



PLASMAPHERESIS, A USEFUL TOOL FOR BETTER OUTCOME OF PATIENTS UNDERGOING THYMECTOMY FOR MYASTHENIA GRAVIS

Dr. Anula Sisodia	Associate professor, Department of Cardio-Thoracic and Vascular surgery, SMS Medical College and Attached Group of Hospitals, Jaipur, Rajasthan, India
Dr. Hemlata Verma	Associate professor, Department of Cardio-Thoracic and Vascular surgery, SMS Medical College and Attached Group of Hospitals, Jaipur, Rajasthan, India
Dr. Sami Anwar Khan	Senior Resident, Department of Cardio-Thoracic and Vascular surgery, SMS Medical College and Attached Group of Hospitals, Jaipur, Rajasthan, India
Dr. Deva Ram	Senior Resident, Department of Cardio-Thoracic and Vascular surgery, SMS Medical College and Attached Group of Hospitals, Jaipur, Rajasthan, India
Dr. R M Mathur*	Senior Professor and Unit Head, Department of Cardio-Thoracic and Vascular surgery, SMS Medical College and Attached Group of Hospitals, Jaipur, Rajasthan, India *Corresponding Author

ABSTRACT

Background: Thymectomy for widespread Myasthenia gravis may be associated with a turbulent postoperative course especially if preoperative circulating acetylcholine receptor autoantibody levels are towering. Plasmapheresis remove these antibodies. The aim of this study was to explore the results of preoperative Plasmapheresis on postoperative course after thymectomy. **Material And Method** This is a retrospective study at tertiary care center where 13 patients of myasthenia gravis were operated in 3 year duration (2017-2020). All patients had undergone 2 cycles of plasmapheresis before surgery. Result was evaluated postoperatively in ICU, at the time of discharge, and at follow up after 7 days, 1 month and 6 month in terms of weaning from ventilator, ICU stay, level of autoantibodies and length of hospital stay, improvement in symptoms, and mortality. **Results** Out of 13 patients 5 (38.46%) were male and 8 (61.54%) were female in the age range of 20 to 60 years. 6 (46.15%) were in stage IIA and 7 (53.85%) in stage IIB. Preoperative autoantibody levels were in the range of 30-50 nmol/ml. Almost total thymectomy was done in all patients. Patients were extubated with in 4-6 hrs after surgery and there was no mortality. Patients were discharged at postoperative day 4-7. **Conclusion** The study shows that preoperative use of plasmapheresis to reduce the autoantibody level is associated with an early extubation, early discharge and less complication after thymectomy.

KEYWORDS : Myaesthesia Gravis, ICU, Thymectomy, Plasmapheresis, Autoantibody, Acetylcholine

INTRODUCTION

Myasthenia gravis is an acquired, autoimmune disease of neuromuscular system¹ in which autoantibodies are formed against acetylcholine nicotinic post synaptic receptors at myoneural junction.² These autoantibodies cause drop in available number of receptors by increasing degradation of receptors, straightaway blocking the receptor sites, and actual degradation of receptor sites through commencement of complement system.³ Once acetylcholine receptor number decreases to 30% of normal, abnormal fatigue of voluntary muscles and weakness appear on repetitive activity. Study have revealed that thymus gland is implicated in myasthenia gravis by producing autoantibodies against acetylcholine receptors.^{4,5}

Symptoms of myasthenia gravis comprise ptosis (ocular involvement), trouble in chewing and swallowing (bulbar involvement), weakness of upper limb, and trouble in walking (Proximal muscle weakness), dyspnea and respiratory failure.

Treatment modalities for myasthenia gravis include Acetylcholine esterase inhibitors, steroids and other immunosuppressive drugs, Human immunoglobulin, plasmapheresis, immunoabsorption and surgical management.

Since thymus is concerned in pathogenesis of myasthenia gravis, getting rid of this gland is the treatment of choice in myasthenia gravis.⁶ Some patients of thymectomy develop myasthenic crisis in postoperative period which may require

intubation and mechanical ventilation⁷ and risks the life of the patient.

Plasmapheresis was introduced in treatment approach of myasthenia gravis by Pinching et al⁸ in 1976, since it remove circulating autoantibodies and alleviates the symptoms, though the benefit is for short term because it cannot prevent synthesis of autoantibodies and it's a well established modality of treatment in myasthenia gravis now.

Plasmapheresis is not only valuable to control acute myasthenic crisis and myasthenia exacerbation⁹ but it can also be used in cold cases preoperatively in patients planned for thymectomy to optimize the patients conditions. d'Empair et al¹⁰ reported significant decrease in time to mechanical ventilation and shorter stay in ICU for myasthenic patients treated by plasmapheresis before thymectomy.

In plasmapheresis, the plasma which is going to be discarded is replaced with albumin or FFP from healthy donor. In this study we exclusively used albumin for exchange to avoid anaphylactic reactions and transmission of infections.

In view of the above findings we retrospectively analyzed the effects of plasmapheresis done preoperatively on postoperative outcome after thymectomy.

MATERIALS & METHODS

A retrospective analysis of 13 patients of myasthenia gravis admitted in SMS Hospital, Jaipur, Rajasthan in the duration of

3 years from August 2017 to August 2020 was done who were subjected to surgical management. All patients were initially evaluated by neurologist and then referred to us for surgical management.

Out of 13 patients, 8(61.54%) were female and 5 (38.46%) were male in the age range of between 20-60 years. Severity of myasthenia gravis was evaluated according to Osserman and Genkin classification.¹¹ 6 patients (46.15%) were classified into stage II A and 7 (53.85%) were in stage II B.

Patient's preoperative evaluation included thorough clinical History and examination, blood investigations including assessment of acetylcholine receptor autoantibody level, chest X-Ray, ECG, CT Scan chest, pulmonary function test, electromyography and 2D echocardiography.

All cases had good motor power, with no evidence of respiratory failure. Ptosis and limb muscle weakness and diplopia were invariably present in all patients. 5 Patients had bulbar muscle involvement and exercise intolerance with dyspnea on exertion. No patient had history of acute myasthenic crisis. All patients were on pyridostigmine and steroids with 3 patients were on azathioprine too.

Preoperatively, spirometry exercises were advised to all patients to improve respiratory muscle strength. As guidelines are not available regarding preoperative plasmapheresis in myasthenia gravis patients undergoing elective thymectomy, therefore we subjected all patients to 2 cycles of plasmapheresis preoperatively, 3-4 days apart and albumin was used to substitute plasma. Plasmapheresis achieved significant reduction in autoantibody level although a definite level of autoantibodies was not fixed. Effect on symptoms and level of autoantibodies were assessed after Plasmapheresis. Pyridostigmine and steroids were continued till the morning of surgery.

Anesthetic Management

Induction was done with thiopentone sodium, fentanyl and single dose of Atracurium. Maintenance was achieved with sevoflurane. Patients were intubated followed by arterial and venous monitoring lines and urinary catheter insertion.

Operative Procedure

Maximal thymectomy was done transsternally by single surgical team in all patients, fatty tissue was removed from root of great vessels to the superior surface of diaphragm and from right phrenic nerve to left phrenic nerve. The specimens were sent for histopathological examination.

Hemostasis was achieved and sternum was approximated after fixing one mediastinal drain. Wound was closed in layers and patient was shifted to ICU on ventilator with no inotropic support.

Post-operative Management

All patients regained consciousness in 2-3 hrs. Intravenous neostigmine and steroid were given and continued 6 hourly on postoperative day 0. Patients were weaned and extubated within 4-6 hrs of surgery.

Oral drug therapy was resumed from postoperative day-1. After removal of mediastinal drain patients were shifted to postoperative ward on postoperative day-2. None of them required phasmapheresis after surgery. Patients were discharged on postoperative day 4-7 on oral pyridostigmine and steroids, which were gradually tapered in follow-up period.

Patient's clinical status improvement in symptoms and autoantibody levels were assessed after surgery in 7 days, 1 month, and 6 month follow up period.

The end points of study were extubation time, ICU stay, hospital stay, postoperative complications, and 6 month mortality.

RESULT

13 patients were enrolled in this study with 8 female (61.53%) and 5 were male (38.46%) (Table 1).

Table 1: Gender

Gender	Number	%
Male	5	38.46
Female	8	61.54
Total	13	100%

Patients were in 25-60 years age group (Table 2).

Table 2: Age

Age	Number	%
20-30	3	23.08
31-40	4	30.77
41-50	4	30.77
>50	2	15.38
Total	13	100%

After history and thorough clinical examination patients were categorized according to Osserman and Genkin classification. 6 (46.15%) patients were in stage II A and 7 (53.85%) patients were in stage IIB (Table 3). Ptosis was invariably present in all the patients and there was no history of acute fulminating myasthenia gravis or acute myasthenic crisis in any patients.

Table 3: Osserman and Genkin Classification

Stage	Number	%
I	0	0.00
IIA	6	46.15
IIB	7	53.85
III	0	0
Total	13	100%

Before undergoing plasmapheresis procedure anti acetylcholine receptor autoantibody level was checked for all 13 patients (Table 4) and the level was in between 10-45 ng/mmol. Autoantibody level was rechecked at 7 days, 1 month, and 6 month of follow-up.

Table 4: Antibody Level before plasmapheresis

Range (nmol/L)	Number	%
1-10	0	0
11-20	2	15.38
21-30	3	23.08
31-40	4	30.77
41-50	4	30.77
Total	13	100%

Patients were extubated with 3-4 hours of surgery. They remained under observation in ICU for 48 hrs. (9 patients) to 72 hrs (4 patients) (Table 5) and then shifted to the postoperative ward. 6 Patients (46.15%) were discharged on postoperative day 4, 3 patients (23.08%) on postoperative day 5, and 4 patients (30.77%) were discharged on postoperative day 7 with oral Prednisolone 10 mg TDS and pyridostigmine 60 mg QID (Table 6).

Table 5: ICU Stay

Hrs.	Number	%
12-48 hrs	8	61.54
48-72 hrs	5	38.46
Total	13	100%

Table 6: Hospital Stay after Surgery

Post of Days	Number	%
4th	6	46.15
5th	3	23.08
7th	4	30.77
Total	13	100%

Histopathological examination revealed thymic hyperplasia in 8 patients (61.54%). Out of 3 thymoma patients (23.08%), one showed thymoma with capsular invasion and for which radiotherapy was included in the treatment regime. Fatty involution was seen in only one case (7.6%) and Normal thymic tissue was seen in one specimen (7.6%) (Table 7).

Table 7: Histopathology of thymus specimen

	Number	%
Normal Tissue	1	7.69
Fatty Involution	1	7.69
Thymic Hyperplasia	8	61.54
Thymoma	3	23.08
Total	13	100%

At one month of follow up 10 patients showed significant improvement in symptomatology and 2 patients revealed that improvement was mild to moderate. These 2 patients had higher level of auto antibodies preoperatively and the level was decreasing slowly. Therefore, it was found that higher autoantibody level may be associated with less improvement in symptoms. At the same time autoantibody level was also checked which showed that it reduced to <5nmol/L in 4 patient (30.77%) while in 9 patients (69.23%) it was between 5-15 nmol/L (Table 8). This decrease in autoantibody level correlated with improvement in symptoms.

Table 8: Acetylcholine receptor auto antibody level at 1 month

nmol/L	Number	%
< 5	4	30.77
5-10	7	53.85
10-15	2	15.38
Total	13	100%

At 6 month follow up, autoantibody level was decreased to less than 5 nmol/L in all except one patient of thymoma who received radiotherapy. Over all there was no mortality, no complication seen and worsening of symptoms was not seen in any patient.

DISCUSSION

Incidence of myasthenia gravis is approximately 140 per 10 lac population.¹²⁻¹³ Overall mortality rate without surgery is 5.3%.¹⁴ Because of playing the main role in pathogenesis of the disease, thymectomy has become the standard treatment modality. But thymectomy may be associated with a stormy postoperative course in terms of myasthenic crisis causing respiratory failure, prolonged ventilation, re-intubation, longer ICU and hospital stay, and mortality. Studies have shown that approximately 3-12% patients develop myasthenic crisis after thymectomy.^{15,16} Chaoying Liu et al demonstrated that occurrence of myasthenic crisis after thymectomy was more if serum acetylcholine receptor antibody levels were high.¹⁷

Although there is no consensus that plasmapheresis before thymectomy improves perioperative outcome¹⁸ yet various studies have shown that preoperative plasmapheresis remarkably facilitates the postoperative recovery with improved outcome^{19,20} while S Saeteng et al found no difference in PPG and NPPG in relation to postoperative outcome.²¹ Nagayasu et al in their landmark study documented that 5 patients suffered myasthenic crisis in non preoperative plasmapheresis group while no patient of

preoperative plasmapheresis group developed this complication within 30 days of thymectomy.²⁰ S Saeteng et al performed one cycle of plasmapheresis one day prior to surgery²¹ but in this study 2 cycles were performed followed by checking the autoantibody level which showed significant reduction in the levels. Then patients were subjected to thymectomy.

Plasmapheresis using fresh frozen plasma as replacement fluid is associated with complications like hypotension, paresthesia, anaphylactic reactions etc.²² However, human albumin is better than FFP as no complications were seen with this during plasmapheresis.²⁰ In the present study, allergic reaction was seen in first patient therefore we exclusively shifted to albumin and completed the research without noticing any side effects. Similar result was also observed by Jason M. Budde et al.²³

In this study most of the patients were extubated within 3-4 hrs of surgery followed by quickly resuming their routine activities like swallowing, chewing, walking etc., improvement was also noticed in respiration during walking, ptosis, and diplopia. S Saeteng et al mentioned that PPG had greater opportunities for immediate or early extubation than those in NPPG²¹ however, El Bawab et al reported no difference in PPG and NPPG in terms of overall median time of mechanical ventilation, ICU stay and hospital stay²⁴ but in our study it was found that overall time of mechanical ventilation, ICU and hospital stay was short.

The frequency of complications after thymectomy as reported by S Saeteng, was 2% in NPPG and 6% in PPG²¹ while according to Vucic and Davis et al it was approximately 24.7%,²⁵ however, in the present study no complications were noted after thymectomy.

Thymus was invariably found involved with some or other pathology and only in one patient thymus was normal. Our histopathological findings were consistent with results shown by Skeie G O et al, showing thymoma presence in 10-15% patients²⁶ and Hohlfeld R et al, showing lymphoid hyperplasia in approximately 70% specimens.²⁷

Seto M et al noticed marked decrease in anti Ach R antibody titers within one month of surgery and is a favorable prognostic sign in patients of myasthenia gravis who have undergone thymectomy.²⁸ Similarly, there was significant reduction in autoantibody titer along with drastic improvement in symptomatology in this study.

At 6 month follow-up, steroid and pyridostigmine were tapered with no evidence of recurrence of symptoms except in one thymoma patient with capsular invasion requiring continuous drug support.

CONCLUSION

Although number of patients included in this study was small but still results suggest that use of preoperative plasmapheresis improves post operative outcomes in thymectomy patient in significant manner.

Abbreviation

ICU- Intensive Care Unit
 FFP- Fresh Frozen Plasma
 PPG - Preoperative Plasmapheresis Group
 NPPG- Non Preoperative Plasmapheresis Group
 Ach R- Acetylcholine Receptor

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Source of Funding: Nil

Ethical Approval: Not required

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