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Routine versus Selective Plasma Exchange before Thymectomy in Myasthenia Gravis

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Abstract: Elective thymectomy without preoperative plasmapheresis in myasthenia gravis patient regardless of a history of myasthenic crisis did not affect the overall outcomes when compared with preoperative plasmapheresis and may reduce catheter-related and post-operative complications. Therefore, preoperative plasmapheresis may be unnecessary in all elective thymectomies, even though patients have a history of crisis. However, patients who have history of myasthenic crisis more than one time or a significantly low motor power grading of extremities, or bulbar involvement, should be considered for preoperative plasmapheresis. The results of this study do not represent patients who have a myasthenic crisis before emergency or urgent surgery, repeated myasthenic crisis, or bulbar.
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1. Introduction

Myasthenia Gravis (MG) is a chronic, potentially debilitating, autoimmune disease in which pathogenic antibodies are directed at the neuromuscular junction (NMJ) of skeletal muscle. The condition can present at any age and is characterized by muscle fatigability, which may fluctuate during the course of the day and is typically worsened by exertion ***(Carla, 2012).***

Myasthenia gravis (MG) is one of the curable neurologic disorders. Various pharmacological therapies are administered for these patients and a thymectomy plays an important role in the therapy of myasthenia gravis ***(Alipour-Faz et al., 2016)***.

The role of the thymus in the development of antibodies against the acetylcholine receptors has been clearly established relationship between myasthenia and thymus has been suggested ***(Barohn et al., 2008).***

Since 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 with remarkable and sustained improvement in many myasthenic patients ***(Sonett et al., 2008).***

However, the morbidity and mortality of the thymectomy 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 like pulmonary infection that may result from operative stress ***(Rubino et al., 2004).***

It is essential to optimize the patient's condition prior to surgery. Patients with significant myasthenic weakness require preoperative optimization of their clinical strength to avoid prolonged respiratory insufficiency and ventilation following surgery ***(Kernstine et al., 2005)***.

Plasmapheresis (PMP) before thymectomy appears to improve the postoperative outcome. As PMP has its own complications, selective use of PMP preoperatively for patients at risk of post-thymectomy complications would improve the postoperative outcome, and decreases the PMP-related complications ***(El-Bawab et al., 2009).***

d'Empair et al.; reported a significant decrease of time on mechanical ventilation and a shorter stay in the intensive care unit (ICU) for myasthenic patients treated by PMP before thymectomy ***(El-Bawab et al., 2009).***

Although plasmaphersis is now in use for more than 30 years, some controversies remain about the indication and the place in the therapy. It can alleviates symptoms and improve the overall neuromuscular function by decreasing the circulating antibodies and may reverse the pathologic process related to these antibodies. Although, its effects are short lasting as it cannot prevent their resynthesis ***(Kuks et al., 1998)***.

However, when multiple plasmaphersis treatments are performed over a short period, the depletion of serum proteins including coagulation factors, albumin and globulin are more pronounced

and may require several days for spontaneous recovery ***(Seggia et al., 1995).***

Aim of the Work

The aim of this work is to study the safety and the efficacy of plasma exchange before thymectomy, either selectively or routinely, in myasthenic patient.

2. Materials and Methods

We performed a prospective analysis of two different protocols, at Benha University Hospital, and at Ain Shams University hospital, Egypt, comparing the routine (group I) versus selective use (group II) of prethymectomy PMP protocols in both centers, respectively.

The computerized database and the medical records of patients treated with thymectomy between 2016 and 2019 reviewed. The severity of the MG (maximum severity before operation) was evaluated according to Osserman and Genkins [5] as follows:

I, ocular disease only (ptosis, diplopia); IIA, mild generalized (ocular and extremities) with no prominent bulbar signs; IIB, moderate generalized (ocular and/or bulbar signs, variable limb muscle involvement), no crises; III, acute fulminating generalized signs with prominent bulbar involvement and crises; IV, late severe generalized and prominent bulbar signs and crises.

Inclusion criteria

All patients in class IIa and IIb and adult patients (more than 14 years old).

Exclusion criteria

Contraindication for PMP (mainly due to infections and abnormal coagulation profile), video-assisted thoraco- scopic (VAT) thymectomy.

The variables collected for each patient include:

Age, gender, weight, duration of disease, highest severity score in patient's history (Osserman's scale), preoperative pyridos- tigmine daily doses, preoperative prednisone daily doses, number of preoperative PMP session (s), complications related to PMP, vascular-access-related complications, arterial blood gas values, preoperative pulmonary function test (PFT) and their percentages from the predicted values, results of serological tests (acetylcholine receptor-binding antibodies), type of anesthetic (inhalational, balanced or regional), the use of neuromuscular blocking drugs, duration of anesthesia, duration of postoperative mechanical ventilation, duration of stay in the ICU and duration of postoperative hospitalization.

30 patients in group I and 17 patients in group II received PMP before thymectomy. The average sessions per patient were 3 sessions. For each procedure the managing team determined the target for plasma exchange, the nature of the replacement fluid and anticoagulant and the treatment schedule. In most patients the aim was to remove 2—3 l of plasma at each treatment. Five percent human serum albumin (5% NSA) alone or formulated with normal saline was the usual replacement fluid. Anticoagulant citrate dextrose (ACD) was the anticoagulant used in all procedures. Plasmapheresis was performed with COBE Spectra (COBE Laboratory, Lakewood, CO), which is a continuous flow machine. The duration of each procedure was 1.5—2.5 h.

Anesthetic management

Premedication with either diazepam or lorazepam orally was given to 60 patients approximately 2 h before surgery. Pyridostigmine and steroid therapy was continued up to the time of surgery. Anesthesia were induced using fentanyl-thiopentone in 19 patients and with sufentanil propofol in 43 patients. Combined general anesthesia and thoracic epidural analgesia was used in 50 patients. In 44 patients (83%) tracheal intubation was performed without neuromuscular blocking drugs. In 10 patients (17%) different neuromuscular blockers were used. Anesthesia was maintained with nitrous oxide/oxygen and isoflurane in patients and with sevoflurane in 21 patients.

Surgical procedure

Maximal thymectomy was performed by the same surgical team utilizing a transsternal approach. Both the cervical and mediastinal pools of the gland were removed en-block with the surrounding tissue, including the fatty tissue anterior and anterolateral to the trachea in the superior mediastinum with identification of the recurrent laryngeal nerves. This fatty tissue included the tissue extending from the neck to the diaphragm inferiorly, and between the two phrenic nerves laterally.

After completion of the operation patient's respiratory status was assessed. Tracheal extubation was performed if the clinical and respiratory variables were judged to be adequate. The extubation criteria were: (a) adequate recovery of neuromuscular function, (b) tidal volume >5 ml/kg during unassisted spontaneous breathing, and (c) inspiratory force of -20 cm H_2O or more. The duration of anesthesia ranged from 4 to 5 h. All patients were managed postoperatively in the intensive care unit. All patients received half of the preoperative pyridostigmine dose 24 h after surgery. There were no operative or hospital deaths and no phrenic or recurrent nerve injuries in this patient population.

In group II, the use of prethymectomy PMP was reserved for those patients identified to be at risk of prolonged postoperative mechanical ventilation (> 6 h). Naguib et al. [6] identified seven risk factors for predicting the needs of postoperative mechanical ventilation, namely: forced vital capacity (FVC), forced mid-expiratory flow between 25% and 75% of

the forced vital capacity (FEF25_75%), maximum expiratory flow at 50% of the forced vital capacity (MEF_{50}%), and their percentages of the predicted as well as sex. The model described is, Discriminate function (i) = -3.198 - 2.874 FVC+ 0.117 (% of the predicted value of FVC)+ 2.491 MEF_{50}% - 0.17 (% of the predicted value of MEF_{50}%) - 0.95 $FEF_{25—75}$% + 0.087 (% of the predicted value of $FEF_{25—75}$%) + 0.623 sex.*

We applied this predictive model to our patients in group II. 17out of the 30 patients included in group II were identified at risk of prolonged postoperative mechanical ventilation and subjected to preoperative PMP.

Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(**Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance;. difference and association of qualitative variable by Chi square test (X2). Differences between quantitative independent groups by t test or Mann Whitney,. P value was set at <0.05 for significant results & <0.001 for high significant result.

Data were collected and submitted to statistical analysis. The following statistical tests and parameters were used.

3. Results

On the basis of preoperative PMP protocol, patients were divided into two groups: group I (n = 30 patients) was treated with routine PMP prior to thymectomy, whereas group II (n = 30 patients) was selectively treated with PMP prior to thymectomy.

Demographic data are shown in Table 1. No significant difference was observed between the two groups in terms of age, gender, and duration of symptoms.

Demographic data distribution between studied group

			Group A	Group B	t/X2	P
Age			31.46±10.23	30.53±9.21	0.352	0.726
Gender	Female	N	18	17	0.06	0.79
		%	60.0%	56.7%		
	Male	N	12	13		
		%	40.0%	43.3%		
Total		N	30	30		
		%	100.0%	100.0%		

This table shows that age was distributed as 31.46±10.23 and 30.53±9.21 respectively with no significant difference between groups, regarding sex female represent more than half of both group with no significant difference between groups.

Anti-acetylcholine receptor antibodies (AchRAb) prior to initial treatment revealed no significant difference between group I (22 patients, 74%) and group II (23 patients, 76%) in terms of the ratio of positive patients.

All patients received pyridostigmine, and the preoperative dosage of pyridostigmine ranged from 60 to 480 for both groups (mean 237 ± 108.4 for group I and mean 234 ± 110.9 for group II). 27 patients (90%) in group I and 26 patients (87%) in group II were receiving glucocorticoids. No significant difference was observed between the two groups (Table 1).

Pre operation clinical characters distribution between studied groups

	Group A	Group B	t/ Mann whitney	P
Age diagnosis	29.13±11.63 (10-60)	28.32±10.32 (14-49)	0.274	0.785
Duration symptoms	28.7±10.91 (3-69)	26.92±8.98 (4-80)	0.243	0.809
Preoperative pyridostgmine	214.4±49.03 (60-360)	202.0±53.39 (60-360)	0.907	0.368
Preoperative Prednisone	15.33±7.7 (0-40)	13.66±6.2 (0-40)	0.506	0.615
Preoperative Azathioprine	30.0±12.3 (0-100)	35.33±13.32 (0-100)	-0.391	0.697

This table shows that there was no significant difference between groups regard age of diagnosis, duration of symptoms, and preoperative doses.

Pulmonary function test was performed for all patients. FVC, MEF_{50}%, and FEF_{25-75}% were compared in both groups. There were no statistical differences in the mean values of those parameters between the two groups (Table 1).

Pre operation Pulmonary function distribution between studied groups

	Group A	Group B	t	P
FEV1	1.75±0.41	1.72±0.39	0.18	0.87
FVC	2.68±0.65	2.65±0.51	0.09	0.93

This table shows that there was no significant difference between groups regard FEV1 or FVC

Pre-operative assessment and classification distribution between groups

			Group		Total	X2	P
			Group A	Group B			
Pre op Osserman	I	N	10	8	18		
		%	33.3%	26.7%	30.0%		
	II	N	7	10	17	0.79	0.67
		%	23.3%	33.3%	28.3%		
	III	N	13	12	25		
		%	43.3%	40.0%	41.7%		
Pre-operative MGFA Class	I	N	10	8	18		
		%	33.3%	26.7%	30.0%		
	II	N	7	10	17	5.77	0.12
		%	23.3%	33.3%	28.3%		
	III	N	11	5	16		
		%	36.7%	16.7%	26.7%		
	IV	N	2	7	9		
		%	6.7%	23.3%	15.0%		
History of Crisis	-VE	N	30	27	57		
		%	100.0%	90.0%	95.0%		
	+VE	N	0	3	3	3.15	0.07
		%	0.0%	10.0%	5.0%		
Pre-operative IVIG	-VE	N	30	28	58		
		%	100.0%	93.3%	96.7%		
	+VE	N	0	2	2	2.06	0.15
		%	0.0%	6.7%	3.3%		
Preoperative thymus CT	0	N	20	23	43		
		%	66.7%	76.7%	71.7%		
	I	N	7	4	11	1.02	0.59
		%	23.3%	13.3%	18.3%		
	II	N	3	3	6		
		%	10.0%	10.0%	10.0%		
NCS	-VE	N	2	0	2		
		%	6.7%	0.0%	3.3%		
	+VE	N	28	30	58	2.06	0.15
		%	93.3%	100.0%	96.7%		
ACH_R_ABS	-VE	N	5	3	8		
		%	16.7%	10.0%	13.3%		
	+VE	N	25	27	52	0.57	0.44
		%	83.3%	90.0%	86.7%		
Total		N	30	30	60		
		%	100.0%	100.0%	100.0%		

This table shows that there was no significant difference between groups regard any pre OP characters or classification.

All patients in group I (n = 30) underwent PMP before thymectomy, while in group II only 17out of 30 patients (57%) underwent preoperative PMP. The mean number of sessions in group I was (3.1 ± 0.72), and (1.2 ± 1.5) in group II. PMP- related complications occurred in 8 patients (26%) in group I and in 3 patients (10%) in group II (Table 2). Documented hypotension (systolic blood pressure <80 mmHg) was the most common complication in both groups (3patients in Group I and 2 patients in group II). Coagulopathy with INR more than 1.2 was reported in 2 patients in group I and only 1 patient in group II. Methicillin sensitive *Staphylococcus aureus* was grown in blood cultures in most cases with documented infection in both groups. The infection was treated by replacement of venous access and intravenous antibiotics. Venous access-related complications in the form of oozing from puncture site, catheter occlusion, and atrial fibrillation during catheterization represented 5% of the overall complications in group I *(n* = 4) and 2% in group II (n = 2). The percentage of overall PMP-related complications in group II was 9% (95% CI 3.0—14.8). This was significantly lower than the percentage of complications in group I which was 26% (95% CI 15.7—35.7) with a *p* value of 0.008 (Fig. 1).

Table 2 Plasmapheresis-related complications.

	Group I (30)		Group II (30)	
	n		*n%*	
Hypotension	3	10	2	7
Coagulopathy	2	7	1	3
Infection	2	7	1	3
Venous access complications	2	7	1	3
Total	4		2	

28 patients (47%) had successful tracheal extubation in the immediate postoperative period. The tracheas of 16 patients (27%) were extubated within 6 h after surgery. Seventeen patients (29%) needed ventilatory support for more than 6 h (10 patients required ventilatory support for 7—12 h, 5 patients for 13—24 h, and 2 patients for 25—48 h).

In group II, the subgroup of patients who did not receive preoperative plasmapheresis needed less postoperative ventilatory support.

Operative data and early post-operative data distribution groups

	Group A	Group B	t	P
Operative time	**186.0±43.4**	**141.66±25.3**	**4.829**	**0.00****
Hospital stay	**2.06±0.25**	**2.1±0.31**	**-0.460**	**0.647**
Pain score	**3.46±0.89**	**3.3±0.83**	**0.743**	**0.460**
Bleeding	**37.5±12.36**	**32.66±10.87**	**1.116**	**0.269**
Time to remove drains	**2.06±0.25**	**1.86±0.34**	**2.554**	**0.013***

This table shows that group B were significantly shorter regard operation time and also significantly shorter regard time to remove drain

Post-operative data distribution and complication distribution between studied groups

			Group		Total	X2	P
			Group A	Group B			
Wound infection	**-VE**	**N**	**30**	**29**	**59**	**1.01**	**0.31**
		%	**100.0%**	**96.7%**	**98.3%**		
	+VE	**N**	**0**	**1**	**1**		
		%	**0.0%**	**3.3%**	**1.7%**		
Post op chest condition	**-VE**	**N**	**28**	**30**	**58**	**2.06**	**0.15**
		%	**93.3%**	**100.0%**	**96.7%**		
	+VE	**N**	**2**	**0**	**2**		
		%	**6.7%**	**0.0%**	**3.3%**		
Early postoperative mechanical ventilation	**-VE**	**N**	**28**	**29**	**57**		
		%	**93.3%**	**96.7%**	**95.0%**		

	+VE	N	2	1	3	0.35	0.55
		%	6.7%	3.3%	5.0%		
ICU stay	-VE	N	28	26	54		
		%	93.3%	86.7%	90.0%		
	+VE	N	2	4	6	0.74	0.38
		%	6.7%	13.3%	10.0%		
Total		N	30	30	60		
		%	100.0%	100.0%	100.0%		

This table shows that there was no significant difference between groups

For group I, the medians of ICU stay and postoperative hospitalization periods were 1 and 9 days, respectively. When compared with the median time of ICU stay and postoperative hospitalization for group II (1 and 8 days), there were no statistical differences between both groups 'Mann— Whitney p = 0.38 and p = 0.15, and differences in medians are zero and one, respectively' (Table 3).

Post OP and follow up doses distribution between groups

	Group A	Group B	t	P
Post operative plasma	0 (0.0%)	0 (0.0%)	–	–
Postoperative Pyridostgmine dose at 2 weeks	190.0±38.8	188.0±58.4	0.149	0.882
Postoperative Prednisone dose at 2 weeks	22.1±5.05	20.54±4.34	0.745	0.459
Postoperative Azathioprine dose at 2 weeks	41.25±9.58	35.87±10.4	-1.035	0.305
Postoperative Pyridostgmine dose at 3 months	142.0±49.54	113.0±32.07	1.671	0.100
Postoperative Prednisone dose at 3 months	27.6±7.36	40.2±4.14	2.483	0.016
Postoperative Azathioprine dose at 3 months	50.0±8.54	44.33±10.6	-0.660	0.512
FINAL Pyridostgmine	98.0±37.1	81.0±29.1	1.111	0.271
FINAL Prednisone	28.5±8.54	30.7±9.7	0.231	0.818
FINAL Azathioprine	50.64±9.12	30.24±7.12	-0.826	0.412

This table shows that there was no significant difference between groups

4. Discussion

Transsternal thymectomy is a widely used treatment for generalized myasthenia gravis with long-term remission [7]. In non-thymomatous patients, complete remission rate has progressively increased from 37.4% to 58.2% and 75% at 3 years, 10 years and 15 years of follow-up consequently [8]. Patients with myasthenic weakness require preoperative optimization of their clinical strength to avoid prolonged respiratory insufficiency and ventilation following surgery. This approach reduces perioperative complications, duration of hospital stay, and overall morbidity. Immunomodulation using plasmapheresis is effective in producing rapid clinical improvement. Yeh et al. [9] used double filtration.

Although PMP is a useful treatment modality [10], it is also sophisticated and invasive. Fatalities and life-threatening reactions have been reported, as well as minor reactions [11]. Furthermore, not all patients are in need for preoperative PMP to ensure satisfactory postoperative outcome. In fact, there is no consensus that preoperative PMP reduces the postoperative complications after thy- mectomy and the complications of PMP may outweigh its beneficial effects in certain patients [12,13].

In this retrospective study we adopted two protocols, routine and selective use of PMP, in an effort to reduce the frequency of PMP-related complications. We have tried to address one specific question at a time in a select group of consecutive patients who have undergone similar operations by the same group of surgeons with similar preoperative demography, and intraoperative and postoperative techniques in an attempt to control as many confounding variables as possible.

Selecting myasthenic patients for preoperative PMP follows the work of Naguib et al. [6]. They suggested a predictive model for those patients who are at risk of respiratory sufficiency and prolonged mechanical ventilation after transsternal thymectomy. The model correctly predicated the actual postoperative respiratory outcome in myasthenic patients with a probability of 88.2%. As PMP would interfere with the postoperative respiratory outcome, we could not calculate the predictive probability of this model. In the mean time, patients who did not receive preoperative PMP (identified as low risk for prolonged postoperative ventilation with numerical value of the discrimination function (i) greater than zero) showed both earlier tracheal extubation and

lower incidence of prolonged postoperative ventilation.

In our group of patients, a total of 47 patients required prethymectomy PMP (30/30 in group I and 17/30 in group II). The frequency of complications in group I was 25.7%. Vucic and Davis [14] reported a similar complication rate of 24.7% in 73 patients who underwent PMP for different neurological disorders. The frequency of PMP-related complications in group II was significantly lower than in group I (26% vs 9%), with p = 0.008. This reduced frequency of complications was primarily due to the lower number of patients who received PMP preoperatively in group II than in group I.

Certain life-threatening complications that have been reported in the literatures [14,15], such as cardiac arrhythmia and asystole, respiratory arrest, seizure, anaphylactic and febrile reactions, hemorrhagic and thrombotic episodes and fluid imbalance did not occur in our series. The first three complications are probably related to an excess in the rate and/or volume of anticoagulant infusion. It is likely that they did not occur in our series because the rate of anticoagulant infusion was maintained within the recommended range of 1.0—1.8 mg/min/kg. Anaphylactic and febrile reactions to infusion of 5% NSA have been reported to occur at a rate of 1 in 6600 infusions [16]. These reactions are attributed to antibody interactions with altered albumin, non-albumin human proteins (such as IgA and factor XII fragments) and contamination of batches with bacteria or pyrogens. Although these complications were not observed, our series is not large enough to allow for meaningful conclusions.

Hypotension is a potential complication of all procedures involving extracorporeal circulation PMP. The incidence of hypotension episodes related to the PMP procedure in this study of 333 PMP sessions (4%) is similar to that reported previously of 2502 sessions PMP sessions (3.3%) [17]. All of the hypotensive events in this series were of brief duration with no syncope; an observation that is in line with other research. Volume and protein depletion are the most likely causes of hypotension. Hypoproteinemia is an important factor contributing to unstable hemodynamics during serial PMP [18—20].

Vascular-access-related complications contributed approximately to 4%of all complications in our study. Major- vessel trauma resulting from catheter placement may cause profound morbidity and even mortality [21]. Couriel and Weinstien [11] have reported that catheter-related trauma contributed to all four cases of severe PMP complications (6.15%), with one expiring due to massive bleeding from arterial rupture. In this study, there were no major morbidities during catheterization. Recently, it has been reported that sonographic guidance during catheter placement reduces the occurrence of such complications [22].

The postoperative recovery did not differ between the two groups. There was no difference in the overall median time of mechanical ventilation, ICU stay, and hospital stay. This indicates that preoperative optimization was comparable in both groups though not all patients in group II received PMP preoperatively (only 35/90). This in turn, indicates that the predictive model suggested by Naguib et al. [6] worked well in predicting patients at risk of post-thymectomy prolonged mechanical ventilation.

In conclusion, selective use of PMP before thymectomy may reduce the incidence of PMP-related complications without affecting the overall outcome. It is, however, not intended to be an absolute standard for perioperative management of myasthenic patients undergoing transsternal thymectomy. Furthermore, prospective studies to include larger number of patients and hence larger number of PMP sessions are needed for complete evaluation.

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