aggressive treatment and timely intervention are of paramount significance in improving the survival rate and living quality of patients with ARDS.

Currently, primary methods for clinical treatment of ARDS include low tidal volume mechanical ventilation to attenuate barotrauma, prone ventilation, conservative fluid management, and delivery of neuromuscular blocking agents [3]. Studies by Wilsterman *et al* [4] have also denoted that continuous administration of neuromuscular blocking drugs substantially improves oxygenated function and lowers mean airway pressure in children with severe acute hypoxic respiratory failure requiring mechanical ventilation. Cisatracurium, a non-depolarizing muscular relaxant with a benzylisoquinolinium structure, is a 1R cis-1-prime R cis-isomer of the highly selective and short-acting neuromuscular junction blocker, atracurium, which primarily blocks the transmission of acetylcholine by binding to cholinergic receptors to achieve muscle relaxation [5]. Nonetheless, to date, randomized controlled trials evaluating the effectiveness and efficacy of cisatracurium delivery for clinical treatment of ARDS patients are still lacking.

Therefore, this research involves a double-blind, randomized clinical trial on ARDS patients admitted to The Third People's Hospital of Honghe Hani and Yi Autonomous Prefecture. Patients were randomly assigned to receive continuous transfusion of cisatracurium or placebo for 48 h to investigate the influence of neuromuscular blocking drug delivery on ARDS treatment.

# METHODS

## Information on patients

A total of 94 patients diagnosed with ARDS and admitted to The Third People's Hospital of Honghe Hani and Yi Autonomous Prefecture ICU from March 2020 to December 2021 were randomly assigned to control and study groups (47 patients each). Among the group of 94 patients, 60 were males while 34 were females (aged between 45 and 75 years old). Based on the severity of ARDS using Berlin definition [6], 74 patients were classified as moderate while 20 were classified as severe. Primary diseases included pneumonia in 52 cases, sepsis in 24 cases, acute severe pancreatitis (ASP) in 10 cases, and trauma in 8 cases. The ethics committee of the hospital approved this study (approval no. 2023-HHZSYIEC-16), and

complied with the guidelines for international studies. All patients and their families were provided with an informed consent form, which they voluntarily signed.

## Inclusion criteria

All patients who met Berlin definition criteria for ARDS [6], aged between 18 and 75 years old, admitted to ICU within 48 h, received mechanical ventilation treatment (partial pressure of oxygen ($PaO_2$): Fio2 (Fraction of Inspired Oxygen) < 150 mmHg).

## Exclusion criteria

Patients with malignant tumors, blood coagulation disorders, rheumatic immune diseases, bronchial asthma, neuromuscular diseases, bromine ion allergy, and incomplete clinical data were excluded.

## Treatments

Two groups of patients received active treatment for ARDS, including routine monitoring of vital signs, anti-infection therapy, enteral and parenteral nutrition support, and fluid management. All patients underwent supine mechanical ventilation with endotracheal intubation employing a breathing machine and with a 30° head of bed elevation. Volume-controlled ventilation was taken with an initial tidal volume set between 6-8 mL/kg, modified based on estimated body weight. When airway plateau pressure exceeded 30 cm $H_2O$, tidal volume was appropriately lowered, but not less than 4 mL/kg. The aim of mechanical ventilation was to keep patient's breathing rate within the range of 16 – 20 breaths/min, $PaO_2$ above 60 mmHg, the pressure of carbon dioxide ($PaCO_2$) between 35 and 50 mmHg, finger pulse oxygen saturation above 95 %, and pH between 7.35 and 7.45.

In the control group, 47 patients received intravenous infusion of fentanyl at a dose of 0.5 μg/(kg·h) for sedation therapy and maintained for 48 h, in addition to routine treatment and mechanical ventilation.

In the study group, 47 patients underwent cisatracurium transfusion at a dose of 0.5-0.8 μg/(kg·h), in addition to routine treatment and mechanical ventilation, starting from time of admission to ICU. After 4 - 6 h, the dose was adjusted to 0.3 - 0.6 μg/(kg·h) using a micro-infusion pump (intravenous drip) and maintained for 48 h.

The treatment period for both groups of patients was from admission to the ICU until they could be transferred to a general ward. The follow-up period was determined based on time of ICU discharge or death during ICU stay for all patients.

### Evaluation of treatment

#### *Mechanical ventilation and ICU-related indicators*

This research compared mechanical ventilation time, ICU stay length, ICU mortality rate (defined as the mortality rate during the ICU stay), incidence of ICUAW (Intensive Care Unit Acquired Weakness, diaphragmatic weakness, difficulty in getting rid of breathing machines, limb paralysis, decreased sensory nerve function, and diminished tendon reflexes), VILI (ventilator-induced lung injury, meeting the diagnostic criteria for diffuse lung damage and extra-alveolar gas damage), and man-machine counteraction (characterized by non-synchronous breathing: the patient exhales while the ventilator is in the air supply phase, and the ventilator stops supplying air when the patient inhales) between study and control groups [7].

#### Blood gas parameters

Analysis of blood gas indicators was carried out using a blood gas analyzer at time of ICU admission and end of treatment in the two groups. Blood gas parameters analyzed include pH value, $PaO_2$, $PaCO_2$, and $SaO_2$.

#### Respiratory mechanics-related indicators

Respiratory function monitor was employed to monitor bedside respiratory mechanics parameters of study and control groups at time of ICU admission and at end of treatment, which encompasses respiratory rate, peak airway pressure, airway occlusion pressure, and static lung compliance [8].

#### APACHEII score and cardiovascular SOFA score

Acute Physiology and Chronic Health Evaluation II (APACHEII) score [9] and Sequential Organ Failure Assessment (SOFA) score [10] were compared between the two groups at ICU admission and after treatment. The APACHE II score consists of three dimensions, namely age, acute physiological pathological changes (including body temperature, heart rate, mean blood pressure, respiratory rate, oxygen saturation, pH, blood bicarbonate, serum sodium, potassium, creatinine, hematocrit (hCT), white blood cell count, Glasgow Coma Scale (GCS)), and chronic health status (assessing history of organ dysfunction or immunosuppression), with a total score of 71.

A greater total score denotes an elevated level of severity and an increased likelihood of mortality while in the ICU. The SOFA score adopts six criteria to reflect function of organ systems, namely respiratory system, blood system, liver system, cardiovascular system, neurological system, and kidney system, with each item scored from 0 to 4 points. A higher total score means a higher risk of death in patients.

### Occurrence of adverse events

Occurrence of adverse events like rash, hypotension, arrhythmia, delirium, ventilator-correlated pneumonia, pneumothorax, and withdrawal syndrome in two groups of patients was recorded and overall incidence rate was calculated.

### Statistical analysis

Data were analyzed with SPSS 22.0 software. Measurement data were represented as mean ± standard deviation (SD) and *t*-test was used for comparisons. Enumeration data were represented as percentages and analyzed using chi-square test. $P < 0.05$ was considered statistically significant.

## RESULTS

### Baseline information

No significant differences in baseline characteristics, including age, gender, ARDS severity, and primary diseases between study and control groups (*p > 0.05*; Table 1).

### Mechanical ventilation and ICU-related parameters

Mechanical ventilation and ICU-associated information of patients subjected to different intervention measures in two groups were compared. Mechanical ventilation duration and ICU stay in study group were significantly shorter ($p < 0.05$), and ICU mortality rate, ICUAW incidence, VILI incidence, and man-machine counteraction incidence were significantly reduced ($p < 0.05$; Table 2).

**Table 1:** Comparison of baseline information between the two groups (n = 47)

| Group | Gender (case) | | Age (years) | Severity grading (case) | | Primary disease (cases) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | | Moderate | Severe | Pneumonia | Sepsis | ASP | Trauma |
| **Study** | 29 | 18 | 53.16±2.38 | 35 | 12 | 25 | 13 | 4 | 5 |
| **Control** | 31 | 16 | 53.02±2.57 | 39 | 8 | 27 | 11 | 6 | 3 |
| *T-value* | 0.184 | | 0.274 | 1.016 | | 1.144 | | | |
| *P*-value | 0.668 | | 0.785 | 0.313 | | 0.2767 | | | |

**Table 2:** Comparison of mechanical ventilation and ICU-correlated parameters between the two groups (n = 47)

| Group | Mechanical ventilation (days) | ICU stay (days) | ICU mortality n (%) | ICUAW incidence n (%) | VILI incidence n (%) | Man-machine counteraction incidence n (%) |
|---|---|---|---|---|---|---|
| Study | 4.68±0.82 | 6.03±0.53 | 5 (10.64) | 2 (4.26) | 3 (6.38) | 1 (2.13) |
| Control | 6.15±0.94 | 7.49±0.68 | 13 (27.66) | 9 (19.15) | 11 (23.40) | 6 (12.77) |
| *T*-value | 8.079 | 11.610 | 4.398 | 5.045 | 5.371 | 3.859 |
| *P*-value | <0.001 | <0.001 | 0.036 | 0.025 | 0.020 | 0.049 |

**Table 3:** Comparison of blood gas indicators in the two groups before and after treatment

| Group | $PaO_2$ (mmHg) | | $PaCO_2$ (mmHg) | | $SaO_2$ (%) | |
|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Study | 53.12±4.48 | 86.41±7.83* | 44.05±5.18 | 36.87±4.25* | 83.33±6.48 | 96.59±10.14* |
| Control | 53.55±4.76 | 71.69±9.01* | 44.11±5.32 | 41.28±5.13* | 82.70±6.91 | 89.67±9.33* |
| *T* | 0.451 | 8.454 | 0.055 | 4.538 | 0.456 | 3.443 |
| *P*-value | 0.653 | <0.001 | 0.956 | <0.001 | 0.650 | 0.001 |

*$P < 0.05$ compared to before treatment

## Blood gas indicators

Before treatment, there was no significant statistical difference in levels of $PaCO_2$, $PaO_2$, and $SaO_2$ between the study and control groups ($p > 0.05$). Subsequently, on treatment, both groups exhibited evident improvements in all indicators, with study group showing significant $PaO_2$ and $SaO_2$ levels and attenuated $PaCO_2$ levels compared with control group ($p < 0.05$; Table 3).

## Respiratory mechanics parameters

Comparisons of respiratory mechanics indicators, which include respiratory rate, peak airway pressure, airway occlusion pressure, and static lung compliance, were done prior to and subsequently on treatment in study and control groups. Before treatment, no statistically significant differences in respiratory rate, peak airway pressure, airway occlusion pressure, and static lung compliance were identified between two groups ($p > 0.05$). Following treatment, all parameters improved, with study group showing more significant improvement in respiratory rate and static lung compliance compared to control group ($p < 0.05$). There was no significant difference in improvement of peak airway pressure and airway occlusion pressure between study and control groups ($p > 0.05$).

**Table 4:** Comparison of respiratory mechanics indicators before and after treatment (n=47)

| Group | Respiratory rate (times/min) | | Peak airway pressure (cm, $H_2O$) | | Airway occlusion pressure (cm, $H_2O$) | | Static lung compliance (mL/cm, $H_2O$) | |
|---|---|---|---|---|---|---|---|---|
| | *Before treatment* | *After treatment* | *Before treatment* | *After treatment* | *Before treatment* | *After treatment* | *Before treatment* | *After treatment* |
| Study | 15.31±1.62 | 20.45±3.13* | 22.13±2.55 | 17.45±3.56* | 3.85±0.43 | 1.74±0.25* | 26.35±3.72 | 37.76±4.18* |
| Control | 15.29±1.71 | 18.78±2.25* | 23.09±2.87 | 18.89±3.81* | 3.81±0.49 | 1.83±0.21* | 25.98±3.49 | 31.12±3.85* |
| *T-value* | 0.058 | 2.970 | 1.714 | 1.893 | 0.421 | 1.890 | 0.497 | 8.010 |
| *P*-value | 0.954 | 0.004 | 0.090 | 0.062 | 0.675 | 0.062 | 0.620 | < 0.001 |

*$P < 0.05$ compared to before treatment

### APACHE II and cardiovascular SOFA scores

Here, APACHE II score and cardiovascular SOFA score of two groups undergoing different regimens were subjected to comparison prior to and following treatment. Results revealed that there was no significant difference in APACHE II score and cardiovascular SOFA score between two groups prior to treatment ($p > 0.05$). Following treatment, study group displayed notably lower APACHE II scores and cardiovascular SOFA scores compared to control group ($p < 0.05$; Table 5).

### Prognosis between two groups

In study group, 5 out of 47 ICU patients who died were excluded, leaving 42 survivors, while in control group, 13 out of 47 ICU patients who died were excluded, leaving 34 survivors. No significant differences in mortality rates between study and control groups at 3, 6, and 12 months following treatment ($p > 0.05$). Total mortality rate in study group was 11.90 %, significantly less than 32.35 % observed in control group ($p < 0.05$; Table 6).

### Incidence of adverse events

Study group had a significantly higher total occurrence of adverse events (23.4 %)

compared to control group, which had an incidence of 12.77 %, ($p < 0.05$). Also, there was no statistical difference in total occurrence of unfavorable incidents between two groups ($p > 0.05$; Table 7).

## DISCUSSION

Acute respiratory distress syndrome is a severe medical condition stemming from a range of factors, its clinical characteristics encompass progressive respiratory distress, refractory hypoxemia, and diffuse pulmonary parenchymal injury [11]. Once diagnosed with ARDS, patients received endotracheal intubation-assisted mechanical ventilation therapy as soon as possible to mitigate symptoms like breathing difficulties. Mechanical ventilation boasts excellent effects on enhancing patient ventilation conditions, but in some patients, shallow and rapid spontaneous breathing may increase work of breathing and oxygen consumption when they do not have conditions for weaning, and primary disease is poorly controlled [12], giving rise to environmental homeostasis imbalance and acid-base imbalance, which poses severe challenges in treatment [13]. For such patients, adjunct use of neuromuscular blocking agents may bring about better clinical benefits.

**Table 5:** Comparison of APACHEII score and cardiovascular SOFA score before and after treatment (n=47)

| Group | APACHEII score | | SOFA score | |
|---|---|---|---|---|
| | *Before treatment* | *After treatment* | *Before treatment* | *After treatment* |
| Study | 21.63±3.18 | 13.04±1.11* | 11.45±2.02 | 6.71±0.72* |
| Control | 21.59±3.22 | 16.77±1.28* | 11.52±2.13 | 9.23±0.84* |
| *T-value* | 0.061 | 15.093 | 0.163 | 15.616 |
| *P*-value | 0.952 | < 0.001 | 0.871 | < 0.001 |

*$P < 0.05$ compared with before treatment

**Table 6:** Comparison of prognosis

| Group | n | 3 months after treatment n (%) | 6 months after treatment n (%) | 12 months after treatment n (%) | Total mortality n (%) |
|---|---|---|---|---|---|
| Study | 42 | 3(7.14) | 2(4.76) | 0(0) | 5(11.90) |
| Control | 34 | 5(14.71) | 4(11.76) | 2(5.88) | 11(32.35) |
| $\chi^2$ | | 1.141 | 1.267 | 2.537 | 4.727 |
| *P*-value | | 0.285 | 0.260 | 0.111 | 0.030 |

**Table 7:** Comparison of incidence of adverse events

| Group | Rash | Hypotension | Arrhythmia | Delirium | Ventilator-associated pneumonia | Pneumothorax | Withdrawal syndrome | Total incidence |
|---|---|---|---|---|---|---|---|---|
| Study | 2(4.26) | 3(6.38) | 1(2.13) | 1(2.13) | 2(4.26) | 1(2.13) | 1(2.13) | 11(23.40) |
| Control | 0 (0) | 1(2.13) | 2(4.26) | 1(2.13) | 1(2.13) | 1(2.13) | 0 (0) | 6(12.77) |
| $\chi^2$ | | | | | | | | 1.795 |
| *P*-value | | | | | | | | 0.180 |

Values are presented as n (%)

Here, the intervention was carried out on patients with ARDS and admitted to the hospital, and subjected to mechanical ventilation and clinical outcomes of study and control groups were compared. It was discovered that study group exhibited significantly shorter mechanical ventilation time and ICU stay, lower ICU mortality rate and incidence rates of ICUAW, VILI, and man-machine counteraction, as well as lower APACHEII and cardiovascular SOFA scores compared to control group ($p < 0.05$). Furthermore, cisatracurium dramatically alleviates severity of ARDS in ICU patients. These outcomes suggest that delivery of cisatracurium effectively boosts recovery of ARDS patients and abates ICU mortality, ICUAW, VILI, and man-machine counteraction incidence rates.

These findings suggested that administration of cisatracurium in conjunction with mechanical ventilation improved health status of ARDS patients and optimized prognosis. Superior muscle relaxation ability of cisatracurium, which is 50 % higher than that of atracurium [14], may explain its efficacy. This approach protects patient's ability to breathe spontaneously and prevents occurrence of ICUAW, VILI, and man-machine counteraction that may result from use of high doses of neuromuscular blocking drugs [15]. This intervention facilitates patient recovery, thereby shortening duration of mechanical ventilation, ICU stay, and reduces ICU mortality.

This study revealed that combination of a placebo and neuromuscular blocking agent, cisatracurium after mechanical ventilation, efficaciously restored blood gas and respiratory mechanics indicators of ARDS patients. However, study group had significantly higher $PaO_2$ and $SaO_2$ levels, lower $PaCO_2$ levels, higher respiratory frequency, and better static lung compliance compared to control group. These findings revealed that cisatracurium ameliorated hypotonic hypoxemia compared to placebo and guarded pulmonary function in ARDS patients. As a short- and fast-acting muscle relaxant, cisatracurium is metabolized via Hoffman pathway within the body, rather than being dependent on organs such as liver or kidneys [16]. Thus, following cisatracurium treatment, ARDS patients displayed significantly higher $PaO_2$, $SaO_2$, respiratory frequency, and static lung compliance than placebo group, whereas level of $PaCO_2$ was significantly compared to placebo group.

In this research, mortality rate at 3, 6, and 12 months after treatment with different methods was also computed and compared between study and control groups. Results revealed that there was no significant difference in mortality rate between study and control groups after treatment, but the overall mortality rate in study group was lower than control group. Incidence of adverse events barely differed between two groups, which is similar to findings by Moss *et al* [17]. This demonstrated that use of cisatracurium did not augment incidence of adverse events in patients with ARDS, indicating safety and reliability. From these findings, cisatracurium not only achieved better clinical efficacy but also showed better short-term prognosis in treatment of ARDS patients undergoing mechanical ventilation. It also reduced mortality rate within a year without dramatically augmenting incidence of adverse events. This further validates finding that cisatracurium is a rapid, effective, and safe treatment option for ARDS patients, and this is worthy of clinical reference as it helps patients achieve early recovery.

**Limitations of this study**

They include a small sample size, single-center, lack of long-term observation and no comparison with other treatments. Future research should increase sample size, use a multi-center randomized design, consider regional/environmental differences, and compare treatments for reliability.

## CONCLUSION

Cisatracurium in ARDS treatment reduces mechanical ventilation and ICU stay, lowers ICUAW, VILI, man-machine counteraction, and mortality rate, enhances blood gas, and respiratory mechanics indices, eliminates hypotonic hypoxemia, and protects lung function. Increased sample size in a multi-centered randomized design with regional/environmental differences will be required to verify the claims of this research.

## DECLARATIONS

*Ethical approval*

The Ethics Committee of the The Third People's Hospital of Honghe Hani approved this study

(approval no. 2023-HHZSYIEC-16).

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yanping Li and Jiping Li contributed equally to this work.

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