

# Observations on the Use of Different Modes of Cisatracurium Administration in Hyperthermic Intraperitoneal Chemotherapy

Jing Zhang

Capital Medical University Affiliated Beijing Shijitan Hospital

Danyang Gao

Capital Medical University Affiliated Beijing Shijitan Hospital <https://orcid.org/0000-0002-8491-5376>

Pengfei Liu

Capital Medical University Affiliated Beijing Shijitan Hospital

Tianzuo Li (✉ [litz@bjsjth.cn](mailto:litz@bjsjth.cn))

Capital Medical University Affiliated Beijing Shijitan Hospital

---

## Research Article

**Keywords:** Cis-atracurium, Intraperitoneal hyperperfusion chemotherapy (HIPEC), Anesthesia, Residual muscle relaxation

**Posted Date:** April 12th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-392323/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Objective:** To investigate the residual effects of cis-atracurium with different administrations in patients with hyperthermic intraperitoneal chemotherapy.

**Methods:** 60 patients undergoing hyperthermic intraperitoneal chemotherapy were randomly divided into two groups with 30 cases in each group. All patients were induced with sufentanil 0.4ug/kg, propofol 2.0mg/kg and cis atracurium 0.2mg/kg. During the operation, sevoflurane and remifentanil were used to maintain anesthesia. BIS value was 45-55. The control group intermittently received cis-atracurium injection with 0.1mg/kg/h. The experimental group received continuous injection of cis-atracurium at a rate of 1.5ug/kg/min. Cis-atracurium was discontinued 30min before the end of the operation, sevoflurane inhalation was stopped 20min before the end of the surgery and remifentanil was discontinued 10min before the end. At the end of the operation, no muscle relaxant antagonism were applied. General information of patients was recorded. Mean arterial pressure (MAP), heart rate (HR), tidal volume (VT), respiratory rate (F), and blood oxygen saturation (SpO<sub>2</sub>) were recorded before anesthesia (T1) , at the time of tracheal catheter extraction (T2). Besides, the total amount of cis-atracurium, the time of recovery of spontaneous tidal volume to 6ml/kg (t1), the time of continuous lifting of the head for 5 s (t2), and the time from the withdrawal of muscle relaxant to the removal of the tracheal catheter (t3) were recorded. Blood gas analysis was also performed to record PaO<sub>2</sub> and PaCO<sub>2</sub> before anesthesia, when leaving the operating room and SICU. Moreover, relevant adverse reactions were recorded.

**Results:** 1) general situation: there was no difference in body weight, operation time, ASA classification and other indicators between the two groups ( $P>0.05$ ). 2) comparison of residual effects of muscle relaxants: the values of t1, t2 and t3 in the experimental group were significantly shorter than those in the control group ( $P<0.05$ ). There was no significant difference between the two groups in PaO<sub>2</sub> and PaCO<sub>2</sub> before anaesthesia, when out of the operating room and when out of SICU ( $P>0.05$ ). 3) hemodynamic comparison: there were no statistically significant differences in mean arterial pressure, heart rate, tidal volume, respiratory rate and blood oxygen saturation between the two groups at time points T1 and T2 ( $P>0.05$ ). 4) comparison of adverse events: no adverse events occurred in either group.

**Conclusion:** Compared with intermittent infusion, continuous infusion of cis-atracurium did not result in significant residual muscle relaxation and no significant histamine release. Therefore, continuous infusion is more suitable for long-term surgery.

## Background

Good muscle relaxation is an important part of general anesthesia. This can ensure a smooth tracheal intubation and provide good conditions for surgical operation, maintaining smooth anesthesia and an uneventful operation. Therefore, muscle relaxation mainly relies on neuromuscular blocking drugs to achieve these <sup>[1]</sup>. At present, there are various types of muscle relaxants available, including depolarizing and non-depolarizing muscle relaxants. Non-depolarizing myorelaxants include rocuronium bromide, vecuronium bromide, atracurium, and cisatracurium. Among them, cisatracurium, without the histamine-

releasing effect of atracurium, is mainly hydrolyzed by esterases, degraded by Hofmann elimination, and is not affected by liver or kidney function or age<sup>[2]</sup>. Thus, it is more commonly used in clinical practice. In addition, hyperthermic intraperitoneal chemotherapy (HIPEC) is the primary treatment modality for patients with peritoneal carcinoma<sup>[3]</sup>. Most patients with peritoneal cancer have advanced tumors and infiltrated abdominal tumor implantation. Thus, the surgery is difficult and prolonged. In addition, HIPEC results in redistribution of body fluids and changes in the internal environment and body temperature. Thus, theoretically, it affects the metabolism of muscle relaxants (myorelaxants). Therefore, our study aims to investigate the effects of two relative common modes of cisatracurium administration in HIPEC.

## Materials And Methods

### 1.1 General information

Sixty patients with peritoneal cancer who underwent HIPEC from June 2018 to June 2019 were selected and randomly divided into two groups of 30 patients each. One group was the control group, with intermittent intravenous administration of cisatracurium, and the other group was the experimental group, with continuous administration of cisatracurium. Inclusion criteria were as follows: ASA classification I–III, age 18–65 years, and signed informed consent form and agreement to be included in this study. Exclusion criteria were as follows: 1) presence of significant preoperative cardiopulmonary, hepatic, and renal insufficiency (including cardiac NYHA class II or higher, respiratory failure, Child-Pugh liver function class B or higher, and chronic renal insufficiency or ongoing dialysis); 2) presence of neuromuscular disorders; 3) presence of allergy to muscarinic drugs; and 4) recent use of drugs that affect neuromuscular conduction (including anticonvulsants, digitalis, diuretics, aminoglycoside antibiotics, and corticosteroids). The study was approved by the Ethics Committee of Beijing Shijitan Hospital, and all patients signed an informed consent form before the study.

### 1.2 Methods

All patients were routinely fasted from food and water before the surgery. After admission to the operating room, intravenous access was initiated, fluids were instituted, and ECG, invasive arterial pressure, oxygen saturation, and electroencephalographic bifrequency index (BIS) were monitored. Anesthesia was induced sequentially with sufentanil 0.4 ug/kg, propofol 2.0 mg/kg, and cisatracurium 0.2 mg/kg (for four-time 95% effective dose [ED], cisatracurium's ED 95% was 0.05 mg/kg). After induction of anesthesia, the patient underwent tracheal intubation and was mechanically ventilated, and EtCO<sub>2</sub> was maintained intraoperatively between 35 and 45 mmHg. Intravenous-inhalation combined anesthesia was chosen for the maintenance of anesthesia. Intraoperatively, sevoflurane inhalation anesthesia was administered with the concentration of volatilization pot output at 1.8–3% and the concentration of 1.8 L/min inhaled oxygen at 50%. Remifentanil was injected continuously at a rate of 0.1–0.2ug/kg/min. A BIS value of 45–55 was maintained. Cisatracurium was added at a rate of 0.1 mg/kg/h intermittently in the control group according to the commonly used clinical dose. Cisatracurium was pumped continuously at a rate of 1.5 ug/kg/min in the experimental group. Cisatracurium was discontinued 30 min before the end of surgery.

Sevoflurane inhalation was discontinued 20 min before the end of surgery. Remifentanyl was discontinued 10 min before the end of surgery. Sufentanil was added at 0.1 ug/kg. The maintenance dose of anesthetics was adjusted at any time during surgery according to the progress of surgery, changes in depth of anesthesia, and changes in hemodynamic indices.

At the end of the procedure, no muscarinic antagonist was administered. The patient was observed for recovery of muscle relaxation. After the patient regained consciousness and reached the tracheal extubation indication, the patient was extubated after the secretions were sufficiently aspirated in the oral cavity and trachea. Indications for extubation were as follows [25,26]: ☐ the patient was conscious and could respond to the call; ☐ cough and swallowing reflexes and muscle strength were restored, and the patient could keep the head raised for 5 s; ☐ spontaneous breathing was restored, tidal volume reached 6 mL/kg, and regular respiratory rhythm was 12–20 cycles/min; and ☐ oxygen saturation (SpO<sub>2</sub>) is > 97% 5 min after discontinuation of oxygen. The patients were sent to the postoperative ICU recovery unit (SICU) for continued observation after the vital signs stabilized.

### **1.3 Observational indicators**

**1.3.1** General information of the patients, including gender, age, body mass index, ASA classification, and duration of anesthesia (min) and operation (min) were recorded. Intraoperative fluid rehydration and urine volume were recorded.

**1.3.2** Patients' vital signs (mean arterial pressure [MAP], heart rate [HR]) and respiratory indices (tidal volume [VT], respiratory rate [F], and SpO<sub>2</sub>) were recorded before anesthesia (T<sub>1</sub>) and at the time of tracheal tube removal (T<sub>2</sub>).

**1.3.3** Total dosage of cisatracurium, time to return to 6 mL/kg of tidal volume for spontaneous breathing (t<sub>1</sub>), time to the ability to hold the head up for 5 s (t<sub>2</sub>), and time from the discontinuation of the inotropes to the removal of the tracheal tube (t<sub>3</sub>) were recorded. Arterial blood gases without oxygen were analyzed using a Gem Premier 3000 blood gas analyzer (IL, USA), and arterial partial pressure of oxygen (PaO<sub>2</sub>) and partial pressure of carbon dioxide (PaCO<sub>2</sub>) were measured before anesthesia, at the time of exit from the operating room, and at the time of transfer from SICU for the assessment of respiratory function.

**1.3.4** For the recording of adverse reactions, patients were observed for adverse events such as skin rash, laryngospasm, bronchospasm, presence of cardiac arrhythmias, and intraoperative hypotension after intravenous cisatracurium injection. Postoperative follow-up was performed to assess whether the patient had intraoperative knowledge.

### **1.4 Statistical methods**

SPSS 19.0 software was used for analysis. Normally distributed data were recorded as mean ± standard deviation, and independent samples t-test was used to compare the normally distributed data of the two groups, while chi-square test was used to compare the count data. P values <0.05 indicated statistical significance.

# Results

## 2.1 General information

The differences between the two groups in terms of age, gender, ASA classification, body mass index, duration of surgery, infusion volume, and urine volume were not statistically significant ( $P > 0.05$ ) and were comparable.

Table 1  
Comparison of basic information between the two groups of patients

Groups N = 30	Age (years)	Sex M/F	Body mass index (kg/m <sup>2</sup> )	ASA classification I/II/III	Surgery time (h)	Intravenous dose of fluid (mL)	Urine output (mL)
Control subjects	47.5 ± 5.8	19/11	23.8 ± 3.9	5/21/4	10.1 ± 2.5	6758 ± 234	826 ± 58
Experimental group	45.9 ± 4.6	16/14	24.4 ± 4.5	7/18/5	9.8 ± 3.2	6428 ± 275	797 ± 68

<sup>a</sup>: statistically significant difference compared to the control group ( $p < 0.05$ )

## 2.2 Comparison of muscle relaxation effects and residual effects between the two groups

Statistical analysis revealed that time to return to 6 mL/kg of tidal volume for spontaneous breathing (t1), time to be able to hold the head up for 5 s (t2), and time from the discontinuation of inotropic drugs to the removal of the tracheal tube (t3) were significantly shorter in the experimental group than in the control group, with statistically significant differences ( $P < 0.05$ ). In contrast, there was no significant difference in PaO<sub>2</sub> and PaCO<sub>2</sub> between the two groups before anesthesia, at the time of exit from the operating room, or at the time of exit from the SICU ( $P > 0.05$ ).

Table 2  
Comparison of muscle relaxation outcomes between the two groups

Groups	N	t1 (min)	t2 (min)	t3 (min)	Cisatracurium amount (mg)
Control subjects	30	39.6 ± 7.8	59.3 ± 9.4	83.4 ± 12.7	64.6 ± 7.5
Experimental group	30	25.4 ± 6.3 <sup>a</sup>	39.8 ± 7.5 <sup>a</sup>	62.1 ± 10.2 <sup>a</sup>	51.8 ± 6.8 <sup>a</sup>

t1: time to recovery of spontaneous respiratory tidal volume to 6 mL/kg; t2: time to the ability to sustain head elevation for 5 s; t3: time from inotropic drug discontinuation to patient's tracheal extubation. <sup>a</sup>: statistically significant difference compared to control group ( $P < 0.05$ ).

Table 3  
Comparison of blood gas results between the two groups of patients

Times	Groups	Pre-anesthesia	At exit from operating room	At exit from SICU
PaO <sub>2</sub> (mmHg)	Control subjects	92.4 ± 6.2	88.6 ± 4.8	90.5 ± 4.7
	Experimental group	91.5 ± 5.3	89.7 ± 4.5 <sup>a</sup>	91.2 ± 5.0
PaCO <sub>2</sub> (mmHg)	Control subjects	39.2 ± 2.8	41.6 ± 4.1	40.6 ± 4.6
	Experimental group	40.0 ± 2.3	41.1 ± 3.9 <sup>a</sup>	40.5 ± 5.0

<sup>a</sup>: statistically significant difference compared to the control group (p < 0.05).

### 2.3 Comparison of patients' hemodynamic indices

A comparison of the hemodynamic parameters between the two groups showed that there was no statistically significant difference in the mean arterial pressure, heart rate, tidal volume, respiratory rate, or oxygen saturation at T1 and T2 time points (P > 0.05).

Table 4  
Comparison of patients' hemodynamic indices

Groups	N	T1		T2	
		Control group	Experimental group	Control group	Experimental group
MAP (mmHg)	30	82.1 ± 13.1	80.3 ± 12.9	87.4 ± 13.7	86.3 ± 14.4
HR (times/min)	30	75.3 ± 13.8	76.9 ± 14.5	84.2 ± 13.5	85.6 ± 15.2
VT (mL)	30	536.5 ± 47.5	521.2 ± 50.1	484.3 ± 50.8	495.6 ± 45.1
F (times/min)	30	12.6 ± 2.7	13.1 ± 1.9	15.2 ± 3.2	14.7 ± 2.8
SpO <sub>2</sub> (%)	30	97.8 ± 2.3	98.4 ± 1.6	95.4 ± 3.7	96.4 ± 3.8

T1: before anesthesia; T2: at tracheal extubation; <sup>a</sup>: statistically significant difference compared with control group (P < 0.05)

### 2.4 Comparison of patient adverse events

There were no intraoperative adverse events in either group.

Table 5  
Comparison of intraoperative adverse events between the two groups of patients

Groups	Rash	Laryngospasm	Bronchospasm	Arrhythmia	Low blood pressure	Intraoperative knowledge
Control group	0	0	0	0	0	0
Experimental group	0	0	0	0	0	0

## Discussion

Sedation, analgesia, and myorelaxation constitute the three elements of general anesthesia. Among them, a good muscle relaxation effect is an important guarantee for a successful operation. Moreover, cisatracurium is a relatively more commonly used non-depolarizing myorelaxant in clinical practice. Compared with other non-depolarizing myorelaxants, such as rocuronium and vecuronium, cisatracurium is stable, is mainly degraded by Hofmann elimination, has no significant accumulation effect, and is less affected by liver and kidney function and age<sup>[2, 4]</sup>. Thus, it theoretically has some advantages for application in prolonged surgery. However, HIPEC has its special characteristics as follows: 1) it is complicated, has a long operation time, and requires prolonged anesthesia to maintain drug administration, which prolongs the half-life of continuous drug infusion; 2) the procedure has extensive trauma exposure and significant intraoperative fluid loss, while HIPEC leads to intestinal dilation, fluid redistribution, and accumulation in the third interstitial space, which affects the apparent distribution of drugs; 3) with HIPEC, the patient's body temperature, metabolic rate, and acidic metabolites all increase, which affect the metabolism of the drug<sup>[5-7]</sup>. Thus, exploring the muscle relaxation effects of different modes of administration of muscle relaxants in this type of surgery and their muscle relaxation residual effects is of great clinical significance to guide the application of muscle relaxants in HIPEC.

The study compared the effects of two different modes of cisatracurium administration on the muscle relaxation effect: intermittent administration and continuous pumping. In the traditional intermittent dosing method, a larger dose is usually administered followed by an additional dose based on clinical experience, theoretical half-life of the drug, intraoperative changes in the patient's airway pressure, presence or absence of body movements, and subjective perception of the surgeon. This mode of administration causes an intermittent and abrupt increase in cisatracurium blood concentration and rapid binding to muscarinic receptors to saturation<sup>[8]</sup>; on the other hand, muscarinic clearance per unit time is accelerated. This mode of administration may thus result in large fluctuations in blood concentration, unstable myorelaxation, and difficulty in estimation of myorelaxation recovery time<sup>[9]</sup>. The other mode of administration is continuous pumping, which can maintain a relatively constant blood concentration, easily control the myorelaxation effect and recovery time, and reduce the occurrence of myorelaxation residuals<sup>[10]</sup>. In this study, the intraoperative cisatracurium dosage was significantly less in the continuous pumping patients than in the intermittent dosing group, and time to recovery of muscle

strength, time to return to normal respiration, and time to extubation of the tracheal tube were all significantly shorter in the continuous pumping group than in the intermittent dosing group, with statistically significant differences. It is suggested that in the intermittent dosing group, whose infusion half-life was prolonged and more difficult to estimate, patients still had a degree of residual muscle relaxation and prolonged extubation time after surgery. In contrast, in the continuous infusion group, the blood drug concentration was relatively stable and there was no significant drug accumulation.

The head-up 5-s test was chosen in the study as the main index to determine the delayed effect of muscle relaxation. Previous reports have mostly used a four-string response ratio ( $\text{TOFR} = \text{T4/T1}$ )  $> 0.7$  as a criterion for neuromuscular recovery [11–12]. Although  $\text{TOFR} = 0.7$  was chosen as an indicator for the termination of muscle relaxation effects in clinical practice, some studies found that even when  $\text{TOFR} = 0.7$ , some patients still had paralysis of the pharyngeal and upper respiratory muscles, weakness in fist clenching, and inability to bite against the upper and lower incisors, which increased the risk of postoperative pulmonary complications [13–14]. In contrast, raising the head for 5 s not only suggests that the patient's respiratory function has largely recovered, but also shows that the patient's airway protection function has recovered, which in turn reduces the risk of aspiration and airway obstruction [15–16]. In the present study, we found that the time from the end of the procedure to head elevation lasting 5 s was significantly shorter in patients in the continuous infusion cisatracurium group, in contrast to some previous studies, which reported that the duration of muscle relaxation effect was significantly longer after continuous infusion of cisatracurium than after intermittently administration. This may be related to the concentration and rate of continuous infusion, the patient's underlying condition, and the type of surgical approach.

In addition, the study also investigated the presence or absence of the histamine-releasing effects of cisatracurium. The comparison revealed no significant changes in the mean arterial pressure or heart rate in patients before and after surgery, while none of the patients in either group experienced adverse events such as rash, flushing, laryngospasm, or bronchospasm during general anesthesia. It was confirmed that prolonged application of cisatracurium, without significant histamine-releasing effects, was safe and effective with continuous infusion.

In conclusion, the duration of muscle relaxation effect is significantly longer after intermittent administration than after continuous infusion of cisatracurium. Thus, continuous infusion is more suitable for prolonged surgery. In addition, there are some shortcomings in this study. The most notable one was the absence of myorelaxation monitor-related indicators, which will be subsequently combined with TOF values to comprehensively assess the pharmacodynamic changes in terms of subjective clinical indicators and objective indicators of myorelaxation monitoring.

## Declarations

### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

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

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

Not applicable.

### **Authors' contributions**

All authors contributed to the completion of this study. JZ and PL collected the patients' data. JZ, DG and PL analyzed the data and wrote the manuscript. TL contributed to the study design. All authors read and approved the final manuscript.

### **Acknowledgements**

Not applicable.

## **References**

1. Wen DX, Ouyang BY, et al. Muscle relaxants[M]. Beijing: People's Medical Publishing House,2007,59-60.
2. Kisor DF, Schmith VD. Clinical Pharmacokinetics of cisatracurium besilate[J]. Clin Pharmacokinet,1999,36(1):27-40.
3. Topgül K, Çetinkaya MB, Çiğdem Arslan N, et al. Cytoreductive surgery (SRC) and hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of peritoneal carcinomatosis: Our initial experience and technical details[J]. Ulus Cerrahi Derg,2015,31(3):138-47.
4. Zheng FK, Cheng ZG. Comparison of Mivacurium and Cisatracurium for Muscle Relaxing Action in Laparoscopic Cholecystectomy [J]. Medical Recapitulate,2015,21(22):4171-4172.
5. Khoronenko VE, Shemetova MM, Drozhzhina OV, et al. Anaesthesia and intensive care during intraoperative intraperitoneal hyperthermic chemotherapy in patients with gastric cancer (literature

- review and own clinical experience)[J]. *Anesteziol Reanimatol*,2015,60(1):50-4.
6. Yang ZM, Zheng XL, Liang HS, et al. The effect of continuous hyperthermic peritoneal perfusion in patients with pseudomyxoma peritoneal on respiratory function, hemodynamics and metabolism parameters[J]. *Beijing Medical Journal*,2014,36(8):639-642.
  7. Meinhold-Heerlein I, Fotopoulou C, Harter P, et al. Statement by the Kommission Ovar of the AGO: The New FIGO and WHO Classifications of Ovarian, Fallopian Tube and Primary Peritoneal Cancer[J]. *Geburtshilfe Frauenheilkd*, 2015,75(10):1021-1027.
  8. Li J, Zhang QG, Liu ZJ, et al. Comparison pharmacodynamics of continuous or intermittent cisatracurium infusion during laparoscopy for deep neuromuscular blockade [J]. *Journal of Clinical Anesthesiology*,2016,32(4):321-324.
  9. Cammu G, Boussemaere V, Foubert L, et al. Large bolus dose vs. continuous infusion of cisatracurium during hypothermic cardiopulmonary bypass surgery[J]. *Eur J Anaesthesiol*,2005. 22(1):25-29.
  10. Guo J, Yuan X, Zhou X, et al. Pharmacokinetics and pharmacodynamics of cisatracurium in patients undergoing surgery with two hemodilution methods[J]. *J Clin Anesth*, 2017,38:75-80.
  11. Kirmeier E, Eriksson LI, Lewald H, et al. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study [J]. *Lancet Respir Med*,2019,7(2):129-40.
  12. Rudolph MI, Chitilian HV, Ng PY, et al. Implementation of a new strategy to improve the peri-operative management of neuromuscular blockade and its effects on postoperative pulmonary complications[J]. *Anaesthesia*,2018,73(9):1067-1078.
  13. Viby-Mogensen J, Claudius C, Eriksson LI. Neuromuscular monitoring and postoperative residual curarization[J],*Br J Anaesth*. 2007,99(2):297.
  14. Feltracco P, Tonetti T, Barbieri S, et al. Cisatracurium- and rocuronium-associated residual neuromuscular dysfunction under intraoperative neuromuscular monitoring and postoperative neostigmine reversal: a single-blind randomized trial[J]. *J Clin Anesth*,2016,35:198-204.
  15. Aytac I, Postaci A, Aytac B, et al. Survey of postoperative residual curarization, acute respiratory events and approach of anesthesiologists[J]. *Braz J Anesthesiol*,2016,66(1):55-62.
  16. Hayes AH, Mirakhur RK, Breslin DS, et al. Postoperative residual block after intermediate-acting neuromuscular blocking drugs[J]. *Anaesthesia*,2001,56(4):312-8.