Use of intravenous immunoglobulin for treatment of neurologic conditions: a systematic review


CRD summary
This review assessed the efficacy and safety of intravenous immunoglobulin (IVIG) in several neurologic conditions. IVIG appeared more effective than placebo in relapsing-remitting multiple sclerosis and idiopathic chronic inflammatory demyelinating polyneuropathy. The evidence to support the use of IVIG for all other neurologic conditions was insufficient. The review was generally well conducted and its conclusions seem reliable.

Authors' objectives
To evaluate the efficacy of intravenous immunoglobulin (IVIG) for neurologic conditions.

Searching
The Cochrane CENTRAL Register and MEDLINE were searched to June 2003; the search terms were reported. The bibliographies of all identified meta-analyses and trials were also checked. Studies available only as abstracts were not eligible for inclusion. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Parallel and crossover randomised clinical trials (RCTs) were included.

Specific interventions included in the review
Studies comparing IVIG with either placebo or an active control were eligible. The active controls in the included studies were plasma exchange, immune absorption, prednisolone and interferon-alpha. All dosage regimens of IVIG were considered.

Participants included in the review
Studies of adults or children with neurologic conditions were eligible for inclusion. The included studies were of individuals with multiple sclerosis (MS), Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, paraprotein-associated polyneuropathy, multifocal motor neuropathy, inclusion body myositis, myasthenia gravis, paediatric head trauma, dermatomyositis, Lambert-Eaton myasthenic syndrome, obsessive compulsive disorder and/or tics, stiff-person syndrome, refractory epilepsy and optic neuritis. The majority of the participants in the included studies had MS or Guillain-Barre syndrome.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. Reported outcomes in the included studies varied across both conditions and studies. The extracted outcomes included disability scores (using a number of different scales), percentage of relapse-free patients, changes in annual exacerbation rate, muscle scores, grip strength, 10-m walk time, 9-hole pegboard test, neurologic disability scores, mortality, time to recovery and myasthenic scores.

How were decisions on the relevance of primary studies made?
Two authors independently reviewed all citations to identify all potentially relevant trials. Any disagreements were resolved through a third reviewer.

Assessment of study quality
Study quality was assessed by the adequacy of randomisation, blinding, and descriptions of withdrawals and drop-outs using the Jadad scale. Each study was allocated a score from 0 (lowest) to 5 (highest). A score of 3 or more was
considered high quality. The authors did not state how many reviewers performed the validity assessment.

**Data extraction**
Two investigators independently extracted the data using a standardised form. Dichotomous data were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Continuous data were expressed as standardised mean differences (SMDs) with 95% CIs.

**Methods of synthesis**

How were the studies combined?
The studies were pooled by neurologic condition in meta-analyses where the authors considered it appropriate, or a narrative summary was provided. When possible, the weighting methods by Curtin were used to pool data of parallel and crossover trials.

How were differences between studies investigated?
The authors stated that statistical heterogeneity was evaluated for each outcome and when significant (p<0.10), potential sources of differences between the studies were investigated. However, the results about heterogeneity were not reported. Subgroup analyses were conducted for some of the disease conditions (type of MS, quality score greater than 3, and disease duration).

**Results of the review**
Thirty-six trials in 37 papers (n=1,994) were included: 20 parallel and 16 crossover.

**MS.**

All studies on MS were double-blinded and achieved a quality score of 3 or greater. The follow-up period ranged from 6 to 27 months.

Compared with placebo, IVIG was associated with a statistically significant improvement on the Expanded Disability Status Scale score after 1 year (SMD -0.46, 95% CI: -0.92, 0.01, p=0.05) in patients with relapse-remitting disease (4 trials, n=167), but not at 2 years (2 trials, n=188). The use of IVIG increased the proportion of relapse-free patients (5 trials, n=296) in relapse-remitting and secondary progressive disease (OR 0.24, 95% CI: 0.10, 0.60) and reduced the number of relapses experienced per year (4 trials, n=254) in relapse-remitting patients (SMD -0.82, 95% CI: -1.54, -0.11).

**Guillain-Barre syndrome.**

The follow-up period ranged from 6 months to 1 year.

No statistically significant difference in the Hughes' disability grading (2 trials, n=398) or in the odds of death (4 trials, n=447) was observed between IVIG and plasma exchange in patients with a symptom duration of less than 14 days. The combination of plasma exchange followed by IVIG had no significant benefit in comparison with either treatment alone (1 trial, n=379).

**Idiopathic chronic inflammatory demyelinating polyneuropathy.**

The follow-up period ranged from 2 to 6 weeks.

Compared with placebo, IVIG was associated with a statistically significant reduction in disability scores (4 trials, n=125; SMD -0.67, 95% CI: -1.04, -0.30), as well as with a higher proportion of patients experiencing clinical improvement as defined by the investigators (4 trials, n=152; OR 4.43, 95% CI: 2.20, 8.91). There was no difference in 10-m walk time, 9-hole pegboard time or disability scores between IVIG and prednisolone (1 trial, n=32), or in the Neuropathy Disability Score between IVIG and plasma exchange (1 trial, n=20).
Paraprotein-associated polyneuropathy.

Compared with interferon-alpha, a greater proportion of patients using IVIG experienced a decrease of 20% or more in the Clinical Neuropathy Disability Score (1 trial, n=20; OR 36.00, 95% CI: 2.72, 476.28) after 6 months; this benefit was also present at 12 months. Overall disability at 4 weeks was significantly reduced by IVIG in comparison with placebo (1 trial, n=22), although there was no statistically significant difference for the primary outcome of that study which was disability at 2 weeks. Patients assigned to receive IVIG experienced an improvement in neuromuscular symptom scores and in sensory capabilities, whereas none of the patients receiving placebo experienced clinically significant changes (1 trial). Further outcomes available from these small studies are available in the paper.

Multifocal motor neuropathy.

Compared with placebo, IVIG led to a statistically significant mean decrease in Neurologic Disability Score (1 trial, n=16) and increased muscle strength (1 trial, n=6).

Inclusion body myositis.

There was no statistically significant difference between IVIG and placebo (2 trials, n=44) for muscle strength, patient's own assessment of improvement, measurement of arm-outstretched time, or electromyographic testing. There was no statistically significant difference in muscle strength between IVIG combined with prednisone and placebo (1 trial, n=37).

Myasthenia gravis.

Statistical analyses were not reported for two of the studies of myasthenia gravis, and one study reported no statistically significant difference between IVIG and placebo on the 42-day change of Quantitative Myasthenia Gravis Score and the Myasthenia Gravis-Activities of Daily Living profile.

Brief summaries of the single studies investigating seven other neurologic conditions were provided, although a synthesis was not conducted.

Authors’ conclusions

The clinical benefits of IVIG seem to vary for the different neurologic diseases. IVIG therapy is effective in relapsing-remitting MS and idiopathic chronic inflammatory demyelinating polyneuropathy, while it appears to have no advantage for secondary progressive MS or inclusion body myositis. There is potential benefit for treatment of multifocal motor neuropathy, myasthenia gravis, dermatomyositis, stiff person syndrome and Lambert-Eaton myasthenic syndrome. The evidence for IVIG therapy in Guillain-Barre syndrome was insufficient.

CRD commentary

This review had clearly stated inclusion criteria with respect to the study design and intervention. A broad definition of participants and outcomes was used. Two relevant databases were searched and no language restrictions were applied; however, there were no specific attempts to locate unpublished studies, thereby introducing the risk of publication bias. Two independent reviewers selected studies and extracted the data. It was not stated whether the quality assessment was performed in duplicate, therefore reviewer error and bias might have been introduced. The authors stated that heterogeneity was investigated but, since the results were not reported, it is difficult to assess whether pooling was appropriate.

While the authors’ conclusions seem reasonable regarding MS, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome and body myositis, the generalisability of these results is unclear given the evidence of clinical heterogeneity and the lack of information on statistical heterogeneity. For the other conditions, the small number of trials and participants is a major limitation. The authors also highlighted that the majority of the trials included were of fairly short duration despite the conditions being chronic, which has implications for generalisability.
Implications of the review for practice and research

Practice: The authors stated that clinical guidelines should consider supporting the use of IVIG in the treatment of relapse-remitting MS. IVIG treatment is not recommended for patients with body myositis.

Research: The authors stated that further trials to determine whether IVIG is effective in neurologic diseases are warranted. Future studies should use standardised validated outcome criteria and avoid surrogate markers in order to enhance the validity and generalisability of the results.

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