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Comparison of Two Different Induction Doses of Atracurium in Myasthenia Gravis in Patients Undergoing Thymectomy

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ABSTRACT

Introduction: Myasthenia gravis is an autoimmune disorder resulting from a decreased number of active acetylcholine receptors at the neuromuscular junction. Thymectomy is one of its current treatments. Due to sensitivity of myasthenic patients to non-depolarizing muscle relaxants and also the interaction of this medication with anti-cholinestrase drugs, determining the dosage of non-depolarizing muscle relaxants for induction of anesthesia is one of the hurdles in thymectomy.

Materials and Methods: Twenty myasthenic patients undergoing transsternal thymectomy were enrolled into the study.They were divided into two groups randomly, and received either 0.25 mg/kg or 0.50 mg/kg of atracurium to facilitate tracheal intubation. Neuromuscular blockade was measured using train of four (TOF) mode of neuromuscular stimulator 15 minutes after administration of atracurium and then each 5 minutes till entered the recovery phase. The time between injection of atracurium and the recovery phase was compared between the two groups.

Results: The two groups were similar with respect to age and gender. The time from the onset of myasthenia gravis to surgery, dosage and duration of pyridostegmine used preoperatively were not significantly different between the two groups.The time from administration of atracurium to recovery phase was not significant between the two groups (P=0.24).

Conclusion: There was no difference between two different doses of atracurium regarding entering the recovery phase, and as the effects of non-depolarizing muscle relaxants are unpredictable in myasthenic patients, we recommend the lower dose to prevent profound skeletal muscle weakness and postoperative complications.

Introduction:

Myasthenia gravis (MG) is a chronic autonomic disease caused by a decrease in functional acetylcholine receptors at the neuromuscular junction due to their destruction or inactivation by circulating

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antibodies (1). Three abnormalities are seen at the neuromuscular junction in myasthenic patients:(a) reduction of the number of acetylcholine receptors and the amount of this reduction correlates to the degree of weakness. (b) Unfolding of the postsynaptic membrane or implification of the folding. (c) Increased gap between the nerve terminal and postsynaptic membrane (2). Weakness and rapid exhaustion of voluntary muscles are the hallmark of this disease. Skeletal muscles innervated by cranial nerves (ocular-phryngeal and laryngeal muscles) are especially vulnerable, as reflected by the appearance of ptosis, diplopia and dysphagia, which are often the initial symptoms of the disease (3).

Treatment for MG includes anticholinestrase drugs, thymectomy, immunosupression, and short-term immunotherapy such as plasmapheresis and administrationof immunoglobulin (4). Thymectomy is intended to induce remission or at least allow for the doses of immunosuppressive medication to be reduced (5). Anesthetists have a special concern in MG because of its interaction with various anesthetic agents, specially neuromuscular blocking drugs and also the effect of the medications used for treatment of MG (6). The decrease of acetylcholine receptors results in an increased sensitivity to nondepolarizing muscle relaxant. Also drugs that used to treat MG such as pyridostegmine can influence the effect of non-depolarizing muscle relaxant and interfere with these drugs (7). Pyridostegmine, a long-acting acetylcholinestrase inhibitor is the first-line therapy acts by inhibiting synaptic acetylcholinestrase, thus overcoming the deficit in receptor density in patients with MG andreduce the sensitivity of the patients to non-depolariziring muscle relaxants (8). So it seems that the dose of relaxant agents has to be reduced. On the other hand perioperative anticholinesterase treatment will modify the response to reversal agents because of already existing acetylcholinesterase and in some cases recovery of neuromuscular function after the administration of a reversal agent has been reported to be prolonged.Atracurium is an intermediate-acting nondepolarizing relaxant, which undergoes organ-independent degradation in plasma by Hofmann elimination at physiological pH and temperature, as well as by nonspecificester hydrolysis (9). Is the use of muscle relaxants safe in myasthenic patients? What is the appropriate dose? What is the impact of preoperative use of pyridostigmine on the use of neuromuscular blocking agents intraoperatively. These questions are very important in anesthesia management of myasthenic patients. Optimal management of the myasthenic patients undergoing thymectomy requires:(a) Knowledge of the physiology and relevant pharmacology of myasthenia gravis in order to understand how the clinical manifestations and treatment of the disease affect anesthesia management. (b) Adequate planning, involving close liaison between neurologist, surgeon, anesthetist and intensivist is necessary so that the patient's neuromuscular function is optimized preoperatively, and postoperative care is organized. (c) Continuous neuromuscular monitoring during anesthesia to manage the changing neuromuscular function that occurs in response to preoperative and intraoperative drug therapy (10). The aim of this study was to compare two different doses of atracurium on muscle relaxation and recovery phase in patient with MG.

Materials and Methods:

Medical Faculty Ethic Committee approval and informed written consent from all patients were obtained. From June 2010 to April 2012, all consecutive patients scheduled for thymectomy because of

MG were enrolled in the study. The exclusion criteria were as follow: patients with diabetes mellitus, hyper and hypothyroidism, systemic lupus erythematosis (SLE), and rheumatoid arthritis (RA).The patients were divided into two groups randomly (group A and group B). The envelop method with random numbers was used. In group A, 0.25 mg/kg of atracurium was injected, and in group B, the dose was 0.50 mg/kg. Bulbar signs and symptoms are primary risk factors for postoperative respiratory difficulties. Patients were assessed by the neurologist and bulbar signs and symptoms including facial weakness, dysphagia, and neck flexion weakness were evaluated. Respiratory muscle strength was also quantified by pulmonary function tests.Pyridostegmine therapy was continued until the morning of surgery and the patients were placed first on the operating list. Anesthesia was induced with fentanyl 3 µ/kg, thiopental 5mg/kg and atracurium (0.25 mg/kg or 0.50 mg/kg). Tracheal intubation was carried 3-5 minute after completion of injection of the atracurium when no muscle contraction were noted in response to stimulation by Train of Four (TOF) mode of nerve stimulator. Anesthesia was maintained with 50% nitrous oxide and 50% oxygen, propofol 50 µg/kg/min and remifentanyl 0.1 µ/kg Standard routine monitoring including ECG, pulse oximetery, Et CO2, IBP, temperature, urine output and neuromuscular monitoring were applied to all patients. Neuromuscular blockade was reversed with neostegmine 0.08 mg/kg and atropine 0.04mg/kg at the end of the surgery when there were four responses to TOF. Following recovery of neuromuscular transmission, N2O was discontinued, and when the patients became conscious and resumed adequate spontaneous ventilation, the trachea was extubated in the operating room.Patients were remained in recovery room for 30 minute, then they were transferred to ICU Neuromuscular monitoring: neuromuscular blockade was assessed using the nerve stimulator. The stimulator delivers a train-of-four 0.1 ms square wave impulse over the ulnar nerve at 0.5Hz. The trachea was intubated when the response to TOF stimulation disappeared. 15 min after the injection of atracurium, TOF was repeated every 5 min till we had four response to TOF (recovery phase) (11). Time from the injection of atracurium to return of four responses of TOF was recorded. Analysis was performed using SPSS/win (version 11.5). Man Whitney U test was used to analyze normally distributed data. P value less than 0.05 was considered significant.

Results:

There were twenty patients with mean age of 30.2±7.9 and female to male ratio of(65%).The patients were similar with respect to age and gender (Table 1) (p=0.36, p=0.64 respectively). The time from the onset of MG and surgery, dosage and duration of pyridostegmine used preoperatively were not significantly different between the two groups (Table 1) (p= 0.89, p=0.23, p=0.75).The time from atracurium administration to appearance of four responses of TOF were 48 min and 43 min in group A and group B respectively (p=0.24) (Table 2). There was no significant difference between the two groups Also the mean duration between induction and recovery phase was 45/5±11/9 minutes (25-65 minutes).

Discussion:

Myasthenia gravis is the prototype of antibody- mediated autoimmune disease.The acetylcholine receptor antibodies accelerated degeneration of the postsynaptic acethylcholine receptors of skeletal muscles and receptor blockade may also be involved (12). Anesthesia

consideration in the MG patients include marked sensitivity to nondepolarizing muscle relaxants, and an increased risk of perioperative respiratory insufficiency requiring prolonged intubation. The unpredictable susceptibility to muscle relaxants in patients with MG requires special consideration for anesthetic management.

Table 1: Average Demographic and preoperative data

Variable	Group A (0.25 mg/Kg)	Group B (0.50 mg/Kg)	P .Value
Age (yr)	28±3.2	32.4±2.8	0.36
Sex Ratio (M/F)	3/7	4/6	0.64
Duration of pyridostigmine used preoperatively (yr)	1.4±0.2	1.5±0.1	0.75
Dosage of pyridostigmine used preoperatively (mg)	282±32	240±26	0.23
Duration between the onset of Myasthenia Gravis and surgery (yr)	1.7±0.2	1.6±0.3	0.89

Table 2: Time to four responses of TOF

Variable	Group A (0.25 mg/Kg)	Group B (0.50 mg/Kg)	P.Value
Duration between induction and recovery phase(minute)	48±3.2	43±4.4	0.24

Various case reports have focused on this problem and suggested several techniques for anesthesia in MG patients such as: reversal of neuromuscular blockad by sugammadex (13), laryngeal mask airway insertion with total intravenous anesthesia without muscle relaxant (14) use of cisatracurim (15), avoiding the use of muscle relaxant and dependence on propofol for tracheal intubation and maintenance of anesthesia (16) , avoidance of muscle relaxant and induction of anesthesia with sevoflorane (17). On the other hand decreasing oravoidance of nondepolarizing muscle relaxant results in inadequate muscle relaxation for intubation and surgery in patients with myasthenia gravis under treatment by acethylcholinestrease. In our study despite the previous case reports, we found that the neuromuscular blockade duration is not significantly different between two dosages (0.25 mg/kg and 0.50 mg/kg) of atracurium for induction of the patients with MG undergoing thymectomy.We observed that the use of atracurium 0.25 mg/kg for airway control resulted in stable intraoperative

conditions and enabled muscle relaxation of patients with MG who had just undergone transsternal thymectomy. So it means that the beneficial effects of the half dose of atracurium is similar to standard dose.

Conclusion:
As the effects of nondepolarizing neuromuscular blockers are highly unpredictable and the distribution of muscle weakness is often uneven, we recommend use of low dose of atracurium in myasthenic patients to prevent profound muscle weakness and postoperative respiratory complications.

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Conflict of interests:

The authors have no conflict of interests**.**

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