Incidence and Risk Factors of Respiratory Complications after Thymectomy in Myasthenia Gravis Patients

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Objective: *To determine the incidence and risk factors for postoperative respiratory complications (PORCs) in myasthenia gravis (MG) patients.*

Material and Method: *Patients who underwent thymectomy at Siriraj Hospital between 2010 and 2014 were retrospectively analyzed. PORCs were defined as 1 delayed extubation (i.e., failed extubationin the operating theater, planned remain intubation); 2 ventilator support requirement (re-intubation or non-invasive positive pressure ventilation) within 24 hours after extubation. Patients' characteristics and perioperative data were recorded and analyzed.*

Results: *Among 134 MG patients, 9.7% developed PORCs. As for risk of PORCs, univariate analysis identified preoperative pyridostigmine consumption (OR 3.82, 95% CI 1.12 to 13.07, p = 0.03), preoperative plasmapheresis (OR 10.82, 95% CI 1.39 to 84.46, p = 0.02), and prolonged operation (OR 1.02, 95% CI 1.00 to 1.03, p = 0.03) were risk factors for PORCs. Multivariate analysis identified preoperative pyridostigmine consumption (OR 6.37, 95% CI 1.32 to 30.88, p = 0.02) and Osserman class III (OR 5.44, 95% CI 1.02 to 24.63, p = 0.04) as predictors of PORCs.*

Conclusion: *MG patients who receive preoperative pyridostigmine alone and those at Osserman class III should be especially monitored for respiratory complications after thymectomy.*

Keywords: *Myasthenia gravis, Thymectomy, Respiratory Complications, Risk factors*

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For almost eight decades since the first reported case by Blalock et al[1], thymectomy has been one of the treatment modalities for patients with non-thymomatous myasthenia gravis (MG). However, myasthenic patients are prone to develop postoperative respiratory complications (PORCs) secondary to several anesthetic agents, including neuromuscular blocking agents (NMBAs) and their antidotes[2], whether given by inhalation or thoracic epidural block. The incidence of PORCs after thymectomy was reported at 29.0 to 47.7%[3-5]. Leventhal et al.[3] identified four risk factors for the need for postoperative mechanical ventilator support; these included history of MG for more than 6 years, chronic respiratory disease, vital capacity less than 2.9 L, and intake of pyridostigmine at more than 750 mg/day. They also proposed a Leventhal scoring system, which was later on proven to have a poor sensitivity of only 22.2 to 35.7%, and positive predictive value of 25 to 50%[6,7]. Therefore this scoring system was not currently used for risk identification for this condition.

Mori et al[8] identified intake of preoperative pyridostigmine ≥240 mg/day as a risk factor for postoperative reintubation. Several other reported risk factors included preoperative bulbar symptoms[9], preoperative serum level of anti-acetylcholine receptor antibody of >100 nmol/L[9], NMBAs usage[6], intraoperative blood loss less than 1,000 mL[9], intake of perioperative corticosteroids[10] and general anesthesia without epidural block[11]. The objectives of this study were to determine the incidence and risk factors for PORCs in myasthenic patients who underwent thymectomy.

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Material and Method

This retrospective descriptive study was approved by the Institutional Review Board (Si 644/2015). Data of myasthenic patients who underwent elective thymectomy from 2010 to 2014 were retrieved. General anesthesia using double-lumen tube with one-

lung ventilation were used with the patients planned for video-assisted thoracotomy (VATs), whereas single-lumen tube in transternal technique. The choice of induction agents, inhalation with or without intermediate-acting muscle relaxant and neuromuscular monitoring were depended on the anesthesiologists' incharge. Epidural analgesia and opioids intravenous were use as standard postoperative pain protocol. All extubated patients received oxygen supplement via face mask or cannula until the first postoperative day. Cholinesterase inhibitors with or without prednisolone were administered until the morning of surgery and restarted via oral, or nasogastric tube in intubated cases, as soon as possible after surgery. Patients' characteristic, severity of the disease (Osserman classification; Appendix 1), anesthetic, surgical, and perioperative data were recorded.

PORCs[8], were defined as 1) delayed extubation (i.e., failed extubationin the operating theater, planned remain intubation); 2) post-extubation ventilator support requirement (re-intubation or non-invasive positive pressure ventilation) within 24 hours due to respiratory failure, including tachypnea (respiratory rate >20 breaths/minute), hypercapnia($PaCO_2$ >50 mmHg), and desaturationt (SpO_2 <90%) despite oxygen supplement.

Statistical analysis

A sample size of 140 patients was determined in order to detect a PORC incidence of 29%[8], with 8% accepted error at a type I error of 0.05. Data were analyzed using PASW Statistics for Windows, Version 18.0 Chicago: SPSS, Inc. Continuous data, such as age, weight, and operative time, were presented as mean and standard deviation. Categorical data, such as gender, preoperative myasthenic medications, and Osserman classification (appendix 1)[9], were presented as numbers and percentages. Unpaired t-test or Chi-square test,with odds ratio (OR) and its 95% confidence interval (CI), was used to assess the relationship between each clinical risk factor and PORCs. The investigators put potential risk factors from previous studies[6,8-11] and other suspected risk factors (severity of disease, type of surgery, intraoperative time, opioids administration) into univariate analysis. Significant variables (p<0.1), except history of plasmapheresis, were entered into a multivariable logistic regression analysis using a backward stepwise method, with PORCs as the dependent variable, to determine the predictors of development of PORCs. Significance was set at a p-value less than 0.05. History of plasmapheresis was excluded in the analysis because of the small number of patients (n = 4).

Results

This study included 134 myasthenic patients with a mean age of 37.8±14.0 years (range, 3 to 76 years) and a preponderance of women (72.4%) (Table 1).The median interval between diagnosis and surgery was 12 months (range, 1 to 204 months). Twenty-four (17.9%) patients had history of respiratory failure and 4 (3.0%) had history of chronic lung disease. Regarding pulmonary function test, only four patients (3.0%) had vital capacity <2.9 L (n = 3) and combined vital capacity <2.9 L and FEV_1 <1.2 L (n = 1). Four patients had a history of plasmapheresis within one week (n = 2) and three months (n = 2) before operation.

Sixty two patients underwent transsternal thymectomy. Mean operative time was 110.3±39.0 minutes. Most of the patients (68.7%) had general anesthesia with endotracheal tube and reduced dose of NMBAs. Half of the population (53.7%) had neuromuscular monitoring by train of four (TOF) during anesthesia (Table 1).

Thirteen patients (9.7%) developed PORCs, which included delayed extubation (n = 6), desaturation (n = 4), and tachypnea (n = 3) (Table 2). In two patients at Osserman stage 3 and who underwent preoperative plasmapheresis, the plan was postoperative mechanical ventilator support and extubationon postoperative days 4 and 11 without any other additional MG treatment. The other four patients who developed PORCs due to residual neuromuscular blockade (rNMB) after reversal were extubated a few hours later. Four patients who underwent VATS thymectomy developed desaturation and two of these patients required reintubation; one patient was reintubated at the operating theater due to rNMB effects and was extubated in the next 3 hours, whereas the other was reintubated at the ward on postoperative day 1 due to mucus plug with atelectasis and was extubated after two days; one patient had desaturation from bronchospasm, which improved with inhaled bronchodilator; and the last patient who received general anesthesia without NMBAs had right-sided pneumothorax 5 h after the operation revision of the intercostal catheter resolved the pneumothorax. In the PACU, three patients developed tachypnea from pain (n = 2) and both pain and pneumothorax (n = 1). Both patients who developed pneumothorax underwent VATS.

Eleven (85%) out of 13 patients underwent

Table 1. Patient characteristics and perioperative data

Variables	Total (n = 134)
Gender; male: female	37 (27.6):97 (72.4)
Age (yr)	37.8±14.0
Body weight (kg)	61.5±15.1
Preoperative medications	
Pyridostigmine	22 (16,4)
Pyridostigmine and prednisolone	112 (83.6)
Pyridostigmine (mg)	
<240: ≥240	44 (32.8): 90 (67.2)
Preoperative plasmapheresis	4 (3.0)
Duration of disease (mo)	
≥72: <72	9 (6.7): 125 (93.3)
Osserman classification	
I, IIA, IIB: III	115 (85.8): 19 (14.2)
Concomitant chronic lung disease	4 (3.0)
History of respiratory failure	24 (17.9)
Anesthetic techniques	
GA with reduced dose of NMBA	92 (68.7)
GA with normal dose of NMBA	15 (11.2)
GA without NMBA	20 (14.9)
Combined GA and RA	7 (5.2)
Intraoperative opioids	
Total morphine equivalent dose (mg)	5.3±4.0
Types of inhalational agents	
None	1 (0.7)
Sevoflurane	77 (57.5)
Isoflurane	45 (33.6)
Desflurane	11 (8.2)
Received Benzodiazepines	60 (40.8)
Train of Four monitoring	72 (53.7)
Type of operation	
Transsternalthymectomy	83 (61.9)
Video-assisted thoracoscopicthymectomy	51 (38.1)
Operative duration (min)	110.3±39.0
Histology	
Thymoma	38 (28.4)
Hyperplasia	47 (35.1)
Atrophy	49 (36.5)

Data presented as mean ± SD or n (%)
GA = general anesthesia; RA = regional anesthesia; NMBA = neuromuscular blocking agent

general anesthesia with muscle relaxant. Among 11 patients, 7 cases (64%) received anesthetics at reduced dosed, whereas 4 cases (36%) received normal dosage of anesthetics. The TOF was monitored before extubation in 6 patients (54.5%). There was no postoperative ventilator complication in patients who underwent combined anesthesia.

Univariate analysis identified receipt of preoperative pyridostigmine consumption (OR 3.82, 95% CI 1.12 to 13.07, $p = 0.03$); preoperative plasmapheresis (OR 10.82, 95% CI 1.39 to 84.46, $p = 0.02$); Osserman class III (OR 3.14, 95% CI 0.86 to 11.08, $p = 0.08$); video-assisted thoracoscopic thymectomy (OR 2.90, 95% CI 0.89 to 9.42, $p = 0.08$) and operative time (OR 1.02, 95% CI 1.00 to 1.02, $p = 0.03$) as risk factors for PORCs (Table 3, 4). Multivariate analysis identified receipt of preoperative pyridostigmine alone (OR 6.37, 95% CI 1.32 to 30.88, $p = 0.02$) and Osserman class III (OR 5.44, 95% CI 1.02 to 24.63, $p = 0.03$) as predictors of PORCs (Table 5).

Table 2. Details of patients with postoperative respiratory complications

Respiratory complications	No	Gender	Age	Stage	Preoperative medication	Type of operation	NMBA	TOF monitoring	Causes	Management
Delayed extubation										
	1	F	45	III	Pyridostigmine& prednisolone	Transsternal	Atracurium (reduced dose)	No	Planned	Extubation (POD4)
	2	F	56	I	Pyridostigmine	Transsternal	Atracurium (reduced dose)	Yes	Residual neuromuscular blockade	Extubation (7 h)
	3	F	57	III	Pyridostigmine& prednisolone	VATS	Cis-atracurium (reduced dose)	No	Planned	Extubation (POD 11)
	4	M	73	IIb	Pyridostigmine	Transsternal	Atracurium (normal dose)	Yes	Residual neuromuscular blockade	Extubation (2 h)
	5	F	37	IIb	Pyridostigmine& prednisolone	VATS	Cis-atracurium (normal dose)	Yes	Residual neuromuscular blockade	Extubation (2 h)
	6	F	60	IIb	Pyridostigmine	VATS	Cis-atracurium (normal dose)	No	Residual neuromuscular blockade	Extubation (3 h)
Desaturation										
	7	F	21	IIb	Pyridostigmine& prednisolone	VATS	Atracurium (reduced dose)	No	Mucus plug	Reintubation (POD 1)
	8	F	32	IIb	Pyridostigmine& prednisolone	VATS	Vecuronium (reduced dose)	Yes	Residual neuromuscular blockade	Reintubation (in OR)
	9	F	23	IIb	Pyridostigmine& prednisolone	VATS	Cis-atracurium (normal dose)	Yes	Bronchospasm	Bronchodilator and Oxygen mask with bag (PACU)
	10	F	26	IIb	Pyridostigmine	VATS	-	-	Right pneumothorax	Revised ICD (5 h after surgery)
Dyspnea										
	11	F	60	IIb	Pyridostigmine	Transsternal	Atracurium (reduced dose)	No	Pain	Morphine
	12	F	62	III	Pyridostigmine& prednisolone	Transsternal	-	-	Pain	Morphine
	13	M	33	III	Pyridostigmine& prednisolone	VATS	Atracurium (reduced dose)	Yes	Pneumothorax & pain	Revised ICD & morphine

VATS = video-assisted thoracoscopic surgery; TOF = Train of Four; POD = postoperative day; ICD = intercostal drainage; PACU = Postanesthesia care unit

Table 3. Pre-operative factors affecting the development of postoperative respiratory complications: univariate analysis

Patient variables	Respiratory complications		Univariate	
	Yes (n = 13)	No (n = 121)	*p*-value	Crude OR
Preoperative medications				
Pyridostigmine	5 (22.7)	17 (77.3)	0.03	3.82 (1.12, 13.07)
Pyridostigmine and prednisolone	8 (7.1)	104 (92.9)		1
Pyridostigmine (mg)				
≤240	4 (9.1)	40 (81.9)		0.90 (0.26, 3.10)
>240	9 (10.0)	81 (90.0)	0.87	1
Preoperative plasmapheresis				
No	11 (8.5)	119 (91.5)		1
Yes	2 (50.0)	2 (50.0)	0.02	10.82 (1.39, 84.46)
Duration of disease (mo)				
≥72	0 (0)	9 (100)		
<72	13 (10.4)	112 (89.6)	-	-
Osserman stage				
I, IIA, IIB	9 (7.8)	106 (92.2)		1
III	4 (21.1)	15 (78.9)	0.08	3.14 (0.86, 11.48)
Concomitant chronic lung disease				
No	13 (10.0)	117 (90.0)		
Yes	0 (0)	4 (100)	-	-
History of respiratory failure				
No	9 (8.2)	101 (91.8)		1
Yes	4 (16.7)	20 (83.3)	0.21	2.24 (0.63, 8.01)

Table 4. Intraoperative factors affecting the development of postoperative respiratory complications: univariate analysis

Patient variables	Respiratory complications		Univariate	
	Yes (n = 13)	No (n = 121)	*p*-value	Crude OR
Type of operation			0.07	
Transsternalthymectomy	5 (6.0)	78 (94.0)	1	
Video-assisted thoracoscopicthymectomy	8 (15.7)	43 (84.3)	0.09	2.90 (0.89,9.42)
Operative duration	133.1±56.3	107.8±36.2	0.03	1.02 (1.00,1.02)
Anesthetic techniques				
GA with reduced dose of NMBA	8 (8.7)	84 (91.3)	-	
GA with normal dose of NMBA	3 (20.0)	12 (80.0)		
GA without NMBA	2 (10.0)	18 (90.0)		
Combined GA and RA	0 (0)	7 (100.0)		
Intraoperative opioids				
Total morphine equivalent dose (mg)	5.9±5.2	5.2±3.8	0.65	
Train of Four monitoring				
No	7 (11.3)	55 (88.7)	0.57	1.40 (0.44,4.41)
Yes	6 (8.3)	66 (591.7)		1

GA = general anesthesia; RA = regional anesthesia; NMBA = neuromuscular blocking agent

Discussion

In this study, the 9.3% incidence of PORCs was lower than that reported by previous studies[3-5,11,12]. Many factors influence the incidence of PORCs, including disease severity and anesthetic technique. Suwanchinda et al[11] have demonstrated

Table 5. Multivariate analysis of the increase postoperative respiratory complications after thymectomy

	p-value	Adjusted OR
Preoperative pyridostigmine	0.02	6.4 (1.3, 30.9)
Osserman class III	0.03	5.4 (1.0, 24.6)

that ventilator support was needed in 29.2% of patients who received combined general and epidural anesthesia, compared with the 77.8% who needed ventilator support after receiving general anesthesia alone. All seven patients who were given combined general and regional anesthesia in their study were extubated at the end of surgery, consistent with the results of another study[6]. The choice of anesthetic agents varied across three studies, including this present work; these were propofol infusion alone[6], fentanyl, and NMBAs[11], and fentanyl alone or morphine with or without NMBAs. All patients who did not receive NMBAs in our study, except for one patient who had desaturation from pneumothorax, did not develop PORCs.

This study revealed that the risk factors for PORCs were preoperative administration of pyridostigmine alone compared with combined pyridostigmine and prednisolone. However, the effect of preoperative steroid therapy for MG on the development of PORCs is still a controversy[9,10,13,14]. Kataoka et al[15], demonstrated that administration of additional perioperative low-dose steroids can lower the risk for PORCs. Wolfe et al[16], have demonstrated in a randomized trial that clinical outcomes within 3 years were better in patients who underwent thymectomy and received prednisolone than those who received prednisolone alone. Mori et al[8], have shown that patients who received preoperative pyridostigmine $\geq$240 mg/day were at risk for postoperative reintubation. Osserman class III was found in this study to be a risk factor for PORCs. Watanabe et al[9], have likewise demonstrated the relationship between Osserman classification and postoperative myasthenia crisis. Leuzzi et al[17], demonstrated that Ossermanclass IIb, III, and IV; history of myasthenic crisis; and duration of symptoms >2 years independently predicted postoperative respiratory failure.

The effect of duration of surgery on PORCs is still controversial[8,9]. In this study, we identified by univariate analysis that duration of surgery was a risk factor for PORCs; this was likely due to the prolonged duration and number of anesthetic exposure. Corresponding to the study of Smith et al[25], the most favorable type of muscle relaxant used in this study was atracurium, which is an intermediate-acting, non-depolarizing muscle relaxant that allowed a rapid rate of recovery from neuromuscular blockade. In some MG patients, the dose of non-depolarizing muscle relaxants was reduced to lessen the sensitivity of the MG patients to the drugs.

The present study showed that history of plasmapheresis was a risk factor of PORCs from univariate analysis,consistent with the other reports[9,17]. Our patients who needed postoperative ventilator support underwent plasmapheresis within one week before surgery due to the severity of their disease. On the other hand, two patients who received plasmapheresis three months prior to surgery did not develop PORCs. Similarly, Saeteng et al[18], was not able to demonstrate any benefit of plasmapheresis before elective thymectomy on PORCs.

Only two patients (1.5%) in our study required prolonged (>24 hour) ventilator support, compared with the 11.5% reported by another study[9]. The differences between these two studies were the anesthetic agents used and duration of operation; our patients received reduced doses of NMBAs and underwent shorter thymectomy (133.1$\pm$56.3 minutes), whereas the patients in the other study received combined general anesthesia and thoracic epidural block without NMBAs and underwent longer thymectomy(203$\pm$98 min).

Four of our patients who underwent neuromuscular monitoring experienced postoperative rNMB. This may be explained by the findings of Takahashi et al[19], who demonstrated in rats that the severity of MG influenced the relationship between TOF ratio and T1, along with changes in the run-down of endplate potentials and those around the neuromuscular junction. Therefore, TOF ratio maynot be an accurate indicator of recovery from NMBAs in MG patients. Further *in vivo* studies are required.

Due to the unpredictable response of MG patients to neuromuscular blocking drugs, a large, randomized controlled study is required to demonstrate the effective use of muscle relaxants without increasing

the risk for postoperative respiratory compromise. In the meantime, we suggest that muscle relaxants should be used carefully with proper neuromuscular monitoring in myasthenia patientsandonly when extremely necessary.

Several case reports and case series have demonstrated the safe use of the new reversal agent, sugummadex, in myasthenic patients receiving rocuronium during anesthesia[20-22]. In addition, anesthesia techniques without the use of NMBAs were proposed; these include combined sevoflurane with thoracic epidural anesthesia[23], and either fentanyl combined with propofol or sevoflurane[24]. However, most of these studies were retrospective and were limited by selection and information bias. A large prospective study will be required to verify our results. A well-controlled study is likewise needed to prove that sugammadex is the best option for myasthenic patients who will undergo surgery.

One limitation of this study was that majority of our patients were in the early stage and had low severity of MG, which meant relatively short duration of disease and small dose of received pyridostigmine.

Conclusion

The incidence of PORCs in myasthenic patients who underwent thymectomy in this study was 9.7%. The significant risk factors for PORCs include preoperative use of pyridostigmine and Osserman class III. The use of muscle relaxant to this kind of patient should be weighed between risk and benefit regarding to patient's safety.

What is already known on this topic?

Myasthenic patients who receive general anesthesia are at risk of PORCs, with a reported incidence of 11-22%. Muscle function monitoring, combined general and epidural anesthesia, avoidance or dose reduction of muscle relaxants were suggested to prevent these adverse outcomes.

What this study adds?

The incidence of PORCs in myasthenic patients who underwent thymectomy in this study was 9.7%. Muscle function monitoring by TOF before extubation did not prevent respiratory complication. Preoperative use of pyridostigmine and Osserman class III were the significant risk factors for PORCs.

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Potential conflicts of interest

None.

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Appendix 1. Osserman classification of Myasthniagravis[9]

Class I	Focal disease (restricted to ocular muscle)
Class IIa	Mild generalized disease, prominent limb involvement
Class IIb	Moderate generalized disease, prominent bulbar involvement
Class III	Acute severe generalized disease with respiratory symptom
Class IV	Severe generalized disease with respiratory symptom

อุบัติการณ์และปัจจัยเสี่ยงต่อภาวะแทรกซ้อนทางระบบหายใจในผู้ป่วยมัยแอสธีเนีย เกรวิส ภายหลังการผ่าตัดต่อมไธมัส

อภิชาต ศุภธรรมวิทย์, ศรัญญา เลิศโกวิทย์, ศิริลักษณ์ สุขสมปอง

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์และปัจจัยเสี่ยงของการเกิดภาวะแทรกซ้อนของระบบหายใจหลังผ่าตัด ในผู้ป่วยมัยแอสธีเนีย เกรวิส*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังในผู้ป่วยมัยแอสธีเนีย เกรวิสที่มารับการผ่าตัดต่อมธัยมัส ณ โรงพยาบาล ศิริราช พ.ศ. 2553 ถึง 2557 คำจำกัดความของภาวะแทรกซ้อนของระบบหายใจหลังผ่าตัดได้แก่ไม่สามารถ ถอดท่อหายใจทันทีหลังเสร็จสิ้นการผ่าตัด หรือ มีการเปลี่ยนแปลงของระบบหายใจที่ต้องให้การรักษา หรือ มีการใส่ท่อหายใจซ้ำ ผู้วิจัยทำการบันทึกข้อมูลของผู้ป่วยและข้อมูลการผ่าตัดจากเวชระเบียน*

ผลการศึกษา: *มีจำนวนผู้ป่วย 134 รายเข้าได้กับการศึกษา พบอุบัติการณ์ของการเกิดภาวะแทรกซ้อนของระบบหายใจ หลังผ่าตัดร้อยละ 9.7 สำหรับปัจจัยเสี่ยงของการเกิดภาวะแทรกซ้อนของระบบหายใจหลังผ่าตัดจากการวิเคราะห์แบบ univariate analysis พบว่าปัจจัยเสี่ยงของการเกิดภาวะแทรกซ้อนของระบบหายใจหลังผ่าตัดได้แก่ผู้ป่วยที่รับประทาน ยาเมสตินอนเพียงชนิดเดียวก่อนผ่าตัด (OR 3.82, 95%CI 1.12-13.07, p = 0.03), มีประวัติเคยได้รับพลาสมาเฟเรซิส มาก่อน (OR 10.82, 95%CI 1.39-84.46, p = 0.02) และระยะเวลาผ่าตัดนาน (OR 1.02, 95%CI 1.00-1.03, p = 0.03) จากการวิเคราะห์แบบ multivariate analysis พบว่าปัจจัยเสี่ยงได้แก่ผู้ป่วยที่รับประทานยาเมสตินอน เพียงชนิดเดียวก่อนผ่าตัด (OR 6.37, 95%CI 1.32-30.88, p = 0.02) และ Osserman class III (OR 5.65, 95%CI 1.10-29.03, p = 0.04)*

สรุป: *ผู้ป่วยที่รับประทานยาเมสตินอนเพียงชนิดเดียวก่อนผ่าตัดและผู้ป่วย Osserman class III มีโอกาสเกิดการเกิดภาวะแทรกซ้อนของระบบหายใจหลังผ่าตัดต่อมธัยมัส*