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ORIGINAL ARTICLE

Clinical Outcome after Thymectomy with or Without Plasmapheresis in Patient with Myasthenia Gravis

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ABSTRACT:

Objective: To compare clinical outcome in patients with myasthenia gravis who underwent thymectomy with or without Plasmapheresis.

Methodology: We studied a total of 47 patients, who were operated on in the period from January 2002 to December 2009 for Myasthenia Gravis .Of these 47 patients, preoperative plasmapheresis was performed in 20 patients (group A) and the remaining 27 patients (group B) had no preoperative plasmapheresis based on non availability of plasmapheresis kit. Outcome in the form of requirement of ventilation, symptomatic improvement, hospital stay and requirement of drugs were assessed at the end of one year and compared between the two groups.

Results: Eighteen out of twenty seven patients (66%) in group B required ventilatory support in the immediate postoperative period, whereas four out of twenty patients (20%) in group A required it. Significant and sustained symptomatic improvement was noted in group A as compared with group B (*P*-0.01).

Conclusion: Preoperative Plasmapheresis in the patients of myasthenia gravis is beneficial and can cause a significant difference in the postoperative outcome.

Key words: Plasmapheresis, Thymectomy, Myasthenia Gravis.

INTRODUCTION:

Myasthenia gravis [1, 2] is a rare autoimmune disorder, which is characterized by easy fatigability and muscular weakness with preferential involvement of ocular and facial muscles. Muscular fatigue is worsened by exercise and alleviated by rest. Clinical symptoms can vary from isolated ptosis, diplopia or mild proximal muscle weakness to severe degree of generalized weakness, bulbar and respiratory muscle weakness which may ultimately result in ventilator dependency. The basic pathogenesis of the disease so far understood is the production of autoantibody against the acetylcholine receptors of the endplate[1, 3], and thereby immunologic destruction and reduction of the number of the receptors. The miniature endplate potential amplitude is decreased, and the endplate potentials are largely subthreshold[1, 3] leading to easy fatigability and weakness. The thymus is believed to play an integral role in pathogenesis of myasthenia. The role of the thymus in the development of antibodies against the acetylcholine receptors has been clearly established and therefore the relationship between myasthenia and thymic abnormalities has been suggested[2, 3]. Thymomas and glandular hyperplasia are the commonest underlying pathologic findings seen in many of these patients. Currently, the detection of 'thymoma-specific' antistratitional antibodies in the peripheral blood and mediastinal imaging by computed tomography (CT) are the most specific diagnostic procedures for the detection of thymoma[4-7]. Considering the management issues, patients with minimal symptoms are usually

treated with anticholinesterase drugs and non-responders require treatment with steroids, immunoglobulins, and immunosuppressants.

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Plasmapheresis that can rapidly deplete the disease-related plasma factors has been found to be very effective in immune modulation by decreasing the circulating antibodies. It reduces antiAchreceptor antibody titer in myasthenia gravis and alleviates symptoms. Although, its effects are short lasting as it cannot prevent their re-synthesis. Considering the role of the thymus in the pathogenesis, complete removal of the thymus has become a standard procedure for the management of myasthenia gravis with remarkable and sustained improvement in many cases [3].However, most patients require management in the intensive care units and prolonged ventilatory support in the postoperative periods due to respiratory insufficiency with an accompanying complication like pulmonary infection [8,9]. These patients often require a high dose of anticholinesterase drugs, steroids, immunosuppressants, evenpostoperative plasmapheresis, irrespective of preoperative clinical status[8, 10–12]. In this study, authors compare clinical outcome in patients with myasthenia gravis who underwent thymectomy with or without plasmapheresis.

METHODS:

We studied 47 consecutive patients of myasthenia gravis, admitted into the Department of Cardio Thoracic Surgery, Post Graduate Medical institute, Lady Reading Hospital, Peshawar, who had undergone trans-sternal thymectomy from January 2002 to December 2009.These patients had a clinical diagnosis of myasthenia gravis with high antiAch receptor antibody titer and myasthenic symptoms controlled with medication. They were classified into five classes (grades), according to the classification by Osserman and Genkins [9] (1, ocular signs only; 2A, generalized mild muscle weakness; 2B, generalized moderate weakness and or bulbar dysfunction; 3, acute fulminating presentation and or respiratory dysfunction; 4, late generalized weakness). Patients with class 2B, 3 or 4 symptoms are included for the study. Patients with the following preoperative risk factors for postoperative ventilation are considered for preoperative Plasmapheresis; 1: Duration of disease > 6 years, 2: History of COPD, 3: Dose requirement of Pyridostigmine >750 mg besides routine examinations, all patients had preoperative chest X-ray, computed tomography scan and detection of circulating autoantibody titer (anti-acetylcholine receptor). Patient's preoperative characteristics are summarized in Table I.

Out of 47 patients, in 20 patients (group A) Plasmapheresis (membrane plasma separation using Plasma Separation Filter; rate of plasma removal (40 ml/kg of body weight daily) was performed preoperatively one day before surgery. In the remaining 27 patients (group B), Thymectomy was done without preoperative plasmapheresis.

Plasma volume was replaced with albumin, fresh frozen plasma and crystalloids. The medications i.e. anticholinesterase drugs, steroids, which the patients were receiving were continued preoperatively; all of them received a morning dosage. However, no sedative was prescribed preoperatively. Induction of anesthesia was done with intravenous propofol (3–10 mg/kg/h) that was maintained with isoflurane, nitrous oxide and oxygen (60:40). Non-depolarizing muscle relaxant (atracurium) was used sparingly under neuromuscular monitoring.

The operations were performed by transsternal technique. Complete removal of all thymic tissue, including cervical and lateral extensions up to the phrenic nerve, was done. Tracheal extubation was performed in the operating room or in the intensive care unit (ICU) when the patient appeared fully conscious and responsive after clinical assessment and nerve stimulation test. The usual dose of pyridostigmine was administered prior to surgery. Pyridostigmine was resumed in the evening after surgery; neostigmine was given intravenously to those patients who were on ventilatory support (perioperative dosage of 1 mg parenteral neostigmine was equated to 30 mg of oral pyridostigmine). After discharge from the hospital, they had regular follow-up visits (first visit one week after discharge; subsequently every month) in cardiothoracic and neurology units. To evaluate postoperative clinical outcome in the two groups, postoperative Osserman grade (0 to q5; 0 is assigned for symptom-free patients) at follow-up visit one year after surgery was subtracted from preoperative Osserman grade (a total of 5 grades) and clinical outcome is calculated on a scale ranging from 4 to 5. Drug dosage reduction was made gradually on follow-up visits depending on clinical stabilization over a period of month.

The statistical analysis was done by using standard statistical software, SPSS software for statistical calculation) (Version-16) for Windows.

RESULTS:

We analyzed the results of thymectomies in group B (no preoperative Plasmapheresis) and group A (with preoperative Plasmapheresis) patients. The results are summarized in Table I, II.

Early results:

In group A (Table I), there were 8 (40%) male patients (mean age, 62.3 years; range, 49–72) and 12 (60%) female patients (mean age, 40.5 years; range, 14–55). The mean time interval between diagnosis and surgery was 4.5 years (range, 2.5–8.5 years). All the patients belonging to Osserman grade were 2B to 4. In group A (Table II), sixteen out of twenty patients were ambulatory and on orals on the first postoperative day. Twelve patients could be discharged on the third or fourth postoperative day. The mean postoperative length of stay was 4.7 days (range, 3–7). Only four patients (20% in group A (Table II) required ventilatory support (mean duration of ventilation was 1.25"0.4 days).

In group B (Table I), 12 (44.4%) patients were male (mean age, 54.5"1; range, 40–64) and 15 (55.5%) patients were female (mean age, 38.6"17.1; range, 17–55). Preoperative Osserman grade was 2B to 4. The mean time interval between diagnosis and surgery was three years (range, 2–5.5 years). 18 out of twenty seven (66.66%) required ventilatory support (mean duration of ventilation was 4.7 days (range, 2–12 days). Fifteen (55.6%) patients developed postoperative wound infection and nine (33.3%) developed pneumonia. The mean postoperative length of stay was nine days (range, 6–18) (Table II). Parenteral neostigmine was administered in all patients on ventilatory support in the postoperative period.

Late results:

In group A, the improvement in the Osserman grade ranged from q2 to q3. Sixteen out of twenty patients were ambulatory and started on orals on the first postoperative day. Oral

anticholinesterase drugs were given half the preoperative dosage which was well tolerated. Subsequent reduction was made in follow-up visits depending on clinical stabilization. Sixteen patients (80%) remained symptom free at one-year follow-up.

In group B, the improvement in the Osserman grade ranged from q1 to q3. Drug dosage could be reduced in fifteen (55.6%) patients postoperatively and completely tapered off in 12 (44.4%); whereas 33.3% required increments in dosage with additional immunosuppression. These 9 (33.3%) patients developed myasthenic crisis.

Patients (in both groups) who were on steroids preoperatively, received the same postoperatively which was subsequently tapered off on clinical improvement. No postoperative mortality was observed in the study period. Demographic data are comparable between the two groups. Anesthetic techniques and operative procedure were similar in both groups. Postoperative morbidity profile was found markedly favorable in regard to the requirement of ventilation (Table II). Postoperative requirement of ventilation and hospital stay were significantly less in group B (*P*-0.05). Eighty percent of patients in group A did not develop any postoperative infection whereas 55.6% of patients in group B developed infection. Clinical improvement in group B in terms of Osserman grade was found to be statistically highly significant (*P* >0.005) (Table II).

DISCUSSION:

Myasthenia Gravis is an autoimmune disease, resulting from the production of antibodies against the acetylcholine receptors of the endplate[1,2,14]. Immunologic attack on synaptic receptors in the muscle causes receptor deficiency. The number of active receptors is reduced either by functional block of the receptors, by neither receptor degradation nor complement-mediated lysis. In myasthenic muscles, the miniature endplate potential amplitude is decreased, and the endplate potentials are largely sub-threshold[14]. There is a decremental response in the action potentials evoked from muscles on repetitive stimulation of peripheral nerves. These patients are usually treated with anticholinesterase drugs. Non-responders required treatment with steroids, immunoglobulins, immunosuppressants, plasmapheresis and surgical removal of the thymus [1, 2, 11].However; controlled trials have not been done to evaluate therapies. The role of the thymus in the development of antibodies against the acetylcholine receptors has been clearly established and therefore the relationships between myasthenia and thymic abnormalities have been suggested[15]. After the reports by Schumacher 1912 and Blalock ET al., In 1941, many series have shown the beneficial effects of thymectomy. Currently, thymectomy is considered a safe and effective procedure in myasthenic patients with or without thymoma, even in the elderly [16]. However, the morbidity and mortality of the procedure still remain the concern among surgeons. Routine postoperative ventilatory support and planned extubation in the ICU have been recommended considering the risk of postoperative respiratory failure and other complications that may result from operative stress [8, 9, 11]. Those patients who require prolonged ventilatory support often fare less favorably so far as the myasthenic symptoms are concerned and require high doses of medications, even periods of plasmapheresis irrespective of preoperative clinical status [8, 10, 11].

Nowadays, in many institutions the surgical strategy in patients with MG is influenced by the suspicion of thymoma based on mediastinal imaging. Currently, CT is thought to be the best

imaging technique in detecting mediastinal abnormalities, but one must be familiar with potential pitfalls and controversies[6]. It is difficult to distinguish lymphoid follicular hyperplasia from thymoma. To obtain the most accurate preoperative diagnosis, a CT scan with contrast should be made and all patient characteristics, especially, age, stage of MG and the presence of antistratitional-antibodies should be assessed[4, 17-19].

Plasmapheresis can improve the overall neuromuscular function by decreasing the circulating antibodies and may reverse the pathologic process related to these antibodies. Unfortunately, the beneficial results are only transient and periodic plasmapheresis treatments are often necessary [20].We believe that by the median sternotomy technique, it is possible to get optimum access for assessment and complete removal of the gland and used in all cases.

Preoperative plasmapheresis in group A has resulted in remarkable improvement in the postoperative morbidity profile in comparison to group B, with less ventilatory requirement and prompts postoperative recovery, thereby reducing the length of hospital stay, particularly in ICUs. The rate of remission was high in group A in follow-up. But the rate of persistence of remission did not differ between the two groups. The mean Osserman grade of patients in group A improved by 2.7 after surgery; where as in group B the improvement was 1.7 after surgery. The change in Osserman grade from before surgery to recent follow-up when compared is highly significant ($p=0.05$).

In the present series, the remission rate at the end of one year after surgery in group A is 80%; whereas in group B (without Plasmapheresis), it is 44.4%. Royce et al. [1] and Cooper and associates [21] in their series of thymectomy,reported an early complete remission rate of 35% and 44.2%, respectively, which is comparable to the result in group B patients (without Plasmapheresis) in our series. Some authors [1, 22] in their series of thymectomy used high doses of steroid perioperatively to improve postoperative outcome; but the results are conflicting. The fewer requirements of medication and overall improvement in physical status and social function in follow-up could be related to beneficial effects of plasmapheresis and surgery on the overall neuromuscular function in myasthenic patients by modifying the abnormalities of the immune system. However, it needs to be seen whether this short-term improvement remains sustained over a prolonged period of time and, therefore, further long-term study is required to substantiate the beneficial effect of the combination of plasmapheresis and surgery.

CONCLUSION:

Preoperative Plasmapheresis in the patients of myasthenia gravis is beneficial and can cause a significant difference in the postoperative outcome.

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Table I: Demographic characteristics of patients in group A and group B

Character	**Group A (*n*=20)**	**Group B (*n*=27)**
Age (mean)	Male = 62.3 years Female =40.5 years	Male = 54.5 years Female = 38.6 years
Sex	Male (*n*=8) Female (*n*=12)	Male (*n*=12) Female(*n*=15)
Time interval between diagnosis and surgery (years)	Range = 2.5 to 8.5 mean =4.5	Range = 2 to 5.5 mean = 2.9
Osserman grade	2B (*n*=8) 3(*n*=8) 4(*n*=4)	2B (*n*=17) 3(*n*=5) 4(*n*=5)
Anticholinesterase therapy	Yes	Yes
Preoperative Plasmapheresis	Yes	No
No. of patients having COPD	08	Nil
No. of patients requiring Pyridostigmine)750 mg	20	Nil
Duration of disease)>6 years	16	Nil

Table II: Postoperative results in group A and group B

	Group A (*n*=20)	**Group B (*n*=27)**	***P*-value**
Hospital stay in days	4.7	9.0	0.035
No. of patients requiring ventilation	04 (20%)	18 (66.6%)	
Postoperative ventilation Requirement in days	1.3	4.7	0.003
Myasthenic crisis	Nil	09 (33.3%)	
Postoperative infection	04 (20%)	18 (66.7%)	
Wound infection	04(20%)	15 (55.5%)	
Pneumonia	02 (10%)	09 (33.3%)	
Improvement in Osserman grade	2.7	1.7	0.005
Drug dosage reduction	16 (80%)	15 (55.6%)	

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