ABSTRACT

Background: Immunoglobulins (IG) are widely used for the treatment of a variety of immune-mediated diseases. The exact mechanism of action remains unknown, but IG modulate the expression and function of Fc receptors, interfere with complement activation and production of cytokines, neutralize pathogenic autoantibodies, and affect the activation and effector functions of B and T lymphocytes. Immunoglobulins are usually delivered intravenously, and are effective in ameliorating motor symptoms, and/or preventing disease progression in immune-mediated neuropathies, including Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy.

Objective: The aim of this systematic review and meta-analysis was to study the potential of IG for the treatment of painful peripheral neuropathy (PPN). The outcome of interest was the percentage of patients with PPN who achieved pain relief following IG administration.

Methods: We performed a systematic literature search on March 17, 2022, in the PubMed database without any publication date restrictions. We also looked for unpublished or ongoing trials in clinicaltrials.org. Pain reduction following IG treatment had to be within the aims (primary or secondary).

Results: The aforementioned literature search strategy revealed five studies (two open-label, three randomized placebo-controlled) eligible to be included. The pooled estimate of the percentage of patients with PPN who received immunoglobulins and reported pain relief was found to be 65% (95% CI 58–71%). The likelihood of achieving pain relief with immunoglobulin treatment was 2.9 times higher (95% CI 1.6–5.2) compared to placebo (p = 0.0003).

Conclusion: The use of IG for the treatment of pain due to peripheral neuropathy has a potential therapeutic benefit. Further studies across patients with different types of painful peripheral neuropathy are needed to better characterize this effect. Registration number on PROSPERO: CRD42022319614.
**Keywords:** Peripheral neuropathy; Pain; Guillain–Barré syndrome (GBS); Chronic inflammatory demyelinating polyneuropathy (CIDP); Intravenous immunoglobulin (IVIG); Subcutaneous immunoglobulin (SCIG); Management

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**Key Summary Points**

The pooled percentage of patients with peripheral neuropathy who received immunoglobulins and reported pain relief was found to be 65% (95% CI 58–71%).

The likelihood of achieving pain relief with immunoglobulin treatment was 2.9 times higher (95% CI 1.6–5.2) compared to placebo ($p = 0.0003$).

Immunoglobulins appear to have a potential for the treatment of pain in patients with peripheral neuropathy, however more studies are needed.

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**INTRODUCTION**

Immunoglobulins (IG) are obtained from the plasma pools of healthy blood donors [1, 2]. Five types of human immunoglobulins have been described, IgG, IgM, IgA, IgD, and IgE with the IgG fraction representing nearly 80% of the total amount of immunoglobulin in the human body [1]. IgG consists of a F (ab')2 fragment that binds to specific antigens and an Fc fragment that exerts effector functions upon binding to Fcγ receptors (FcγRs) [1].

IG are widely used for their immunomodulatory properties for the treatment of a variety of immunedeficiencies and autoimmune diseases [1, 3]. The exact mechanism of action remains unknown, although it is known that IG modulates the expression and function of Fc receptors, interferes with complement activation, preventing complement-mediated cell death and tissue damage [1, 3, 4], neutralizes pathogenic autoantibodies, and affects the activation and effector functions of B and T lymphocytes. Additionally, IG inhibits the activation of monocytes and macrophages, and induces anti-inflammatory cytokines and a direct neutralization effect on innate inflammatory cytokines [5, 6].

For many years, immunoglobulins were preferably administering intravenously, but, in recent years, subcutaneous administration has also been chosen. IG administration may cause adverse events, which most frequently include an injection site reaction, a mildly increased body temperature, and headache. Administration of intravenous immunoglobulin (IVIG) has been shown to have a beneficial effect on ameliorating motor symptoms and/or preventing disease progression of immune-mediated peripheral neuropathies, such as Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and multifocal motor neuropathy [7–10]. IVIG contributes to the treatment of motor symptoms in multiple ways. In particular, through anti-idiotypic effects, it reduces the circulating pathogenic antibody levels (i.e., anti-GM1 IgM) and interferes with antibody-mediated complement deposition in nerves [3]. IVIG also interferes with B-cell receptors on antibody-specific clones, as described in patients with CIDP [11].

Clinical experts using IG in their clinical practice have observed that the latter may have a potential for the treatment of chronic pain in various conditions [12]. These observations have led to the completion and publication of the first clinical trials. The aim of this study was to systematically review the role of IVIG in the treatment of painful peripheral neuropathy (PPN).

**METHODS**

**Protocol Registration**

This review was initially registered to PROSPERO, an international prospective register database of systematic reviews in health and social care. The registration number was CRD42022319614.
Literature Search Strategy

A systematic literature search was performed on March 17, 2022, in the PubMed database, without any publication date restrictions. For the PubMed search, we used three medical subject heading (MeSH) terms in either the abstract or the title. Term A was “pain” OR “painful”. Term B was “neuropathy” OR “neuritis” OR “polyneuropathy” OR “mononeuritis” OR “neuronopathy” OR “CIDP” OR “polyradiculoneuropathy” OR “polyradiculopathy”. Term C was “IVIG” OR immunoglobulin” OR “immune globulin”. We also searched at clinicaltrials.gov, a resource provided by the U.S. National Library of Medicine for unpublished trials. For the search, we used the same MeSH terms as above. The filters “with results” AND “completed” were applied. No publication date filter was applied. The reference lists of included articles were further screened to identify further studies that may fall within the scope of this review.

Inclusion Criteria

Articles eligible to be included in this review were required to meet the following criteria:

1. Human subjects were involved.
2. The full article was written in the English language.
3. Pain management was within the primary or secondary aims of the IG use
4. Papers were of adequate methodological quality, as described below.

Exclusion Criteria

Articles meeting the following criteria were excluded from our review:

1. Non-original articles (i.e., review articles, letters, medical hypotheses, etc.).
2. Trials with less than 10 patients per treatment arm.
3. Duplicate articles or papers from the same research teams describing the same patient population.

All article abstracts were screened three times repeatedly in a blinded fashion. Those found to meet any of the exclusion criteria were removed, and any controversies were dealt with consensus during a face-to-face meeting, in which the abstracts were reviewed. All remaining papers were screened again as a full article by at least three reviewers, and conflicts were settled as previously noted.

Quality Assessment of Included Studies

The risk of bias was independently assessed by two of the authors. For the evaluation of randomised controlled trials (RCTs), we used the Cochrane Collaboration's tool [13, 14], which contains seven evidence-based criteria evaluating selection bias; random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and other biases [13]. RCTs were considered to be of low risk of bias if low risk of bias was scored in all key domains, unclear risk of bias if low or unclear risk of bias was scored for all key domains, and high risk of bias if high risk of bias was scored for one or more key domains.

The Joanna Briggs Institute Critical Appraisal Checklist was used for the evaluation of case series, which contains ten items [15]. We considered “High risk of bias” studies that met up to 4 of the quality criteria, “Moderate risk of bias” studies that met 5–7 of the quality criteria, and “Low risk of bias” studies that met 8–10 of the quality criteria.

Data Collection Process

After the identification of eligible literature, relevant data were extracted from each study in a structured coding scheme using Excel, and included population size, gender and age distribution, the cause of PPN, the means of diagnosis of the polyneuropathy, the duration of RCT, the response to treatment, the way of assessment of effectiveness, the side effects associated with the treatment, the dropouts associated with the treatment, and the follow-up period of the patients, where applicable. When there was uncertainty considering how
Data should be interpreted or utilized, at least three authors discussed the study in question to meet consensus.

**Data Synthesis**

This study used aggregated data where possible, and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16].

**Statistical Analysis**

Meta-analysis of the pooled proportions was conducted in the R language [17] using the default settings of the ‘metaprop’ package. The meta-analysis of odds ratios was conducted using the RevMan programme [18], as suggested by the Cochrane Collaboration Group. Heterogeneity between studies was assessed using the $I^2$ statistic [19]. Data were analyzed using a fixed effects model.

**Compliance with Ethical Guidelines**

This study is based upon studies published prior to the present review. Thus, there are no ethical concerns with respect to this study.

**RESULTS**

The literature search strategy resulted in the identification of 280 articles. After the eligibility assessment, 175 articles were excluded. In total 5 papers met the inclusion criteria [20–24]. These studies were published between 2015 and 2021. The study selection process is illustrated in the PRISMA Chart (Fig. 1).

Of the included studies, three were placebo-controlled randomized controlled trials and two were retrospective open-label studies. In four studies, IG were administered intravenously, while in one study IG were administered subcutaneously. Two studies included patients with CIDP, one study patients with diabetic periph-

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*Fig. 1 PRISMA chart*
| Study       | Type of study | n (IG/placebo) | Disease | Means of diagnosis | IG type | IG dose and frequency | Means of determining PNP response to treatment | F/U period |
|------------|---------------|---------------|---------|--------------------|---------|----------------------|--------------------------------|-----------|
| Kuitwaard  | Retrospective open label | 77 | CIDP | EFNS/PNS criteria | IV | 2 g/kg over 5 days | Self-report | NR |
| Liu [20]   | Retrospective open label | 32 | Apparently autoimmune SFN | Symptoms and skin biopsy. Had autoimmune disease comorbidity | IV | ≥ 1 g/kg/4 weeks (range: 1.3–2.0 g/kg/4 weeks) | NRS > 30% reduction | 3 months |
| Hartung [21] | RCT | 115/57 | CIDP | EFNS/PNS criteria | SC | 0.2 g/kg or 0.4 g/kg weekly for 24 weeks | NRS score reduction by 1 point | 6 months |
| Jann [22]  | RCT | 11/12 | DPN | Toronto Diabetic Neuropathy Expert Group criteria (symptoms and abnormal NCS or symptoms and abnormal SFN test) | IV | 2 g/kg over 5 days | NRS > 50% reduction | 4 weeks |
| Geerts [23] | RCT | 30/30 | Idiopathic SFN | Symptoms and skin biopsy. Normal NCS-only length-dependent pattern | IV | 2 g/kg over 2 days and additional 3 g/kg over 6 weeks | Self-report | 3 months |

*RCT* randomized controlled trial, *IG* immunoglobulin, *CIDP* chronic inflammatory demyelinating polyneuropathy, *SFN* small fiber neuropathy, *DPN* diabetic peripheral neuropathy, *NCS* nerve conduction studies, *IV* intravenously, *SC* subcutaneously, *PNP* peripheral neuropathic pain, *NRS* numerical rating scale, *F/U* follow-up
eral neuropathy (DPN), and two patients with small fiber peripheral neuropathy. The characteristics of the included studies are summarized in Table 1.

The quality assessment of the included papers is available as Supplementary material.

Response to IG Treatment

Figure 2 shows the pooled response to IG administration in patients with PPN who received treatment with IG, following the meta-analysis of the five available studies assessing 265 patients. The pooled response to treatment was 65% (96% CI 58–71%). There was substantial heterogeneity across the included studies ($I^2 = 90\%$).

As demonstrated in Fig. 3, the likelihood of responding was 2.9 times higher (95% CI 1.6–5.2) with the administration of IG in comparison to the placebo ($p < 0.0003$). This was not a statistically significant difference. There was substantial heterogeneity across the included studies ($I^2 = 62\%$).

Adverse Events

Common adverse events of IG use included headache, nausea, and dizziness [20, 24]; however, no more dropouts have been reported in the IG-receiving groups compared to placebo [24].

DISCUSSION

In our systematic review and meta-analysis, we looked into the potential of the use of IG administration for the management of PPN. We showed that the use of IG increases the likelihood of ameliorating pain in comparison to placebo by almost three times. This is of particular importance for patients suffering from PPN and for the clinicians treating those patients, as it adds another potential treatment to their armament.

The advantage of our work is that we included papers of adequate methodological quality with well-defined populations of patients suffering from PPN. The diagnoses of peripheral neuropathy (DPN), and two patients with small fiber peripheral neuropathy. The characteristics of the included studies are summarized in Table 1.

The quality assessment of the included papers is available as Supplementary material.

Response to IG Treatment

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| Study          | Events | Total | Proportion | 95%-CI     | Weight (fixed) | Weight (random) |
|----------------|--------|-------|------------|------------|----------------|-----------------|
| Geerts 2021    | 13     | 30    | 0.43       | [0.25; 0.63]| 15.6\%         | 20.3\%          |
| Jann 2020      | 7      | 11    | 0.64       | [0.31; 0.69]| 5.4\%          | 16.6\%          |
| Hartung 2020   | 100    | 115   | 0.87       | [0.79; 0.93]| 27.5\%         | 21.3\%          |
| Lu 2018        | 10     | 32    | 0.31       | [0.16; 0.50]| 14.5\%         | 20.1\%          |
| Kuitwaard 2015 | 50     | 77    | 0.65       | [0.53; 0.75]| 37.0\%         | 21.7\%          |
| **Fixed effect model** | **265** |       | 0.65       | [0.58; 0.71]| 100.0%         | --              |
| **Random effects model** |       |       | 0.60       | [0.37; 0.80]| 100.0%         | --              |

Heterogeneity: $I^2 = 90\%$, $\chi^2$ = 1.0495, $p < 0.01$

![Fig. 2](https://example.com/fig2.png)

Pooled response to immunoglobulin administration in patients with painful peripheral neuropathy

![Fig. 3](https://example.com/fig3.png)

Metanalysis results as illustrated in the forest plot regarding the percentage of patients with painful peripheral neuropathy who responded to immunoglobulin administration compared to placebo

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neuropathy had to be based on established and widely accepted criteria. We only included studies where pain management was within the aims of the study after IG administration. Moreover, we searched for unpublished or ongoing trials in order to limit the possibility of not including gray literature.

Although the meta-analysis showed that IG have a potential to treat PPN, our results should be interpreted with caution, given some important limitations. Firstly, the included studies assessed patients with different underlying types of peripheral neuropathy, with the exemption of the studies conducted by Hartung et al. [22] and Kuitwaard et al. [20], who both reported the effectiveness of IG in patients with CIDP. This poses a risk that the underlying pathophysiological mechanisms of the PPN are different. Secondly, the studies we included had different treatment protocols, as well as the researchers used different methods to determine response to treatment (i.e., one point change in Pain Intensity Numerical Rating Scale [24] or 30% reduction of the intensity of pain [21]). Thirdly, the studies followed patients for different periods, and therefore we could not assess the effectiveness of pain at a specific time point after treatment with IG. Finally, a more comprehensive search using other databases rather than PubMed alone may have produced a greater number of articles suitable for final analysis.

Despite these limitations, further well-designed placebo-controlled RTCs are needed to determine the effectiveness of IG in the treatment of PPN. Such studies should focus on immune-mediated neuropathies, given the fact that IG has already a proven effectiveness in treating motor symptoms in such neuropathies. Using widely accepted ways to evaluate pain before and post-treatment at many time points is of utmost importance.

CONCLUSION

The use of IG for the treatment of PPN has a potential therapeutic benefit. Further studies across patients with PPN of different aetiologies are needed to better characterize this effect.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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