Effect of SIRS, Sepsis and Chemotherapy on Rocuronium Muscle Relaxation: A Case Series and Literature Review

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Case Report

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Abstract

Background

Studies have shown that systemic inflammatory response syndrome (SIRS), sepsis and chemotherapy can attenuate the muscle relaxing effect of rocuronium, prolong the onset of muscle relaxation as well as shorten the maintenance and recovery time. However, there are few reports on this phenomenon.

Case presentation

Case 1 was a 47-year-old Chinese male with gastric remnant cancer, who had a sudden onset of abdominal pains after SOX chemotherapy, and underwent an emergency abdominal CT suggesting gastrointestinal perforation. An emergency abdominal exploratory surgery was performed, after which the intraoperative recovery of spontaneous breathing and abdominal muscle tension occurred several times. Case 2 was a 71-year-old Chinese male who underwent an emergency borehole drainage for a sudden cerebral hemorrhage. His intraoperative mechanical ventilation mode showed multiple respiratory waveform changes, which were considered as the recovery of spontaneous breathing. Case 3 was a 43-year-old Chinese female diagnosed with breast cancer, who underwent a radical elective breast cancer surgery after a chemotherapy through the AC-T regimen. Intraoperatively, a significant muscle fibrillation was developed during lymph node dissection.

Conclusion

Systemic inflammatory response syndrome (SIRS), sepsis and chemotherapeutic factors could be associated with a poor effect of intraoperative rocuronium muscle relaxation, whose specific mechanisms need to be further clarified.

Background

Rocuronium is one of the non-depolarized muscle relaxants (NDMRs) commonly used in general anesthesia, which exerts muscle relaxation by competitively binding to acetylcholine receptors (AChR) on the endplate membrane at neuromuscular junctions and antagonizing acetylcholine (ACh). It is characterized by a rapid onset, dose-based durations, no side effects, no active metabolites or toxins, and hepatic clearance. Factors that may affect the pharmacokinetics and pharmacodynamics of rocuronium and its mechanism of action have been reported in previous studies, such as gender, age, obesity, hypothermia, hepatic and renal insufficiency as well as inhaled anesthetics.\textsuperscript{[1–8]} It has also been shown that systemic inflammatory response syndrome (SIRS), sepsis and chemotherapy can attenuate the muscle relaxing effect of rocuronium, prolong the onset of muscle relaxation as well as shorten the maintenance and recovery time.\textsuperscript{[11,23,24]} However, studies on its related mechanisms are rarely
mentioned. Inspired by the following case series (Table 1), the mechanism of the effect of SIRS, sepsis and chemotherapy on rocuronium muscle relaxation will be reviewed and discussed in this article.

Case Presentation

Case 1

1. Medical History Summary

The patient was a Chinese male aged 47, with a height of 170cm, a weight of 54kg and an ASA physical status of Level 1. He was admitted to the hospital with an abdominal discomfort for 1 month as the main reason, and was diagnosed to have a gastric remnant cancer. The patient underwent "radical total gastrectomy, vagus nerve dissection, laparoscopic exploration and abdominal drainage as well as irrigation", together with 3 courses of SOX chemotherapy (oxaliplatin + tegeo) 2 years ago. The abdominal discomfort appeared almost one month ago without any obvious cause. Since the onset of the disease, he had poor diets and sleep, but had not lost any significant weight. The patient had a history of hypertension for 5 years, who had not been taking antihypertensive drugs regularly, but had a moderate blood pressure control. He denied the history of diabetes mellitus, coronary heart disease, food or drug allergy, hepatitis or tuberculosis and smoking or alcohol consumption.

After admission to the hospital for gastroscopy, abdominal CT, PET-CT and other related examinations, multiple metastases of gastric cancer were considered. The patient was treated with SOX chemotherapy regimen with an intravenous oxaliplatin infusion of 200mg, taking tegeo capsules orally 3 capsules/time, 2 times/day. On the second day after chemotherapy, the patient suddenly felt bloated with an urge to defecate after dinner, together with sudden severe abdominal pains after straining to defecate, which persisted without relief. Repeat emergency abdominal CTs suggested a gastrointestinal perforation. Therefore, "intestinal resection, enterostomy, intestinal perforation repair, abdominal adhesion release and abdominal flushing as well as drainage" were performed in the emergency. Preoperative blood gas analysis: PH: 7.458, PCO$_2$: 32.2mmHg, Hct: 32%, tHb: 10.8g/dL, Na$: 133.6mmol/L, K$: 4.61 mmol/L, Glu: 6.30 mmol/L, Lac: 2.21 mmol/L.

2. Anesthesia and Surgical Procedure

Admission to the operating room: The patient was admitted at a lateral recumbent position with significant abdominal pains, a heart rate of 120 beats/min, a blood pressure of 150/110 mmHg and SpO$_2$ of 97%. He was clearly conscious and had a painful face.

Induction and maintenance of anesthesia: 2mg of midazolam, 16mg of etomidate, 15ug of sufentanil and 30mg of rocuronium were given for the induction of anesthesia. 3min after induction, the BIS value was 40 and his eyelash reflex disappeared. After a rapid intravenous injection of 40ug of remifentanil and
3mg of propofol, a visual laryngoscopic tracheal intubation was performed. Vital signs were stable during intubation, with a heart rate of 90 beats/min and a blood pressure of 115/85 mmHg immediately after intubation. 0.37mg/kg.h of propofol and 0.0074mg/kg.h of remifentanil were pumped intravenously with 2% sevoflurane inhaled to maintain the BIS value at 40–50. 0.003mg/kg.h of norepinephrine was pumped to maintain the blood pressure at 20% of the basal value.

Intraoperative condition: After 20min of anesthesia induction, the ventilator indicated that the patient's spontaneous respiration was restored, with a respiratory rate of 12 breaths/min, a tidal volume of 300ml and a BIS value of 45. After confirming that there was no abnormality in the intravenous infusion route, 10mg of rocuronium was infused as a supplement dose. 2min later, there was no significant change in the spontaneous respiratory rate or tidal volume. 10mg of rocuronium was infused additionally, the spontaneous respiratory rate remained unchanged at 12 breaths/min and the tidal volume was reduced to 200ml. After another 2min of continuous observation, the ventilator indicated that his spontaneous breathing was still present. We replaced the former rocuronium with another ampoule of the latest production date, and another 10mg was infused. Meanwhile, manually-controlled ventilation and intermittent recruitment were performed and the ventilator mode was switched from VCV to PCV. The patient's spontaneous breathing disappeared and his respiratory waveform returned to normal under mechanical ventilation mode. No further recovery of the patient's spontaneous breathing had occurred. During this period, BIS value was maintained between 40 and 50 with a muscle relaxation detector applied. The results suggested that T1 was elevated by up to 20% at one time when the patient showed a recovery of spontaneous breathing. During the preparation for an abdominal closure, the operator indicated abdominal muscle tension, and three doses of additional 10mg of rocuronium was added at 2-min intervals until a good muscle relaxation was achieved. After the completion of peritoneal suturing, the anesthetic maintenance medication was reduced. 4mg of ondansetron was given intravenously, and all maintenance medication was discontinued at the start of skin sealing. Immediately after the operation, the patient’s breathing recovered, who opened his eyes naturally, could respond correctly to verbal commands, and had a tidal volume >350ml. The tracheal tube was removed only 25min after the last addition of rocuronium. The patient was well awakened and could respond spontaneously, who was transferred to the PACU for observation. The patient was questioned in the PACU and it was confirmed that he had no intraoperative awareness. 20min later, the patient returned to the ward.

Postoperative condition: After returning to the ward, a blood gas analysis was performed: PH: 7.315, PCO₂: 38mmHg, PO₂: 145.3mmHg, HCO₃⁻: 18.90mmol/l, Hct: 36%, tHb: 12.1g/dL, Na⁺: 134.7mmol/L, K⁺: 3.79 mmol/L, Glu: 7.5mmol/L, Lac: 1.94mmol/L. The patient presented a decrease in serum cholinesterase level to as low as 1541 U/L, a drop of leukocytes to 0.43×10⁹/L and a progressive decrease in platelets, together with anemia, recurrent fever and hypokalemia after a surgery, which were probably caused by chemotherapy, postoperative immune deficiency and severe infection. Symptomatic supportive treatments such as blood transfusion, platelet supplementation, leukocyte elevation, potassium supplementation and anti-infection were actively given. The patient was also given a thoracentesis and a drainage for bilateral pleural effusion. Half a month after the operation, the patient
was discharged after thoracic and abdominal drains were withdrawn, after which his condition was relatively stable and he could eat on his own.

Case 2

The patient was a Chinese male aged 71, with a height of 174cm, a weight of 70kg and an ASA physical status of Level . He was admitted to the hospital as an emergency patient with "cerebral hemorrhage" due to a sudden onset of confusion for 12h, accompanied by nausea and vomiting for 5 times, which were non-jetting and the stomach contents were mixed with blood. The diagnosis of "cerebral hemorrhage from the left basal ganglia region into the ventricles" was confirmed through a multi-row CT scan of the skull and brain, meanwhile "left stereotactic minimally-invasive borehole drainage and external ventricular drainage" were performed on an emergency basis. The patient's preoperative blood biochemistry, liver functions and other test results were not significantly abnormal, and leukocytes shown in his blood routine were 10.74×10^9/L with a neutrophil percentage of 0.9. On admission, he was in a deep coma, with a body temperature of 39°C, a heart rate of 120 beats/min, a respiration rate of 25–30 breaths/min and a blood pressure of 196/83 mmHg. The induction of anesthesia was given with 20mg of etomidate, 20ug of sufentanil and 40mg of rocuronium. Intravenous pumping of 0.43mg/kg.h propofol, 0.0057mg/kg.h remifentanil and the inhalation of 1% sevoflurane were used to maintain anesthesia. Intraoperatively, multiple respiratory waveform changes were observed in his mechanical ventilation mode, which was considered as the recovery of spontaneous breathing, and 20mg of rocuronium was added every 20min, but human-machine confrontation still occurred frequently. Muscle relaxation monitoring during this period showed that T1 was between 10% and 20%. As the patient was suspected to be insensitive to rocuronium, he was given 10mg of supplemented cisatracurium instead. The procedure ended 40min later and the patient's spontaneous breathing resumed. The patient was transferred to NSICU with tracheal intubation afterwards due to his advanced age and the fact that his consciousness had not recovered, who continued to be treated with CPAP-mode assisted ventilation. The patient still had an elevated leukocyte and neutrophil percentage postoperatively, but the rest of the test results were unremarkable. Symptomatic supportive treatments such as anti-infection treatment, dehydration to a lower cranial pressure and nerve nutrition were also given. As the patient remained in a light coma with tubes, a tracheotomy was performed one week later, and he was transferred back to the local hospital for continued treatments after half a month.

Case 3

The patient was a Chinese female aged 43, with a height of 160cm, a weight of 67kg and an ASA physical status of Level . She was diagnosed with left breast cancer in the hospital and underwent an elective “radical left mastectomy” after 4 weeks of chemotherapy with doxorubicin and cyclophosphamide combined with paclitaxel (AC-T). The patient was routinely monitored for vital signs after entering the operating room. Anesthesia was induced sequentially with 20mg of intravenous
etomidate, 25ug of sufentanil and 40mg of rocuronium. Anesthesia maintenance was conducted with 0.45mg/kg.h propofol, 0.012mg/kg.h remifentanil, an intravenous pump and an inhalation of 1% sevoflurane. During the operation, 10mg of rocuronium was added 10min before an axillary lymph node dissection, but a significant muscle fibrillation was still noted by the surgeons during the lymph node dissection. At this point, the muscle relaxation monitor indicated that T1 had recovered to 10%. 10mg of additional rocuronium was given at 2min intervals, and the muscle fibrillation disappeared. The last dose of rocuronium was given 30min before the end of the operation, and the continuous infusion of general anesthetic drugs was stopped at the time of skin suturing. After the patient's spontaneous breathing, consciousness, choking reflex and swallowing reflex were restored, the tracheal tube was removed and the patient was sent to the PACU. Upon questioning, it was learned that the patient had no intraoperative awareness, who recovered well after surgery and was discharged one week later.

Table 1
Basic Characteristics and Rocuronium Usage for Three Patients

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47</td>
<td>71</td>
<td>43</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>54</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>ASA Physical Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity / Nationality</td>
<td>Han / Chinese</td>
<td>Han / Chinese</td>
<td>Han / Chinese</td>
</tr>
<tr>
<td>Surgery Type</td>
<td>Emergency</td>
<td>Emergency</td>
<td>Selective</td>
</tr>
<tr>
<td>Duration of Surgery, min</td>
<td>155</td>
<td>112</td>
<td>98</td>
</tr>
<tr>
<td>Average dosing interval, min</td>
<td>30</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Satisfactory-supplementary dose, mg</td>
<td>30 (ROC)</td>
<td>10 (CIS)</td>
<td>20 (ROC)</td>
</tr>
<tr>
<td>Interval from final dose to extubation, min</td>
<td>25</td>
<td>Unextubated</td>
<td>30</td>
</tr>
<tr>
<td>Total dose at extubation, mg</td>
<td>90mg (ROC)</td>
<td>100 (ROC) + 10 (CIS)</td>
<td>70 (ROC)</td>
</tr>
</tbody>
</table>

ASA, American Society of Anesthesiologists; ROC, rocuronium; CIS, cisatracurium.

Discussion

There are many possible reasons for the poor effect of muscle relaxants during surgeries. Based on the factors influencing the effect of rocuronium, the possible mechanisms of rocuronium in SIRS, sepsis and chemotherapy leading to a reduced muscle relaxing effect were reviewed in this article, and the perioperative management of related surgeries were discussed to provide ideas for anesthesia of potential patients with high risk characteristics.
1. Influencing Factors of Rocuronium

Rocuronium is a non-depolarized muscle relaxant that acts as a competitive antagonist of AChR and provides a neuromuscular blockade by competing with ACh for AChR on the endplate membrane at neuromuscular junctions. There are many factors that could influence the effect of rocuronium, such as gender, age, obesity, hypothermia, hepatic and renal insufficiency, together with inhaled anesthetics (Table 2). The mechanisms of actions of these factors have been reported in several studies, but the effect of SIRS, sepsis and chemotherapy on rocuronium has been less studied.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of Publication</th>
<th>Factor</th>
<th>Type of Research</th>
<th>Conclusion</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xue et al. [1]</td>
<td>1997</td>
<td>Gender</td>
<td>Prospective Cohort study</td>
<td>Women were significantly more sensitive to rocuronium than men; the clinical duration of rocuronium was prolonged among women.</td>
<td>Possibly related to the differences in body composition, distribution volume and plasma protein concentration, etc.</td>
</tr>
<tr>
<td>Furuya et al. [2]</td>
<td>2012</td>
<td>Age</td>
<td>Prospective Cohort study</td>
<td>The duration of rocuronium-induced intense neuromuscular block is markedly prolonged among older patients</td>
<td>Rate of plasma clearance for rocuronium decreases with age increasing.</td>
</tr>
<tr>
<td>Puhringer et al. [3]</td>
<td>1995 2004</td>
<td>Obesity</td>
<td>Prospective Cohort study</td>
<td>Rocuronium injected in obese patients has a shorter onset of action. Among morbidly obese patients, the duration of action of rocuronium is significantly prolonged when it is dosed according to real body weight. Therefore, the dosage should be assessed on the basis of an ideal body weight rather than the real one in clinical practice.</td>
<td>Obese people have larger absolute lean body masses and fat masses, together with a decreased proportion of muscle mass and body water than the nonobese. Due to obesity, both liver functions and protein binding may also be altered.</td>
</tr>
<tr>
<td>Leykin et al. [4]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaufort et al. [5]</td>
<td>1995</td>
<td>Hypothermia</td>
<td>Prospective Cohort study</td>
<td>Hypothermia prolongs the duration of action of rocuronium and delays spontaneous recover.</td>
<td>Altered pharmacokinetics, such as a decreased clearance, play an important role.</td>
</tr>
<tr>
<td>Reference</td>
<td>Year of Publication</td>
<td>Factor</td>
<td>Type of Research</td>
<td>Conclusion</td>
<td>Mechanism</td>
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</tr>
<tr>
<td>Magorian et al.⁶</td>
<td>1995</td>
<td>Liver Disease</td>
<td>Prospective Cohort study</td>
<td>The duration of action of rocuronium is prolonged among patients with liver diseases.</td>
<td>The volume of distribution of rocuronium and its elimination half-life increase due to liver diseases, but not its clearance.</td>
</tr>
<tr>
<td>Robertson et al.⁷</td>
<td>2005</td>
<td>Renal Failure</td>
<td>Prospective Cohort study</td>
<td>The duration of action of rocuronium increases significantly among patients with renal failure.</td>
<td>Patients with renal failure have a decreased clearance of rocuronium.</td>
</tr>
<tr>
<td>Liu et al.⁸</td>
<td>2013</td>
<td>Inhaled Anesthetics</td>
<td>Randomized Controlled Trial</td>
<td>Inhaled anesthetics enhance the neuromuscular blocking effect of NDMRs and prolong the duration of inhibitory action as well as the recovery from neuromuscular blockade.</td>
<td>The synergistic mechanism between inhaled anesthetics and NDMRs remains to be elucidated.</td>
</tr>
</tbody>
</table>

### 2. Mechanism of SIRS, Sepsis and Chemotherapy

In Case 1, no poor muscle relaxation was observed at the time of the elective radical gastric cancer surgery 2 years ago. However, in consideration of the emergency admission and relevant chemotherapy history, the poor effect of rocuronium during this emergency surgery might be related to factors such as sepsis and chemotherapy.

Gastrointestinal perforation is one of the common surgical emergencies. Several studies have demonstrated that in general anesthesia for acute abdominal surgeries, more muscle relaxants were often needed to satisfy surgical needs than normal patients.⁹ An excessive release of cytokines and mediators in patients with an acute abdomen often causes SIRS, which subsequently leads to the development of sepsis. It has been stated in recent consensus guidelines that sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.¹⁰ Although SIRS is no longer a part of the diagnostic process of sepsis, it remains a common feature of patients with sepsis. Narimatsu et al. have long demonstrated that the stage of sepsis dependently and differentially
attenuates the effect of non-depolarized neuromuscular blockade on rat diaphragms in vitro.\textsuperscript{[11]} This suggests that factors related to sepsis can attenuate the muscle relaxing effect of NDMRs including prolonging the onset of muscle relaxation as well as shortening maintenance and recovery time. The exacerbation of sepsis could lead to liver and kidney dysfunctions and reduce cholinesterase activity, together with inflammatory factors affecting the binding of muscle relaxants to plasma proteins, thereby affecting the distribution, metabolism and clearance of muscle relaxants.\textsuperscript{[10]}

The patient's test results in Case 1 showed a significant decrease of serum cholinesterase level. Serum cholinesterase, produced by the liver, mainly refers to butyrylcholinesterase (BChE), which is the main enzyme in plasma that degrades ACh. Decrease in the serum cholinesterase level and activity of patients with sepsis, as well as the significant decrease in acetylcholinesterase (AChE) activity at neuromuscular junctions, can lead to an increase in the ACh concentration at neuromuscular junctions. Together with systemic inflammation that can lead to the upregulation of AChR in muscles,\textsuperscript{[12]} the blocking effect of rocuronium is in turn antagonized (Fig. 1). Wu Jin et al. found in a rat model with cecal ligation and puncture that sepsis could decrease the activity of AChE at neuromuscular junctions, thereby strengthening the antagonistic actions of neostigmine on rocuronium.\textsuperscript{[13]} Among them, oxidative damage to reactive oxygen species (ROS) induced by oxidative stress as well as the mitochondrial and organ function damage can be involved in the process of AChE activity reduction.\textsuperscript{[14, 15]} Severe metabolic acidosis may also affect the AChE activity of patients.\textsuperscript{[16]} In addition, sepsis can cause ischemia and hypoxia in the tissues and organs, meanwhile decreasing blood supply to muscles, which reduce the ability of plasma proteins to bind muscle relaxants and weaken muscle relaxation. In an inflammatory state, the plasma concentration of α1-acid glycoprotein (α1-AGP) increases, which binds cationic drugs including muscle relaxants, and can also lead to resistance to neuromuscular blocking drugs.\textsuperscript{[17]}

The patient with cerebral hemorrhage in Case 2 can be diagnosed with non-infectious SIRS due to his high fever, shortness of breath, leukocytosis and tachycardia. Non-infectious SIRS, a well-known phenomenon accompanied with various acute brain injuries, reflects the extent of tissue damage and predicts adverse outcomes of patients with cerebral hemorrhage.\textsuperscript{[18]} Combining Case 1 with Case 2, it has also been suggested that muscle tonicity caused by the inability of muscle relaxants, which blocks muscle contraction at neuromuscular junctions, may be associated with an intracellular Ca\textsuperscript{2+} overload. It is well known that the intracellular calcium level in skeletal muscles is a key factor in the regulation of contraction and diastole. Based on a rat model with an acute gastric perforation-induced peritonitis, Zhang et al. demonstrated increased cytokines, free radicals and T-cell infiltration induced by inflammation in skeletal muscle tissues interfered with the expression and function of sarcoplasmic reticulum calcium pump (SERCA) as well as a decreased Ca\textsuperscript{2+} uptake in the sarcoplasmic reticulum, thereby attenuating the effect of neuromuscular blockers, leading to the tonic contraction of abdominal wall muscles.\textsuperscript{[19]} In this context, SERCA is one of the main proteins regulating the calcium ion level in skeletal muscle cells, mainly transporting Ca\textsuperscript{2+} from the cytoplasm to the sarcoplasmic reticulum.\textsuperscript{[20]} Sathish et al. found that inflammatory factors could downregulate the SERCA level in myocytes.\textsuperscript{[21]}
Hobai et al also observed a decrease of SERCA level in myocytes of mice with an endotoxic shock.[22] Therefore, in SIRS, inflammatory factors can cause abnormalities to SERCA functions or downregulate protein expression in skeletal muscle cells, reduce Ca\(^{2+}\) uptake in the sarcoplasmic reticulum, lead to the onset of an intracellular Ca\(^{2+}\) overload, and eventually diminish the intraoperative rocuronium muscle relaxation effect (Fig. 1).

1. Sepsis can lead to a decrease in butyrylcholinesterase (BChE) level and activity as well as acetylcholinesterase (AChE) activity, resulting in an increase in ACh concentration at neuromuscular junctions. Systemic inflammation can lead to the upregulation of AChR in muscles, which subsequently antagonizes the blocking effect of rocuronium.

2. SIRS can cause abnormal SERCA functions or a downregulated protein expression, reduce Ca\(^{2+}\) uptake in the sarcoplasmic reticulum, lead to an intracellular Ca\(^{2+}\) overload and ultimately attenuate the muscle relaxation effect of rocuronium.

Zanjani AP et al. found that neoadjuvant chemotherapy resulted in a longer time to achieve the clinical effect of deep block with muscle relaxants and a shorter recovery time after block.[23] Wang T. et al. also showed that patients receiving a preoperative neoadjuvant chemotherapy had a prolonged rocuronium onset of actions, a shorter clinical duration of actions and an increased intraoperative rocuronium dosage.[24]

Oxaliplatin, a common neoadjuvant chemotherapeutic agent, is commonly used in the first-line treatment of advanced colorectal cancer, which can cause peripheral nerve damage and skeletal muscle dysfunctions. It has been found that oxaliplatin increases the release of neurotransmitters from motor nerve terminals by modulating voltage-gated Na\(^{+}\)-channels, which leads to the hyperexcitability of motor nerves, a process that can be antagonized by Na\(^{+}\)-channel blockers.[25] Through in vitro studies on sciatic nerve fibers, Kagiava et al. demonstrated that oxaliplatin was also able to induce functional abnormalities in voltage-gated potassium channels by decreasing the expression of TREK-1 and TRAAK channel types as well as increasing the expression of the pro-excitatory K\(-\)-channels.[26] Shulze and collaborators, on the other hand, found that although an acute exposure to oxaliplatin had no effect on neuronal cells, but a prolonged exposure to it produced spontaneous changes in intracellular Ca\(^{2+}\) with an increased amplitude of phospho-inositide-mediated Ca\(^{2+}\) responses, probably due to the alteration of the endoplasmic reticulum Ca\(^{2+}\) load. [27] Furthermore, oxaliplatin can induce oxidative stress,[28] evoke axonal mitochondrial swelling and vacuolization and cause mitochondrial dysfunctions, which leads to electron transport chain disruption and cellular energy failure in neurons.[29] All of the above mechanisms may cause abnormal neuromuscular functions for patients, thereby affecting the muscle relaxing effect of rocuronium.

The standard chemotherapy drugs for patients with a breast cancer are anthracyclines combined with taxanes, mainly including doxorubicin (DOX), cyclophosphamide and paclitaxel,[30] among which paclitaxel may cause peripheral neuropathy, resulting in distal limb motor weakness.[31] DOX mediates
oxidative stress through chemically-reactive oxygen-containing molecules, inhibits mitochondrial oxidative phosphorylation, disrupts the intracellular respiratory chain and energy production in striated muscles, resulting in an increased intracellular calcium level and an enhanced skeletal muscle fiber tone, thereby inducing muscle weakness.\[32\] Meanwhile, several early clinical and experimental studies have demonstrated that antitumor drugs for chemotherapy have a direct hepatotoxic effect, leading to a decrease in serum cholinesterase activity.\[33\] It was found in a study that cyclophosphamide caused an acquired decrease in serum cholinesterase activity, which in turn prolonged succinylcholine-induced muscle paralysis.\[34\] Cisplatin, which is the same platinum complex as oxaliplatin, inhibits AChE activity in camel retinas with a rapid reversible time-dependent inhibition of serum cholinesterase activity produced.\[35\] It is hypothesized that anti-cancer chemotherapeutic drugs may also affect the effect of muscle relaxants such as rocuronium by inhibiting serum cholinesterase.

In addition, a significant postoperative anemia, leukopenia and low platelets were developed in the patient in Case 1, suggesting that the patient was in an immunocompromised state. Studies have shown that severe immune deficiencies are often developed in patients with malignant tumors after chemotherapy. Bone marrow suppression, one of the major side effects of chemotherapy, often leads to the development of anemia, leukopenia and thrombocytopenia.\[36\] As a sign of SIRS, leukopenia is associated with an increased risk of deaths compared with leukocytosis. Among patients with sepsis, a decreased bone marrow production or an increased destruction and leukocyte-platelet interaction as well as the formation of bacterial neutrophil-extracellular traps (NETs) may cause leukopenia and thrombocytopenia.\[37\] As early as 1994, Fassoulaki et al. showed that a prolonged neuromuscular blockade could be obtained after a single bolus dose of vecuronium for patients with an acquired immunodeficiency syndrome.\[38\] However, due to the poor quality of that study, it is difficult to conclude whether there is resistance to non-depolarized muscle relaxants, despite a reasonable correlation between immunodeficiency and muscle relaxation effect. Thus, the effect of immunodeficiency on muscle relaxants still needs to be further explored.

3. Perioperative Management

In the above three cases, the patients had different diseases and physical states, whose final outcomes were different, but all of them showed a poor intraoperative effect of rocuronium, such as the recovery of spontaneous breathing, muscle tension and fibrillation. Specific dosing guidelines have been proposed for NDMRs in no study, such as rocuronium during general anesthesia for different surgical procedures. Therefore, when the muscle relaxation effect is not satisfactory, additional drug doses can be useful, but there is also a risk of drug residues due to postoperative muscle relaxation. Therefore, how to well manage the perioperative period when patients themselves have possible influences on the effect of muscle relaxation is worth discussing, such as SIRS, sepsis and chemotherapy.

Preoperative evaluation: Patients with cancers often suffer from immunosuppression due to their own diseases, chemotherapy, malnutrition and psychological stress, which induce apoptosis in immune cells and thus exhibit immune hypofunction. While improving the rate of radical tumor resection, preoperative
systemic neoadjuvant chemotherapy can also have toxic effects on multiple organ systems and may affect heart, lung, kidney and liver functions. Anesthesiologists should concern about patients’ acute abdomen and other appropriate symptoms before an emergency surgery for patients undergoing chemotherapy, and should also be aware of the possible toxic effects of their neoadjuvant chemotherapy. Preoperative ECG, cardiac ultrasound, lung CT, abdominal ultrasound and laboratory tests such as routine blood count, coagulation, biochemistry and liver functions are needed to accurately assess a patient’s cardiopulmonary reserve and physiological status related to liver and kidney functions, so as to provide information for preoperative evaluations and the selection of anesthesia techniques.\cite{39}

Intraoperative management: In addition to routine intraoperative monitoring, patients may require continuous invasive arterial blood pressure monitoring and CVP monitoring due to chemotherapy-induced toxicity, extensive surgeries or blood loss to allow a timely observation of hemodynamic fluctuations.\cite{39} In case of a massive blood loss, blood volume should be replenished as soon as possible and electrolyte ion disturbances should be corrected. Intraoperatively, rocuronium can be administered through continuous infusion using a closed-loop muscarinic target-controlled injection system and be monitored with a muscle relaxation monitor. Under the train of four stimulation (TOF) electrical stimulation mode, patients’ degree of neuromuscular blockade is objectively assessed by stimulating their ulnar nerves in the wrists and monitoring the response pattern of their thumb adductor muscles, thus providing an insight into the dose adjustment and an adequate recovery of their neuromuscular transmission, enabling an individualized maintenance of neuromuscular blockade for each patient.\cite{40} The recommendation for rocuronium infusion at steady-state blocks during a standard anesthesia can range from 0.24 to 0.96 mg/kg per hour (mean = 0.6 mg/kg per hour).\cite{41–44} Intraoperative temperature monitoring is also crucial, as not only bleeding is controlled by regulating the optimal temperature, but infection can also be reduced, thus improving the prognosis.\cite{45}

Postoperative analgesia: Acute perioperative pains are a result of surgical traumas, inflammation and sympathetic nervous system hyperresponsiveness. The current perioperative multimodal analgesia is mainly composed of regional anesthesia, opioids and NSAIDs. Among them, regional anesthetic analgesic protocols, including spinal anesthesia, epidural anesthesia, fascial plane blocks and peripheral nerve blocks, provide superior analgesia, improve the quality of early recovery and reduce postoperative cardiopulmonary complications, thus reducing the length of hospital stay. In addition, they can also attenuate surgical stress and reduce the use of perioperative opioids.\cite{46}

**Conclusion**

In conclusion, we hypothesize that patients' own SIRS, sepsis and chemotherapy factors could be related to the phenomenon of a poor intraoperative rocuronium muscle relaxation effect, which can lead to a longer onset of muscle relaxation effect, a shorter clinical duration of actions and an increased intraoperative consumption of rocuronium. However, further studies and more literature reports are needed to optimize the doses of individualized muscle relaxants and clarify specific mechanisms for
such patients. In the perioperative management of such procedures, anesthesiologists should be more careful and considerate, so as to ensure safety and promote an early recovery at the same time.

Declarations

Consent for Publication

A written informed consent was obtained from patients for the publication of this case series.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article. Further information can be requested from the author.

Competing Interests

All the authors declared no competing interests.

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Ethical approval and consent to participate

Not Applicable.

Authors’ Contributions

Chenxi Liu drafted the manuscript; Xuesong Song were responsible for the revision of the manuscript for important intellectual content; Siqi Liu and Hang Yang participated in data analysis, interpretation of data and follow-up. All authors read and approved the final manuscript.

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References


**Figures**
Figure 1

Mechanism of sepsis and SIRS leading to a diminished rocuronium muscle relaxation