

**Resistance to non-depolarizing neuromuscular blocking agents****Dong-Min Hyun<sup>1</sup>, Young-Mu Kim<sup>1</sup>, Jae-Ho Lee<sup>1</sup>, Jin Sun Kim<sup>1</sup>, Hong Seuk Yang<sup>2\*</sup>**<sup>1</sup>*Department of Anesthesiology and Pain Medicine, Gangneung Asan Hospital, Gangneung, Gangwon-do, Republic of Korea*<sup>2</sup>*Department of Anesthesiology and Pain Medicine, Daejeon Sun Hospital, Daejeon, Republic of Korea***Received: 22-10-2019 / Revised: 31-01-2019 / Accepted: 10-02-2020****ABSTRACT**

The authors experienced three cases of the resistance to the nondepolarizing neuromuscular blocking agents (NMBAs), rocuronium. There are many factors that affect NMBAs such as steroid, endocrine or autoimmune diseases which are thyroid disease, parathyroid disease, myasthenia gravis and etc., and anticonvulsant medication. However, in these three cases, the patients did not have any neuromuscular disorder, except certain drug administration, smoking, endocrine disorder and fever. In this study, we report three cases of the resistance to rocuronium where the resistance duration was much shorter than known and we should be aware of the importance of neuromuscular monitoring.

**Key words:** Non-depolarizing neuromuscular blocking agents; Resistance; Rocuronium.

© The Author(s). 2020 Open Access. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**INTRODUCTION**

In the anesthetic management for the operation, the neuromuscular blocking agents are important medications that are useful for the endotracheal intubation and the improvement of the surgical view. Therefore, selecting appropriate neuromuscular blocking agents and monitoring the neuromuscular function to achieve adequate action time according to the operation time would allow efficient maintenance of the anesthetic management. The duration of action of the neuromuscular blocking agents is affected by the shape, type, and blood flow of the muscles, and there is a large difference depending on the muscles. In particular, expression and duration of the action in the diaphragm and the adductor pollicis muscle differ. [1] It will also be affected by the "up and down regulation" of the nicotinic acetylcholine receptor, which is the site of action of the neuromuscular blocking agents, and the long-term administration of anticonvulsants and hormones for endocrine disorders or steroids. [2-4]

Resistance to the neuromuscular blocking agents can be explained as a delayed onset time, an incomplete muscle relaxation or early recovery of neuromuscular blocks, despite enough dose of neuromuscular blocking agents. [5]

Along with the literature review, the authors report cases where the patients suspected of such change had very short action time.

**CASE REPORTS****Case 1**

A 67-year-old male patient (height: 167 cm; weight 60.8 kg) was admitted for posterior lumbar interbody fusion with bone graft due to spinal stenosis lumbar 3–5. The patient had a history of benign prostate hypertrophy with 5mg of terazosin and lumbar pain with non-steroid anti-inflammatory drugs. He had a 30-year history of smoking (1/2 ~ 3/4 pack/day) and alcohol consumption (3–4 times/week, 1 bottle of soju). No abnormal findings was found in the results of preoperative complete blood cell count, kidney function test, electrolyte and coagulation test (Table 1). No specific findings was found on chest X-ray and electrocardiography (ECG). The patient entered the operation room without premedication and was monitored with non-invasive blood pressure (NIBP), ECG and oxygen saturation (SpO<sub>2</sub>). Sixty mg of lidocaine and 100mg of propofol were injected for general anesthesia. After confirming that the eyelash

\*Address for Correspondence

**Dr. Hong Seuk Yang**

Department of Anesthesiology and Pain Medicine,  
Daejeon Sun Hospital, Daejeon, Republic of Korea.

**E-mail:** [hdm27@hanmail.net](mailto:hdm27@hanmail.net)

reflex was absent, assisted ventilation was initiated with mask ventilation. Once assisted ventilation was stable, N<sub>2</sub>O/O<sub>2</sub> 2 L/min (FiO<sub>2</sub> 0.5) + desflurane 12.0 volume% was given using 1:1:12 technique. Then 50mg (0.82 mg/kg) of rocuronium was administered after confirming that the patient is stable. In 3 minutes, the patient was intubated. Anesthesia was maintained with N<sub>2</sub>O/O<sub>2</sub> 2 L/min (FiO<sub>2</sub> 0.5) + desflurane 5.0–8.0 volume%. After checking the modified Allen's test on the left hand to confirm the collateral circulation of hand, an arterial catheter was inserted at left radial artery for continuous blood pressure monitoring and an 18-gauge intravenous line was inserted in right antecubital vein with plasmalyte A. After inducing general anesthesia, the patient was laid in a prone position for the spinal surgery. Thirty minutes after the start of surgery (1 hour after prone position), the blood pressure was dropped below 80–85 mmHg for systolic pressure/50–60mmHg for diastolic pressure. To increase the blood pressure, 10mg of ephedrine was administered 3 times for every 10 minutes, but there was no effective response. One hundred µg of phenylephrine was administered 5 times for every 10 minutes, but there was still no effective response. Intravenous line was checked for adequate fluid infusion and there was no problem. Norepinephrine was continuously administered at 0.05–0.2 µg/kg/min to maintain stable blood pressure, and blood pressure was maintained with systolic pressure of 85–110 mmHg / diastolic pressure of 50–70 mmHg. Through this process, SpO<sub>2</sub> was temporarily dropped to 90%. Increasing FiO<sub>2</sub> to 70% resulted in the gradual recovery of SpO<sub>2</sub> upto 95%. As there were no other abnormal signs, no further management was provided, and FiO<sub>2</sub> was changed to 50% (Table 2). During the above process, the changes in spontaneous respiration were observed in the capnography, 40 minutes after the first administration of rocuronium, and 30mg of rocuronium was administered. But the same changes in spontaneous respiration were observed in the capnography after 10 minutes, and 20mg of rocuronium was administered additionally. After that, 30 mg of rocuronium was administered 3times at the intervals of 20–30 minutes. One hundred ninety mg of rocuronium was administered in total during 2 hours and 40 minutes of the operation duration. At the end of the operation, no additional rocuronium was administered. When the operation was finished, the patient was laid in supine position and all anesthetic medications were stopped. While ventilating with 100% oxygen, the patient was allowed to recover the responsiveness to the verbal instruction, such as opening his eyes and mouth and taking deep breath. Then, 120 mg (2 mg/kg) of sugammadex was

administered and the endotracheal intubation was removed after 3 minutes. The patient was moved to the post anesthetic care unit (PACU) after 10 minutes and transferred to the general ward after an hour. The operation duration was 2 hours and 30 minutes, and the anesthetic duration was 3 hours and 20 minutes. During the operation, the operation room temperature was 22–23°C, the patient's esophageal body temperature was maintained at 35.5–37.0°C, and the end-tidal carbon dioxide (EtCO<sub>2</sub>) was maintained at 30–35 mmHg, the fluids of 700ml Ringer's lactate and 800ml plasmalyte A were administered, hemoglobin was maintained 13.8mg/dl, and no transfusion was given as the estimated blood loss was below 400ml.

### Case 2

A 27-year-old female patient (height: 160.2 cm; weight: 61.9 kg) was admitted for grave's disease and scheduled for the total thyroidectomy. The patient was at 26 +1 week's gestation. She was diagnosed with grave's disease in February 2014 and has been administering 10mg of methimazole. In January, 2018, the thyroid hormone level was not stably controlled, so the medication was increased from 10 mg to 40mg of methimazole. However, the thyroid hormone level was still not controlled and the medication was changed to 400 mg of propylthiouracil. In August 2018, the free T4 level fell within the normal range, so the medication was adjusted from 400 mg of propylthiouracil to 30mg of methimazole. In the previous 2 months of the operation, the thyroid function test was maintained with normal range [Table 3]. There was no unusual medical history and there were no abnormal findings in the results of preoperative complete blood cell count, kidney function test, electrolyte test, and coagulation test [Table 1]. The patient entered the operation room without premedication and was monitored with NIBP, ECG and SpO<sub>2</sub>. Pre-oxygenation with 100% oxygen (flow rate : 10L/min) was applied for 2 minutes. Sixty mg of lidocaine and 100mg of propofol were injected for general anesthesia with rocuronium 50 mg (0.81 mg/kg) as a muscle relaxant for endotracheal intubation. The patient was intubated after performing 3 minutes of manually controlled ventilation. The anesthesia was maintained with Air/O<sub>2</sub> 2.5L/min (FiO<sub>2</sub> 0.4) + sevoflurane 2.0–3.0 volume%. After induction of the general anesthesia, skin preparation and surgical drape were done for the operation and the operation was started. Thirty minutes after the induction of general anesthesia, a diaphragm movement (hiccup) was observed in the capnography, indicating a spontaneous respiration, so 10mg of rocuronium was administered. However, after 10 minutes, the changes in the spontaneous respiration were observed again in

the capnography, and 10mg of rocuronium was administered. After another 10 minutes, a diaphragm movement was observed and capnography revealed spontaneous respiration, so bolus dose of rocuronium was increased to 20 mg. After that, 10 mg of rocuronium was administered at the intervals of 10–15 minutes. One hundred twenty mg of rocuronium was administered in total over 2 hours. During the operation, the systolic pressure was maintained about 95–110 mmHg and the SpO<sub>2</sub> was maintained about 99–100% and EtCO<sub>2</sub> was maintained about 29–32mmHg. When the operation was finished, all anesthetic medications were stopped. While ventilating with 100% oxygen, the patient was allowed to recover the responsiveness to the verbal instruction, such as spontaneous respiration, clenching fist, and opening her eyes. Fifteen mg of pyridostigmine and 0.4mg of glycopyrrolate were administered to reverse the neuromuscular blocking agents. After 3 minutes, the patient was extubated. The patient recovered from general anesthesia in the post anesthetic care unit (PACU) for 30 minutes and transferred to the general ward. The operation duration was 2 hours and 40 minutes, and the anesthetic duration was 3 hours. Total fluid input was 900ml of Ringer's lactate, and the urine amount was not measured. During the operation, the transfusion was not given to the patient as the estimated blood loss was below 100ml.

### Case 3

A 77-year-old female patient (height: 165 cm; weight: 65 kg) was admitted for femur neck fracture and scheduled for bipolar hip joint arthroplasty. The patient had a history of hypertension and had an operation in the lumbar regions 10 years ago. In the preoperative evaluations, pericardial effusion was detected in the chest computed tomography and D-dimer level and erythrocyte sedimentation rate (ESR) were elevated (17.33µg/ml, normal range: <0.50 µg/ml; ESR: 64mm/hr). There were no abnormalities in other laboratory test results (Table1) and electrocardiography. Due to the patient's request, the operation was performed under general anesthesia. The patient entered the operating room without premedication and was monitored with NIBP, ECG and SpO<sub>2</sub>. Pre-oxygenation with 100% (flow rate: 10L/min) oxygen was applied for 2 minutes. Sixty mg of lidocaine, 100mg of propofol and 50 mg (0.82 mg/kg) of rocuronium were injected for general anesthesia. In 3 minutes, the patient was intubated. After intubation, the esophageal body temperature probe was inserted and the esophageal body temperature was measured to be 36.7–37.3°C. The anesthesia was maintained with N<sub>2</sub>O/O<sub>2</sub> 1.0 L/min

(FiO<sub>2</sub> 0.5) + desflurane 6.0–8.0 volume% using a low flow anesthesia technique. The skin preparation and surgical drape were done and the operation was started about 20 minutes after the induction of anesthesia. A spontaneous respiration pattern was observed in the capnography 30 minutes after the induction of anesthesia, so 20 mg of rocuronium was administered. Thirty minutes later, a recovery sign of spontaneous respiration was observed in the capnography, and the neuromuscular function assessment device (TOF watch EX, Organon Ltd., Ireland) was applied. The train of four (TOF) showed T3 count, so 20 mg of rocuronium was additionally administered. Soon after, there was no TOF response and the capnography showed controlled mechanical ventilation (Fig. 1A). Twenty minutes later, the clefts in plateau portion of capnography (Fig. 1B) was observed, but no TOF response was observed in TOF monitor. After another 20 minutes, the spontaneous respiration pattern was observed in the capnography, and T1 and T2 counts were observed in the TOF monitors (Fig. 1C). After the clefts occurred in the plateau portion of the capnography along with the diaphragm movement, about 10–15 minutes were required to have the T1 count in the TOF monitor. Although an abnormality was observed in the plateau portion of the capnography, SpO<sub>2</sub> and EtCO<sub>2</sub> level were maintained within the normal range (SpO<sub>2</sub>: 99–100%; EtCO<sub>2</sub>: 29–32 mmHg), and the anesthetic depth and vital signs were stably maintained. Ten minutes later, the operation was finished and anesthetic medications were stopped. While ventilating with 100% oxygen, TOF count of 2 and 3 were consecutively observed within 1 minute, so 120 mg (2mg/kg) of sugammadex was administered. After 3 minutes, TOF ratio was recovered to 1.0, and the patient was able to open her eyes and mouth, take deep breathing and respond to verbal instruction. The patient was extubated, recovered from general anesthesia in the PACU for an hour and transferred to the general ward. The operation duration was 1 hours and 45 minutes, and the anesthetic duration was 2 hours and 30 minutes. The total fluid input was 300 ml Ringer's lactate and 700 ml plasmalyte A. During the operation, blood loss was estimated to be below 300 ml and urine output was estimated to be 50 ml.

### DISCUSSION

The neuromuscular blocking agents is widely used for the general anesthesia because of easiness of airway intubation, limited patient movement during the operation, reduced use of other anesthetic agents, and it is one of the major drugs in the general anesthesia. The resistance to these neuromuscular blocking agents is common in the cases of burns, immobilization,

denervation, infectious diseases. The patients administered with medications for anticonvulsant therapy such as corticosteroids, phenytoin and carbamazepine are said to have resistance to the neuromuscular blocking agents due to the interaction of the medications.<sup>[3,4]</sup> However, a large amount of the neuromuscular blocking agents was used in these cases because of a much shortened action duration of the neuromuscular blocking agents, even though the patients did not have any medications that may have interaction or any underlying diseases that have resistance to neuromuscular blocking agents. In particular, it is important to not only select the appropriate neuromuscular blocking agents but also monitor the neuromuscular function, as there may be a specific response to individual differences.<sup>[6]</sup> For the endotracheal intubation during the induction of anesthesia, NMBAs are administered at least twice as much as ED<sub>95</sub>. The ED<sub>50</sub> of rocuronium is 0.147 mg/kg and the ED<sub>95</sub> of rocuronium is 0.305 mg/kg. Intubation dose of rocuronium is 0.6–0.9 mg/kg, and the duration of clinical action is about 40–50 minutes. To maintain this, rocuronium is administered at a dose of 0.1 mg/kg.<sup>[7]</sup> In the above three cases, rocuronium for the endotracheal intubation was administered at 0.82–0.83 mg/kg, but a spontaneous respiration due to a diaphragm movement was observed at 30–40 minutes. Despite the maintenance dose was administered at 0.2–0.4 mg/kg, which is higher dose than usual maintenance dose, a spontaneous respiration was observed within 15 to 30 minutes. In the first case, there was no unusualness except 5mg of terazosin due to patient's underlying disease, benign prostate hyperplasia, and smoking. In patients who smoke more than 10 cigarettes a day, approximately 25% more of the dose is required to maintain 90–98% of the neuromuscular block for 60 minutes in vecuronium, a non-depolarizing neuromuscular blocking agents similar to rocuronium.<sup>[8]</sup> However, in this case, more than twice of the usual maintenance dose of rocuronium was administered even though the patient only smoke 1/2–3/4 pack/ day, and this cannot be simply explained by smoking alone. Furthermore, as the systolic blood pressure was decreased to 80 mmHg after 1 hour of being in a supine position, ephedrine and phenylephrine were administered to increase the blood pressure, but did not react to maintain an effective blood pressure. The blood pressure was maintained by administering norepinephrine. The action duration of rocuronium may have been shortened as ephedrine and phenylephrine promoted the expression by increasing the cardiac output, and norepinephrine caused hemodynamic effects and increased cardiac output.<sup>[9]</sup> It has been reported that

the action expression time of rocuronium is shortened when phenylephrine, an alpha-adrenergic agonist, is administered.<sup>[10]</sup> In the case 1, the patient was being administered with ephedrine, phenylephrine and norepinephrine due to the hemodynamic instability and smoking, and with alpha-adrenergic antagonist for the treatment of benign prostate hyperplasia. It is thought to be also important to consider whether these medications can affect rocuronium. In the second case, hyperthyroidism and pregnancy may be factors affecting the neuromuscular blocking agents. When the patient have hyperthyroidism, metabolic rates are increased, leading to changes such as hypertension, tachycardia, increased cardiac output, and etc. These factors may affect the neuromuscular blocking agents. It is reported that the expression and the action duration of rocuronium is reduced by approximately 25–50% when the free T<sub>3</sub> and the free T<sub>4</sub> values are significantly higher in the patient's preoperative thyroid function tests.<sup>[11]</sup> Pregnancy can affect the neuromuscular blocking agents due to increased body weight, body fluid, blood volume and distribution volume in the body, and increased glomerular filtration rate. It is known that the action duration of rocuronium in the pregnant women is not different from that in non-pregnant women or may be even longer in the second trimester. This is because, while rocuronium is metabolized in the liver, the blood flow is increased in the early pregnancy, but the blood flow is reduced by 20% in the second trimester of the pregnancy, resulting in a slowed metabolic rate and a longer duration of action.<sup>[12,13]</sup> In the case 2, even though the history of hyperthyroidism and pregnancy (26 weeks of gestation) were the conflicting factors with neuromuscular blocking agents, it took less time for the neuromuscular blocking agents to act. This may be presumed to be that the patient's metabolic rate may have been still elevated because the duration of the normal thyroid function was short as 2 months although the free T<sub>4</sub> level was reduced to the normal range due to hyperthyroidism, and the patient decided to have an operation as fatigue, throbbing and burning symptoms persisted.<sup>[14-15]</sup> These reasons may have contributed to the shortened action time of the neuromuscular blocking agents. In the third case, a small amount of pericardial effusion was observed in the thoracic computed tomography, but not in the transthoracic echocardiography. There was no specific finding other than elevation of pre-operative D-dimer, and the patient did not have specific history other than taking antihypertensive drugs for the hypertension. Moreover, there was no specific symptom other than having an upper limit of the body temperature measured in the lower esophagus (37.3°C) at the

beginning of the operation, which can be predicted to be a mild fever. It is reported that the plasma clearance is increased by 11.3% in the neuromuscular blocking agents whenever the body temperature is decreased by 1°C, and it is known that there is a difference in the action duration of the neuromuscular blocking agents according to body temperature.<sup>[14,15]</sup> However, the body temperature of 37.3°C is difficult to be considered as a high temperature outside the normal body temperature range, and there is a possibility that the action duration of the neuromuscular blocking agents to be shortened, but it is a unique point that the action duration was excessively reduced than the known action time as in this case. The patient's increased erythrocyte sedimentation rate (ESR) of 64 mm/h may suggest that the possibility of reduced effect of the neuromuscular blocking agents by increased metabolic rate due to inflammation reaction or infection. Like in the case 3, there was no actual change upon the train of four in the adductor pollicis muscle despite a change that could predict the restoration of a spontaneous respiration with the changes in the capnography was observed. It is predicted that this is due to the difference in the response to the neuromuscular blocking agents of the diaphragm and adductor pollicis muscle.<sup>[1]</sup> In fact, the results of the neuromuscular monitoring and the changes in the capnography did not match. In the results of the authors' monitoring in the case 3, the T1 count began to appear in the train of four watches after a significant change in the carbon dioxide curve (Fig.1C). A fault in these three cases is that the neuromuscular monitoring devices such as TOF were not used in the case 1 and 2. Of course, the recovery of the spontaneous respiration can be predicted through the capnography, and the degree of reversal of the neuromuscular block can be estimated, but using the neuromuscular monitoring device would enable a more

accurate judgment by assessing the reversal of the neuromuscular block in particular and allowing numerically express the effect of the neuromuscular blocking agents. In addition, as rocuronium used in these cases was a generic drug, rocuronium® (Ilung pharmaceuticals Co., Seoul, Korea), problems that may have occurred during the drug manufacturing processor problem of reduced drug potency compared to the original drug should be considered at one point. However, considering that other patients who were administered with rocuronium with the identical serial number did not have problems, it can be inferred that there was no problem with the drug potency or the drug activity. Third, the susceptibility to the neuromuscular blocking agents may be different in each patient. As these differences may be present without any specific disease or abnormality, using a direct neuromuscular monitoring device would allow to confirm a more accurate change in the use of neuromuscular blocking agents.<sup>[6]</sup> The neuromuscular blocking agents are one of the most commonly used drugs in the general anesthesia. Even though many things, such as drugs, patient's accompanying disease, patient's condition, or genetic factors, are known to interact with the neuromuscular blocking agents, it is predicted that many factors are yet to be discovered. By experiencing and presenting the patients where cardiogenic drug such as vasopressors, smoking, hyperthyroidism, or mild fever as in these cases are predicted to be affected in the shortened duration of action, the resistance of the neuromuscular blocking agents that is seen in few cases and is not fully understood, needs to be carefully studied. Furthermore, when using the neuromuscular blocking agents, the neuromuscular monitoring devices should be applied together at initial monitoring to detect these changes early and to take appropriate action.

**Table 1: Results of Preoperative Laboratory Test**

	Case I		Case II		Case III	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Hb (g/dl)	13.3	11.3	11.7	9.5	12.5	11.1
Hct (%)	41.2	33.8	34.4	28.5	36.1	32.8
Plt (x10 <sup>3</sup> /ul)	264	298	210	178	302	264
PT (INR)	0.94	-	1.01	-	1.02	-
APTT (sec)	30.3	-	28.0	-	30.2	-
Calcium (mg/dl)	8.0	8.1	8.1	7.1	8.2	8.0
Glucose (mg/dl)	172	97	81	110	175	118
Creatinine (mg/dl)	0.74	0.58	0.27	0.29	0.52	0.46
Sodium (mEq/L)	138.0	137.0	136.0	136.0	137.0	135.0
Potassium (mEq/L)	3.9	3.7	3.6	3.2	3.7	4.1

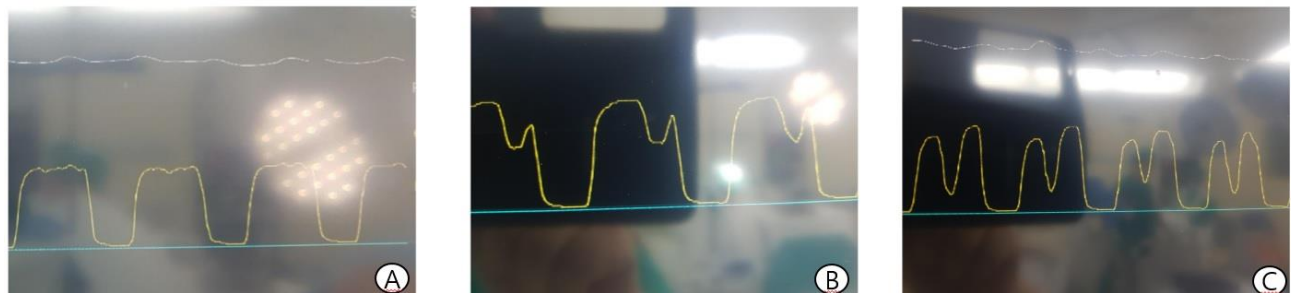
Chloride (mEq/L)	105	104	106	106	101	102
Total bilirubin (mg/dl)	1.07	1.22	0.48	0.45	0.98	0.70

**Table 2: Results of Arterial Blood Gas Analysis at 100 and 140 Minutes after Induction of Anesthesia**

	After 100 min (FiO <sub>2</sub> : 50%)	After 140 min. (FiO <sub>2</sub> : 70%)
pH	7.40	7.39
PaCO <sub>2</sub> (mmHg)	37	39
PaO <sub>2</sub> (mmHg)	56	71
SaO <sub>2</sub> (%)	89	94
Sodium (mEq/L)	138	38
Potassium (mEq/L)	3.1	3.6
Ionized Calcium (mg/dl)	3.89	4.13
Glucose (mg/dl)	148	246
Hb (g/dl)	12.9	13.8
Hct. (%)	38	41

**Table 3: Results of Thyroid Function Test**

	5/29	8/9	8/17	9/5	9/7	9/10	9/13
TSH	< 0.04	< 0.04	< 0.04	< 0.04	< 0.04	< 0.04	< 0.04
fT4	2.9	1.6	1.5	1.3	1.4	1.1	0.86
TSH-R-Ab	> 40.0	35.4	-	-	-	-	-
PTH-intact	-	-	-	-	35.4	25.2	-



**Figure 1:** These figures show the capnography during surgery. (A) The capnography after rocuronium injection via intravenous line. (B) Clefs were observed in the plateau portion of the capnography when the action of muscle relaxants is subsided and the sign of spontaneous respiration returns. (C) The capnography when T1 is observed in the TOF monitor.

## REFERENCES

1. Bragg P, Fisher DM, Shi J, Donati F, Meistelman C, Lau M, et al. Comparison of twitch depression of the adductor pollicis and the respiratory muscles. Pharmacodynamic modeling without plasma concentrations. *Anesthesiology* 1994; 80: 310-9.
2. Martyn JA, White DA, Gronert GA, Jaffe RS, Ward JM. Up-and-down regulation of skeletal muscle acetylcholine receptors. Effects on neuromuscular blockers. *Anesthesiology* 1992; 76: 822-43.
3. Soltesz S, Fraisl P, Noe KG, Hinkelbein J, Mellinghoff H, Mencke T. Dexamethasone decreases the duration of rocuronium-induced neuromuscular block: a randomised controlled study. *European journal of anaesthesiology* 2014; 31: 417-22.
4. Soriano SG, Sullivan LJ, Venkatakrishnan K, Greenblatt DJ, Martyn JA. Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy. *British J. of anaesthesia* 2001; 86: 223-9.
5. Fink H, Lupp P, Mayer B, Rosenbrock H, Metzger J, Martyn JA, et al. Systemic inflammation leads to resistance to atracurium without increasing membrane expression of acetylcholine receptors. *Anesthesiology* 2003; 98: 82-8.

6. Ortiz-Gomez JR, Palacio-Abizanda FJ, Fornet-Ruiz I. Failure of sugammadex to reverse rocuronium-induced neuromuscular blockade: a case report. *European journal of anaesthesiology* 2014; 31: 708-9.
7. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. *Anesthesiology* 1993; 79: 913-8.
8. Teiria H, Rautoma P, Yli-Hankala A. Effect of smoking on dose requirements for vecuronium. *British journal of anaesthesia* 1996; 76: 154-5.
9. Kuipers JA, Boer F, Olofsen E, Bovill JG, Burm AG. Recirculatory pharmacokinetics and pharmacodynamics of rocuronium in patients: the influence of cardiac output. *Anesthesiology* 2001; 94: 47-55.
10. Won YJ, Shin YS, Lee KY, Cho WY. The effect of phenylephrine on the onset time of rocuronium. *Korean journal of anesthesiology* 2010; 59: 244-8.
11. Apiliogullari S, Duman A, Ogun C, Gok F. The statistical power in the study of onset and duration of rocuronium in hyperthyroidism and euthyroidism patients. *Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques* 2009; 12: 232.
12. Atherton DP, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clinical pharmacokinetics* 1999; 36: 169-89.
13. Jun IJ, Jun J, Kim EM, Lee KY, Kim N, Chung MH. Comparison of rocuronium-induced neuromuscular blockade in second trimester pregnant women and non-pregnant women. *Int. J. of obstetric anesthesia* 2018; 34: 10-4.
14. Caldwell JE, Heier T, Wright PM, Lin S, McCarthy G, Szenohradszky J, et al. Temperature-dependent pharmacokinetics and pharmacodynamics of vecuronium. *Anesthesiology*.2000; 92: 84-93.
15. Heier T, Caldwell JE, Sessler DI, Miller RD. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. *Anesthesiology*.1991;74: 815-9.

**How to cite this Article:** Hyun DM, Kim YM, Lee JH, Kim JS, Yang HS. Resistance to non-depolarizing neuromuscular blocking agents. *Asian Pac. J. Health Sci.*, 2020; 7(1):74-80.  
**Source of Support:** Nil, **Conflict of Interest:** None declared.