

Anaesthesia for Thymectomy in Myasthenia Gravis

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Myasthenia gravis is a chronic autoimmune disorder of neuromuscular transmission in which acetylcholine receptor antibodies attack the postsynaptic membrane of the neuromuscular junction leading to fluctuating but progressive weakness and easy fatigability of voluntary skeletal muscle, with improvement following rest. The process most likely originates in the thymus. Thymectomy improves the cause of disease and can increase the remission rate. Anaesthesia in patients with myasthenia Gravis is one of the greatest challenges for an anaesthesiologist. To achieve the proper preoperative evaluation and preparation, intraoperative monitoring and management, and postoperative care, the anaesthesiologist must be aware of the pathophysiology of disease and the pharmacology of the patient treatment and drugs used per operatively. Our experience of anaesthesia in thirty patients of myasthenia Gravis undergoing thymectomy over a period 20 months is being presented here. Propofol was used for induction of anaesthesia and endotracheal intubation. Anaesthesia was maintained with IPPV with O₂, N₂O 50% each and halothane 0.5-1% . No muscle relaxant was used low dose of intravenous opioids was used for analgesic and all patients were extubated on the operation table. Recovery was rapid after completion of transternal thymectomy. Reversal (neostigmine+atropine) was given before extubation even though no muscle relaxant was used. Patients were shifted to ICU postoperatively. No patient required postoperative ventilation of lungs. Postoperatively. Diclofenac Sodium 75mg I.M 8 hourly was used for analgesia.

Key words: Myasthenia gravis, thymectomy, muscle relaxant

Myasthenia Gravis is a chronic autoimmune disorder of neuromuscular transmission in which acetylcholine receptor (AChR) antibodies attack the postsynaptic membrane of the neuromuscular junction leading to fluctuating but progressive weakness and easy fatigability of voluntary skeletal muscle with improvement following rest¹. The worldwide prevalence of the disease is 1 per 20,000 to 30,000 of the population. More common in women than in men in 6:4 ratio². People of any age may be affected, but in women highest incidence occurs in third decade; in men in fifth or sixth decade.

Although the cause of the disease is unknown, the role of immune responses in its pathogenesis is well established. Circulating acetylcholine receptor antibodies are present in 80-90% of patients with generalized form of myasthenia gravis. There is a breakdown in tolerance of T&B cells to the acetylcholine receptor. This lack of tolerance activates T-helper cells which produce antibodies specific for acetylcholine receptors. The process most likely originates in the thymus, as 90% of patients have histologic abnormalities of the thymus gland, including thymoma, hyperplasia or atrophy. These antibodies damage the postsynaptic membrane via a complement mediated reaction. This results in increased degradation and decreased formation of acetylcholine receptors.

Any skeletal muscle or group of muscles may be affected, although there is a predilection for muscles innervated by cranial nerves, which leads to diplopia, dysphagia, dysarthria and pulmonary aspiration. Peripheral muscle involvement may cause weakness, clumsiness and difficulty in holding up the head or in walking. Respiratory muscle and limb weakness are rare at the onset of the disease³. The classification of myasthenia Gravis is based

on skeletal muscle groups affected as well as the age of onset.

Diagnosis relies on history, signs, "Tensilon" test, electromyographic signs of impaired neuromuscular transmission, and serum acetylcholine receptor antibody titration. Apart from the antiacetylcholine receptor antibody assay, no single test is specific for myasthenia gravis; it is rather their combined results that can confirm diagnosis⁴.

Therapeutic approach varies from patient to patient and as far as possible, should be adapted to each individual. Treatment strategies⁵ for myasthenia gravis that are currently in use are:

- Enhancement of neuromuscular transmission with acetylcholine esterase inhibitors.
- Short term immunotherapies, including plasma exchange, and intravenous immunoglobulin therapy.
- Immunosuppression
- Surgical thymectomy

The range of therapies differ with respect to efficacy, timing and side effects⁶. Symptomatic drugs such as anticholinesterases improve muscle strength but seldom restore it to normal. Immune therapy includes immune suppressive drugs, plasma exchange, immunoglobulin and thymectomy⁷.

Thymectomy is indicated in most patients unless the symptoms are minimal or the weakness is confined to the extraocular muscles or the patient is elderly⁸. Thymectomy improves the course of disease and can increase the remission rate⁴. Thymectomy is beneficial and should be considered for all patients with thymoma associated myasthenia gravis. However, in cases with non-

thymomatous autoimmune myasthenia gravis, thymectomy is recommended only for patients below 55-60 years and within the first 6-12 months of disease duration. Thymectomy alone results in remission in about one-third of patients, but in addition most patients require symptomatic anticholinesterase drugs to prolong the action of acetylcholine at the muscle end plate.

Anaesthesia in patients with myasthenia gravis is one of the greatest challenges in clinical anaesthesiology. Since many drugs used in anaesthesia affect the activity of neuromuscular conduction mechanism, the anaesthetist should be aware of pathophysiology of disease and of the effect which these drugs have on it⁹. The specific anaesthetic considerations that must be addressed include careful preoperative assessment and preparation, preoperative appropriate monitoring and other agents used during surgery and postoperative pain relief and ventilatory management. We present our experience of anaesthesia in patients of myasthenia gravis undergoing thymectomy at cardiac surgery department, Mayo Hospital, Lahore over a period of twenty months.

Materials and methods

In this study all the patients both male and female diagnosed case of myasthenia gravis coming to cardiac surgery department, Mayo Hospital, Lahore for thymectomy were included. These patients were previously treated with anticholinesterases, pyridostigmine (Mestinon, Amygra) dose ranging from 60mg TDS to 60mg QID and corticosteroid (deltacortril) 30mg to 60mg daily. These patients were also taking tablet Neo-K, one tablet TDS.

Incentive spirometry and chest physiotherapy was also started. On the day of operation the patients were given following treatment.

- Injectable antibiotics (Inj. Zinacef 1.5mg I/V stat + Inj. Gracil 500mg I/V stat).
- Inj. Zantac 50mg I/V Stat
- Anticholinesterase, pyridostigmine (Amygra) 60mg oral with sip of water.
- Corticosteroids (prednisolone) 6 tablets oral stat (for all or only for patients on steroids)
- Chest physiotherapy was done.
- The patients were nebulized with normal saline.

No sedative or narcotic was given as premedication. On arrival in the operating room, I/V cannula No.18 was inserted on right hand and I/V line maintained with Hartman's solution. Left radial artery was cannulated for invasive blood pressure monitoring ECG and SPO₂ monitoring applied.

After preoxygenation, anaesthesia was induced with Propofol 2.5mg/kg body weight intravenous bolus. The patients were easily intubated without relaxant. If difficulty while intubation was observed, Halothane was added to deepen the anaesthesia and intubation attempted

again with further bolus of Propofol. Nasogastric tube was passed. Patient was maintained on intermittent positive pressure ventilation with a mixture of oxygen and nitrous oxide 50% each and Halothane 0.5-1%.

Central venous line was secured on right internal jugular vein with single lumen CVP line (Cavafix single lumen).

Volatile based anaesthesia was used for maintenance of anaesthesia. No muscle relaxant was used. Intravenous narcotic analgesics in very low dose was used for analgesia. Thymectomy was done through median sternotomy.

At the end of surgery, all anaesthetic agents were stopped and patients were ventilated with 100% oxygen. The patients were brought back to spontaneous breathing. Reversal (neostigmine+ atropine) was given even though no muscle relaxant was used. After adequate reversal and patient regaining full consciousness, the patient was extubated on the operating table. Patient was shifted to ICU. Propped up in bed and oxygen inhalation (5-6 litres) given with face mask.

Postoperative analgesia was given with Diclofenac sodium 75mg I/M (intramuscular) 8 hourly.

ECG, SpO₂ and invasive blood pressure monitoring continued in ICU. Anticholinesterase was administered through nasogastric tube till oral feeding started. Incentive spirometry and chest physiotherapy was continued post operatively.

Results

Out of thirty patients, 18 female and 12 males were studied. Age of female patients ranged from 11-35 years (mean 22 years), while ages of male patients were between 20-39 years (mean 25 years). Preoperatively all patients were taking anticholinesterase, Pyridostigmine (Amygra) 60mg four times a day. 23 patients were on corticosteroids (prednisolone) 30 to 60mg per day. Only two patients were on immunosuppressants. Tab imuran 50mg three times a day. Patients on corticosteroids showed serum potassium level between 3-3.5mEq/lit. They were regularly taking potassium replacement as Tab. Neo K, three times a day.

Twenty patients presented with dysphagia and dyspnoea 8 patients presented with ptosis and diplopia and two patients with muscle weakness. Three patients had thymoma while rest of patients had normal thymus on CT scan. Five patients had thymic hyperplasia.

All but 4 patients were intubated in first attempt after single bolus dose of Propofol. In these 4 patients mild coughing was observed. In them, halothane was added to deepen anaesthesia and patients were intubated after a second dose of Propofol. Good operating conditions were achieved with halothane 0.5-1% and without a muscle relaxant. Recovery was rapid. All patients started breathing spontaneously. All patients were extubated within 20-30min after surgery was completed. No patient required

post operative ventilation of lung. The recovery was uneventful.

Discussion

Myasthenia gravis is a disease of great significance to anaesthesiologist because it affects the neuromuscular junction and because of the potential interaction between the disease, treatment of disease and neuromuscular blocking drugs. Treatment of myasthenia gravis with cholinesterase inhibitor can influence the response to both depolarizing and nondepolarizing neuromuscular blocking drugs¹⁰. To avoid all these, regional anaesthesia is preferred in myasthenics where possible, but for thymectomy trachea is to be intubated and lungs ventilated. For this, different anaesthetic techniques can be used. As such no specific anaesthetic technique is superior to others for patients with myasthenia. Both inhaled and intravenous anaesthetics have been used successfully¹¹. Patients should not undergo thymectomy while in crisis¹². So they are admitted while in remission or admitted to optimally control their physical and emotional condition prior to surgery. Concomitant autoimmune, respiratory and cardiac disorders should be evaluated and managed accordingly. Breathing exercises, incentive spirometry and chest physiotherapy are started preoperatively.

Patients benefit from care by coordinated team, including neurologist, intensivist, anaesthetist and surgeon¹². Regarding the continuation of anticholinesterase therapy there are again two schools of thoughts. According to one, anticholinesterase should be withheld on the morning of surgery so that the patient is weak and can be easily intubated; it also avoids interaction with other drugs.

According to current mode, anticholinesterase therapy is continued until anaesthesia⁷. Induction of anaesthesia is achieved with intravenous short acting barbiturate or Propofol. Inhalational induction can also be achieved with sevoflurane. As halogenated inhaled anaesthetics depress neuromuscular transmission in myasthenic patients, neuromuscular blocking drugs may not be required^{13,14}. Anaesthesia may be deepened using a potent inhaled anaesthetic. This provides good intubating and operating conditions¹⁴. Myasthenic patients are more sensitive than normal patients to the neuromuscular depressant effects of the potent inhaled anaesthetics. In patients with myasthenia gravis, isoflurane at 1.9 MAC end tidal concentration induced a neuromuscular block of 30-55% whereas halothane at 1.8MAC induced a block of 10-20%. Both agents produced fade in the train of four ratio of 41% and 28% respectively^{14,15}.

Integrated electromyographic monitoring of train of four response of adductor pollicis demonstrated that myasthenics are more sensitive than non myasthenics to the neuromuscular depressant effects of Isoflurane¹⁴. As these volatile anaesthetics are easily administered and withdrawn, they are the most commonly used anaesthetic drugs for patients with myasthenia gravis. Using them,

recovery from anaesthesia is rapid with minimal postoperative residual muscle weakness or respiratory depression^{14,16}. The tremendous variability in the response of myasthenic patients to the different types of neuromuscular blocking drugs warrants their routine use in anaesthesia. The uncontrolled or poorly controlled myasthenic patient is extremely sensitive to nondepolarizing muscle relaxant^{17,18}. Even small defasciculating doses of nondepolarizing muscle relaxants can produce significant respiratory muscle paralysis and respiratory depression¹⁹. The response of myasthenic patient to succinylcholine is unpredictable depending on individual patient, severity of myasthenia gravis and the treatment. The untreated myasthenic patient is resistant to effects of succinylcholine. On the other hand patient treated with anticholinesterases may show resistant, prolonged or normal responses to succinylcholine^{20,21,22,23}. Moreover, treatment of myasthenia with anticholinesterases can influence the response to both depolarizing and nondepolarizing neuromuscular blocking drugs¹⁰.

However, in some cases, patients with myasthenia gravis cannot tolerate the cardiovascular depressant effects of potent inhaled anaesthetics, in which case muscle relaxants may be used with careful monitoring and titrated in 1/10-1/20 of usual dose. Atracurium in such situations is preferred to produce relaxation with minimal risk of prolonged post operative paralysis because of its short elimination $\frac{1}{2}$ life of 20 minutes, small volume of distribution, lack of cumulative effect, high clearance, Hofman degradation^{24,25,26,27,28}. ED₅₀ of atracurium in patients with myasthenia gravis is approximately 1/5th of that in normal patients¹⁷.

Different analgesic technique may be employed such as intravenous analgesics, or regional anaesthesia and/or neuraxial narcotic administration (epidural anaesthesia, combined with high general anaesthesia). Reduced doses of opioids are used as the myasthenic patients are very sensitive to the respiratory depressant effects of opioids. The analgesic effect of morphine and other opioid analgesics has been reported to be increased by anticholinesterases, so, analgesic be reduced by one third in the patients receiving anticholinesterase therapy.

A combined anaesthetic technique is shown to be safe and cost effective alternative to balanced anaesthesia as it provides optimal operating condition, post operative analgesia, less rate of post operative ventilatory support and shorter hospital stay^{29,30,31,32}. In one study epidural anaesthesia with Propofol provided stable haemodynamics during operation and rapid emergence³³.

In another study using isoflurane only for anaesthesia, the recovery from anaesthesia was also rapid with minimal post operative residual muscle weakness or respiratory depression¹⁴.

Myasthenic patients should be extubated when they are responsive and able to generate negative respiratory pressure of more than 20cm H₂O. After extubation, they

are carefully observed in recovery room or ICU. Cases of mild respiratory depression may be treated with parenteral anticholinesterase; more severe cases may require reintubation of trachea and mechanical ventilation of lungs.

Laventhal's scoring system for predicting need of postoperative ventilation of lungs in myasthenics was not found useful in patients with myasthenia gravis undergoing transternal thymectomy^{29,34}. However, expiratory weakness, by reducing cough efficacy and ability to clear secretions was shown to be the main predictive determinant. Techniques that may be useful in reducing postoperative ventilatory failure include preoperative plasma exchange and high dose perioperative steroid therapy.

Our patients were young, their disease optimally controlled. Propofol was used for induction only. Anaesthesia was maintained with halothane (0.5-1%). Analgesia was provided with low dose opioid. The intubating and operating conditions were good with this volatile based anaesthesia. Muscle relaxants were not required. Recovery was rapid. All of our patients required spontaneous breathing and were extubated on the operating table within 20-30 minutes after surgery was completed. No patient required postoperative ventilatory support.

Conclusion

Patient can be successfully intubated and anaesthesia was maintained without any muscle relaxant even painted has taken anticholinestrace dose in the morning of operation.

References

1. Drachman DB. Myasthenia gravis: Review article. *N Engl J Med* 1994; 330: 1797.
2. Pourmand R. Myasthenia gravis. *Dis Mon* 1997; 43(2): 65-109.
3. Evoli A, Batocchi AP, Tonali P. A practical guide to the recognition and management of myasthenia gravis. *Drugs* 1996; 52(5): 662-70.
4. Czaplinski A, Radziwill AJ, Steck AJ. Acute aspects of myasthenia gravis treatment. *Pol Merkuriusz Lek* 2003; 14(81): 256-60.
5. Graves M, Katz JS. Myasthenia gravis. *Curr Treat Options Neurol* 2004; 6(2): 163-171.
6. Blobna M, Mann R. Anaesthesia in patients with myasthenia gravis. *Anaesthetist* 2001; 50(7): 484-93.
7. Havard CW, Fonseca V. New treatment approaches to myasthenia gravis. *Drugs* 1990; 39(1): 66-77.
8. Roelofse JA. Anaesthesia for thymectomy in myasthenia gravis. *SAfr Med J* 1981; 60(16): 619-20.
9. Baraka A, Taha S, Yazbeck V et al. Vecuronium block in the myasthenic patient. *Anaesthesia* 1993; 48: 588.
10. Lorimer M, Hall R. Remifentanyl and Propofol total intravenous anaesthesia for thymectomy in myasthenia gravis. *Anaesth Intens Care* 1998; 26: 210.
11. Wilkin KB, Bulkley GB. Thymectomy in the management of myasthenia gravis. *Adv Surg* 1999; 32: 105-33.
12. Nilsson E, Poloheimo M, Muller K et al. Halothane induced variability in the neuromuscular transmission of patients with myasthenia gravis. *Acta Anaesthesiol Scand* 1989; 33: 395.
13. Rowbottom SJ. Isoflurane for thymectomy in myasthenia gravis. *Anaesth Intens Care* 1989; 17: 444-7.
14. Nilsson E, Muller K. Neuromuscular effect of influence in patients with myasthenia gravis. *Acta Anaesthesiol Scand* 1989; 33: 395.
15. Nisevic V, Duric D. Anaesthesia for thymectomy in patients with myasthenia gravis. *Med Pregl* 2000; 53(9-10): 506-9.
16. Smith Ce, Donati F, Bevan DR. Cumulative dose response curve for atracurium in patients with myasthenia gravis. *Can J Anaesth* 1989; 36: 402.
17. Eisenkraft JB, Book WJ, Papatestas AE. Sensitivity to vecuronium in myasthenia gravis: a dose response study. *Can J Anaesth* 1990; 37: 310.
18. Haider Ali AM, MacGregor B, Stewart M. Myasthenia gravis presenting with Dysphagia and postoperative ventilatory failure. *J Laryngol Otol* 1998; 112: 1194.
19. Abel M, Eisenkraft JB, Patel N. Response to suxamethonium in a myasthenic patient in remission. *Anaesthesia* 1991; 46: 30.
20. Valinhoult LEH, Robertson EN, Booy KHDJ. Response to suxamethonium during Propofol - fentanyl - N2O/O2 anaesthesia in a patient with active myasthenia gravis receiving long term anticholinesterase therapy. *Anaesthesia* 1994; 49: 509.
21. Barka A. Suxamethonium block in the myasthenic patient: Correlation with plasma cholinesterase. *Anaesthesia* 1992; 47: 217.
22. Baraka A, Baroody M, Yazbeck V. repeated doses of suxamethonium in the myasthenic patient. *Anaesthesia* 1993; 48: 782.
23. Baraka A, Dajani A. Atracurium in myasthenics undergoing thymectomy. *Anesth Analg* 1984; 64: 1127.
24. Ramsay F, Smith GD. Clinical use of atracurium in myasthenia gravis. *Can Anaesth Soc J* 1985; 32: 642.
25. Bell CF, Forence AM, Hunter JM et al. Atracurium in the myasthenic patient. *Anaesthesia* 1984; 39: 961.
26. Hunter JM, Bell CF, Florence AM et al. Vecuronium in the myasthenic patient. *Anaesthesia* 1985; 40: 848.
27. Sanfilippo M, Fierro G, Cavalletti MV et al. Rocuronium in two myasthenic patients undergoing thymectomy. *Acta Anaesthesiol Scand* 1997; 41: 1365.
28. Chevalley C, Spitiopoulos A, dePerrot M, Tschopp JM, Licker M. Perioperative medical management and outcome following thymectomy for myasthenia gravis. *Can J Anaesth* 2001; 48(5): 446-51.
29. Suwanchinda V, Yok-Ubol B, Prakanrathna U, Udophum Thurak S. Combined thoracic epidural with light general anaesthesia for thymectomy in myasthenia gravis. *J Med Assoc Thai* 1995; 78(11): 605-10.
30. Burgess FW, Wilcosky B. Thoracic epidural anaesthesia for transternal thymectomy in myasthenia gravis. *Anesth Analg* 1989; 69: 529.
31. Gorbach MS. Analgesic management after thymectomy. *Anesthesiol Rep* 1990; 2: 262.
32. Abe S, Takenchi C, Kaneko T, Maeda M, Saitoh Y, Hikawa Y, Yasuda K. Propofol anaesthesia combined with thoracic epidural anaesthesia for thymectomy for myasthenia gravis - a report of eleven cases. *Masni* 2001; 50(11): 1217-20.
33. Eisenkraft JB, Papatestas AE, Kahn CH et al. Predicting the need for postoperative mechanical ventilation in myasthenia gravis. *Anesthesiology* 1986; 65: 79.