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Surgical outcome in thymic tumors with myasthenia gravis after plasmapheresis – a comparative study

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Abstract

Plasmapheresis has been used widely in the treatment of myasthenia gravis and also in symptomatic thymectomized patients with short-term clinical improvement. But the utility of preoperative plasmapheresis in the outcome has not been widely studied. The authors analyzed its impact in the surgical outcome of thymic tumors with myasthenia gravis. We studied a total of 19 patients, who were operated on in the period from January 2000 to July 2006 for thymic tumors with myasthenia gravis. Of these 19 patients, preoperative plasmapheresis was performed in 10 patients (group B) and the remaining nine patients (group A) had no preoperative plasmapheresis based on risk factors for requirement of postoperative ventilation. 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. Six out of nine patients (67%) in group A required ventilatory support in the immediate postoperative period, whereas two out of ten patients (20%) in group B required it. Significant and sustained symptomatic improvement was noted in group B as compared with group A \((P<0.01)\). Preoperative plasmapheresis in the patients of thymic tumors with myasthenia gravis is beneficial and can cause a significant difference in the postoperative outcome.

Keywords: Thymic tumors; Myasthenia gravis; Plasmapheresis

1. Introduction

Myasthenia gravis 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 sub-threshold [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.

Considering the management issues, patients with minimal symptoms are usually treated with anticholinesterase drugs and non-responders require treatment with steroids, immunoglobulins, and immunosuppressants. 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 antiACh receptor 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 [4, 5]. These patients often require a high dose of anticholinesterase drugs, steroids, immunosuppressants, even postoperative plasmapheresis, irrespective of preoperative clinical status [4, 6–8].

In our study, we combined plasmapheresis and thymectomy in patients with preoperative risk factors for postoperative ventilation.
2. Methods

We studied 19 consecutive patients of myasthenia gravis, admitted into the Department of Cardio Thoracic and Vascular Surgery, Institute of Post Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital, Kolkata, West Bengal, India who had undergone trans-sternal thymectomy from January 2000 to July 2006. These patients had a clinical diagnosis of myasthenia gravis with high antiAch receptor antibody titer and myasthenic symptoms controlled with medication. These patients had radiological evidence suggestive of thymic mass. 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. H/o 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). Patients’ preoperative characteristics are summarized in Table 1. Out of 19 patients, in 10 patients (group B) plasmapheresis (membrane plasma separation using Plasma Separation Filter; rate of plasma removal = 40 ml/kg of body weight daily) was performed preoperatively over a period of five days. In the remaining nine patients (group A), 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 perioperatively.

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 trans-sternal technique. Complete removal of all thymic tissue, including cervical and lateral extensions up to the phrenic nerve, was done. Thymic enlargement was present in all cases; a few of them were nodular. 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 on the next morning 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 +5; 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.

2.1. Statistical analysis

The statistical analysis was done by using standard statistical software, SPSS (a software for statistical calculation) (Version-10.5) for Windows. The values were expressed as mean ± standard deviation wherever applicable. \( \chi^2 \)-test was used for non-parametric data. A \( P \)-value < 0.05 was considered as statistically significant.

3. Results

We analyzed the results of thymectomies in group A (no preoperative plasmapheresis) and group B (with preoperative plasmapheresis) patients. The results are summarized in Table 2.

3.1. Early results

In group A (Table 1), 4 (44.4%) patients were male (mean age, 54.5 ± 1; range, 40–64) and 5 (55.6%) 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–

Table 1: Demographic characteristics of patients in group A and group B

<table>
<thead>
<tr>
<th>Character</th>
<th>Group A (n = 9)</th>
<th>Group B (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>Male – 54.5 ± 1; female – 38.6 ± 17.1</td>
<td>Male – 62.3 ± 11.9; female – 40.5 ± 18.2</td>
</tr>
<tr>
<td>Sex</td>
<td>Male – (n = 4); female – (n = 5)</td>
<td>Male – (n = 4); female – (n = 6)</td>
</tr>
<tr>
<td>Time interval between diagnosis and surgery (years)</td>
<td>Range – 2 to 5.5; mean = 2.9</td>
<td>Range – 2.5 to 8.5; mean = 4.5</td>
</tr>
<tr>
<td>Osserman grade</td>
<td>2B (n = 5)/3(n = 2)/4(n = 2)</td>
<td>2B (n = 4)/3(n = 4)/4(n = 2)</td>
</tr>
<tr>
<td>Anticholinesterase therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Preoperative plasmapheresis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No. of patients having COPD</td>
<td>Nil</td>
<td>4</td>
</tr>
<tr>
<td>No. of patients requiring pyridostigmine &gt; 750 mg</td>
<td>Nil</td>
<td>10</td>
</tr>
<tr>
<td>Duration of disease &gt; 6 years</td>
<td>Nil</td>
<td>8</td>
</tr>
</tbody>
</table>
5.5 years). Six out of nine (67%) required ventilatory support (mean duration of ventilation was 4.7 days (range, 2–12 days). Five (55.6%) patients developed postoperative wound infection and three (33.3%) developed pneumonia. The mean postoperative length of stay was nine days (range, 6–18) (Table 2). Parenteral neostigmine was administered in all patients on ventilatory support in the postoperative period.

In group B (Table 1), there were 4 (40%) male patients (mean age, 62.3 years; range, 49–72) and 6 (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 Oslerman grade were 2B to 4.

In group B (Table 2), eight out of ten patients were ambulatory and on orals on the first postoperative day. Six 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 two patients (20% in group B (Table 2) required ventilatory support (mean duration of ventilation was 1.25 ± 0.4 days).

### 3.2. Late results

In group A, the improvement in the Oslerman grade ranged from +1 to +3. Drug dosage could be reduced in five (55.6%) patients postoperatively and completely tapered off in 4 (44.4%); whereas 33.3% required increments in dosage with additional immunosuppression. These 3 (33.3%) patients developed myasthenic crisis.

In group B, the improvement in the Oslerman grade ranged from +2 to +3. Eight out of ten 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. Eight patients (80%) remained symptom free at one-year follow-up. 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. The majority in our series had thymic hyperplasia with lymphoid follicle formation having germinal center. Only two (22.2%) cases in group A and one (10%) in group B had thymoma on histopathological examination.

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 2). Postoperative requirement of ventilation and hospital stay were significantly less in group B (P < 0.05). Eighty percent of patients in group B did not develop any postoperative infection whereas 66.7% of patients in group A developed infection. Clinical improvement in group B in terms of Oslerman grade was found to be statistically highly significant (P = 0.005) (Table 2).

### 4. Discussion

Myasthenia gravis is an autoimmune disease, resulting from the production of antibodies against the acetylcholine receptors of the endplate [1, 2, 10]. 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 receptor degradation or complement-mediated lysis. In myasthenic muscles, the miniature endplate potential amplitude is decreased, and the endplate potentials are largely sub-threshold [10]. 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, 7]. 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 relationship between myasthenia and thymic abnormalities have been suggested [11]. Since the reports by Schumacher 1912 and Blaick 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 [12]. 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 [4, 5, 7]. 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 [4, 6, 7].
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 [13].

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 B has resulted in remarkable improvement in the postoperative morbidity profile in comparison to group A, with less ventilatory requirement and prompt postoperative recovery, thereby reducing the length of hospital stay, particularly in ICUs.

The rate of remission was high in group B 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 B improved by 2.7 after surgery; whereas in group A the improvement was 1.7 after surgery. The change in Osserman grade from before surgery to recent follow-up when compared is highly significant (<0.05). In the present series, the remission rate at the end of one year after surgery in group B is 80%; whereas in group A the improvement was 44.4%. Roeye et al. [14] and Cooper and associates [1] 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 A patients (without plasmapheresis) in our series. Some authors [1, 15] 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.

References