Use Of Intravenous Immunoglobulin And Management Of Anesthesia For Preparation To Thymectomy In A Case With Myasthenia Gravis That Was Intractable To Classical Treatment Modalities

M Aksun, N Karahan, L Y?l?k, S Ture, E Damar, E Y?lmaz, T Adan?r, G Aran, A Gurbuz, G Akhan

Citation

M Aksun, N Karahan, L Y?l?k, S Ture, E Damar, E Y?lmaz, T Adan?r, G Aran, A Gurbuz, G Akhan. *Use Of Intravenous Immunoglobulin And Management Of Anesthesia For Preparation To Thymectomy In A Case With Myasthenia Gravis That Was Intractable To Classical Treatment Modalities*. The Internet Journal of Anesthesiology. 2008 Volume 20 Number 2.

Abstract

Myasthenia gravis (MG) is a rare, autoimmune disease. In our study we aimed to present multidisciplinary approaches of neurology, cardiovascular surgery and anesthesia departments and the successful anesthesia technique in our patient who received intravenous immunoglobulin (IVIG) therapy due to chronic MG and then underwent thymectomy. Thymectomy is beneficial in ~40-90% of MG patients. Besides thymectomy, anticholinesterases, corticosteroids, immunosuppressives and plasma exchange (PE) often improve the prognosis of patients with life threatening symptoms. IVIG might be an alternative to PE in the prethymectomy preparation of MG patients with generalized involvement but not more severe than type II B and thymectomy should be performed within 10 days after IVIG treatment as the effect of IVIG is temporary.A 48 years old female patient having the diagnosis of MG for 10 years and evaluated as class II B according to Osserman classification received prydostigmine, prednisolon and azatiyoprin therapy previously. Despite the treatment, through last 3 months complaints of patient were increased. For this reason the patient was scheduled for thymectomy and 400 mg/kg IVIG therapy for 5 days was started preoperatively. Four days later, the patient was taken into thymectomy. In anesthesia induction 3 mg/kg propofol and 100 µg fentanyl was used, but no sedative and neuromuscular blocking agent (NMB) was used. Case was ventilated with %50 O_2 - % 50 N_2O combination and 2% Sevoflurane for 5 minutes. There wasn't any unfavorable response to intubation. While considering previous steroid treatment, patient was applied 250 mg prednisolone. During the operation there was no need for NMB. After the operation, successful tracheal extubation was achieved in the operating room and the patient transferred to the cardiovascular surgery intensive care unit (CSICU). Case was given O_2 supply for a time. She was discharged to the ward 2 days later and then she was discharged home 5 days later.Multidisciplinary approach and the successful anesthesia technique were effective in discharge of our MG case after thymectomy following IVIG treatment without any problem. PE can be applied in longer time and due to some associated complications, hospitalization time prolongs (10 days) and cost increases. On the other hand, IVIG treatment can be applied in a shorter time (5 days) but it is more expensive. For this reason we think that comparative studies in large series are needed and case selection must be done appropriately. Selected MG cases can be operated successfully with preoperative IVIG use especially with multidisciplinary approach and successful anesthesia management. By this way, also hospitalization times, cost and complication can be decreased.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease with antibodies directed against the acetylcholine receptor at the neuromuscular junction ([1]). Although MG is rare, prevalence rates for MG have increased over time, likely due to improvements in diagnosis and treatment. Recent prevalence rates approach 20/ 100,000 ([2,3]). The onset of MG is influenced by gender and age in a bimodal fashion. In patients younger than 40, women predominate with a ratio of 7:3. In the fifth decade, new cases of MG are evenly distributed between men and women. After age 50, new cases of MG are slightly more common in men with a ratio of 3:2 ([3]).

Myasthenia gravis is characterized clinically by increasing fatigue with exercise. The symptoms range from isolated ptosis, diplopia or mild proximal muscle weakness to severe

generalized weakness and ventilator dependence ([4]). The thymus is thought to play a major role in the pathogenesis of myasthenia gravis. Autoantibodies associated with myasthenia gravis are directed at the acetylcholine receptor in the neuromuscular junction, resulting in a decrease in acetylcholine receptors.

Current treatment strategies in MG include anticholinesterases, steroid, immunosupressants, thymectomy and plasmapheresis (PE) ([5,6]). The use of intravenous immunoglobulin (IVIG) in MG has been investigated for more than a decade ([6]). Some patients do well on only anticholinergic inhibitors such as pyridostigmine to relieve symptoms and steroids to treat the autoimmunity. In other patients, it is necessary to consider treatment with immunosuppressive therapy to relieve the progressive evolution of myasthenic symptoms ([4,7]). Most patients respond well, but despite immunosuppressive treatment with prednisone and/or azatioprine, a subset of patients continue to have moderate to severe generalized myasthenic symptoms. In this difficult subgroup of patients with chronic MG that is poorly controlled with standard immunosuppression, further therapy with IVIG or PE can be considered ([7]). IVIG has many effects on immunological function but its mechanism of action is unknown ([6]). The application of IVIG in the treatment of MG was reported initially in 1984 ([6]).

Thymectomy as an adjunctive treatment is considered the standard of care, with the best results occurring in younger patients who have had myasthenia gravis for a short period of time and the medical treatment failed ([4]).

Anesthetists have a special interest in MG because of its interaction with various anesthetic agents and because many myasthenics require a thymectomy to control their disease ([1]).

In our study we aimed to present multidisciplinary approaches of neurology, cardiovascular surgery and anesthesia departments and the successful anesthesia technique in our patient who was applied IVIG therapy due to chronic MG and then underwent thymectomy.

CASE PRESENTATION

Our case was a 48-year-old female who was admitted to another hospital 10 years ago with complaints of lisping, difficulty in opening her mouth and holding her head in upright position. She was diagnosed as myasthenia gravis and categorized as Class II B according to Osserman classification. Pyridostigmine 60 mg tid and prednisolon 30 mg per day were initiated as pharmacotherapy. Her complaints deteriorated over time and dosages were increased as pyridostigmine 60 mg q4h and prednisolon 60 mg per day. Her symptoms were relieved for 3 years and the dose of prednisolon therapy was reduced to 20 mg per day with cessation of pyridostigmine. But her complaints recurred and pyridostigmine was initiated again with a dose of 60 mg whereas the dose of prednisolon was increased. After a while, 1000 mg of mycophenolate mofetil (CellCept® Roche) was started. She used this medication for a period of 1 year. But, because of the lack of availability of this drug, her medication was switched to azathioprine 3x1, prednisolon 50 mg and pyridostigmine 60 mg q4h. During the last 3 months her symptoms of dysphagia, dyspnea and easy fatigability worsened in spite of the therapy. She was hospitalized by the Department of Neurology. Thymectomy was planned according to the decision of the council constituted by Departments of Neurology, Cardiovascular Surgery and Anesthesia. Intravenous immunoglobulin (IVIG) therapy for 5 days was started preoperatively. Four days after, patient was taken into thymectomy. In anesthesia induction 3 mg/kg propofol and 100 µg fentanyl was used, but no sedative and neuromuscular blocking agent (NMB) was used. Case was ventilated with %50 O_2 - % 50 N_2O combination and 2% Sevoflurane for 5 minutes. There wasn't any unfavorable response to intubation. While considering previous steroid treatment, patient was applied 250 mg prednisolone. Supplementary dose of propofol was administered 1 mg/kg before the median sternotomy. During the operation there was no need for NMB. The surgery took 90 min following induction of anesthesia and the thymus was removed uneventfully. After the operation, successful tracheal extubation was achieved in the operating room and the patient transferred to the CSICU. Case was given O_2 supply for a time. Analgesia was provided with intravenous paracetamol infusion. She was discharged to the ward 2 days later and then she was discharged home 5 days later.

DISCUSSION

Current treatment is based on enhancing neuromuscular transmission, suppression of the immune system, decreasing the levels of circulating antibodies and thymectomy in MG ([1,8]). Anticholinesterases are the mainstay of treatment. Pyridostigmine is usually preferred to neostigmine because it has a longer duration of action and fewer muscarinic side effects. These drugs improve transmission by slowing the

breakdown of acetylcholine, so prolonging its action. Most patients respond well to anticholinesterases and for those with only ocular disease, other drug treatments are often unnecessary. Corticosteroids are second line agents, and it is suggested they may worsen results of thymectomy in adults. Consequently, they may be withheld pending surgery. If they are used, the doses tend to be large so additional steroid cover may be needed perioperatively. Other immunosuppressive agents such as azothiaprine, cylophosphamide and cyclosporin, have been used but their serious side-effects limit their use. PE and IVIG are used when a patient is in crisis, or to optimize neuromuscular function preoperatively. PE works by clearing the acetylcholine receptor antibodies from the circulation, whereas the mechanism of action of IVIG is less clear. IVIG may exert its effects by altering antibody production, binding of antibodies or prevention of interaction with the neuromuscular junction. ([1]).

Huang et al ([6]) conducted a clinical trial including six patients to assess the effect of IVIG in the preparation of thymectomy for patients with MG. Six consecutive patients of type IIB MG treated with IVIG at a dose 0.4 g/kg daily for 5 days as ours before thymectomy were enrolled in their study. All patients responded positively to this treatment. Improvement began to occur 1–9 days after starting the injection and reached a maximum in 3–19 days. In their study five patients underwent thymectomy from 10 to 13 days after starting the IVIG treatment. The patients were sent to recovery room and extubated 5.5–8 h after surgery without any respiratory complication. The six patients they chose in their study were relatively stable, with short duration of disease, without crisis and cardiopulmonary embarrassment. They concluded that IVIG might be an alternative to PE in the prethymectomy preparation of MG patients, and thymectomy should be performed within 2 weeks after IVIG treatment to minimize the perioperative complications.

Seggia et al ([6],[9]) investigated the effects of PE in the preparation for thymectomy. They found significant improvement in respiratory function and muscular strength in patients thymectomized after PE and concluded that PE should be considered as a coadjuvant to thymectomy in the treatment of MG. Arsura et al. ([6],[10]) reported that in 12 patients with MG treated with IVIG at a dose of 0.4 g/kg/day for 5 days, 11 patients improved. Cosi et al. ([6],[11]) noted that a temporary improvement could be achieved in 26 of 37 patients (70.3%) receiving IVIG with the same dose.

IVIG has been utilized in a number of autoimmune neuromuscular disorders it is thought to act by down regulation of autoantibodies and/or induction of anti-idiotypic antibodies. In MG, IVIG may provide short-term improvement in strength for MG exacerbations and crises, for surgical preparation in patients who are poor PE candidates because of vascular access issues, and in patients with septicemia. Pretreatment with acetaminophen and diphenhydramine may reduce the frequency and severity of idio-syncratic reactions with IVIG using. Side effects include volume overload, particularly for patients with cardiomyopathy or valvular heart disease, solute-induced renal failure, especially in patients with preexisting renal insufficiency or diabetic nephropathy, and idiosyncratic reactions such as fever, chills, nausea, vomiting, vascular headaches, and aseptic meningitis. High infusion rates may be associated with thrombosis and stroke ([3],[12],[13]).

Calhoun and associates ([4]) conducted a retrospective review of patients with myasthenia gravis who underwent transcervical thymectomy to identify outcomes and incidence of complications. Of the 100 patients, 88 had surgery. Six patients were lost to follow-up; two others died more than four years after surgery, one of cardiac arrest and the other of a cerebrovascular accident. A total of 78 patients were available for long-term follow-up. Almost all patients experienced an improvement in Osserman grade, with patients younger than 40 years of age demonstrating the greatest improvement. Ninety percent of the patients took pyridostigmine and 33 percent took prednisone preoperatively. Following thymectomy, only 46 percent took pyridostigmine, and 27 percent took prednisone. Patients who underwent surgery within nine months of the diagnosis of myasthenia gravis demonstrated a statistically significant improvement in postoperative Osserman grade. The authors concluded that early thymectomy for nonthymoma― associated myasthenia gravis was a useful adjunct to medical management, especially in younger patients.

Multidisciplinary approach and the successful anesthesia technique were effective in discharge of our MG case after thymectomy following IVIG treatment without any problem. PE can be applied in longer time and due to some associated complications (hemolysis, bleeding diathesis, catheter-related venous trombosis, fever, chills, hypotension, tachycardia and nausea/vomiting), hospitalization time prolongs (10 days) and cost increases. On the other hand,

IVIG treatment can be applied in a shorter time (5 days) but it is more expensive ([7,14]). For this reason we think that comparative studies in large series are needed and case selection must be done appropriately.

In conclusion; Selected MG cases can be operated successfully with preoperative IVIG use especially with multidisciplinary approach and successful anesthesia management. By this way, also hospitalization times, cost and complication can be decreased.

CORRESPONDENCE TO

Uzm.Dr.Murat AKSUN Erzene Mah. 116/10 Sok. No:7/11 Bornova-IZMIR/TURKEY Tel: 0552 3631614 – Fax:0232 2434848 E-mail= murataksun@yahoo.com

References

1. White MC, Stoddart PA. Anesthesia for thymectomy in children with myasthenia gravis. Pediatric Anesthesia 2004 14: 625–635
2. Phillips LH 2 nd. The epidemiology of myastenia gravis. Ann NY Acad Sci. 2003;998:407–412.
3. Juel VC and Massey JM. Myasthenia gravis. Orphanet J Rare Dis. 2007; 6;2:44. Review.
4. Calhoun RF, Ritter JH, Guthrie TJ, et al. Results of transcervical thymectomy for myasthenia gravis in 100 consecutive patients. Ann Surg October 1999;230: 555-561.
5. Drachman DB. Myasthenia gravis. N Engl J Med 1994;330:1797–810.
6. Huang CS, Hsu HS, Kao KP, et al. Intravenous immunoglobulin in the preparation of thymectomy for myasthenia gravis. Acta Neurol Scand 2003; 108: 136–138.
7. Rogener J, Ravnborg M, Hermansen I et al. Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. Artif Organs 2001; 25: 967-973.
8. Baraka A. Anesthesia and critical care of thymectomy for myasthenia gravis. Chest Surg Clin N Am 2001; 11: 337–361.
9. Seggia JC, Abreu P,Takatani M. PE as preparatory method for thymectomy in myasthenia gravis. Arq Neuropsiquiatr 1995; 53: 411–415.
10. Arsura EL, Bick A, Brunner NG, Namba T, Grob D. High dose intravenous immunoglobulin in the management of myasthenia gravis. Arch Intern Med 1986;146:1365–1368.
11. Cosi V, Lombardi M, Piccolo G, Erbetta M. Treatment of myasthenia gravis with high-dose intravenous immunoglobulin. Acta Neurol Scand 1991; 84: 81–84.
12. Tan E, Hajinazarian M, Bay W, et al. Acute renal failure resulting from intravenous immunoglobulin therapy. Arch Neurol 1993, 50:137-139.
13. Caress JB, Cartwright MS, Donofrio PD, et al. The clinical features of 16 cases of stroke associated with administration of IVIg. Neurology 2003, 60:1822-1824.
14. Qureshi AI, Suri FK. Plasma Exchange for Treatment of Myastenia Gravis: Pathophysiologic Basis and Clinical Experience. Therapeutic Apheresis 2000; 4 : 280-286.

Author Information

Murat Aksun
Specialist in II. Anesthesiology, Izmir Ataturk Training and Research Hospital

Nagihan Karahan
Clinic Chief in II. Anesthesiology, Izmir Ataturk Training and Research Hospital

Levent Y?l?k
Specialist in Cardiovascular Surgery, Izmir Ataturk Training and Research Hospital

Sabiha Ture
Specialist in III. Neurologia, Izmir Ataturk Training and Research Hospital

Ertan Damar
Specialist in II. Anesthesiology, Izmir Ataturk Training and Research Hospital

Engin Y?lmaz
Assistant in II. Anesthesiology, Izmir Ataturk Training and Research Hospital

Tayfun Adan?r
Specialist in II. Anesthesiology, Izmir Ataturk Training and Research Hospital

Gulcin Aran
Specialist in II. Anesthesiology, Izmir Ataturk Training and Research Hospital

Ali Gurbuz
Clinic Chief in Cardiovascular Surgery, Izmir Ataturk Training and Research Hospital

Galip Akhan
Clinic Chief in III. Neurologia, Izmir Ataturk Training and Research Hospital