

Title: Dual neuromuscular monitoring in juvenile myasthenia gravis undergoing thoracoscopic thymectomy - Report of four cases.

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Abstract:

Differential neuromuscular blockade between muscles has been reported in healthy subjects, but information on this phenomenon in patients with juvenile myasthenia gravis (JMG) is scarce. The degree of muscle weakness between different muscles in MG patients varies from person to person. Single stimulations of the orbicularis oculi and pollicis longus muscles in the same patient are variable and do not give reproducible results.

We anaesthetised four girls with MG (Osserman stage II-B) undergoing video-assisted thoracoscopic thymectomy (VATT). We administered propofol, fentanyl or remifentanyl and vecuronium or cisatracurium during an average anaesthetic period of 155 minutes. Isoflurane was used in one case. A method of dual neuromuscular monitoring is described to assess intraoperative neuromuscular status more accurately. We conclude that undergoing VATT in addition to propofol, remifentanyl and cisatracurium anaesthesia and double neuromuscular monitoring provides safe operating conditions and serves as a tool for early recovery in juvenile MG patients.

Keywords:

Total intravenous anaesthesia, thoracoscopic thymectomy, juvenile myasthenia gravis, neuromuscular monitoring, myasthenia score, neuromonitoring, acetylcholine receptor antibodies.

Introduction:

Juvenile myasthenia gravis (JMG) is an autoimmune disease caused by the formation of autoantibodies against elements of neuromuscular transmission. Acetylcholine receptor antibodies, in addition to titin and muscle-specific kinase antibodies, affect the function of the acetylcholine receptor on the postsynaptic nicotinic membrane[1]. The overall incidence of MG is approximately 3-4: 1,000,000. Its prevalence is 60-100 per 1,000,000. MG rarely occurs in childhood. Approximately 10% of the incidence and prevalence is in people aged 16 years or younger [22]. Exact figures on the incidence and prevalence of juvenile MG are not available. A discrepancy between electrical and clinical neuromuscular recovery is often seen in healthy patients compared to MG patients [19,23]. The primary therapy for congenital, infantile and juvenile MG is the administration of acetylcholinesterase inhibitors[5]. If medical treatment fails, the surgical treatment of juvenile MG is thymectomy [2,3].

Children are candidates for surgery if they have a short history, progressive disease, and Osserman stage I to II-B. Thymectomy can be performed by video-assisted thoracoscopic thymectomy (VATT). We describe the anaesthetic management of four cases of juvenile MG undergoing VATT.

Methods:

We anaesthetised four girls with MG. Preoperative symptoms are listed in Table 1. All were operated using the VATT technique.

Table 1. Patient data and preoperative scoring system

Case	1	2	3	4
Age Years	12	9	12	14
Weight Kiloqram	60	29	45	67
Osserman classification	II-B	II-B	II-B	II-B
Pyridostigmin dose mg	600	80	360	0
Acetylcholin Antibody (nmol/l)	24	0,03	18,7	210
Vital capacity %	90,7	79 4	55 1	89
FEV1 %	109	94,2	58,2	95
Muscle weakness [4,5]	3	2	4	3
Case	1	2	3	4
Ptosis	+	+	+	-
Diplopia	+	-	-	+
Dysphagia	+	+	+	+
Dysarthria	+	+	+	+

Case report 1:

This girl presented with progressive MG for 8 months with myasthenic crisis. Pyridostigmine had to be increased to 600 mg daily. Preoperatively she had mild arm weakness, ptosis, diplopia, dysphagia and dysarthria. We tried to reduce the dose of pyridostigmine preoperatively, but diplopia and dysphagia worsened, so we had to administer pyridostigmine (300 mg) before surgery. For induction of anaesthesia and tracheal intubation, we administered propofol (2.5 mg/kg), fentanyl (0.025 mg) and vecuronium (0.5 mg) to achieve complete neuromuscular blockade. Neuromuscular blockade was monitored at the ulnar nerve with an NS 252 relaxometer. A 35 Charriere left Robertshaw tube was used for one-lung ventilation. To maintain anaesthesia, we administered isoflurane (0.6%) and a bolus of fentanyl (0.025 mg) i.v. We did not need to administer additional vecuronium during surgery. At the end of surgery, we antagonised the residual effects of the neuromuscular block with pyridostigmine (1.0 mg) i.v. We were able to extubate the patient within 30 minutes. On the first postoperative day, a severe myasthenic crisis occurred requiring endotracheal intubation and mechanical ventilation. While on mechanical ventilation in the ICU, we were able to reduce the dose of pyridostigmine to about 600 mg per day. After successful weaning from the ventilator, she was maintained on the 600 mg daily dose of pyridostigmine. We discharged this girl from the ICU on postoperative day 6.

Case Report 2:

This 9-year-old girl presented with myasthenic symptoms for 3 months with rapid progression. During induction, three repeated 0.5 mg vecuronium bolus injections were required to achieve complete neuromuscular block. We also used 0.5 mg vecuronium at 45, 55 and 60 minutes. The morning dose of pyridostigmine was administered intraoperatively via a gavage tube. At the end of surgery, the remaining neuromuscular block was antagonised with 1.0 mg of pyridostigmine. The maintenance dose of pyridostigmine was not increased postoperatively. The ICU stay was one day.

Case report 3.

In this 12-year-old girl, two months elapsed between the onset of symptoms and the diagnosis of myasthenia gravis. The pre-anaesthetic status showed a reduction in respiratory capacity. The patient was premedicated with promethazine per os. For induction and maintenance of anaesthesia we used a target of 2.75 µg/ml propofol and 0.1 µg/kg/min remifentanyl. The

morning dose of pyridostigmine was given by gastric tube. We used cisatracurium 0.02 mg/kg for complete muscle relaxation and intubated with a 28 Charriere double lumen tube. We used a total of 1.59 mg of cisatracurium until the end of anaesthesia. We extubated this girl when the TOF ratio on the adductor pollicis longus was 96%. The time between the end of surgery and extubation was 5 minutes.

The girl remained in the ICU. On postoperative day 3, her myasthenic status changed dramatically. She developed respiratory insufficiency and had to be reintubated.

Case Report 4:

This 14-year-old girl presented with the strength-dependent symptoms of diplopia, dysphagia and dysarthria. Her acetylcholine antibody titer was (210 nmol/l). For induction and maintenance of anaesthesia we used a target of 3.5 µg/ml propofol, 0.5 µg/kg remifentanyl and 0.02 mg/kg cisatracurium. Depth of anaesthesia was assessed with an EEG monitor (Narkotrend), while neuromuscular blockade was monitored with TOF Guard (Biometer) at the ulnar nerve and TOF Watch SX (Biometer) at the facial nerve. After induction we used a 35 Charriere left double lumen tube for intubation. From TOF ratio 25 we started continuous infusion of cisatracurium at 1.0 µg/kg/min. The continuous infusion of cisatracurium was stopped just before the endoscopic removal of the thymus. At the end of the operation, the girl was extubated without complications and was discharged from the ICU after one day without pyridostigmine medication.

All descriptive data of the anaesthetics are shown in the following table.

Table 2: Management of anaesthesia

Case	1	2	3	4
Management	bA, tNMM	TIVA, tNMM	TCI, 2qNMM, EEG	TCI, 2qNMM, EEG
Propofol (mg/kg)	2.5	11,2	15,8	18,7
Isofluran MAC (Vol.%)	0,6	0	0	0
Fentanyl (µg/kg)	13	26	0	0
Remifentanyl (µg/kg)	0	0	53,5	29,4
Vecuronium (µg/kg)	8,33	103,44	0	0
Cisatracurium (µg/kg)	0	0	35,4	84,1
Duration of anesthesia	235	145	125	90
Duration of SLV	140	90	100	70
Duration of surgery	150	100	105	75
Pyridostigmin mg (iv)	1	1	0,15	0
Pyridostigmin mg GT	0	20	90	0
DLT Charriere	35	26	28	35
ICU length of stay	6	1	6	1

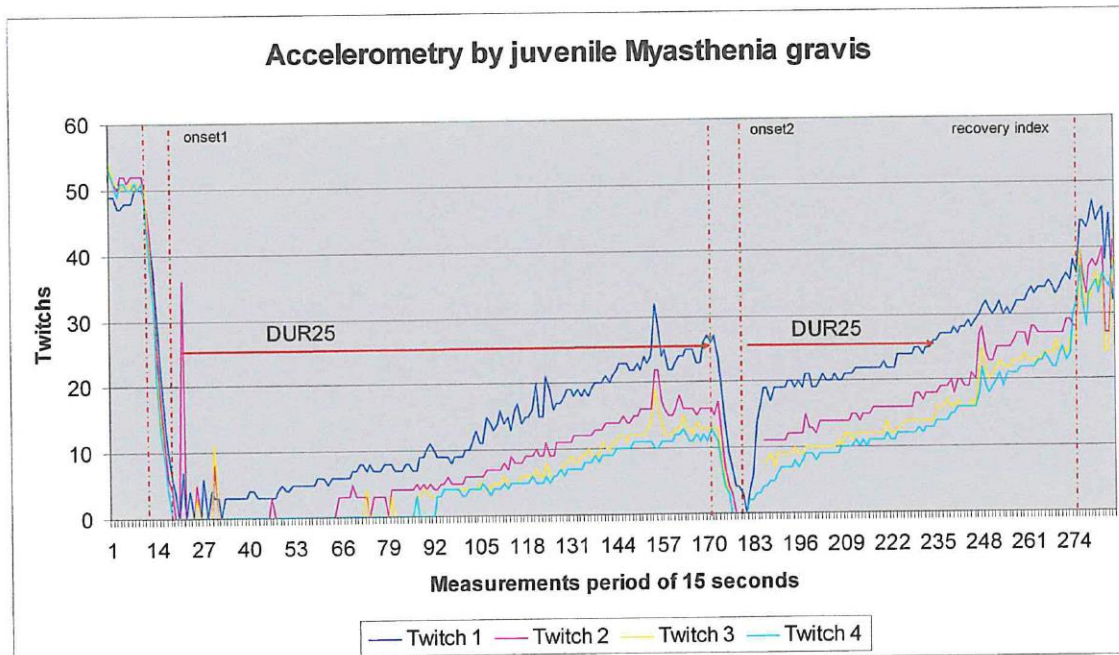
Legend: bA=balanced anaesthesia, TIVA=total intravenous anaesthesia, tNMM=tactile neuromuscular monitoring; 2qNMM=double qualitative neuromuscular monitoring, TCI= target controlled infusion, EEG = neuromonitoring; GT=gastric tube

A neuromuscular score was obtained during the preoperative evaluation. In order to apply a neuromuscular scoring system, we performed an arm and foot exertion test, fist clenching

test, and examination for ptosis and diplopia. A spirometric evaluation is mandatory to assess the involvement of the respiratory muscles. A chest radiograph was used to assess cardiopulmonary status and to measure tracheal diameter to select the most appropriate double lumen tracheal tube. The double lumen tube was required to provide one-lung ventilation during the VATT procedure. Premedication was promethazine 1.0 mg/kg. After induction of anaesthesia, but before injection of any muscle relaxant, we calibrated the muscle relaxation monitoring device using optimal supramaximal stimulation of the adductor pollicis longus and orbicularis oculi muscles. Neuromuscular monitoring was performed by measuring acceleration with piezoelectric transducers (Biometer). The nerves were stimulated with 0.2 ms square pulses every 15 seconds with a pause of 1 minute. Neuromuscular data were recorded on a memory card using TOF Reader software. For accelerometry we used TOF Guard and TOF Watch SX or Innervator NS 252 (Fisher Parkell) for visual assessment of forearm contractions. The slow TOF mode is a continuous stimulation with four 0.2 ms square twitch pulses and a pause of 5 minutes. The correct position of the double lumen tube was confirmed by auscultation and bronchoscopy. The use of a double lumen tube is advantageous compared to the use of a bronchial blocker during single lung ventilation because it allows broncho-alveolar mucus aspiration. The gas flow consisted of air/oxygen in a 50/50 ratio. During VATT, normoventilation was maintained with a target etCO_2 between 33 and 35 mmHg. No PEEP or low flow was applied to the blocked lung. Arterial pO_2 was greater than 100 mmHg at all times and mean arterial oxygen saturation was 98%. Haemodynamic conditions were stable. Vecuronium injection was triggered by measurement of the TOF response, resulting in an intubation dose of 30.03 $\mu\text{g/kg}$. The girls were intubated after achieving a twitch height < 10% of baseline and a TOF < 25%. After administration of vecuronium, the onset of action of approximately 1 minute was not shortened to 35 minutes, nor was the duration of action prolonged in this patient. However, we found a prolonged recovery index of 30 minutes after three repeated doses totalling 17.24 $\mu\text{g/kg}$. In addition, 51.15 $\mu\text{g/kg}$ of pyridostigmine was administered at the end of the procedure. Cisatracurium was used at a dose of 0.02 mg/kg to achieve good intubation conditions. The infusion of cisatracurium was stopped at the time of complete muscle relaxation. No further muscle relaxants were administered until duration 25 (DUR25). The use of 20% of 2x ED 95 cisatracurium resulted in a faster onset of action (mean=2:10 minutes). After DUR25, 4.15 $\mu\text{g/kg/min}$ of cisatracurium was administered. After stopping the cisatracurium infusion, the relaxation index at 10 minutes did not differ from that of healthy girls. Propofol (12.05 mg/kg), fentanyl (1.95 $\mu\text{g/kg}$) or remifentanyl (41.44 $\mu\text{g/kg}$) was used during a mean anaesthesia time of 155 minutes. In the TCI technique, we also installed EEG neuromonitoring (Narkotrend). Throughout the procedure, the children were kept in a D2 EEG level. For postoperative analgesia we used pentazocin at an average of 1.26 mg/kg or 0.05 $\mu\text{g/kg/min}$ remifentanyl continuously. To assess postoperative pain, we used an analogue visual scale from 1 to 10. Our aim was a maximum pain level of 2 to 3.

Results:

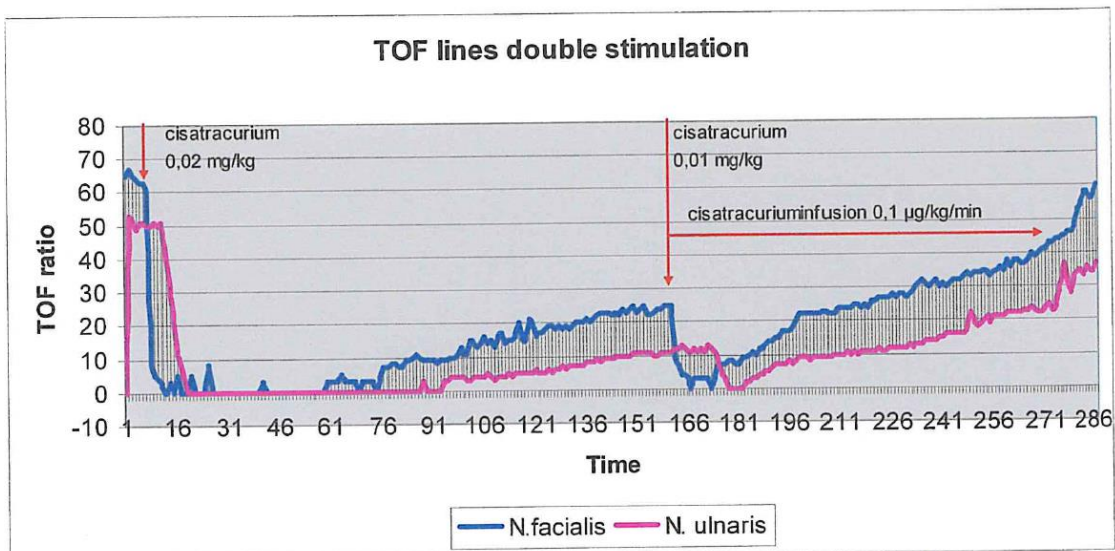
Figure 1: Mono-Accelomyometry Ulnar Nerve



Legend: supramaximal stimulation (165 s); first onset time (150 s); first DUR 25 (38:15 min); second onset time (150 s); second DUR 25 (32:00 min); second point DUR 25; recovery index time=duration 75

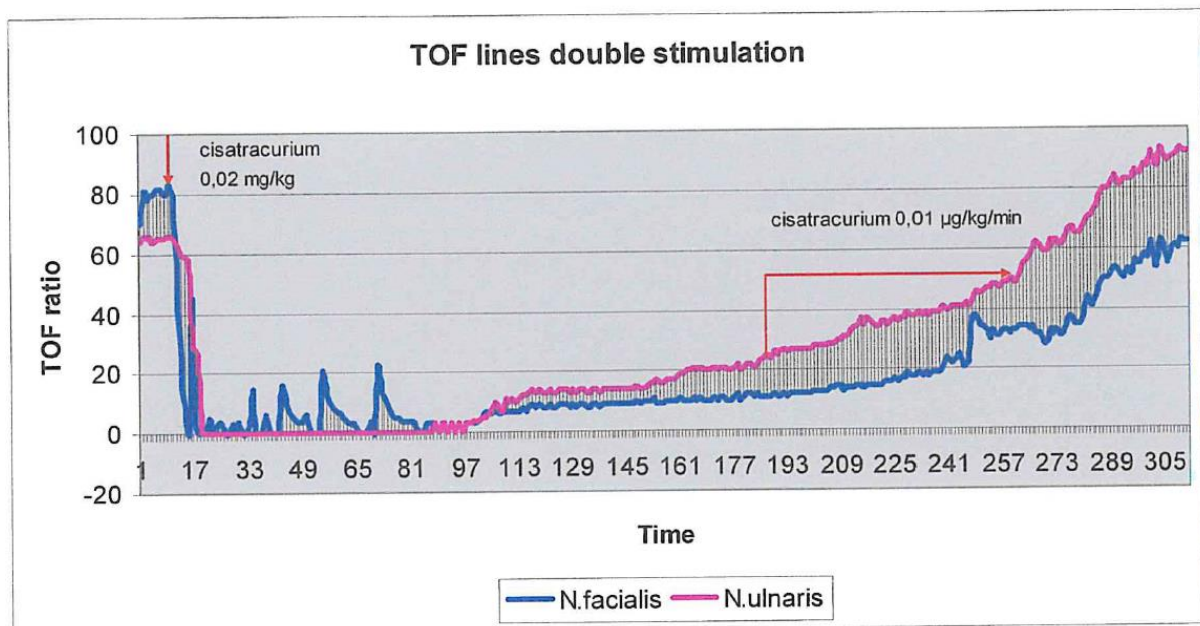
The duration of supramaximal stimulation was 2:45 minutes. The time from administration of cisatracurium (0.02 mg/kg) to twitch O and TOF ratio O was 2:30 minutes. The time from cisatracurium to DUR 25 was 38 minutes and 15 seconds. The second onset time after administration of cisatracurium (0.01 mg/kg) was again 2:10 minutes. Cisatracurium was then administered continuously (0.1 µg/kg/min). We switched the TOF monitoring to slow mode stimulation for 20 minutes. 32 minutes passed until the second DUR25. The infusion was stopped. The TOF ratio (T4/T1) was 84%. The recovery index was 10:15 minutes. We administered a total of 1.59 mg of cisatracurium during anaesthesia. We extubated this girl 5 minutes after the end of surgery with a TOF ratio of 96%.

Figure 2: TOF double stimulation. Facial and ulnar nerves



The difference between the TOF graphs is the area between the curves. This area corresponds to the TOF ratio. The girl presented with a generalised form of myasthenia with reduced respiratory capacity. The TOF response curve of the periocular muscles lies above the response curve of the adductor pollicis. At the beginning of anaesthesia, the onset time is shorter in the ocular muscles. Comparison of the amplitudes of the muscle responses shows that the oculi response curve is larger and that the TOF quotient is greater than 0.5 (TOF N. facialis > TOF N. ulnaris).

Figure 3: TOF double stimulation



This picture shows both TOF curves of stimulation in a girl with the generalised form of MG with diplopia, dysphagia and dysarthria. The TOF quotient is less than 0.5 (TOF N. ulnaris > N. facialis) because the response curve of the adductor pollicis muscle is above that of the periocular muscles. In untreated patients with MG, spontaneous wasting occurs in the absence of muscle relaxants. The degree of muscle weakness varies between different muscles in MG patients. Single stimulations of the orbicularis oculi and pollicis longus muscles in the same patient are variable and do not give reproducible results. Better results are obtained by monitoring TOF at both sites. The relationship between the two TOF measurements allows a better assessment of the true neuromuscular status.

Furthermore, in MG there is no neuromuscular safety reserve tested by tetanic stimulation and double burst stimulation. In MG, the use of tetanic stimulation and double burst stimulation does not give better results than TOF. The slow TOF mode is preferred because it reduces neuromuscular fatigue during stimulation.

Discussion: The juvenile form of MG is very rare. Only 10% of patients with myasthenia gravis are younger than 16 years [22]. The progressive form of MG and the short time from symptom onset to diagnosis are indications for surgical therapy in these children. The advent of video-assisted thymectomy has reduced surgical trauma and length of hospital stay. Single-lung ventilation with adequate neuromuscular blockade is essential for this procedure [6,7]. Compared with isoflurane anaesthesia, the intravenous technique resulted in favourable recovery conditions in juvenile myasthenic girls [8-10]. The use of inhalational anaesthetics may not be safe due to immunological interactions of different autoantibodies after anaesthesia [11, 123]. We have previously reported that propofol does not interact with the motor endplate [13, 14]. The degree of muscle weakness between different muscles in MG patients varies individually [4, 21]. The use of supramaximal stimulation (approximately 10 to 2 mA) prevents the decline from fading in MG [18]. Single stimulations

of the orbicularis oculi and pollicis longus muscles in the same patient are variable and do not give reproducible results. We have used accelerometers, but we have not found any differences between the measurements on these nerves to predict relaxation, unlike other authors [19,20].

The measurements at two sites and the calculation of the relaxometric quotients of the muscle responses gave us a very good assessment of the status of neuromuscular blockade. A TOF quotient of 1.0 indicates inadequate blockade and the dose of cisatracurium should be increased. A TOF less than 0.5 indicates excessive blockade and the cisatracurium infusion must be stopped. The TOF quotient is determined by the magnitude of the TOF value. However, it is important to note that the TOF quotient only compares the two curves. Because of the multiple manifestations of muscle weakness, double stimulation gives the most reliable results, which helps to achieve the goal of early extubation.

We prefer cisatracurium to vecuronium because of its organ-independent elimination. In addition, the elimination of cisatracurium is not influenced by the state of neuromuscular recovery. The recovery index of cisatracurium is approximately 11 minutes and is independent of the total cumulative dose. Our intubation dose was comparable to the experience of other authors [15,16]. Response to neuromuscular blocking agents is variable in myasthenic children [11,17].

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