ORIGINAL ARTICLE

Preoperative Plasmapheresis Improves Post-thymectomy Outcome in Myasthenia Gravis

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ABSTRACT

Background: Thymectomy in generalized Myasthenia gravis patient may be associated with a stormy postoperative course, especially if preoperative circulating acetylcholine receptor autoantibody levels are high. Plasmapheresis removes these antibodies. So, the aim of this study was to analyze the results of preoperative Plamapheresis on postoperative course of thymectomy patients of myasthenia gravis.

Material and Method: This is a single center retrospective study at our tertiary center in which a total number of 13 cases of myasthenia gravis patients were operated in 3 year duration (2017-2020). All patients had undergone 2 cycles of plasmapheresis before surgery. Outcome was assessed 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 and improvement in symptoms.

Results: Out of 13 case 5 (38.46%) were male and 8 (61.54%) were female in the age range of 20 to 60 years. 6 patients (46.15%) were in stage IIA and 7 patients (53.85%) in stage IIB. Preoperative autoantibody levels were in the range of 30-50 nmol/ml. Maximal thymectomy was done in all cases. 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: Acetylcholine; Autoantibody; ICU; Myaesthenia Gravis; Plasmapheresis; Thymectomy.

INTRODUCTION

Myasthenia gravis is an acquired, autoimmune disease of neuromuscular system[1] in which autoantibodies are formed against acetylcholine nicotinic post synaptic receptors at myoneural junction[2].

These autoantibodies cause reduction in available number of receptors by accelerating degradation of receptors, directly blocking the receptor sites, and actual degradation of receptor sites through activation of complement system[3].

Once acetylcholine receptor number decreases to 30% of normal, abnormal fatigue of voluntary muscles and weakness appear on repetitive activity. It was found that thymus gland is involved in myasthenia gravis by producing autoantibodies against acetylcholine receptors[4,5].

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

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

Since thymus is involved in pathogenesis of myasthenia gravis, removal of this gland is the treatment of choice in myasthenia gravis[6].

Some cases of thymectomy develop myasthenic

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crisis in postoperative period which may require intubation and mechanical vrentilation[7] and risks the life of the patient.

Plasmapheresis was introduced in treatment strategy of myasthenia gravis by Pinching et al[8] in 1976, since it removes circulating autoantibodies and alleviates the symptoms. Plasmapheresis is now a well established modality of treatment in myasthenia gravis and American society for Apheresis recommends it as category I based on strong consensus of class III evidence[9-11].

Phasmapheresis is not only very useful to control acute myasthenic crisis and myasthenia exacerbation[12] but it can also be used in cold cases preoperatively in patients planned for thymectomy to optimize the patients conditions. d'Empair et al[13] 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 albu min or FFP from healthy donor. In our study we exclusively used albumin for exchange to avoid anaphylactic reactions and transmission of infections.

In view of removal of circulating autoantibodies and improving the symptoms, we retrorospectively analyzed the effects of plasmapheresis done preoperatively on postoperative outcome after thymetomy.

MATERIAL AND METHODS

We performed a retrospective analysis of 13 cases of myasthenia gravis admitted in SMS Hospital, Jaipur, Rajasthan in the duration of 3 years from August 2017 to August 2020 and were subjected to surgical management. Patients were initially evaluated by neurologist and then referred to us for surgical management.

Out of 13 cases, 8 (61.54%) cases were female and 5 (38.46%) cases were male. The age range was between 20-60 years. Severity of myasthenia gravis was evaluated according to Osserman and Genkin classification[10]. 6 cases (46.15%) were classified into stage II A and 7 cases (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, and electromyography.

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, spirometery exercises were advised to all patients to improve respiratory muscle strength. All 13 cases were subjected 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 not to the normal level and we did not fixed the level to which the autoantibody level to be achieved. Effect on symptoms and level of autoantibodies were assessed after Plasmapheresis. We continued pyridostigmine and steroids till the morning of surgery.

ANESTHETIC MANAGEMENT

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

OPERATIVE PROCEDURE

We performed maximal thymectomy through midline sternotomy approach in all cases i.e. thymus was excised completely; fatty tissue was removed from root of great vessels to the superior surface of diaphragm and from right phrenic nerve to left phrenic nerve.

Whole excised tissue was 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

In ICU, all patients regained consciousness in 2–3 hours. 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 restarted from postoperative day-1. After removal of mediastinal drain patients were shifted to postoperative ward on postoperative day-2. No patient 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.

RESULTS

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

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

After history and clinical examination patients were categorized according to Osserman and Genkin classification. 6 (46.15%) patients were in stage IIA 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.

Before undergoing plasmapheresis procedure antiacetylcholine 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.

In all the patients maximal thymectomy was done through midline approach with clearance of all fatty and thymic tissue from Right phrenic to left phrenic nerve and from infrathyroid region to the superior surface of diaphragm.

All 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).

Histopathological examination revealed that most commonly thymic hyperplasia was present 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).

At one month of follow up 10 patients showed significant improvement in symptoms present before surgery 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, 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 was matched with improvement in symptoms.

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.

Table 1: Distribution of Patients according to Gender

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

Table 2: Distribution of Patients according to Age

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

Table 3: Distribution of Patients as per Osserman and Genkin Classification

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

Table 4: Antibody Level before plasmapheresis in patients

Range (nmol/L)	Number of patients	%
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%

Table 5: Postoperative ICU stay in patients

Hrs.	Number patients	%
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 patients	%
4^{th}	6	46.15
5^{th}	3	23.08
7^{th}	4	30.77
Total	**13**	**100%**

Table 7: Histopathology of thymus specimen

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

Table 8: Acetylcholine receptor auto antibody level at 1 month

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

Myasthenia gravis is a chronic disease of neuromuscular system causing skeletal muscle weakness. Usually it affects muscles of eye, face, swallowing and respiratory system[14].

Incidence of myasthenia gravis is approximately 140 per 10 lac population[15,16].

The overall mortality rate for these patients is 0.27/100,000 and in ICU mortality is approximately 5.3%[17,18].

Management of myasthenia gravis usually revolves around drug therapy i.e. acetylcholine esterase inhibitors, steroids, immunoglobulins, and other immunosuppressant drugs but it becomes a challenge for clinicians to treat severe forms and fulminating forms of myaesthenia gravis because even with the use of various treatment modalities including plasmapheresis, improvement is only mild to moderate.

Patients may get benefit in terms of symptoms improvement but continue to have problems with day to day activities. Also, drugs are not without side effects.

Knowing that thymus is the main culprit organ in

pathogenesis of myaesthenia gravis, it was proposed that removal of thymus gland may improve the patient[6].

But, thymectomy is associated with a stormy postoperative course in terms of respiratory failure, prolonged ventilation, re-intubation, longer hospital stay and mortality especially if preoperative autoantibody levels are very high.

Size of these autoantibodies is longer than the glomerular pores of kidney to be excreted in urine. Therefore, plasmapheresis comes in the picture as it can directly remove these autoantibodies from circulation[19-22] and if we do it preoperatively it will help in early extubation of patient and bring Immunoglobulin levels to nearly normal.

In some patients autoantibodies directed against muscle specific kinase (Musk) also appear in circulation[19] and these autoantibodies produce plasmablast. Removal of these B-lymphocytes in such cases does not exclude recurrence of myasthenia gravis[23].

It was observed that approximately 94% of patients after a primary set of five plasma exchange procedure showed improvement[24].

In severe cases, and if patient is on ventilator, addition of plasmapheresis helps to wean the patient from ventilator, although the effect is short-term and requires repeated sets of plasmapheresis[25].

Various studies showed that plasmapheresis before thymectomy remarkably facilitates the post-operative period and improved the outcome of patients[26-29].

Therapeutic Plasma exchange has positive recommendation for treatment of myasthenia gravis based on strong consensus of class II evidence and in the category I of American society for apheresis[18-20].

Looking into the benefits of plasmapheresis in acute myasthenic crisis and severe generalized form, we decided to use this modality preoperatively rather than using in patients on ventilator postoperatively.

We found that our patients were extubated with in 3-4 hrs. of surgery and they quickly resumed their day to day activities like chewing, swallowing walking, no respiratory distress, ptosis, diplopia etc. very quickly within one month.

Thymus was invariably involved with some or other pathology and only in one case histo-pathological examination of thymus was normal.

Our histopathological findings were consistent with studies done by Skeie G O et al, showing thymoma presence in 10-15% of cases and Hohlfeld R et al, showing lymphoid follicular hyperplasia in approximately 70%[31].

Plasmapheresis is also not without complication. Using fresh frozen plasma as placement increases the risk of anaphylaxis, transfusion-transmitted infections, hemolysis etc.

In our 1st patient we found allergic reaction to FFP during plasmapheresis, so we used albumin in all patient. In our study we have not seen any mortality, similar result was also observed by Jason M. Budde et al.[32] and No patients experienced significant complications related to the operation.

Maximal thymectomy ensures complete removal of thymic and ectopic thymic tissues therefore maximal thymectomy was our procedure of choice.

At one month follow up, 11 patient (84.61%) showed significant improvement in their symptoms and 2 patients (15.38%) which were thymoma showed partial recovery.

SUMMARY

Severity of symptoms of myasthenia gravis depends on the load of circulating autoantibodies, higher the level more will be destruction of post synaptic nicotinic receptors therefore more will be symptoms. Thymectomy leads to decrease in autoantibody level only in postoperative period and it is a gradual decline hence it is associated with high morbidity, respiratory failure, and sometimes acute myesthenic crisis.

Preoperative Plasmapheresis reduces the available autoantibody level prior to surgery, and then thymectomy shuts the production of new auto antibodies, therefore, this overall reduction in the circulating load of auto antibodies reflects into a better outcome after surgery

Although our study is very small in terms of number of patients included but still we found that use of preoperative plasmapheresis improves post operative outcomes in thymectomy patient.

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