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REVIEW

Effectiveness of Intravenous Immunoglobulin for Management of Neuropathic Pain: A Narrative Review

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Abstract: Administrations of intravenous immunoglobulin (IVIG), an immune-modulating blood-derived product, may be beneficial for managing neuropathic pain. Here, we review previous studies to investigate the effectiveness of IVIG in managing neuropathic pain due to various neurological disorders. The electronic databases PubMed, Scopus, Embase, and the Cochrane Library were searched for studies published up to February 2020. Two reviewers independently assessed the studies using strict inclusion criteria. Ten studies were included and qualitatively analyzed. The review included patients with pain due to complex regional pain syndrome (CRPS), diabetic polyneuropathy, and others, such as postherpetic neuralgia and trigeminal neuralgia. We found that IVIG may be one of the beneficial options for managing neuropathic pain from various neurological disorders. In the four articles reviewed, no major adverse effects were reported, and the trend was toward a positive pain-reducing effect in eight articles. However, to confirm the benefits of IVIG on reducing neuropathic pain, more high-quality studies are required.

Keywords: neuropathic pain, intravenous immunoglobulin, complex regional pain syndrome, diabetic polyneuropathy

Introduction

Neuropathic pain is caused by damage of the peripheral or central nervous system and affects 7–10% of the general population.[1] Its typical characteristic is burning or electrical sensation and pain induced by non-painful stimuli, such as light touching.[1–3] It occurs in various neurological disorders, such as diabetic polyneuropathy, chemotherapy-induced painful neuropathy, complex regional pain syndrome (CRPS), spinal pain, trigeminal neuralgia, postherpetic neuralgia, and other painful neuropathies.[1–3] Neuropathic pain is frequently refractory to several treatment methods, such as oral medication (anti-inflammatory drugs, tricyclic antidepressant, and anticonvulsant drugs), physical therapy, and procedures.[4–6] Chronic neuropathic pain can also greatly impair patients' quality of life and cause depression, anxiety, and sleep disturbances.[7–9]

Neuropathic pain is associated with neuroinflammation.[10,11] In patients with neuropathic pain, regardless of the underlying etiology, pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin 1, are overexpressed.[10,11] Administration of intravenous immunoglobulin (IVIG), an immune-modulating blood-derived product, may be beneficial for managing neuropathic pain.[12,13] IVIG

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has anti-inflammatory effects, probably induced by the suppression of pro-inflammatory cytokines, blockade of the Fc receptor, and enhancement of antibody catabolism.[12–14]

To date, several previous studies have evaluated the effectiveness of IVIG for controlling neuropathic pain due to various neurological disorders.[10,15–17] However, the effectiveness of IVIG for pain-reducing effect is debatable. In addition, there has been no review about the effectiveness of IVIG for managing neuropathic pain due to various neurological disorders. Here, therefore, we review previous studies to investigate the effectiveness of IVIG for managing neuropathic pain due to various neurological disorders.

Methods

Two authors (D.P. and M.C.C) independently performed the literature search using the electronic databases PubMed, Scopus, Embase, and the Cochrane Library. Differences in their search results were resolved through a discussion. In PubMed, a search of ((“Immunoglobulins, Intravenous”[Mesh]) AND (“Neuralgia”[Mesh] OR “Nervous System Diseases”[Mesh] OR “Pain”[Mesh])) was performed. In Scopus, Embase, and the Cochrane library, a search of ((“Intravenous Immunoglobulin” OR “IVIG”) and (“neuralgia” OR “neuropathic pain” OR “nervous system diseases”)) was performed. The search was limited to articles published up to February 29, 2020. Only studies on the effects of IVIG on pain in patients with neuropathic pain were included. Data extraction was performed by two independent reviewers (D.P and M.C.C) (Figure 1).

Results

A total of 4127 potentially relevant articles were found in the primary literature search. After reading the titles and Abstracts and assessing them for eligibility based on the full-text articles, four articles were finally included in this review

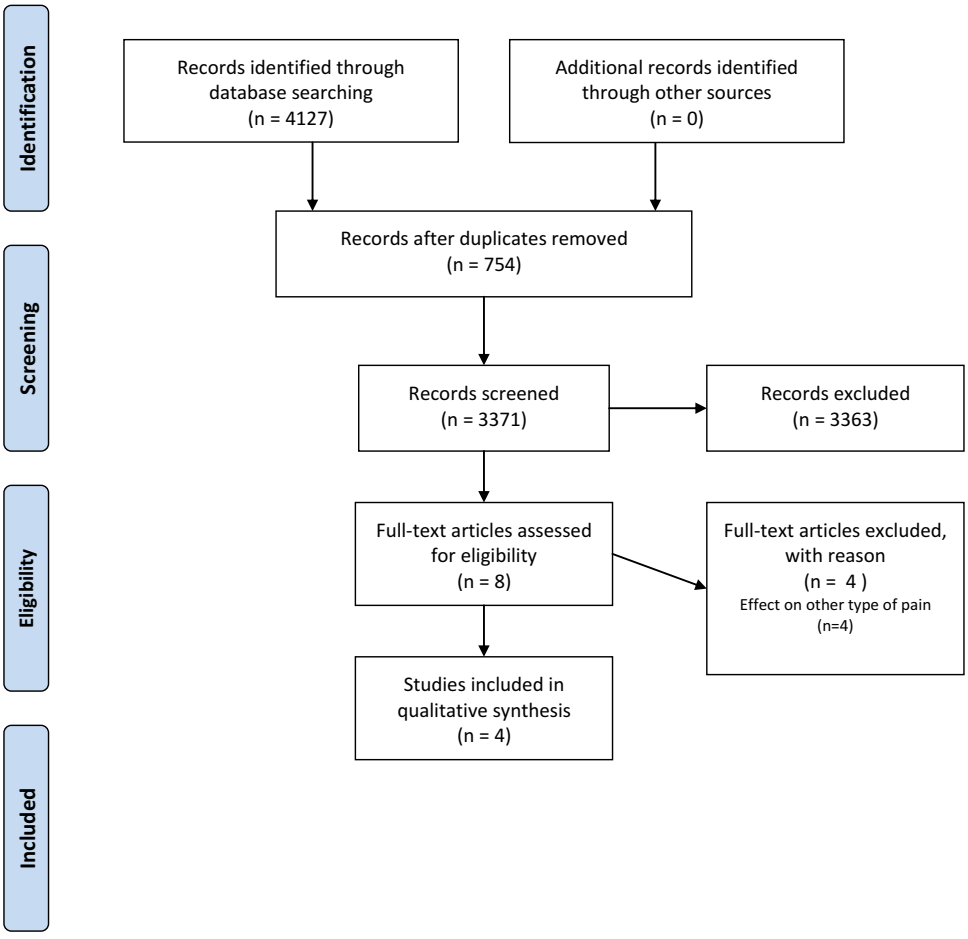

Figure 1 Flowchart of this study using PRISMA Flow Diagram.**Notes:** Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 6(7): e1000097. doi:10.1371/journal.pmed1000097.[16] Creative Commons license and disclaimer available from: (http://creativecommons.org/licenses/by/4.0/legalcode).

Table 1 Summary of the Included Studies

#	First Author, Years	Study Design	Number of Patients (E/C)	Treatment Compared with IVIG	IVIG Protocol	Pain Measurement Methods	Outcome Measurement Time, Months	Summary of Outcome	Diagnostic Methods
Complex regional pain syndrome									
1	Goebel, 2010[15]	Randomized crossover study	13	–	0.25 g/kg/day * 2 days	Average 24 hour pain intensity score on an 11-point NRS (0–10)	6 to 19 days after each infusion session	Decline in VAS score of 1.6 after IVIG treatment was more than placebo.	Diagnosis of Complex Regional Pain Syndrome I or II according to Budapest research criteria.
2	Goebel, 2017[16]	RCT	111 (55/56)	-	Total 0.5/kg	NRS pain value	6–42 days after the treatment	No significant effect	Diagnosis of Complex Regional Pain Syndrome I or II according to Budapest research criteria.
Diabetic polyneuropathy									
3	Jann, 2020[17]	RCT	23 (11/12)	Placebo	0.4 g/kg/day for 5 days	VAS, NPSI	4 weeks after the treatment	≥50% pain reduction: 63.6% (IVIG) vs 0% (placebo)	Diagnosis confirmed as per the Toronto Diabetic Neuropathy Expert Group criteria[17]
Various neurological disorders									
4	Goebel, 2002[10]	Single-arm prospective study	130	-	Total 9–18 g over 1 week	Average 24 hour pain intensity score on an 11-point NRS (0–10)	Within 2 years after the treatment	24.1% showed >70% of initial pain	Patients were diagnosed according to IASP (International Association for the Study of Pain) guidelines[10]

Abbreviations: E, experimental group; C, comparison group; IVIG, intravenous immunoglobulin; RCT, randomized controlled trial; VAS, visual analogue scale.

(Table 1).[10,15–17] Among 4127 articles, only four articles were included in this study. Among the included articles, IVIG was used for evaluating the effect of reducing pain due to CRPS in two studies,[15,16] diabetic polyneuropathy in one study,[17] and neuropathic pain due to various disorders, including CRPS, postherpetic neuralgia, posttraumatic neuropathy, phantom limb pain, and spinal pain in one study.[10]

CRPS

To date, two previous studies evaluated the effect of IVIG for controlling pain due to CRPS.[15,16] The first author in these two studies was Goebel. In 2010, Goebel et al[16] investigated the effectiveness of IVIG in 13 patients with CRPS. Their study design was a randomized, placebo-controlled, double-blind, crossover trial. The authors gave each infusion to patients for two consecutive days. Changes in the degree of pain were measured 6 to 19 days after the initial treatment and crossover treatment. In the results, a decline in VAS score of 1.6 was higher after IVIG treatment than after placebo. In 2017, Goebel et al[15] reported the effectiveness of IVIG in patients with moderate to severe chronic CRPS sustained for 1 to 5 years (IVIG group, n = 55; Placebo group, n = 56). Pain intensity was measured on VAS as a primary outcome, and quality of life was evaluated as a secondary outcome. IVIG was administered on days 1 and 22 after randomization. However, after 6 weeks of IVIG, no statistically significant difference was found between the IVIG and placebo groups in pain intensity or quality of life.

Diabetic Polyneuropathy

Only one study (2020) evaluated the pain-relieving effect of IVIG on diabetic polyneuropathy.[17] Jann et al[17] recruited 11 patients in the IVIG group and 12 patients in the placebo group and conducted an RCT. One month after IVIG, 7 of 11 patients (63.6%) showed more than 50% reduction in the initial pain, but none of patients in the placebo group (0%) showed more than 50% reduction in the initial pain. They concluded that IVIG is an efficacious treatment for patients with neuropathic pain due to diabetic polyneuropathy.

Others

One prospective observational study evaluated the effectiveness of IVIG for controlling pain from various neurological disorders.[10] In 2002, Goebel et al[10] (prospective observational study) recruited 11 patients with CRPS, five patients with postherpetic neuralgia, six patients with trigeminal neuralgia, 12 patients with posttraumatic or unknown etiology neuropathic pain, three patients with phantom limb pain, and 21 patients with spinal pain. Of 58 patients, 14 (24.1%) showed more than 70% reduction in the initial pain while 11 (19.0%) showed 25–75% reduction in the initial pain.

Adverse Effects

No major adverse effects were observed after IVIG treatment in any study included in our review. However, a few minor adverse effects were reported. Goebel et al[15] reported adverse effects of IVIG as headache, nausea, light-headedness, tiredness, pain elevation, and infusion site reaction. However, of the nine severe adverse events in that study, four occurred after IVIG and five occurred after saline administration. Jann et al[18] also reported a few adverse effects of IVIG. In that study, however, one patient developed mild dermatitis psoriasiform in the treatment arm while one patient from the placebo group developed mild "influenza".[17] These studies included in our review suggest that there are no significant side effects of IVIG.

Discussion

Out of four previous studies, except for one study (Goebel et al in 2017: CRPS), IVIG significantly alleviated neuropathic pain. Results of these studies suggest IVIG as a good therapeutic option for alleviating pain due to various neurological disorders.

Although it has not been definitely demonstrated, IVIG may work by binding to perineural pro-inflammatory cytokines or by hindering pro-inflammatory cytokines mRNA expression in neurons, macrophages, and glial cells.[10,19,20] In several previous studies, IVIG was demonstrated to have anti-inflammatory effect by suppressing various pro-inflammatory cytokines.[21,22]

Regarding CRPS, two studies have been reported.[15,16] However, the effects of IVIG on CRPS in both studies showed contradictory results, possibly attributed to the following causes. First, the number of patients in the studies was different. In 2017, Goebel et al enrolled 111 patients with CRPS.[15] However, in 2010, Goebel et al enrolled only 13 patients with CRPS.[16] Second, the duration of CRPS was different in both studies. IVIG treatment exerts a modulation effect on immune activation. Although the mechanism of CRPS is not exactly known, it differs depending on the time course of disease between acute and chronic stages. Considering that steroids, a potent immunomodulator, are more effective in the acute stage of CRPS than in the chronic stage, pathomechanism due to the immune response

contributes a little more to the acute stage of CRPS than to the chronic stage.[23–28] The disease durations were 2.4 ± 0.9 and 1.6 ± 0.7 years in studies conducted in 2017 and 2010, respectively.[15,16] Therefore, the greater effect of IVIG in the study by Goebel et al in 2010[16] compared to 2017[15] may be explained by the enrollment of patients in a relatively early phase of CRPS. Moreover, elevated cytokine levels in blood serum seem to be associated with the occurrence of neuropathic pain in patients with CRPS.[29] IVIG infusion reduces the levels of some cytokines, and this effect of IVIG seems to alleviate pain. However, in order to find out the exact effect of IVIG on CRPS, additional studies with a larger number of patients and different time periods may be required.

As for diabetic polyneuropathy, only one RCT was conducted despite its result being positive.[17] Furthermore that study had a small number of patients. Accordingly, it is hard to draw a conclusion on the use of IVIG for managing pain due to diabetic polyneuropathy. Moreover, evidence is lacking on various neurological disorders other than CRPS, and diabetic neuropathy, despite some positive pain-reducing results reported in one study. That study was limited in that they did not evaluate the effect of IVIG in each neurological disorder separately.[10]

Conclusions

This narrative review shows that IVIG may manage neuropathic pain due to various neurological disorders. In the four articles reviewed, no major adverse effects were reported, and the trend was toward a positive pain-reducing effect. To confirm the benefits of IVIG on reducing neuropathic pain, more high-quality studies are required, because only four studies are included. Moreover, the protocols for IVIG infusion used in each study were heterogeneous; therefore, the most effective protocol for IVIG infusion for controlling neuropathic pain should be evaluated in the future. Also, pain-reducing effect is known to be initiated at 1 or 2 days after IVIG infusion, but the time when the maximal pain relief occurs and the duration of its pain-reducing effect have not been clearly known.[12] Studies on changes in the effectiveness of IVIG over time would be helpful to elucidate the most appropriate protocol for IVIG infusion.

Abbreviations

IVIG; intravenous immunoglobulin (IVIG), PPS; postpolio syndrome, CRPS; complex regional pain syndrome, TNF-α; tumor necrosis factor-α, VAS; visual analogue scale, RCTs; randomized controlled trials.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author Contributions

Min Cheol Chang: Made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, acquisition of data, revision of manuscript and critical revision of manuscript for intellectual content. Donghwi Park: Made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, acquisition of data, revision of manuscript and critical revision of manuscript for intellectual content.

Both authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors drafted or wrote, or substantially revised or critically reviewed the article. All authors have agreed on the journal to which the article will be submitted, reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage, and agree to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors report no conflicts of interest in this work.

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