

Evidence for Use of Intravenous Immunoglobulin and Plasma Exchange in Generalised Myasthenia Gravis



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In 1895, Friedrich Jolly described the electrophysiological feature of fading response of muscles to prolonged electrical stimulation, which is characteristic of the fatigue of myasthenia gravis (MG).¹ MG is an autoimmune disorder of neuromuscular junction transmission that causes fluctuating, painless muscle weakness. It most commonly presents with ocular weakness, manifesting as binocular diplopia and asymmetrical ptosis. In 15% of cases, it remains purely ocular; in the remaining 85% it becomes generalised, usually by descending to involve bulbar, neck, limb and, sometimes, respiratory muscles. Severe involvement of respiratory or bulbar muscles may lead to a myasthenic crisis, necessitating intubation and mechanical ventilation.

The impairment of neurotransmission in MG is usually caused by antibodies to postsynaptic nicotinic acetylcholine receptors (AChRs) which reduce the number of functional AChRs.² Around 15% of patients with generalised MG do not have detectable AChR antibodies.³ Sera from a fraction of these AChR antibody-negative patients contain antibodies to muscle-specific tyrosine kinase (MuSK), although the pathogenic role of the latter have not been established.⁴ Loss of tolerance to self-antigens appears to be important in MG.⁵ T cell tolerance to self-antigens is established in the thymus, and thymic abnormalities are common in MG – 65% of patients have thymic hyperplasia and 10% have thymomas.⁶ B cell and T cell activation are involved in the pathogenesis and immunoregulation of MG.^{7,8}

In the past 70 years, advances in treatment have reduced the mortality of MG from 70% between 1915 and 1934⁹ to less than 5% now.¹⁰ Furthermore, the prevalence of MG has risen from around five per million population between 1915 and 1934,⁹ to about 200 per million now,¹¹ although part of this is due to improved detection of AChR antibodies. Apart from improvements in pulmonary support and ventilation, most of the decrease in mortality has been due to the development of effective treatments based on the

understanding of the pathophysiology of MG.

This review will examine and summarise the evidence of the short-term immunomodulatory treatments intravenous immunoglobulin (IVIg) and plasma exchange (PE) in the treatment of generalised MG.

Intravenous immunoglobulin

The mode of action of intravenous immunoglobulin (IVIg) in MG is not completely understood, but key mechanisms include the neutralisation of activated complement, interference of signalling via Fc receptors, modulation of proinflammatory cytokines and suppression of idiopathic antibodies.^{12,13} IVIg was first used in MG in the mid 1980s.^{14,15}

IVIg showed an improvement of more than 70% in MG in two reviews, which collated results from previously published uncontrolled studies.^{16,17} In addition, two open studies of severe generalised MG with a total of 21 patients showed improvement with IVIg in all patients.^{18,19} IVIg has comparable effectiveness to PE in preoperative thymectomy preparation of patients with MG.^{20,21}

Five randomised controlled trials (RCTs) comparing IVIg with placebo or other treatments in MG have been carried out (Table 1).²² Two trials compared IVIg to placebo. In the first trial of 15 patients with mild to moderate generalised MG, no significant difference between the two groups was observed at six weeks.²³ In the second trial of 51 patients with acute exacerbation of generalised MG, IVIg resulted in significant improvement in muscle strength (measured by the Quantitative MG Score for Disease Severity [QMG score])²⁴ only in the group of patients with severe disease, with a mean difference in the QMG score on day 14 of -3.40 (95% confidence interval [CI] -5.74 to -1.06).²⁵ Two trials compared IVIg to PE. In the first with 87 patients with acute exacerbation of generalised MG, no significant change in muscle strength was observed between day 0 and day 15 between the two treatment groups. In addition, similar efficacy of IVIg was observed

Table 1: Major randomised controlled trials comparing different types of treatment in generalised myasthenia gravis

Trial	Patients	Intervention	Outcome
Wolfe GI 2002 ²³	15 with stable mild or moderate MG	IVIg v placebo	No significant difference
Zinman 2007 ²⁵	51 with acute exacerbation of MG	IVIg v placebo	Significant improvement in muscle strength in group with severe disease
Gajdos 1997 ²⁶	87 with acute exacerbation of MG	IVIg v PE	No significant difference
Rønager 2001 ²⁷	12 with stable moderate or severe MG	IVIg v PE	No significant difference
Cochrane group ²² (personal communication)	33 with acute exacerbation of MG	IVIg v oral methylprednisolone	No significant difference

IVIg = intravenous immunoglobulin, MG = myasthenia gravis, PE = plasma exchange

whether 1.2g/kg or 2g/kg of IVIG was used.²⁶ In the second trial which had a crossover design with 12 patients with moderate to severe generalised MG in a stable phase, no significant difference between the two groups was detected after 1 and 4 weeks of treatment.²⁷ The Cochrane group also reported that an unpublished RCT comparing IVIG to oral methylprednisolone, which was obtained through personal communication, in 33 patients with acute exacerbation of generalised MG did not show any significant difference between the two treatment arms.²² Finally, another RCT comparing two doses of IVIG in 173 patients with acute exacerbation of generalised MG did not show any significant difference in efficacy between 2g/kg and 1g/kg of IVIG.²⁸

The RCTs of IVIG in generalised MG only show limited evidence that it is effective (class I evidence).²² In acute exacerbation of generalised MG, only one RCT showed efficacy of IVIG over placebo.²⁵ In chronic generalised MG, there is insufficient evidence to determine whether IVIG is effective as the number of patients in each of the two trials was very small.^{23,27} No meta-analysis of the RCTs were possible due to major methodological differences between the trials.²² Common adverse events of IVIG include fever, headache, nausea, and allergic reaction. A severe anaphylactic reaction might occur in patients with IgA deficiency. Volume overload may occur in cardiomyopathy and solute-induced renal failure may occur in patients with pre-existing renal impairment.²⁸ Serious adverse events include thrombosis and stroke, which are associated

with high infusion rates.²⁹ However, adverse events from IVIG appeared less severe than those from PE.^{26,27}

Plasma exchange

Therapeutic PE is an extracorporeal blood purification technique designed to remove large molecular weight particles from plasma. Its mechanism of action is thought to involve the removal of circulating antibodies, immune complexes, cytokines, and other inflammatory mediators.³⁰ In MG, the concentration of AChR and MuSK antibodies have been shown to fall with PE.^{31,32} PE was first used in MG in the mid 1970s.³³

Several relatively large open studies of 20 or more patients each have demonstrated a beneficial effect from PE in MG. Most of the patients in these trials were already on other immunosuppressive / immunomodulatory therapy, or started on these therapies after PE. Of a total of 166 patients with generalised MG, 130 patients (78%) were reported to have improved with PE.³⁴⁻³⁸ Three fairly large retrospective studies totalling 84 patients with generalised MG reported improvement with PE in 81 patients (96%).³⁹⁻⁴¹ Another retrospective study comparing PE with IVIG in myasthenic crisis showed that the ventilatory status at two weeks and the functional outcome after one month was better in the PE group.⁴² One non-randomised trial comparing different PE protocols in generalised MG did not reveal any significant difference in efficacy between the treatments.⁴³ Prethymectomy plasmapheresis improves outcome after thymectomy in MG.^{44,45}

One RCT of PE plus prednisolone versus prednisolone alone in 14 patients with generalised MG did not show any significant difference in muscle strength between the two treatment groups after one month.⁴⁶ Two RCTs comparing daily and alternate-day PE in generalised MG have not shown any difference in efficacy between the treatments.^{47,48}

The small number of patients in the RCT of PE in generalised MG makes it difficult to draw any definite conclusion on its effectiveness in generalised MG, despite the fact open or retrospective studies have been encouraging.⁴⁹ However, as mentioned above, a large trial has shown that it is as effective as IVIG in acute exacerbation of MG (class I evidence).²⁶ Most adverse events of PE are related to issues of vascular access such as thrombosis, infection, pneumothorax and, rarely, air embolism. Excessive fluid volume shifts can lead to hypotension or fluid overload and congestive cardiac failure. Citrate infused for anticoagulation may lead to disturbances in acid-base homeostasis and hypocalcaemia.³⁰

Conclusions

IVIg and PE are both used to achieve rapid (days to weeks), temporary improvement in generalised MG. Each treatment is useful as an interim measure while waiting for corticosteroids and other long-term immunosuppressants to take effect. As IVIG is easier to administer and associated with fewer adverse events than PE, and the efficacy of the two treatments are similar, the former is commonly preferred to the latter.⁵⁰ ♦

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