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REVIEW

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Comparative efficacy of low dose, daily versus alternate day plasma exchange in severe myasthenia gravis

A randomised trial

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Abstract *Objective* To evaluate the comparative efficacy of low dose daily versus alternate day plasma exchange in patients with severe myasthenia. *Methods* Thirty three patients with myasthenia gravis (Osserman's stage II b and III) were randomized to receive alternate day (n = 17) or daily low dose plasma exchange (n = 16). Plasma exchange were carried on each patient, number of exchanges varying subject to their requirements and 20-25 ml/kg plasma was removed during each session. Myasthenia gravis disease scale (MGDS) score was evaluated before and after the procedure. Time to wean off ventilator, removal of nasogastric tube and total duration of hospital stay were also assessed. *Results* There was no statistically significant difference between daily vs. alternate day group with regards to change in MGDS score, percentage change in MGDS score, and complication rates. A decreased hospital stay was observed in patients on daily plasma exchange which almost reached statistical significance. *Conclusion* We conclude from our study that daily and alternate day plasma exchange are similar in their efficacy and complication rates, however the daily schedule could be a preferred modality due to decreased hospital stay.

Key words myasthenia · plasma · daily · alternate day · schedule · score

Introduction

Myasthenia gravis (MG), is an autoimmune disease characterized by fatigable muscle weakness, diurnal variation of symptoms and a favorable symptomatic response to acetylcholine esterase inhibitors (AChEI) [1]. Circulating antibodies to acetylcholine receptors are detectable in most patients with MG and are reported to play a major role in the pathogenesis of the disease [2]. Remission in the symptoms of MG can be induced using immunosuppressant drugs, or by modalities which either neutralize or remove the circulating acetylcholine receptor antibodies (AChRAb)[3]. Plasma exchange (PE) is used in the management of myasthenic crisis [4], for management of acute exacerbation of MG (particularly in patients with bulbar or severe generalized symptoms), for optimizing the clinical state prior to thymectomy, and for patients who do not adequately respond to standard treatment [5–7]. The role of PE in the management of these conditions in MG has been endorsed by the National Institute of Health (NIH,USA) in its consensus statement [8], despite the fact that only class III evidence exists to support the role of PE in management of MG [9]. The exact mechanism of action of PE in myasthenia remains unknown; however,

its most likely role is in the removal of circulating auto-antibodies. There is no consensus on the schedule, the number of PEs in MG, or the replacement fluids used. There are many different methods of PE such as centrifugation technique, immunoadsorption, and double filtration plasmapharesis, which have all been used for PE successfully. There are not many studies which have evaluated the efficacy of daily versus alternate day PE in MG. In the present study we tried to evaluate the efficacy of low dose daily against alternate day PE in MG patients, using conventional centrifugation method for plasmapheresis.

Material and Methods

Patients of MG were recruited from Neurology and Neuroimmunology clinics, causualy and the neurology wards of All India Institute of Medical Sciences (AIIMS), New Delhi from January 2002 to December 2003, in this prospective randomized study, on an intention to treat basis. The study was approved by the institutional ethics committee and was performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki. The diagnosis of MG was made on a typical history and clinical signs of fatigable muscle weakness, and responsiveness to AChEI drugs. They were classified into definite, probable, and possible MG according to established diagnostic criteria [1]. Patients with generalized, probable or definite MG with crisis requiring endotracheal intubation or assisted ventilation, or significant bulbar symptoms requiring nasotracheal tube, i.e., Osserman's stage II b and III, patients with generalized MG who were bed bound because of the weakness, were included in the study. Patients with ocular myasthenia and those with significant contraindications for PE such as cardiac disease, uncontrolled hypertension, renal or hepatic disease, and septicemia were excluded from the study. Patients who voluntarily opted for intravenous immunoglobulins (IVIg) as their treatment modality were also excluded from the study. Written informed consent was obtained from all patients before inclusion in the study.

Clinical evaluation

All the patients were evaluated using a standard pre-structured format. A detailed clinical history was taken from all the patients, which included, as well as the demographic data, age at onset, duration, and distribution of the disease. Information was obtained on symptoms of other autoimmune disease (if any), and the factors responsible for clinical deterioration. A detailed treatment history was taken from all patients and a note was made of the type, dose and duration of treatment with immunosuppressant drugs. Examination included a detailed neurological examination, including testing for objective evidence of muscle fatigue. A myasthenia gravis disease scale (MGDS) score was assigned to all patients. This was an eight itemed score, (duly validated by us in bilingual MG patients and controls), including assessment of patients on severity of ptosis, diplopia, dysphagia, dysphonia, chewing difficulty, and weakness of pelvic girdle, shoulder girdle and neck muscle on a scale of 0 to 4. A score of zero meant normal and a score of four meant maximum disability on that particular item, the maximum score being 32. Each of the above mentioned variables in the MGDS carried equal weight. All subjects underwent routine serum biochemistry, haemogram, workup for systemic vasculitis and collagen vascular disorders, thyroid function tests and AChR antibody assay. Repetitive nerve stimulation test (RNST), radiography of chest PA view and contrast enhanced CT was done in all patients.

After confirmation of diagnosis, clinical evaluation and obtaining a written consent, the patients who were recruited in the trial were subjected to plasma exchanges. They were assigned to receive daily or alternate day of plasma exchange (PE), randomly by using computer generated numbers into 2 groups. If a patient received more than one course of PE on same or different admissions, fresh random numbers were allocated each time, therefore such patient had a possibility of falling in the 'daily' or 'alternate' group.

PE protocol

PE was performed using the Hemonetics MCS 3p – discontinuous centrifugation system, after obtaining negative reports of Hepatitis B Ag, Anti Hepatitis C antibodies, and Elisa for HIV. Hemonetics Plasmapheresis set no. 622 or 627 was used. The set was discarded after single use. Patients were assigned to receive at least 5 sessions of PE, (under cardiopulmonary monitoring). If the clinical condition of the patient demanded more or less PE it was permitted according to the decision of the treating physician. Peripheral vascular access (antecubital vein) was used in 17 patients and central access (femoral, subclavian, internal jugular) in 16 patients. Central access was used only if peripheral access was not available. Targeted plasma exchange during each session was 20-25 ml/kg of plasma, replenished with fresh frozen plasma (FFP) or 5% albumin (in patients who developed reaction to FFP, or when there was non-availability of plasma of a matching blood group). Citric acid (ACD-A) was used as an anticoagulant. AChR antibody levels were obtained before PE in all the patients. Owing to financial constraints a repeat estimation of AChR Abs was not done after each procedure.

Following plasmapharesis, the patients were evaluated daily for any change in their motor power using the MRC grading by assessors blinded to the treatment regimen. Improvement was also rated on functional aspects such as time taken for removal of nasogastric tube, time taken to extubation, to weaning from ventilator, ability to get up from a sitting position, walk and raise arm above the shoulder level. A note was made of number of days spent in intensive care unit (ICU), in hospital, and the complications encountered as a result of MG and PE. Patients were evaluated at base line, 2 weeks, 4 weeks or at the time of discharge following plasma exchanges, whichever was later by a reviewer who was blinded to the treatment regimen. The two groups were compared for the improvement in the MGDS score at 2 weeks, 4 weeks and/or discharge and for the clinical improvement in the condition of the patient. The days spent in the hospital, in the ICU, the number of days the patient required ventilatory support, and the complications in the two groups were also compared between the groups. A change in MGDS scores at discharge by more than 40% was taken as significant.

Statistical methods

The demographic data and the clinical details were tabulated in MS Excel spreadsheet and the data were cross checked for any keyboard errors. The variables were evaluated descriptively using EPIINFO version 6.04 D and SYSTAT version 7.0, which is the standard protocol used at bio-statistics department, AIIMS. Quantitive variables were assessed for approximate normal distribution. The two groups were compared using the Mann Whitney's test when the variables were non-parametric and chi square test when parametric variables were evaluated. In this study a statistically significant difference was considered if the p value was 0.05 or less.

Results

In the present study forty four patients presented to us with myasthenic crisis during the study period of whom four patients declined to participate in the study, and opted for the alternate day PE and seven patients opted for IVIG. Therefore 33 patients with myasthenia gravis were recruited in the present study, of whom 17 patients were randomized to receive alternate day and 16, daily PE. The two groups were comparable in their demographic and clinical details, antiacetylcholine receptor antibodies positivity, their baseline MGDS score, median duration of illness and median duration of exacerbation. Of those assigned to alternate day PE, 10 were in Osserman's stage II b and 7 in stage III whereas 11 and 5 patients respectively were in Osserman's stage IIb and III in the daily PE group. Bulbar symptoms, without respiratory involvement were present in 21 patients at the onset of treatment, of whom 10 were in alternate day PE and 11 in daily PE group. Seven patients in alternate day PE group and five patients in daily PE group required ventilator support at the onset of treatment (Stage III) and 4 patients (2 in each group) required ventilator support while receiving PE. There was evidence of either significant bulbar and/or respiratory muscle weakness in all the patients. No statistically significant difference was observed in the demographic or clinical details among the groups. All the patients in both the groups were receiving AChEI in comparable doses. Amongst the patients who were receiving steroids and azathioprine, the doses of these medications were also similar in the two groups. In our study, radiological/histopathological evidence of thymoma was present in 18 patients (10 in alternate day PE group and 8 in daily PE group), while in 13 patients either the gland was normal or had benign hyperplasia. Thymus gland was not visualized in two patients (Table 1).

Average number of treatment sessions carried out in each group was similar (Table 2). A total 161 treatment sessions were carried out in 33 patients, of which 85 (17 treatments) were in alternate day PE group, and 76 (16 treatments) in daily PE group. ($p = 0.71$). Each patient received 1–8 exchanges (5.0 ± 1.83 in alternate day PE group and 4.75 ± 1.48 in daily PE group), depending upon the clinical condition of the respective patient and tolerance to PE. The distribution of the mean number of exchanges was thus similar in the two groups. The average amount of plasma removed for each patient was comparable in the two groups, as was the average amount of plasma removed per kilogram body weight of the patient. Two patients received 5% albumin as replacement fluid instead of FFP; one because of unacceptable side-effects to transfusion of FFP and the other because of non-availability of FFP of that blood group.

The clinical response to plasma exchange in the two groups of PE are shown in Tables 3, 4 and 5. Absolute MGDS score, change in MGDS score, and percentage change in MGDS scores from baseline till the time of discharge did not show any statistically significant change between the two groups (Table 3). Improvement in MGDS and functional grading were observed in 26 patients (78.7%). Of these, improvement in MGDS score by more than 40% was observed in 21 patients, 11 in group with alternate PE and 10 in group with daily PE (Table 4). Less than 40% improvement was seen in 5 patients. All these five patients had significant bulbar symptoms, three patients were on ventilator and were eventually weaned off ventilator, the nasogastric tube was removed in one patient and another patient showed 22.2% improvement in MGDS score though he did not

Table 1 Baseline clinical and demographic characteristics of patients randomized to alternate day or daily PE treatment groups

Variable	Alternate day PE (n = 17)	Daily PE (n = 16)	P value
Mean age (yrs) ± SD, median age	34.88 ± 9.67, 35	37.00 ± 12.71, 35	0.86
Osserman's Stage II b	10	11	
Stage III	7	5	0.55
Baseline MGDS score Mean ± S.D, median	15.11 ± 4.93, 15	16.06 ± 3.94, 16	0.34
Median duration of illness	30 months	30 months	
Median duration of exacerbation	0.8 / months	1 month	
AchE I dose before Plasma exchange (mg), Mean ± S.D, median	237.32 ± 70.91, 240	290.62 ± 95.32, 285	0.11
Number of patients receiving steroids	11	9	0.62
Dose of steroids before PE (mg), Mean ± S.D, median	29.09 ± 18.27, 30	22.22 ± 17.69, 15	0.42
Number of patients receiving azathioprine	9	8	0.87
Dose of azathioprine before PE (mg), mean ± S.D, median	72.22 ± 36.32, 50	100.00 ± 37.79, 100	0.12
Evidence of thymoma (radiological/histopathological)	10	8	0.61
Normal Thymus / Benign Hyperplasia	6	7	0.62
Thymus status not known	1	1	0.96
Thymectomy	11	10	0.9

Table 2 Details of plasma exchange in patients randomized to alternate day or daily PE

Variable	Alternate day PE (n = 17)	Daily PE (n = 16)	P value
Amount of plasma removed (ml), mean ± SD, median	1061.07 ± 118.11, 1108.00	1010.80 ± 280.00, 1095.95	0.88
Plasma removed each session (ml/kg) mean ± SD, median	21.09 ± 3.88, 20.23	18.72 ± 3.54, 19.12	0.08
Total number of sessions	5.0 ± 1.83	4.75 ± 1.48	0.71
Venous access Periph	9	8	0.87
Central	8	8	
Total units of FFP received	23.17 ± 9.81	20.68 ± 10.06	0.51

Table 3 Primary Outcome Measures in patients randomized to alternate day or daily PE

Variable	Alternate day PE (n = 17) mean ± SD	Daily PE (n = 16) mean ± SD	P value
Absolute MGDS score at 2 weeks	11.76 ± 6.00	10.75 ± 5.55	0.62
Absolute MGDS score at 4 weeks	7.94 ± 3.91	10.19 ± 5.21	0.17
Absolute MGDS score at discharge	7.94 ± 3.91	10.19 ± 5.21	0.17
Change in MGDS score at 2 weeks	6.17 ± 4	5.87 ± 4.33	0.98
Change in MGDS score at 4 weeks	7.17 ± 5.18	5.87 ± 4.33	0.53
Change in MGDS score at discharge	7.17 ± 5.18	5.87 ± 4.33	0.53
Percentage change in MGDS score at discharge	42.01 ± 28.26	38.40 ± 27.99	0.52

Table 4 Change in MGDS score at discharge in patients randomized to alternate day or daily PE

MGDS Score	Alternate day PE (n = 17)	Daily PE (n = 16)	Total (n = 33)	P value
No change	2	2	4	1.0
<40% improvement	3	2	5	1.0
>40% improvement	11	10	21	0.9
Expired	1	2	3	0.6

Table 5 Secondary Outcome Measures in patients randomized to alternate day or daily PE

Variables	No. of patients	Alternate day PE	Daily PE	P value
Median duration of hospital stay in days	33	26 (n = 17)	17.5 (n = 16)	0.054
Median duration of ET tube in days	17	14.5 (n = 10)	10.5 (n = 7)	0.213
Median duration of RT feeds in days	19	22 (n = 11)	14.5 (n = 8)	0.076

report any subjective improvement. MGDS score was unchanged in 4 patients, of whom 2 were in each group. One patient who did not show any improvement in MGDS score was given plasma exchange just before thymectomy for stabilization of symptoms. Another patient who was enrolled twice in the study was randomized to receive daily PE in the first session and alternate day PE in the second. The interval between the two treatment sessions was three weeks. This patient showed slow improvement over a month, only after receiving IVIg and could then be weaned off the ventilator. Plasma exchange was not effective in a total of 6 patients (18.1%), 2 in alternate day PE group and 4 in daily PE group. Of these, three patients expired during the course of their hospital stay, and were considered as non responders. Plasma exchange had to be stopped after first PE in one patient, who was in alternate day PE group, and later had to be switched over to IVIg as he developed hypotension before the second plasma exchange. The other two patients did not show any response to PE, in any of the parameters mentioned above and had to be switched over to IVIG.

No statistically significant difference in the two groups was seen with respect to duration of endotracheal tube or nasogastric tube requirement. There was no statistically significant change in medication in the two groups following PE . The change in the requirement for AChEI drug dosage and frequency, as well as the dosage of immuno-suppressive agents was also not statistically significant in the two groups. The median duration of stay in the hospital was less in the daily PE group which was almost significant ($p < 0.054$) (Table 5). The mean duration of stay was less in the daily treatment group and this almost reached statistical significance as well.

Transient hypotension was seen in 6 patients (18.1%), three in each group of alternate and daily plasma exchange which was corrected within 3–5 minutes after rapid saline infusion in all the patients (Table 6). Symptomatic hypotension causing cessation of PE was not observed in any of the patient. Technical difficulty was faced in one patient, assigned to receive daily PE, because of difficulty in main-

Table 6 Complications of therapy in patients randomized to alternate day or daily PE

Complications	Alternate day PE (n = 17)	Daily PE (n = 16)	Total (n = 33) %
Hypotension	3	3	6 (18.1%)
DVT	1	2	3 (9%)
Hypoalbuminemia	0	0	0 (0%)
Reaction to FFP	0	1	1 (3%)
Deranged Liver Function Test	0	0	0 (0%)
Sinus Tachycardia	1	0	1 (3%)
Technical difficulties	1	0	1 (3%)
Deaths	1	2	3 (9%)
Generalised Aesthenia	2	0	2 (6%)
Bleeding Tendencies	0	0	0 (0%)

taining central access. There were 3 deaths of which one was in alternate day PE and two in daily PE group. One patient died from pulmonary oedema (non cardiogenic), a second patient had cardiac arrhythmia (asystole) 12 hours after the procedure and could not be revived. The third patient died from multi-system organ dysfunction following septicaemia.

Discussion

From this randomized study, we conclude that daily and alternate day PE are equally effective in management of severe MG, with a trend towards better response with daily PE. The procedures are comparable not only in their efficacy but also in the incidence of adverse events. Daily plasma exchange might be the preferred mode to induce remission in severe myasthenia considering that the duration of stay in hospital is less with this procedure.

Plasma exchange is considered an established method of inducing remission in myasthenic crisis, ever since its introduction [10]. A Cochrane review has commented that there is evidence of short term benefit of PE in several case series of myasthenic crisis, and randomized controlled trials are required to generate evidence in favour of PE [11]. PE has also been found to be of benefit in stabilizing the symptoms of patients with MG just prior to thymectomy [12–14].

Previous studies have assessed a change in the circulating acetylcholine antibodies titres, the vital capacity (VC), or the functional vital capacity, as a measure of improvement in patients with MG on PE. We chose to observe the changes in the ADL and MGDS as a more robust indicator of responsiveness to PE in MG. In a similar study, by Yeh and Chiu [15] benefit of doing daily PE over alternate day PE, has been reported; however, this change was not statistically significant. The study evaluated, among other aspects the vital capacity of the patients before and after the procedure. We on the other hand compared the duration of endotracheal intubation in our patients. Vital capacity measurements would have indicated change in the condition of our patients, even in those cases who were not intubated; however, in our trial, those patients who were not intubated were on nasogstric tube for dysphagia. The time taken to the removal of the nasogastric tube was also similar between the two groups. This indicates that the evaluation of the time to extubation/removal of the nasogastric tube was probably an adequate measure of improvement, at least in the power of the bulbar musculature.

Double filtration plasmapharesis (DFP) used by Yeh and colleagues is an elaborate process, requiring a higher technical expertise. The equipment is costlier, but this procedure is claimed to reduce albumin loss. The conventional centrifugation system, used by us, despite being cost effective causes slightly more albumin loss. Efficacy of plasma exchange, DFP and immuno-adsorption has been compared and all the procedures have been found to be equally effective [16, 17]. As we used low dose plasma exchange in the present study a significant albumin loss was not a constraint as is exhibited by the fact that none of our patient had hypoalbuminaemia.

The amount of plasma removed (20–25ml/kg) per session of PE in our study was lower when compared the amounts in other reports. PE in our centre has been done since early 1980s using this regimen with good results [18]. Our patients might be responding to 'low dose' PE because of genetic or racial differences from the rest of the world. The present study used the same dose and we noted good response in 81.8% patients, which is similar to other reports [5, 19, 20]. Removal of 40–50 ml/kg during each session is supported by studies of PE on patients with acute inflammatory polyneuropathy, [21] but studies using removal of 0.5, 0.8, 1 and 1.5 times the plasma volume per session, in MG patients have not found significant difference between various regimens and there are no randomized trials to support any particular regimen [5, 6, 22].

The hypotheses advocating the use of alternate day over daily PE is based on the presumption that with the former procedure there is time for the extravascular stores of immunoglobulins to equilibrate with the intravascular compartment. There has been poor correlation between the circulating levels of immunglobulins and the severity of disease, therefore, probably there are other reasons that cause an improvement in MG patients after PE which are yet unknown. It is possible that alternate day PE keeps the circulating levels of immunoglobulins at a

persistently low level, which results in an improvement which is comparable with the alternate day regimen. There is, however, no conclusive evidence for this hypothesis.

Patients with thymoma showed as good a clinical response after PE as those without thymoma, similar to other studies [23]. One of our patients with thymoma did not respond to two cycles of PE (daily in the first and alternate day in the second). He subsequently responded to IVIg therapy. Various studies have reported IVIg to be as efficacious as PE for induction of remission in MG patients [24–26]. In our centre PE is the preferred mode of treatment for MG as it is cheaper for the patient, despite higher incidence of complications. A cost analysis comparing the two procedures, considering the cost of the machine, the PE set, maintenance and staff for PE, might be of help in deciding which modality is actually cheaper.

In our study important outcome measures were the days spent on ventilator, duration on nasogastric tube, duration of ICU stay and the duration of hospital stay of the patient, measures governing the cost of treatment which have not been evaluated in the earlier studies. A notable difference was observed in the duration of hospital stay in patients who received daily PE, which almost reached statistical significance. We believe that daily PE is likely to induce remission faster compared with those receiving alternate day PE. In a retrospective study comparing PE, DFP, and immunoadsorption in Taiwan, similar observation was made [27].

To conform to the intention to treat pattern, analysis was also carried out by excluding those patients who could not complete the protocol, but no statistically significant difference in primary or secondary outcome measures between the two groups was observed. The procedures were comparable in their safety norms. Hypotension, was equally distributed between the two groups and was much higher than that reported by others (2.7%–7.1 %) [5, 27, 28]. This difference could be due to the differences in equipment used for PE, the body composition of patients, or maybe because of significant malnutrition because of prolonged bulbar myasthenic symptoms. These complications were, however, transient, reversible and did not alter the treatment protocol. There were three deaths in our study, the patients who expired had a relatively higher MGDS score and the precipitating factor in all the three was pulmonary infection. Two of these patients had stopped their steroid on their own. The non cardiogenic pulmonary oedema in one patient and the cardiac arrhythmia observed in the other patient could be a direct result of PE itself, however the third death was probably due to high 'pre study' morbidity.

Comparable efficacy of daily versus alternate day PE in MG, as found in our study is important in developing countries like ours as it can bring down the cost of treatment and the in-hospital time. Shorter hospital stay would also reduce the risk of nosocomial and other infections and duration of venous access which may expose them to the risk of deep venous thrombosis. We acknowledge that due to our small sample size our study may have a type II error in interpretation of results. Our primary objective was to evaluate the efficacy of the two procedures and its impact on the duration of stay in the hospital. The duration in the hospital was lower in the daily PE group which almost reached statistical significance, therefore the study does is not actually a completely 'negative' study. Studies using larger number of patients are required to reach any definite conclusion in MG patients and also ascertain the best method of exchange vis-à-vis, the cost involved.

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