

Neuromuscular Monitoring at the Orbicularis Oculi May Overestimate the Blockade in Myasthenic Patients

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Background: In most publications about myasthenia, monitoring neuromuscular blockade during anesthesia is recommended. In healthy patients, the relation of blockade between muscles has been established, but there is little information about the relation in myasthenic patients. Our objective was to investigate whether the relation between the orbicularis oculi and adductor pollicis muscles is the same in healthy patients and myasthenic patients.

Methods: After anesthesia was induced with 4–6 mg/kg thiopental and 2 µg/kg fentanyl, followed by 2% sevoflurane and 60% nitrous oxide in oxygen, 10 healthy patients and 10 myasthenic patients received 0.025 and 0.01 mg/kg vecuronium, respectively. Neuromuscular monitoring was performed with use of accelerometry at the orbicularis oculi and the adductor pollicis muscles by stimulating the temporal branch of the facial nerve and the ulnar nerve.

Results: The relation of blockade between these two muscles was not the same in healthy patients and myasthenic patients: in healthy patients, the maximum neuromuscular blockade with 0.025 mg/kg vecuronium was less in the orbicularis oculi than in the adductor pollicis (median 72% vs. 91%; $P < 0.05$); in contrast, in myasthenic patients, the blockade with 0.01 mg/kg vecuronium was greater in the orbicularis oculi than in the adductor pollicis (median 96% vs. 62%; $P < 0.05$).

Conclusion: Neuromuscular monitoring at the orbicularis oculi may overestimate blockade in myasthenic patients. Extubation must be performed when the muscle most sensitive to neuromuscular blocking agents is recovered. Therefore, neuromuscular monitoring at the orbicularis oculi is recommended to avoid persistent neuromuscular blockade in patients with myasthenia gravis. (Key words: Acceleration; myasthenia gravis; nondepolarizing neuromuscular blocker; Osserman classification.)

IN anesthetic management of patients with myasthenia gravis, neuromuscular monitoring is recommended and performed commonly in the forearm muscles. Consequently, knowledge regarding the effect of neuromuscular blocking agents is restricted to these muscles. In myasthenic patients, however, the ocular muscles are affected most commonly,¹ and neuromuscular blockade (NMB) is expected to be deeper in the orbicularis oculi compared with the adductor pollicis muscles. This is in

contrast with healthy patients, who responded considerably less to neuromuscular blocking agents at the orbicularis oculi compared with the adductor pollicis muscle.^{2–4} Therefore, we hypothesize that the relation between these two muscles is not the same in healthy patients and myasthenic patients. To study this hypothesis, we compared the degree of NMB in these two muscles in healthy patients and myasthenic patients.

Methods

After approval by the Ethics Committee of Kanazawa University (Kanazawa, Japan) and informed consent were obtained, we conducted this study in 10 healthy patients and 10 myasthenic patients who were scheduled to undergo minor surgery or thymectomy. All myasthenic patients showed a positive reaction to intravenous injection of 10 mg edrophonium. Myasthenic patients were classified into two subgroups ($n = 5$ for each): ocular-type patients (Osserman classification type I⁵) and generalized-type patients (type II). In generalized-type patients, preoperative electromyography with 3-Hz stimulation at the deltoid muscle showed waning. Anticholinesterase or steroid therapy, if necessary, was continued until the morning of surgery. Hydroxyzine, 50 mg, and atropine, 0.5 mg, were administered intramuscularly 1 h before induction of anesthesia. Anesthesia was induced with 4–6 mg/kg thiopental and 2 µg/kg fentanyl, followed by 2% sevoflurane and 60% nitrous oxide in oxygen. The trachea was intubated after topical anesthesia, without administration of a neuromuscular blocker. The lungs were ventilated so that end-tidal carbon dioxide pressure was maintained between 35–45 mmHg. Skin temperature over the forehead and the thenar region was kept at 32 or 33°C.

Neuromuscular monitoring was performed by measuring the acceleration of the orbicularis oculi and adductor pollicis muscles. Electrodes were placed 2 cm anterior to the ear lobe and at the wrist. The piezoelectric transducers (TOF Guard; Biometer International, Odense, Denmark) were fastened to the external half of the upper eyelid with use of adhesive tape and to the distal phalanx of the thumb. The temporal branches of the facial nerve and the ulnar nerve were stimulated with train-of-four (TOF) square pulses of 0.2-ms duration, which were greater than that needed to produce a maximal response (60 mA). The nerves were stimulated every 15 s. At the eyelid, the transducer measured the acceleration gener-

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ated by circumferential contraction of the orbicularis oculi muscle.² After the patients had rested for more than 10 min to allow the response to stabilize, baseline recordings of the TOF ratio, which were calculated as $100 \times T_4/T_1$ (%) were taken, where T_1 and T_4 were the first and fourth responses after TOF simulation. After baseline measurements were recorded, either 0.025 mg/kg (healthy patients) or 0.01 mg/kg (myasthenic patients) vecuronium was administered intravenously. Responses of the orbicularis oculi and adductor pollicis muscles were monitored continuously. Maximum block was calculated according to the following definition: maximum block was the maximum of $(1 - T_1/\text{baseline } T_1)$. After maximum block, the inspired concentration of sevoflurane was decreased to 0.5–1.5%. Neuromuscular data for the orbicularis oculi and adductor pollicis muscles were recorded on a memory card of the TOF Guard. All graphical and numerical neuromuscular data were obtained with use of TOF Guard Reader software (Biometer International).

Preoperatively, binding and blocking antibodies to acetylcholine receptors (AChRs) were measured in myasthenic patients. The laboratory methods were as follows.

Binding Antibody

α -Bungarotoxin labeled with ^{125}I were bound to prepared antigenic human AChRs (^{125}I -AChR). Sera from patients were incubated with ^{125}I -AChR, and complex materials were precipitated by incubation with anti-human immunoglobulin G. Radioactivity was measured by γ -counter.⁶

Blocking Antibody

Sera from patients and controls were incubated with prepared antigenic AChRs, followed by incubation with ^{125}I -labeled α -bungarotoxin, and aliquots were applied to sepharose columns to measure the percent inhibition of toxin binding with AChRs.⁷

Statistical Analysis

Parametric data are presented as mean \pm SD, and nonparametric data are presented as the median (range). Parametric data were analyzed with use of the *t* test, and nonparametric data were analyzed with use of the Wilcoxon signed rank test or the Mann-Whitney test. A *P* value less than 0.05 was considered to be significant.

Results

Characteristics of the myasthenic patients are shown in table 1. All patients recovered from the anesthesia with no sequelae. There were no significant differences between healthy patients and myasthenic patients with respect to age (51 ± 14 and 49 ± 17 yr, respectively), body weight (58 ± 9 and 59 ± 15 kg, respectively), height (159 ± 12 and 158 ± 12 cm, respectively), time of sevoflurane inhalation (22 ± 6.4 and 20 ± 1.9 , respectively), or gender ratio (5 men:5 women for each group).

Before administration of vecuronium, TOF ratios were more than 100% in both muscles in all healthy patients but were less than 100% in some myasthenic patients (table 2). Significant differences were seen between healthy patients and myasthenic patients in both of the two muscles in baseline TOF ratio. Compared with ocular-type myasthenic patients (type I), the generalized type myasthenic patients (type II) showed smaller TOF ratios in both muscles, but the differences were not significant.

After administration of vecuronium, maximum block was significantly less in the orbicularis oculi than in the adductor pollicis muscles in healthy patients (table 3). In contrast, the block was significantly greater in the orbicularis oculi than in the adductor pollicis muscles in myasthenic patients. Compared with generalized-type myasthenic patients, ocular-type myasthenic patients showed significantly less block in the adductor pollicis muscle.

Table 1. Characteristics of Patients with Myasthenia Gravis

Patient No.	Age/Gender	Osserman Classification	Pyridostigmine/Prednisolone (mg/day)	Duration of Disease (yr)	Binding Antibody* (pmol/ml)	Blocking Antibody† (%)
1	62/M	I	90/—	0.5	12.4	24.5
2	71/M	I	180/—	0.4	5.8	0
3	25/F	I	—/2.5	23	0.4	10.0
4	66/F	I	—/—	4	0.8	8.7
5	62/F	I	—/—	1	9.4	12.6
6	39/M	II	120/5	0.2	<0.1	8.7
7	49/F	II	—/—	20	<0.1	0
8	15/M	II	210/—	0.1	<0.1	0
9	48/F	II	120/—	0.2	<0.1	0
10	55/M	II	180/—	0.8	318	28.4

* Normal < 0.37. † Normal < 10%.

Table 2. Differences in Baseline Train-of-four Ratio

	Train-of-four Ratio (%)	
	Orbicularis Oculi	Adductor Pollicis
Normal patients (n = 10)	107 (100–114)	116 (101–130)
Myasthenic patients (n = 10)	84 (51–108)*	89 (55–125)*
Ocular type (n = 5)	87 (51–108)	100 (74–112)
Generalized type (n = 5)	79 (57–94)	83 (55–125)

Values are median (range).

* $P < 0.05$ versus normal patients. There were no significant differences between the two muscles or between the two types in myasthenic patients.

Ocular type = Osserman classification type I; generalized type = Osserman classification type II.

Discussion

In healthy patients, maximum NMB was significantly less in the orbicularis oculi than in the adductor pollicis muscle. In contrast, in ocular-type myasthenic patients, maximum NMB was significantly greater in the orbicularis oculi. In generalized-type myasthenic patients, maximum NMB was not significantly different between the two muscles. Therefore, the relation of NMB between the two muscles was not the same in healthy patients and myasthenic patients. In addition, the relation was not the same in ocular-type and generalized-type myasthenic patients. These differences between healthy patients and myasthenic patients and between ocular-type and generalized-type myasthenic patients were impressive findings in the current study. Such observations have not been reported previously.

In healthy patients, maximum NMB was significantly less in the orbicularis oculi than in the adductor pollicis muscle after administration of 0.025 mg/kg vecuronium. This finding coincides with the results of previous studies.^{2,3} In those studies, maximum NMB was considerably less in the orbicularis oculi than in the adductor pollicis muscle after administration of 0.04–0.06 mg/kg vecuronium. Therefore, our finding confirms the differential effects of vecuronium on the orbicularis oculi *versus* the adductor pollicis muscle in healthy patients. These differences can be attributed to different muscle fiber composition (fast *vs.* slow),^{8,9} fiber size,^{10,11} or junctional receptor density.¹²

Conversely, in myasthenic patients, maximum NMB was significantly greater in the orbicularis oculi than in the adductor pollicis muscle. Therefore, the relation of NMB between these two muscles differed in healthy patients and myasthenic patients. These findings indicate that data of the differences between muscles, which have been measured in healthy patients, may not be the same in myasthenic patients. The relation between these two muscles in myasthenic patients differed according to the Osserman classification type. The differential effect of vecuronium on the orbicularis oculi *versus* the adductor pollicis muscle was significant only in ocular-type myasthenic patients. The differential response in

Table 3. Differences in Maximum Block

	Orbicularis Oculi (%)	Adductor Pollicis (%)
Normal patients (n = 10)	72 (26–85)	91 (43–97)*
Myasthenic patients (n = 10)	96 (40–100)	62 (0–100)*
Ocular type (n = 5)	83 (40–100)	11 (0–67)*
Generalized type (n = 5)	100 (90–100)	93 (61–100)†

Values are median (range).

* $P < 0.05$ versus orbicularis oculi. † $P < 0.05$ between ocular-type and generalized-type myasthenic patients.

Ocular type = Osserman classification type I; generalized type = Osserman classification type II.

ocular-type myasthenic patients can be attributed to the significant decrease in safety margin of neuromuscular transmission in the ocular muscles. Conversely, in generalized-type myasthenic patients, the safety margin is decreased throughout the body, including the ocular and the adductor pollicis muscles.

The data of 0–67% NMB in the adductor pollicis muscle in ocular-type myasthenic patients show that 0.01 mg/kg vecuronium was not appropriate for these patients, which may have influenced our study. However, several studies that used a cumulative technique have shown that the ED₉₅ of vecuronium is 0.005–0.044 mg/kg in myasthenic patients.^{13–16} Furthermore, in this study, all ocular-type myasthenic patients showed clinically fair muscle relaxation during surgery. Therefore, our results have clinical relevance, even if the relatively small dose of vecuronium in myasthenic patients had some influence on our findings.

This study shows that the relation of NMB between the orbicularis oculi and the adductor pollicis muscles is not the same in healthy patients and myasthenic patients. It follows that at least one, and possibly both, of these muscles do not reflect respiratory muscle function as in healthy patients. During surgery, NMB in myasthenic patients would be overestimated when the orbicularis oculi is monitored, which could lead to insufficient paralysis for surgical purposes. However, extubation must occur when the muscle most sensitive to neuromuscular blocking agents has recovered. Therefore, neuromuscular monitoring at the orbicularis oculi is recommended to avoid persistent neuromuscular blockade in myasthenic patients.

References

1. Miller JD, Lee C: Muscle disease, Anesthesia and Uncommon Disease, 3rd edition. Edited by Katz J, Benumof JL, Kadis LB. Philadelphia, WB Saunders Company, 1990, pp 590–644
2. Rimaniol JM, Dhonneur G, Sperry L, Duvaldestin P: A comparison of the neuromuscular blocking effects of atracurium, mivacurium, and vecuronium on the adductor pollicis and the orbicularis oculi muscle in humans. *Anesth Analg* 1996; 83:808–13
3. Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. *ANESTHESIOLOGY* 1990; 73:870–5
4. Abdulatif M, El-Sanabary M: Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles. *Br J Anaesth* 1997; 79:24–8

5. Osserman KE, Genkins G: Studies in myasthenia gravis: Review of a twenty-year experience in over 1200 patients. *Mount Sinai J Med* 1971; 38:497-537
6. Lindstrom JM, Seybold ME, Lennon VA, Whittingham S, Duane DD: Antibody to acetylcholine receptor in myasthenia gravis: Prevalence, clinical correlates, and diagnostic value. *Neurology* 1976; 26:1054-9
7. Mittag T, Kornfeld P, Tormay A, Woo C: Detection of anti-acetylcholine receptor factors in serum and thymus from patients with myasthenia gravis. *N Engl J Med* 1976; 294:691-4
8. Paton WDM, Zaimis EJ: The action of d-tubocurarine and decamethonium on the respiratory and other muscles in the cat. *J Physiol (London)* 1951; 112:311-31
9. Jewell PA, Zaimis E: A differentiation between red and white muscle in the cat based on responses to neuromuscular blocking agents. *J Physiol (London)* 1954; 124:417-28
10. Ibebunjo C, Wall LW: Muscle fibre diameter and sensitivity to neuromuscular blocking drugs. *Br J Anaesth* 1993; 71:732-3
11. Ibebunjo C, Srikant CB, Donati F: Duration of succinylcholine and vecuronium blockade but not potency correlates with the ratio of endplate size to fibre size in seven muscles in the goat. *Can J Anaesth* 1996; 43:485-94
12. Martyn JAJ, White DA, Gronert GA, Jaffe RS, Waud JM: Up-and-down regulation of skeletal muscle acetylcholine receptors. *ANESTHESIOLOGY* 1992; 76: 822-43
13. Buzello W, Noeldge G, Krieg N, Brobmann GF: Vecuronium for muscle relaxation in patients with myasthenia gravis. *ANESTHESIOLOGY* 1986; 64:507-9
14. Eisenkraft JB, Book WJ, Papatestas AE: Sensitivity to vecuronium in myasthenia gravis: A dose-response study. *Can J Anaesth* 1990; 37:301-6
15. Nilsson E, Meretoja OA: Vecuronium dose-response and maintenance requirements in patients with myasthenia gravis. *ANESTHESIOLOGY* 1990; 73:28-32
16. Baraka A, Tabboush Z: Neuromuscular response to succinylcholine-vecuronium sequence in three myasthenic patients undergoing thymectomy. *Anesth Analg* 1991; 72:827-30