INFORMATION BRIEF (RAPID REVIEW)

PLASMA EXCHANGE PROCEDURE FOR MYASTHENIA GRAVIS

Malaysian Health Technology Assessment Section (MaHTAS)
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PURPOSE

To provide brief information on the effectiveness, safety and cost-effectiveness of plasma exchange procedure for patients with myasthenia gravis following a request from the Director of Medical Practice Division, Ministry of Health Malaysia.

BACKGROUND

Myasthenia gravis (MG) is an autoimmune disease, a disorder of neuromuscular transmission, which presents with weakness and fatigability of skeletal muscles. The weakness increases with repetitive physical activity and improves with rest. Women between the second and third decades and men between the sixth and seventh decades are predominantly affected.[1] The incidence of the disease is 4.1 to 30 cases per million person-years, and the prevalence rate ranges from 150 to 200 cases per million people.[2] It is estimated to affect about 60,000-80,000 people in the United States and about 700,000 people worldwide.[3]

The disease is clinically classified into two main categories: restrictive ocular MG commonly affecting ocular muscles, and generalised MG affecting multiple muscles sets which accounts for about 80% of all MG.[3] The basic pathology in MG is binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor (AChR).[4] The neuromuscular junction consists of a nerve terminal and motor end plates on the muscle fibres separated by the synaptic space (Fig. 1A). It is the site of impulse transmission between nerve terminals and muscle fibres. This process requires the release of presynaptic acetylcholine (ACh) and subsequently binding to a postsynaptic ACh receptor (AChR). The neuromuscular junction in patients with MG have only one-third of the AChR compared with normal persons. The synaptic space is widened, and the folds at the motor end plate simplified (Fig. 1B). In MG, the reduction in number of AChR leads to a reduction in the amplitude of the end-plate potential generated. Action potentials of reduced amplitude are unable to trigger muscle fibre contraction in some fibres. When widespread involvement of neuromuscular junction occurs, weakness is clinically manifested.[1,2]

There are four treatment modalities for myasthenia gravis: anticholinesterase agents to preserve acetylcholine in the synaptic spaces, surgical thymectomy, immunosuppression, and short-term immunotherapies that include plasma exchange and intravenous immunoglobulin (IVIg).[1] Acetylcholinesterase inhibitors may be sufficient to manage the mildest presentations of MG, but generalised forms usually require long-term treatment with corticosteroids and immunosuppressant, thymectomy, IVIg, or plasma exchange.[5]

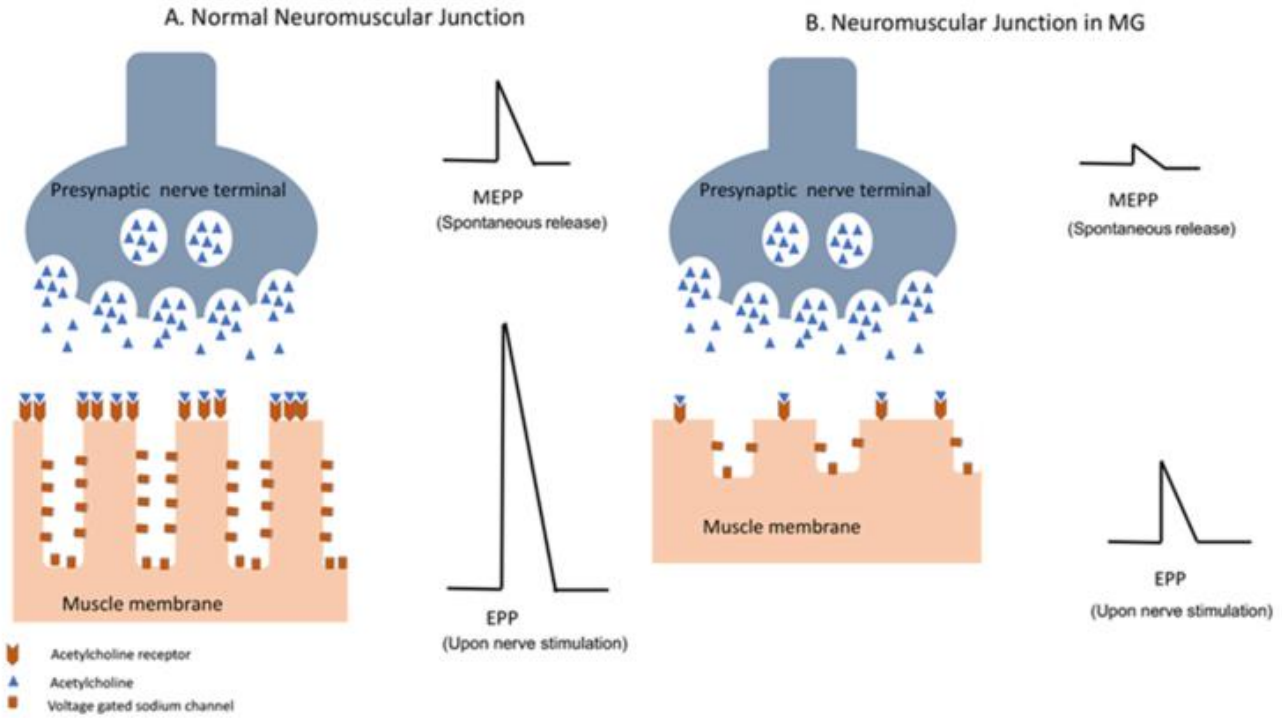

Figure 1. Neuromuscular transmission in normal individuals (**A**) and in patients with MG (**B**). Decreased density of the acetylcholine receptor (AChR) and complement-mediated damage to the postsynaptic membrane in MG patients result in decrease in miniature end plate potential (MEPP), which occurs with spontaneous release of AChR vesicles, as well as endplate potential (EPP) in response to nerve action potential of the presynaptic membrane. Diminished amplitude of EPP in MG results in impaired neuromuscular transmission.[2]

Technical features

Plasma exchange (PLEX) is used to effectively remove the circulating antibodies to acetylcholine receptors, for short-term treatment of life-threatening events such as respiratory insufficiency or dysphagia in MG patients. The procedure consists of filtering venous blood and removing plasma constituents, including normal and pathogenic immunoglobulins, and replaced with fresh-frozen plasma or albumin.[6] A large volume of replacement fluid is required to replace the similar amount of plasma extracted.[7] The clinical response correlates with a decrease in the levels of the circulating antibodies' titres. Studies reported that clinical improvement is observed by day 14 after treatment, which is similar to IVig, but major changes were detected as early as three days after treatment or by the last day of PLEX treatment. With this rapid response, PLEX may be the preferred treatment in situations such as threatening myasthenic crisis. However, it is perceived to be a complex treatment requires vascular access, hospital admission, with risk of allergic reactions, infections and other many complications.[7,8] Apart from PLEX, another technique for plasmapheresis is double-filtration plasmapheresis (DFPP). Double-filtration plasmapheresis consist of a first filter to separate plasma from blood (a plasma separator) and a second filter to separate albumin from larger molecules in the plasma (a plasma fractionator). The procedure selectively remove pathogenic substances without the need for plasma supplementation. The advantage of DFPP is that the volume of substitution fluid can be minimised compared to PLEX. [6,7]

EVIDENCE SUMMARY

A total of 1,328 titles were retrieved from the scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from general search engines [Google Scholar and US Food and Drug Administration (USFDA)], using the search term; myasthenia gravis, plasma exchange and plasmapheresis. Last search was conducted on 7 March 2022. Five articles were found to be relevant and included in this review which comprised of three systematic review and meta-analysis studies, each looking into efficacy and safety of plasma exchange, pre-thymectomy plasmapheresis and double-filtration plasmapheresis for the treatment of MG. A safety analysis of plasma exchange treatment and one systematic review on economic costs were also added.

EFFICACY/ EFFECTIVENESS

Effectiveness of plasma exchange

Ipe *et al.* (2021) conducted a systematic review and meta-analysis to assess the comparative efficacy and safety of therapeutic plasma exchange against available treatment modalities and/or untreated patients on studies published between 1997 and 2017. A total of 64 articles were included for a systematic literature review and 11 articles for a meta-analysis. Six studies comprised of two prospective, randomised trials and four retrospective analysis reviewed the effectiveness of PLEX and IVIg in the treatment of acute MG. Across four studies of 292 patients, the pooled estimate based on a random effects model was +19% response risk difference, which **indicates in favour of PLEX compared to IVIg in acute MG (p = 0.002)**. Evidence suggested that those treated with PLEX experience shorter ventilation times but longer hospitalisation compared to IVIg. Four retrospective studies demonstrated the outcomes in 73 patients with MG who received PLEX prior to thymectomy compared to 120 patients without immunomodulatory treatment. Pre-thymectomy PLEX significantly increased speed of post-operative recovery, improves long-term response rate and magnitude, and decreased incidence of crisis during follow-up. Other factors such as timing, frequency and route of venous access influence in optimising PLEX procedure. MG crisis patients who received early PLEX (0-2 days from admission) gave a significant shorter hospital stay (6 days versus 14 days; $p < 0.001$) compared to those who received delayed PLEX (> 2 days from admission). Among acute MG patients, shorter hospital stay was reported in those received PLEX procedure via peripheral venous access than through a central venous line (median: 9 days [range: 6-10] versus 12 days [range: 8-18], $p = 0.002$). Data from seven studies consisted of 1,073 patients were analysed for all-cause mortality in acute MG between PLEX and IVIg. The pooled estimate based on a random effects model was a +1.5% mortality risk difference (indicate higher mortality risk in PLEX) but was not statistically significant ($p = 0.264$). In the pre-thymectomy, the use of PLEX has not been shown to significantly affect mortality compared to untreated patients. In myasthenic crisis, PLEX with corticosteroid treatment is associated with significantly lower mortality than treatment with corticosteroids alone. All-cause mortality was significantly higher in patients who received delayed versus early PLEX (adjusted odds ratio 1.86, $p < 0.0001$). Certain adverse events were identified in PLEX procedure included cardiovascular complications (hypotension, fluid overloading, arrthymias, myocardial infarction, and cardiac arrest),

systemic infections, renal failure, and citrate reactions. This study illustrated a higher response rate with PLEX in acute MG patients and patients undergoing thymectomy.[3]

Reis *et al.* (2019) conducted a systematic review and meta-analysis on experimental and observational studies, to evaluate the effectiveness of plasmapheresis during the preoperative period before a thymectomy for the treatment of MG and the outcome during the postoperative period. Seven studies were included comprising of two randomised clinical trial (RCT) and five retrospective studies, involving 360 patients with MG that underwent thymectomy in between 1975 and 2011. The risk of bias in RCT was assessed with Cochrane Collaboration criteria while for the case-control studies, analysis using the Robins-I tool was performed. Overall case-control studies have high risk of bias and both the RCTs biases risk were ranked uncertain. Meta-analysis of five studies involving 243 patients showed preoperative plasmapheresis did not decrease the myasthenic crisis in the postoperative period (RR 0.36, 95% CI 0.08 to 1.66; I^2 = 44%; p = 0.13). In three studies involving 172 patients, the mortality rate was not altered for those who received plasmapheresis during the preoperative period (RR 0.72, 95% CI 0.11 to 4.62; I^2 = 0%; p = 0.44). Plasmapheresis did not reduce pneumonia in the postoperative period (RR 0.28, 95% CI 0.07 to 1.09; I^2 = 27%; p = 0.25) but there was a tendency towards protection against its occurrence. However, plasmapheresis during the preoperative period increased bleeding in the patients compared to those in the control group (mean difference 34.34 ml; 95% CI 24.93 to 43.75; I^2 = 0%; p = 0.57). Other outcomes evaluated showed, those patients who had plasmapheresis reported (i) the need for mechanical ventilation (MV) was lower; (ii) shorter hospital stay; (iii) shorter stay in the ICU; and (iv) shorter MV time. Due to high degree of heterogeneity among the studies, meta-analysis evaluation for these outcomes were not performed. Subgroup analysis of two studies involving 82 patients showed that plasmapheresis performed during the preoperative period in patients with severe disease (Osserman stage III and IV) decreased the myasthenic crisis postoperatively (RR 0.12, 95% CI 0.02 to 0.65). This study demonstrated that plasmapheresis during the preoperative period prior to a thymectomy may reduce myasthenic crisis during the postoperative period in patients with severe disease but may produce little or no difference in patients with less advanced disease (Osserman stage II).[9]

Effectiveness of double-filtration plasmapheresis

A systematic review and meta-analysis had been conducted by a group of researchers from China to evaluate the efficacy of double-filtration plasmapheresis (DFPP) treatment of MG. Multiple databases had been used to locate the clinical research articles on randomised controlled trials (RCTs) and quasi-randomised trials (clinical controlled trial [CCTs]) up to June 2019. Nine studies (seven RCTs and two CCTs) consisted of 329 patients were selected for both systematic review and meta-analysis. Two of the studies had low risk of bias, five studies with moderate risk of bias and two studies with high risk of bias based on Cochrane risk of bias. As a primary outcome measured, the analysis showed that based on five studies comprising 192 patients, the clinical MG remission rate after DFPP treatment was significantly higher than that in the control group (OR = 4.33, 95% CI 1.97 to 9.53; *p* = 0.0003, I^2 = 0%). Another three studies which consists of 136 patients reported that quantitative MG (QMG) score descent range was significantly higher than that of the control group (MD = 37.64, 95% CI 36.33 to 38.95). The duration of hospital stay for MG patients after DFPP treatment was significantly decreased (MD = –5.71, 95% CI –8.30 to –3.12) based on three studies with 136 patients evaluated in the analysis. Three out of nine studies

showed that the time to MG remission after DFPP treatment was significantly decreased (MD = –3.50, 95% CI –7.62 to –0.61; $p < 0.01$, $I^2 = 100\%$). Hence, the analysis concluded that DFPP may be a beneficial option for MG patient due to its efficacy in improving clinical MG remission rate, reducing QMG scores and shorter duration of hospital stay.[6]

Organisation

Ipe *et al.* (2021) reviewed three sets of prominent United States (US) and European (EU) professional guidelines and guidance statements that recommended the use of therapeutic plasma exchange in one or more of MG clinical situations. The guidance from the MG Foundation of America (MGFA), guidelines from the European Federation of Neurological Societies (EFNS) and American Society of Apheresis (ASFA) **all recommended the use of therapeutic plasma exchange in cases of severe acute MG, including myasthenic crisis, and in preparation for thymectomy**. However, 2011 guidelines from the American Academy of Neurology (AAN) concluded that there is not enough evidence to support or refute the use of therapeutic plasma exchange in MG citing a lack of randomised, controlled clinical trials with masked outcomes. The MGFA Task Force, ASFA, and EFNS describe therapeutic plasma exchange and IVIg as equally effective, but tentatively suggest potential advantages for each. No strong recommendation for one over the other is given. The EFNS guidelines stated that IVIg may be preferred due to fewer and less severe side effects, while the MGFA Task Force suggests that therapeutic plasma exchange is more effective.[3]

The MGFA Task Force published an international consensus guidance for the management of MG in 2016 and updated the guidance in 2020 without any additional changes on PLEX. It is recommended that PLEX and IVIg are appropriately used as (i) a short term treatments in patients with MG with life-threatening signs such as respiratory insufficiency or dysphagia; (ii) in preparation for surgery in patients with significant bulbar dysfunction; (iii) when a rapid response to treatment is needed; (iv) when other treatments are insufficiently effective; and (v) prior to beginning corticosteroids if deemed necessary to prevent or minimise exacerbations. Plasma exchange cannot be used in patients with sepsis. Both, PLEX and IVIg are probably equally effective in the treatment of severe generalised MG and PLEX may be more effective than IVIg in muscle-specific tyrosine kinase MG (MuSK-MG). The use of IVIg as maintenance therapy can be considered for patients with refractory MG or for those in whom immunosuppressive (IS) agents are relatively contraindicated. Plasma exchange and IVIg are used as short-term treatment for impending and manifest myasthenic crisis and in patients with significant respiratory or bulbar dysfunction.[4]

SAFETY

Ebadi *et al.* (2012) reported detail safety analysis of PLEX treatment from a randomised clinical trial (RCT) conducted. The aim was to provide guidance to those considering PLEX for MG treatment by reporting the methodology and adverse events. In the primary RCT, 84 patients with moderate-to-severe MG [determined by Quantitative Myasthenia Gravis Score (QMGS) of >10.5 units] were randomised to treatment with PLEX or IVIg from 2007 to 2010.[10] A total of 42 patients were treated with PLEX for a total of 203 procedures. The PLEX treatment was performed on an apheresis device (Spectra Optia and COBE Spectra: Terumo BCT, Lakewood, Colorado). Each patient received up to five PLEX procedures with 1 plasma

volume per procedure were used. Treatments were given every other day with breaks allowed for weekends for most patients. Albumin 5% was used as the replacement fluid. To prevent citrate reactions, 0.5 gram of 10% calcium gluconate was added to each 500ml of 5% albumin bottle. Peripheral venous access was performed for draw access and return procedure. While, central venous access was conducted for patients who did not have adequate peripheral venous access. The central venous catheter (CVC) line was removed immediately after the fifth (the last) PLEX procedure in the apheresis unit. Assessment with QMGS was done on the 14th day after treatment was completed. Adverse events were documented up to 30 days after treatment. Only 40 patients completed PLEX treatment. Majority, 90% received treatment in an outpatient setting and 83% completed PLEX using peripheral venous access. The mean time for each procedure was 105.6 minutes (range: 75.4 – 153.3 minutes). Those on PLEX, 57% patients responded to treatment with a reduction in QMGS of 4.7 ± 4.9 units (95% CI 3.2 to 6.2) at day 14 after the end of treatment (based on a predefined decrease in QMGS ≥ 3 units). During the procedure, 55% patients had no complications. The remaining 45% had mild-to-moderate reactions that did not require cessation of treatment in which the majority were citrate reactions and related to peripheral vascular access. Two patients had severe adverse events: one patient had a myocardial infarction possibly exacerbated after the second procedure, and one was unrelated to PLEX. This study indicated that PLEX treatment for MG is effective in 57% of patients, with mild-to-moderate reactions to procedure, safe to be performed in the outpatient setting using peripheral venous access, and each session lasted for about two hours.[8]

The systematic review by Ipe *et al.* (2021) reported no significant increase in mortality risk for PLEX compared to other MG treatment modalities. Adverse events related to PLEX procedure involved vascular, cardiac complications, infection, and citrate reactions. Evidence suggested that using peripheral venous access and early PLEX treatment associated with lower adverse events rates. However, IVIg was associated with a lower risk of potentially serious adverse events.[3]

Only one study analysed in one systematic review study showed that among the 15 patients undergone DFPP, three patients had adverse reactions: two with hypotension and one with haematoma.[6]

COST-EFFECTIVENESS (If any)

Landfeldt *et al.* (2020) conducted a systematic review (SR) of economic costs (henceforth costs) associated with MG on published articles up until March 18, 2020. The SR was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The quality and risk of bias of non-randomised studies were assessed with the Newcastle-Ottawa Scale (NOS). Identified cost estimates were inflated and converted to 2018 United States (US) dollar ($). A total of 16 studies were identified consist of 12 retrospective and 1 prospective observational cohort study, 1 cross-sectional observational study, and two modelling studies. Five of 16 articles were based on publicly accessible data from the National (Nationwide) Inpatient Sample (NIS) part of the Healthcare Cost and Utilization Project (HCUP) in the US. Estimates of costs for MG treatment were found from eight countries across four continents (Europe, North America, South America, and Asia). Across studies, the mean per-patient annual direct medical cost of

illness ranged from $760 in Japan to $28,780 in the US. Main drivers of the direct medical cost of illness were IVIg, PLEX, myasthenic crisis, mechanical ventilatory support and hospitalisations. Based on claims data, the mean per-patient cost per hospitalisation ranged between $2,550 and $164,730. The mean per-patient indirect cost of MG was estimated at $80 and $3,550. The mean per-patient cost of IVIg as a treatment for MG crisis was estimated at $6,620 in Canada and $90,760 in the US. Corresponding estimates for PLEX were $4,990 and $116,470, respectively. In addition, the median per-patient hospital cost of IVIg and PLEX in the US at $28,080 and $35,450 in patients with MG, and $45,100 and $71,520 in those with MG crisis. In Germany, the mean per-patient total cost of illness (including direct medical, informal care, and indirect costs) was estimated at $19,000. In the US, the mean per-patient annual direct medical cost of illness vary by age, ranging from $9,100 in patients 0-19 years of age to $23,820 in those older than 65 years. Nine of 16 (56%) of included studies were judged to have low risk of bias as assessed using the NOS, however results should be interpreted with caution as observational studies may still have lack of quality.[5]

CONCLUSION

Available evidence demonstrated that plasma exchange procedure has clinical benefit in the treatment of acute myasthenia gravis and in improving thymectomy outcomes. This procedure has side effects of mild-to-moderate reactions which involved vascular, cardiac complications, infection, and citrate reactions that should be considered. There was no significant increase in serious adverse events or mortality risk across studies in patients receiving plasma exchange procedure.

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