

Plasmapheresis vs. immunoglobulin in autoimmune neurologic diseases: a meta-analysis

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Abstract

Objectives: to evaluate the efficacy and safety of human immunoglobulin versus plasmapheresis in the management of autoimmune neurologic diseases. Likewise, length of hospital stay and duration of ventilator support were compared.

Methods: Randomized controlled trials and analytical observational studies of more than 10 cases, were reviewed. Cochrane Neuromuscular Disease Group trials, MEDLINE, EMBASE, HINARI Ovid, the Database of abstracts of reviews of effectiveness and the Economic evaluation Database were searched as data source. Reference lists were examined for further relevant articles. A random-effect model was used to derive a pooled risk ratio.

Results: 725 articles were found and 27 met the criteria for a population studied of 4717 cases: 14 articles were about Guillain Barré syndrome, 10 of Myasthenia Gravis, one of Sydenham Chorea, one of Chronic inflammatory demyelinating polyneuropathy, and one of PANDAS. No evidence was found in favor of any of the two treatments as regards effectiveness (OR 0.94, IC 0.63 – 1.41, $p=0.77$) or ventilator support time; IGIV had a significant better safety profile than plasmapheresis (OR 0.70, IC 0.51 – 0.96, $p=0.03$) and patients needed less time of hospital stay ($p=0.03$).

Conclusions: There is no evidence for superiority in the effectiveness of immunoglobulin or plasmapheresis in the management of autoimmune neurologic diseases. Nevertheless, patients treated with immunoglobulin have statistically significant less adverse effects, a shorter hospital stay and a tendency of less ventilator support time. These premises could lead to fewer costs for health services but an economic study should be done.

INTRODUCTION

In the last three decades, the treatment of autoimmune neurologic diseases has notably improved as a result of a better understanding of physiopathology. Many of the conditions are due to a loss of immunological tolerance of self-antigens, induced by T or B Cells. The autoimmune phenotype and clinical presentation vary depending on the target cell and the organ affected but generally, all of them have an altered immune response(1). As they share the same physio-pathological basis, the treatment aim is to improve the immunological disturbance(2). This is one of the reasons why plasma exchange, plasmapheresis (PE) or the application of intravenous immunoglobulin (IVIG), have shown to be effective in most of these pathologies as has been demonstrated in different trials (3, 4). Both treatments seem to be effective but the use of PE is restricted due to the requirement of specific equipment and personnel trained in the management of extracorporeal circulation and there might be severe complications that can endanger the patient's life (3). In the other way, IVIG has the advantage that it is less invasive. (5) The decision to carry out a treatment with IVIG or with PE implies an extensive knowledge of the disorders to be treated, the therapeutic effects and the undesirable side effects of each of these therapies. Currently, in the scientific literature there are some revisions and meta-analyses about the effectiveness of each of these methods, but none has been issued comparing the two.

The aim of this study was to carry out a meta-analysis to evaluate the existing evidence that compares the effectiveness (analytical studies) and the side effects of PE versus IVIG in the management of autoimmune neurologic disorders. As secondary objectives, lengths of hospital stay and ventilator support time were studied.

MATERIALS AND METHODS

A systematic review of literature and a meta-analysis of data were carried out following the PRISMA declaration. We included randomized controlled trials and analytical observational studies that compared management with PE vs. IVIG in relation to effectiveness and safety, in patients with autoimmune neurologic diseases.

The following databases were consulted: Cochrane Neuromuscular Disease Group trials in The Cochrane Library Oxford (30/May/2013), MEDLINE (January 1960–May 2013), EMBASE (January 1980–May 2013); HINARI, Ovid, Database of abstracts of reviews of effectiveness (DARE) and Economic evaluation Database (NHS EED). The MeSH terms used were: “polyradiculoneuropathy, Chronic inflammatory demyelinating”, “Guillain-Barré Syndrome”, “Myasthenia Gravis”, “Pediatric, Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections”, “Sydenham's Chorea”, “Fulminant demyelinating disease of the nervous system”, “multiple sclerosis”, “secondary progressive multiple sclerosis”, “transverse myelitis”, “Neuromyelitis optica”, “Acute disseminated encephalomyelitis”, “Multifocal motor neuropathy”, “Polineuropathy associated with monoclonal gammopathy of unknown significance, Immunoglobulin A, G, M”. Each of these terms was cross-referenced with the following MeSH terms: “plasmapheresis” “immunoglobulin, intravenous”. Additionally, each of the MeSH terms was translated into DeCS (Health Sciences Descriptors), a tool that contains the structured and trilingual vocabulary used for indexing articles in Spanish, English and Portuguese.

The search was restricted to humans and articles published in English, French, Portuguese and Spanish. There were no restrictions about the age of the patients. Reference lists were examined for further relevant articles that the electronic search did not mark. To review articles difficult to access or to obtain data not published, the authors were contacted.

Two authors independently evaluated the eligibility of all studies by checking the title and the abstract to determine whether they met all of the inclusion criteria. Disagreements were resolved by discussion or in consultation with third party authors. When they were ambiguous, the complete articles were analyzed to determine their pertinence. The levels of evidence of each of the articles were established with the Oxford Centre for Evidence-based Medicine 2011 criteria

The publications that reported statistical analysis like relative risk (RR) and odds ratio (OR) with the respective confidence intervals (CI), or that in their content provided information to calculate them (number of subjects exposed, number of subjects not exposed, and type of outcome in each case), were included for the meta-analysis. In order to establish an adequate basis for comparison, the sample size had to be of 10 or more patients. Articles, that included information published by another study, were excluded.

The primary Outcome was defined as effectiveness of management according to commonly used methods. The number of patients who improved was taken and not the episodes in which there were changes. Specifically, positive results were defined thus: for Guillain Barré syndrome (SGB) improvement in Hughes scale four weeks after starting the treatment or the randomization (6). In Myasthenia Gravis (MG), changes in the Myasthenia muscle score (MMS), or quantitative Myasthenia Gravis score (QMGS) between day one and 15 days after the treatment began or the randomization was done (7). In Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), the improvement in the Neuropathy Disability Scale (NDS) in the sixth week after starting the treatment or the evaluation of the *Inflammatory Neuropathy Cause and Treatment scale (INCAT)* (8). For the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) the global assessment scale applied at the beginning and a month after the treatment was taken into account. In the case of Sydenham Chorea, the improvement after a month was evaluated with the chorea scale (9). We did not find articles referring the treatment in other diseases.

Statistical analyses

Effectiveness and adverse events data were analyzed using the Comprehensive Meta-Analysis program, version 2 (Biostat, Englewood, NJ, 2004). Calculations were carried out for the whole group of articles depending on the binary data available, regardless of the autoimmune neurologic disease: number of subjects and risk data (OR and RR with the corresponding 95% CI). Effect size was calculated based on raw data given by case-control and cohort studies. Different study designs were used to compute the same effect size since the effect size had the same meaning in all studies and were comparable in relevant aspects to observe improvement and adverse effects. Thus, this study was able to transform all values into log values (log odds ratio and standard error), which were used in the pooled analysis. This approach prevented the omission of studies that used an alternative measure thus preventing the bias of loss of information. A sensitivity analysis was done in which the meta-analysis results of the studies as a whole was compared to the same meta-analysis with one study excluded in each round to determine how robust the findings were. It was also done to evaluate the impact of decisions that lead to different data being used in the

analysis and whether the conclusions reached might differ substantially if a single study or a number of studies were omitted.

Additional meta-analyses were done, for specific studies with complex data structure and noncumulative results if the information to calculate the different effect size was not completely independent. To compare effects across subgroups we typically use subgroup as the unit of analysis in an independent meta-analysis.

Heterogeneity was calculated by means of Cochran's (Q) and Higgins's (I²) tests. The last was expressed as a ratio ranging from 0% to 100% and it was qualitatively classified as low (25%), moderate (50%), and high (75%). Publication bias was determined using Funnel plots and Egger's regression asymmetry tests, and additional tests were applied if it was found.

ORs were grouped by weighing individual ORs by the inverse of their variance. For each analysis, the final effect OR and 95% CI were obtained by means of both random and fixed effect models. The selection of the computational model was made based on the assumption that the studies shared a common effect size. The random effect model was preferred because it assumes that there is a distribution of true effect sizes rather than one true effect and assigns a more balanced weight to each study. It was also used because all the studies were considered to be unequal in terms of specific autoimmune neurologic diseases. For the evaluation of the length of hospital stay and ventilator support time, we analyzed the standardized mean difference with 95% confidence intervals (CI) accepting $p < 0.05$ as a statistically significant difference.

The publication bias was determined using Funnel plots and Egger's regression asymmetry test. Additional tests were applied if these two indicated publication bias. Finally, a cumulative analysis was made to evaluate the weight of the different studies.

RESULTS:

725 articles were initially retrieved but only 27 were included for data analysis according to the inclusion criterion previously established (figure 1). Of the studies included (Appendix e-1), 14 corresponded to SGB (2545 cases, age: 4–85 years), 10 to MG (2112 cases, age: 18–84 years), one to CIDP (19 patients, age: 22–52 years), one to PANDAS (29

patients, age: 5.8–13 years) and one to Sydenham Chorea (12 patients, age: 5–14 years). The total of patients evaluated in these studies was 4717 (table 1).

IVIG was applied in doses of 0.4 grams/kg/day or a total of 2 grams/kilogram. PE was applied in three to six sessions during a time period of 7 to 14 days, with an exchange of 200 to 250 ml/kg of plasma.

Effectiveness:

14 of the 27 articles reported effectiveness data with the criteria defined previously (7-20). The remaining 13 studies were excluded because they did not provide the number of patients who showed improvement (21-31), the evaluation of improvement was subjective (given by the patient) or it was not reported in a scale of degree of functional disability or of muscular weakness (32) and the results were reported in episodes and not in number of patients(33).

The study of effectiveness of all the diseases as a group, did not evidence any statistically difference in favor of any of the two therapies (OR 0.94, IC 0.63–1.41, $p=0.77$) (figure 2). The results did not change after the sensitivity analysis. The different measures for heterogeneity calculated for the analysis were as follows: Q-Value: 16.95; degree of freedom (Q): 13; p -value= 0.20; I-squared: 23%. The analyses using the funnel plot and Egger's regression asymmetry ($p = 0.51$; intercept to: -0.51) did not evidence any publication bias (appendix e-2).

We included additional analysis, to study independently analytical observational studies and controlled clinical trials and no significant differences were observed in the effectiveness of any of the two therapies ($p= 0.19$ y $p=0.88$, respectively). We also investigated the effectiveness in SGB and to MG studies, separately; there was no significant statistical difference with any of the two treatments ($p=0.44$ y $p=0.22$ respectively) (appendix e-2). The other diseases could not be evaluated because of insufficient data.

Adverse Effects:

17 articles reported adverse effect data (7, 9, 12, 13, 15, 17, 18, 22-30, 33). The other 10 studies were excluded because they did not have complete data of adverse effects in the

two groups (8, 10, 14, 16, 19-21, 31, 32) or the adverse effects were reported by episodes and not in number of patients (11).

The adverse events described were very diverse in both intervention groups (Table 2.). The severity could not be established because it was not categorized in the articles. Taking into account these premise, the analysis presented was done related to the frequency of the side effects and not about the severity of them.

The analysis showed that patients managed with IVIG had less adverse effects than those who received PE (OR 0.70, IC 0.51 – 0.96, $p= 0.03$) (figure 3). In the sensitivity analysis, when Mandawat study was excluded (relative weight: 32.87%), the difference was no longer significant (appendix e-3). The different measures for heterogeneity calculated for the analysis were as follows: Q-Value: 18.11; degree of freedom (Q):16; p -value= 0.32; I-squared: 11%. The analyses using the funnel plot and Egger's regression asymmetry ($p=0.56$; intercept to-0.25) did not evidence any publication bias (appendix e-3).

When the evaluation by design was done, a significant difference was found ($p=0.00$) favoring IVIG in analytical observational studies; there was not any difference in experimental studies ($p=0.69$). In the evaluation by diseases, there was no significant difference in SGB ($p=0.3$) nor in MG ($p= 0.15$). It was not possible to evaluate other diseases because there was not enough data.

Length of hospital stay:

Twelve articles evaluated the length of hospital stay(15, 16, 21-24, 26, 27, 29, 31-33). The standardized mean difference (SMD) between the two therapies shows that patients treated with IVIG spent in average less time of hospitalization than those managed with PE (SMD= -2.92, IC95%: -5.48; -0.35 $p=0.03$). The different measures for heterogeneity calculated for the analysis were as follows: Q-Value: 3776.19; degree of freedom (Q): 12; p -value= 0.00. The analyses using funnel plot and Egger's regression asymmetry ($p = 0.23$; intercept to10.76) did not evidence any publication bias (appendix e-4).

In general, patients with SGB, required more days in hospital than those with MG in both groups of treatments. When the evaluation by design or by diseases, limited to SGB and to

MG studies, were done, there was no significant statistical difference with any of the two treatments (appendix e-4).

Ventilator support time

Seven articles showed mechanical ventilation data in average requirement days (10, 16, 20, 22, 25, 30, 33). The analysis of the articles about ventilator support time by the SMD showed that patients with IVIG required less time than patients who received PE but no statistical difference was found. The results did not change after the sensitivity analysis. The different measures of heterogeneity calculated for the analysis were as follows: Q-Value: 730.03; degree of freedom (Q): 6; p-value= 0.00. The analyses using funnel plot and Egger's regression asymmetry (p = 0.60; intercept to -5.59) did not evidence any publication bias (appendix e-5).

When the evaluation by design or by diseases, limited to SGB and MG studies, were done, there was no significant statistical difference with any of the two treatments (appendix e-5).

DISCUSSION

This is the first meta-analysis study that compares effectiveness and adverse side effects between the IVIG and PE therapy for the management of autoimmune neurologic disorders and this is the strength of our study. Our results indicate that both treatments are equally effective in terms of symptom improvement but IVIG has a lower profile of side effects than PE (OR 0.70, IC 0.51 – 0.96, p= 0.03) and patients needed less days of hospital stay (p=0.03). When each disease was considered individually, there were not differences regarding effectiveness or adverse side effects. Also, as we include analytical observational studies and experimental studies, an additional meta-analysis was done regarding each design and it was observed that both therapies were similar in effectiveness; in observational studies, adverse side effects reported were less with IVIG than with PE therapy.

These findings show an important impact because they provide data for the discussion on which of the two treatments may be better. They also help to assume that any of them should be offered or considered for the treatment of the autoimmune neurologic diseases because of the improvement of patients' symptoms and their high level of safety. The ease of use and the need of fewer requirements with respect to equipment and personnel of IVIG in relation to the EP could incline the balance towards the former method.

Multiple clinical studies and meta-analysis, have evaluated PE or IVIG against placebo or other treatments, individually or in specific disease. Positive effects have been found with significant effectiveness and relatively few side effects. (3, 4, 6)

In a systematic review and meta-analysis, PE was effective in patients with mild, moderate and severe SGB, regardless of the evolution time of the disease (3). In the meta-analysis of Gajdos P et al, no adequate clinical trials were found to determine whether PE improves the short- or long-term prognosis for chronic MG or MG exacerbation. However, the case series included, reported a short-term benefit of PE management for myasthenic crisis; no significant difference was found between management with PE or with IVIG in one clinical trial (34). Subsequently, a review of IVIG in MG, concluded that there was no sufficient data to determine the effectiveness of IVIG in chronic MG: in six controlled trials evaluated (35).

The review by Cortese conclude that the diseases with the best data on PE efficacy and most frequently used, include CIDP, SGB, MG (both moderate–severe and prethymectomy), paraproteinemic polyneuropathies (IgG/IgA), Multiple Sclerosis (acute relapses), and Lambert-Eaton syndrome (36).

In guidelines based on the evidence of treatment with IVIG and with PE, the effectiveness of these two treatments has been described in SGB and CIDP and their uses have been recommended. The evidence is insufficient for the use of IVIG in children, as well as in Sydenham Chorea and PANDAS but it is probably effective in MG. The evidence is insufficient with PE for MG (preoperative and crisis), Sydenham Chorea and PANDAS (4, 37).

In relation to safety, adverse effects have been described in about 5% of patients treated with IVIG and 7% to 18 with PE (22, 38). It is noteworthy that most of the studies only make a description of the symptoms but few of them mention details regarding severity.

According to our results, the evaluation of the direct and indirect costs and the cost-benefit of both therapies become important, especially for health services. Nagpal evaluated the direct costs of the two methods by a meta-analysis and evidenced that the cost of IVIG was 60% higher than that of PE (PE: \$6,204; IVIG: \$10,165) (39). When adverse events are included, the short-term cost average with PE in MG was \$101,140 per patient as compared to \$78,814 of IVIG (40).

Our study has potential limitations. There is a possibility that some studies may have been missed despite our extensive search strategy, although this is unlikely. The main limitation pertains to the quality of the evidence (not all the studies included were randomized controlled trials) and the heterogeneity of studies principally due to their sample size. Finally, some studies reported the experience in the treatment of episodes and not related to patients so they have been excluded from the analysis.

This meta-analysis invites to go deeper in the pathophysiology to find common paths both of presentation and of managements and carry out much larger studies that permit the analysis of effectiveness and safety.

AUTHOR CONTRIBUTIONS

Dr. Paola Ortiz-Salas: was responsible for study design, identification of papers for systematic review, analysis and interpretation of data, drafting of the manuscript and revising the final version of the manuscript.

Dr. Alberto Velez-van-Meerbeke participated in study design, study supervision, statistical analysis and interpretation of data, as well as in the drafting of manuscript and revising the final version of the paper.

Dr. Camilo Alberto Galvis: collaborated for identifying papers for systematic review, collection and analysis of data.

Dr. Jesus Hernan Rodriguez Quintana participated in study design, in obtaining funding as well as in the drafting of the manuscript.

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