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The Effect of Perineural Injection Treatment with 5% Dextrose on Clinical Improvement in Patients with Peripheral Neuropathy: A Systematic Review and Meta-Analysis

Gabriella Bamba Ratih Lintin[1,2], Yose Waluyo[1*], Wa Ode Sri Nikmatiah[1], Nuralam Sam[1]

[1]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[2]Department of Anatomy, Faculty of Medicine, Tadulako University, Palu, Indonesia
*Corresponding Author: Yose Waluyo. Email: yose.waluyo@med.unhas.ac.id

ABSTRACT:

Introduction: Peripheral neuropathy is a global health problem with an increasing prevalence. Perineural Injection Therapy (PIT) is effective in the management of peripheral neuropathy through the mechanisms of inflammatory modulation and nerve function repair.

Objective: To evaluate the effectiveness of PIT in the management of peripheral neuropathy.

Methods: The databases used were ScienceDirect, PubMed, and Cochrane. Included articles were Randomized Controlled Trials (RCTs) with PIT 5% dextrose in sterile water (D5W) interventions in patients with peripheral neuropathy published within the last 10 years and assessing clinical improvement. Risk of bias was assessed based on the National Institutes of Health Assessment. Meta-analyses were conducted using Review Manager 5.4.1.

Results: PIT with D5W with a dose range of 1ml to 6ml provided significant improvements in SSS (MD = -4.58; 95% CI = -10.40 to -0.57, p=0.0004, I2=0%), FSS (MD = -2.82; 95% CI = -4.35 to -1.30, p=0.0003, I2=4.4%), VAS (MD = -1.29; 95% CI = -1.88 to -0.69, p<0.0001, I2=0%) up to more than 3 months after the intervention. However, it did not provide a significant effect on SNCV (MD = 0.46; 95% CI = -0.04 to 0.96, p=0.94, I2=0%), DML (MD = -0.20; 95% CI = -0.40 to 0.01, p=0.06, I2=0%), MNCV (MD = 0.77; 95% CI = -1.84 to 3.38, p=0.56, I2=0%), and quick-DASH (MD = -12.44; 95% CI = -37.19 to 12.30, p=0.32, I2=0%).

Conclusion: PIT with D5W has the potential to be an effective complementary intervention in the management of peripheral neuropathy.

1. INTRODUCTION

Peripheral neuropathy is one of the most common neurological conditions. Peripheral neuropathy can be clinically classified based on anatomical patterns, symptoms, and the results of electrodiagnostic studies for axonal and demyelinating diseases. Peripheral nerves consist of motor, sensory, and autonomic nerve fibers.[1] This condition can affect peripheral nerves, resulting in various symptoms and signs, including pain, paresthesia (subjective complaints such as tingling, numbness, or crawling sensations), sensory disturbances, weakness, and changes in gait.[2] One of the purposes of peripheral neuropathy treatment is

to control neuropathic pain.[2] Perineural Injection Treatment (PIT) is one of the latest advances in regenerative medicine. PIT targets neurogenic inflammation in the subcutaneous nerves, which can potentially cause pain. This therapy has been further refined by Lyftogt, who uses dextrose injections to provide significant pain control in a series of 300 cases of Achilles tendinopathy.[3,4]

In adults, symptoms of chronic neurological diseases are one of the most common reasons for medical visits, and evaluation of sensory disorders, including peripheral neuropathy, is one of the five main reasons for neurological consultation. The prevalence of peripheral neuropathy in the general population is 2.4% and increases with age to approximately 8% in those over 55 years of age.[5]

PIT is performed through subcutaneous injection of 5% dextrose in sterile water (D5W) around the dysfunctional nerve. The use of dextrose in pain management has gained attention due to its non-inflammatory properties at concentrations below 10%. Several recent studies have shown that dextrose has the potential to reduce pain and contribute to the improvement and recovery of connective tissue function. However, the rapid improvement in symptoms after PIT administration indicates that the main therapeutic effect is likely to originate from a sensorineural mechanism, rather than simply a regenerative or proliferative effect on the tissue. Clinically, pain reduction is generally reported within a short period of time, namely within hours to 1–2 days after injection, which is temporally inconsistent with the time required for tissue repair processes to occur. Therefore, it is suspected that dextrose acts directly on sensory nerve fibers by modulating pain neuron activity. Subcutaneous injection of dextrose without local anesthesia has been shown to rapidly reduce hyperalgesia and allodynia in the injected area, indicating a significant neuromodulatory effect on the peripheral nervous system.[5,6] A systematic review is needed to compile and evaluate the latest findings, thereby providing a more complete picture of the effectiveness of PIT with D5W in peripheral neuropathy.

2. METHOD

Data Collection

Data collection in this study was conducted using the methodological guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for a more transparent and comprehensive systematic review. Two reviewers (G.B.L., Y.W.) selected studies from several leading online search engine databases, including *PubMed, ScienceDirect*, dan *Cochrane Library*. The keywords used for literature search were "*Perineural Injection Treatment*" OR "*Dextrose 5%*" OR "*Dextrose Injection*" OR "*Glucose*" OR "*Glucopuncture*" OR "*Perineural Therapy*" OR "*D5W Injection*" AND "*Peripheral Nerve Injury*" OR "*Peripheral Nerve Entrapment*" OR "*Neuropathy Management*" OR "*Peripheral Neuropathy*" OR "*Nerve Entrapment*" OR "*Nerve Injury*".

Eligibility Criteria

Included studies were published randomized controlled trials (RCTs) that had been completed. These studies involved (P) Patients with a diagnosis of peripheral neuropathy aged 18-60 years, no other diagnosed medical conditions, and not taking any medications; (I) Patients receiving perineural injection therapy with 5% dextrose; (C) Patients receiving perineural injection therapy with other medications such as corticosteroids, mecobalamin, platelet-rich plasma (PRP) or normal saline. (O) The outcomes assessed included Visual Analog Scale (VAS), Symptom Severity Scale (SSS), Functional Status Scale (FSS), Sensory Nerve Conduction Velocity (m/s), Distal Motor Latency (DML), Quick-DASH, Motoric Nerve Conduction (MNCV). Only literature published in the last 10 years and written in English were included in this review. Studies in the form of commentaries, case reports, case series, review articles, editorial letters, and abstracts were excluded. This study was approved by PROSPERO CRD420251110621.

Study Selection

Keywords were used to identify potentially relevant studies, which were included in the literature review. Duplicates were then removed using the *Rayyan.ai* application, and reviewers screened all studies obtained based on their titles and abstracts. All screening stages were conducted using the *Rayyan.ai* program. A comprehensive assessment was also conducted on full-text studies that potentially met the eligibility criteria mentioned earlier. During the selection process, reviewers routinely held discussions to reach agreement on any differences or doubts that arose. If differences could not be resolved at the scheduled consensus meeting, they were discussed further via social media and online platforms as soon as they were identified.

Data Extraction

Each study included in this review is described in a separate table, and the data are presented in another table. Characteristics for each study in this review include: 1) Author and year of publication; 2) Sample size; 3) Mean age of participants; 4) Frequency of intervention; and 5) Brief description of the intervention and comparison/control. Meanwhile, the extracted study data are presented in the following order: 1) Author and year of publication; 2) Measurement scale; 3) Time of measurement; 4) Measurement outcomes by intervention and control groups; and 5) p-value.

Quality Assessment

Risk of bias in RCTs was assessed using the National Institutes of Health (NIH) Assessment for Risk of Bias and implemented in Review Manager 5.4.1. This instrument was used to qualitatively evaluate the risk of bias in the performance, participant attrition, detection, selection, and reporting of results in our systematic reviews. Results were then classified as unclear, low risk, or high risk. A study was considered low risk only if all domains for that outcome were rated low. A study was considered high risk when at least one aspect of the findings or multiple domains were considered unclear and significantly reduced confidence in the results. If all domains were unclear, it was considered unclear. We independently evaluated the risk of bias to produce a summary, followed by a discussion of the findings.

Meta-Analysis

Meta-analysis was conducted using Review Manager 5.4.1. Each assessment parameter was assessed individually based on the dose of PIT with D5W (≤3mL vs >3mL) and based on the length of follow-up (≤3 months vs >3months). Under a random-effects model, pooled effect sizes were computed as the Mean Difference (MD) with 95% confidence intervals. Heterogeneity was assessed using the I^2 statistic, where values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively.

3. RESULTS

Article Selection

An initial search of three electronic databases (PubMed, Cochrane Library, and ScienceDirect) yielded 61 articles. After duplication screening using Rayyan.ai, 12 articles were found, leaving 49 articles. The authors then conducted an initial screening by reading the titles and abstracts of these 49 articles, yielding 16 articles eligible for further analysis. However, approximately 2 articles were inaccessible due to the lack of free full text, leaving only 15 articles eligible for eligibility. After full-text screening, 6 articles were excluded due to not meeting the inclusion criteria and incomplete data. Ultimately, this review included a total of 8 studies. The search flow and selection methods are summarized in Figure 1.

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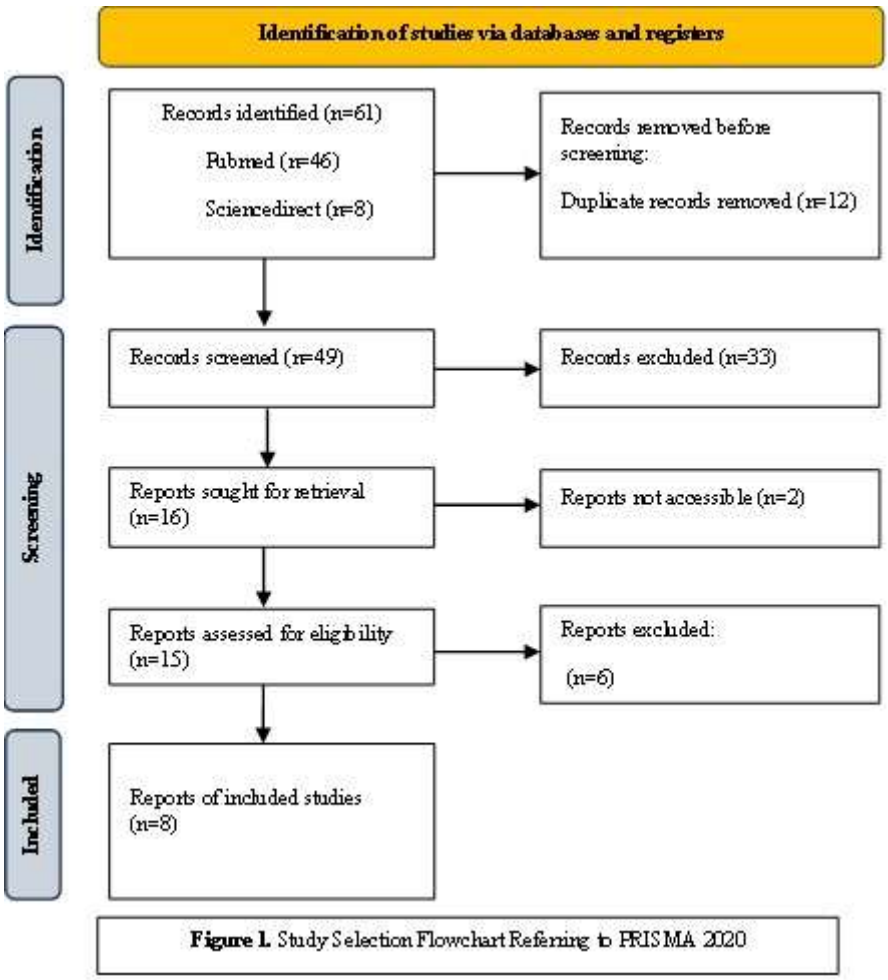

Figure 1. Study Selection Flowchart Referring to PRISMA 2020

Table 1. Characteristics of Research Subjects

No	Study (Author, Year)	Study Design	Number of Participants		Age (mean±SD)		Frequency of Intervention	Intervention	Comparison
			IG	CG	IG	CG			
1	Wu *et al.* (2017)[7]	RCT	30	30	58.47±2.33	58.10±1.93	Single dose injection	PIT with 5 ml D5W	5ml normal saline (NS)
2	Kaplan *et al.* (2022)[8]	RCT	20	20	43.6±13.5	38.1±10.7	Single dose injection	PIT with 5 ml D5W	5ml normal saline (NS)
3	Chen *et al.* (2020)[9]	RCT	17	16	55.5±2.2	56.5±2.3	Single dose injection	PIT with 5 ml D5W	PIT with 5 ml corticosteroid (3mL [10mg/mL] triamcinolone acetonidec mixed with 2mL normal saline)

4	Uslu *et al.* (2024)[10]	RCT	17	16	46.05±5.26	48.13±5.39	Single dose injection	PIT with 5 ml D5W	PIT with 3 ml corticosteroid (2.63 mg betamethasone sodium phosphate + 5 mg betamethasone dipropionate)
5	Wu *et al.* (2018)[11]	RCT	27	27	58.6±2.2	54.3±2.0	Single dose injection	PIT with 5 ml D5W	PIT with 3 ml (10 mg/ml) triamcinolone acetonide
6	Abdallah *et al.* (2025)[12]	RCT	40	40	45.8±7.5	46.9±6.2	Single dose injection	PIT with 5 ml D5W	PIT with 1ml triamcinolone 40 mg + 1ml 1% lidocaine
7	Sugihartono *et al.* (2024)[13]	RCT	12	12	18-80 years		Single dose injection	PIT with 1 ml D5W	PIT with 1ml mecobalamin
8	Nasiri *et al.* (2023)[14]	RCT	21	21	45.00±19.00	47.5±16.00	Single dose injection	PIT with 2 ml D5W	PIT with 1ml methylprednisolone acetate

Table 2. Results from various studies

No	Study (Author, Year)	Measurement Scale	Time of Measurement	Results		Significancy (p-value)
				Intervention Group	Control Group	
1	Wu *et al.* (2017)[7]	*Visual Analog Scale* (VAS)	Pre Intervention	6.67±1.64	6.56±01.64	0.81
			Month 1	4.60±1.92	5.64±1.92	<0.001
			Month 3	3.57±1.64	4.70±2.52	<0.001
			Month 6	2.43±1.64	4.59±2.52	<0.001
		Symptom Severity Scale (SSS)	Pre Intervention	30.20±6.85	28.07±10.57	0.36
			Month 1	20.83±5.81	22.37±9.64	<0.001
			Month 3	17.60±4.38	20.50±11.06	<0.001
			Month 6	15.30±3.29	21.60±11.28	<0.001
		Functional Status Scale (FSS)	Pre Intervention	21.87±3.78	19.93±5.26	0.11

			Month 1	14.17±3.94	18.00±5.75	0.09
			Month 3	12.90±2.85	16.77±6.46	0.005
			Month 6	11.43±2.52	17.07±6.74	0.03
		Sensory Nerve Conduction Velocity (m/s)	Pre Intervention	33.76±5.53	33.83±4.93	0.96
			Month 1	35.46±6.41	34.08±4.98	0.04
			Month 3	36.29±5.81	33.72±5.64	0.003
			Month 6	36.75±6.52	34.08±5.71	0.004
		Distal Motor Latency (DML)	Pre Intervention	4.89±1.31	4.68±0.82	0.45
			Month 1	4.68±1.26	4.72±0.82	0.22
			Month 3	4.64±1.20	4.72±0.82	0.20
			Month 6	4.53±1.10	4.64±0.88	0.43
2	Kaplan *et al.* (2022)[8]	*Visual Analog Scale* (VAS)	Pre Intervention	6.7±4.2	6.5±4.5	0.27
			Week 2	4.8±4.2	5.5±1,8	<0.001
			Month 1	2.7±3.8	6.6±1.6	<0.001
			Month 3	1.5±3.2	6.9±1.7	<0.001
		Quick-DASH	Pre Intervention	46.2±24.4	43.8±14.8	0.71
			Week 2	34.1±24.6	32.5±14.9	0.75
			Month 1	16.4±16.5	37.3±13.9	0.001
			Month 3	5.2±9.4	40.5±15.2	<0.001
		Motoric Nerve Conduction (MNCV)	Pre Intervention	40.3±6.2	49.5±3.5	<0.001
			Month 1	46.1±6.8	49.5±3.0	<0.001
			Month 3	50.7±7.5	49.8±3.3	<0.001
3	Chen *et al.* (2020)[9]	*Visual Analog Scale* (VAS)	Pre Intervention	6.0±1.65	5.8±0.80	0.709
			Month 1	4.4±2.47	3.5±2.80	0.488
			Month 3	3.4±2.06	3.6±2.40	0.657
			Month 4	3.3±2.47	4.0±2.00	0.309
			Month 6	3.6±2.47	4.0±2.00	0.709

		Quick-DASH	Pre Intervention	38.1±17.73	37.4±15.20	0.901
			Month 1	24.9±14.84	23.5±14.80	0.873
			Month 3	24.9±22.26	23.8±15.60	0.631
			Month 4	24.2±17.73	28.7±16.80	0.657
			Month 6	25.9±19.79	28.1±18.80	0.901
		Motoric Nerve Conduction (MNCV)	Pre Intervention	16.1±8.66	19.7±10.40	0.127
			Month 1	13.0±8.25	14.2±9.20	0.136
			Month 3	12.9±9.48	14.5±8.40	0.326
			Month 6	14.8±7.83	13.5±8.80	0.081
4	Uslu *et al.* (2024)[10]	*Visual Analog Scale* (VAS)	Pre Intervention	5.81±0.98	6.13±0.95	0.278
			Week 1	1.63±1.08	2.51±0.51	0.016
5	Wu *et al.* (2018)[11]	*Visual Analog Scale* (VAS)	Pre Intervention	6.3±1.56	6.2±1.04	0.743
			Month 1	4.2±1.56	4.2±2.08	<0.001
			Month 3	3.3±1.04	3.6±1.56	<0.001
			Month 4	2.8±1.56	3.9±1.56	<0.001
			Month 6	2.0±1.56	4.5±2.08	<0.001
		Symptom Severity Scale (SSS)	Pre Intervention	28.2±6.24	27.6±7.27	0.435
			Month 1	19.8±4.68	22.5±8.83	0.016
			Month 3	16.4±3.64	19.8±6.24	<0.001
			Month 4	15.9±3.12	21.2±6.76	0.002
			Month 6	14.7±3.12	23.7±8.31	0.128
		Functional Status Scale (FSS)	Pre Intervention	20.7±5.72	19.7±4.16	0.435
			Month 1	15.0±4.16	16.1±5.20	0.008
			Month 3	12.9±2.60	15.0±4.16	<0.001
			Month 4	12.2±3.12	15.9±4.16	0.002
			Month 6	11.4±2.08	16.6±4.16	0.063
		Sensory Nerve Conduction Velocity (m/s)	Pre Intervention	32.3±5.72	32.7±6.76	0.837

			Month 1	34.2±6.24	34.7±7.27	0.850
			Month 3	34.6±6.24	35.4±7.27	0.512
			Month 6	34.9±6.76	33.9±6.76	0.203
		Distal Motor Latency (DML)	Pre Intervention	5.2±1.56	5.4±1.56	0.698
			Month 1	5.0±1.56	5.0±1.04	0.253
			Month 3	4.8±1.04	4.9±1.04	0.792
			Month 6	4.8±1.04	5.0±1.56	0.828
6	Abdallah *et al.* (2025)[12]	*Visual Analog Scale* (VAS)	Pre Intervention	8.6±0.9	8.4±0.8	0.201
			Month 1	2.9±1.2	3.1±1.6	0.528
			Month 3	6.4±1.4	6.9±2.0	0.199
			Month 6	6.7±1.2	7.5±2.1	0.397
		Symptom Severity Scale (SSS)	Pre Intervention	32.0±5.8	31.4±4.4	0.604
			Month 1	16.9±3.8	17.3±5.4	0.702
			Month 3	23.2±3.8	25.2±6.8	0.135
			Month 6	25.5±3.7	27.1±5.9	0.150
		Functional Status Scale (FSS)	Pre Intervention	23.2±2.7	22.9±3.0	0.670
			Month 1	11.5±2.3	11.9±3.3	0.531
			Month 3	15.1±2.8	16.4±4.5	0.124
			Month 6	19.5±2.1	20.4±3.6	0.176
		Sensory Nerve Conduction Velocity (m/s)	Pre Intervention	31.8±1.6	31.3±1.5	0.100
			Month 1	35.1±1.5	34.8±1.9	0.435
			Month 3	34.4±1.7	34.1±1.4	0.391
			Month 6	33.1±1.2	32.7±1.5	0.192
		Distal Motor Latency (DML)	Pre Intervention	4.5±1.7	4.6±1.5	0.781
			Month 1	4.0±1.2	3.9±1.3	0.722
			Month 3	4.1±1.3	4.3±1.7	0.556
			Month 6	4.2±0.6	4.5±0.8	0.062

7	Sugiharto *et al.* (2024)[13]	*Motoric Nerve Conduction* (MNCV)	Pre Intervention	56.00±14.19	51.00±10.48	0.337
			Week 2	56.08±12.27	52.00±11.13	n/a
		Distal Motor Latency (DML)	Pre Intervention	3.81±0.93	3.86±0.84	0.892
			Week 2	3.70±0.89	3.75±0.70	n/a
		Sensory Nerve Conduction Velocity (m/s)	Pre Intervention	45.00±11.31	50.33±16.67	0.369
			Week 2	44.00±11.87	51.16±16.65	n/a
8	Nasiri *et al.* (2023)[14]	*Visual Analog Scale* (VAS)	Pre Intervention	8.00±2.97	8.00±2.97	0.906
			Month 1	4.00±2.22	3.00±2.22	0.373
			Month 3	2.00±3.71	3.00±2.97	0.894
		Symptom Severity Scale (SSS)	Pre Intervention	36.00±6.67	38.00±6.67	0.427
			Month 1	28.00±11.12	23.5±7.41	0.94
			Month 3	20.00±4.45	22.00±7.41	0.266
		Functional Status Scale (FSS)	Pre Intervention	26.00±8.15	29.5±5.93	0.632
			Month 1	17.00±5.93	18.00±8.15	0.668
			Month 3	14.00±5.93	15.00±5.93	0.733

Characteristics of the studies included

Outcome data were drawn from 8 studies using a randomized controlled trial (RCT) design. One RCT compared PIT with D5W and a corticosteroid solution (betamethasone)[10], three RCTs compared PIT with D5W and a corticosteroid solution (triamcinolone)[11,12,15], two RCTs compared PIT with D5W and normal saline[7,8], one RCT compared PIT with D5W and mecobalamin[13], and one RCT compared PIT with D5W and methylprednisolone acetate.[14] All were administered by single-dose injection (Table 1).

Main Outcome and Data Analysis

This review evaluates the effects of PIT administration in the management of peripheral neuropathy. The outcome parameters used to assess the effects before and after intervention varied between studies, including VAS[7–12,14], SSS[7,11,12,14], SNCV[7,11–13], DML[7,11–13], FSS[7,11,12,14], QuickDASH[8,9], MNCV[8,9,13].

The effect of perineural injection treatment with D5W based on doses of D5W (≤3mL vs >3mL)

Symptom Severity Scale

Only one article assessed the effect of PIT with D5W at a dose of ≤3 ml on SSS assessment parameters. In that article, PIT with D5W at a dose of ≤3 ml did not have a significant effect on SSS compared to controls (p=0.29); similarly, PIT with D5W at a dose of >3 ml also did not have a significant effect on SSS compared to controls (p=0.11). Overall, PIT with D5W at either

a dose of ≦3 ml or >3 ml did not have a significant effect on SSS compared to controls (MD = -1.42; 95% CI = -2.92 to 0.30, p=0.06) (Figure 2). There was no subgroup heterogeneity (I^2=0%) in this analysis.

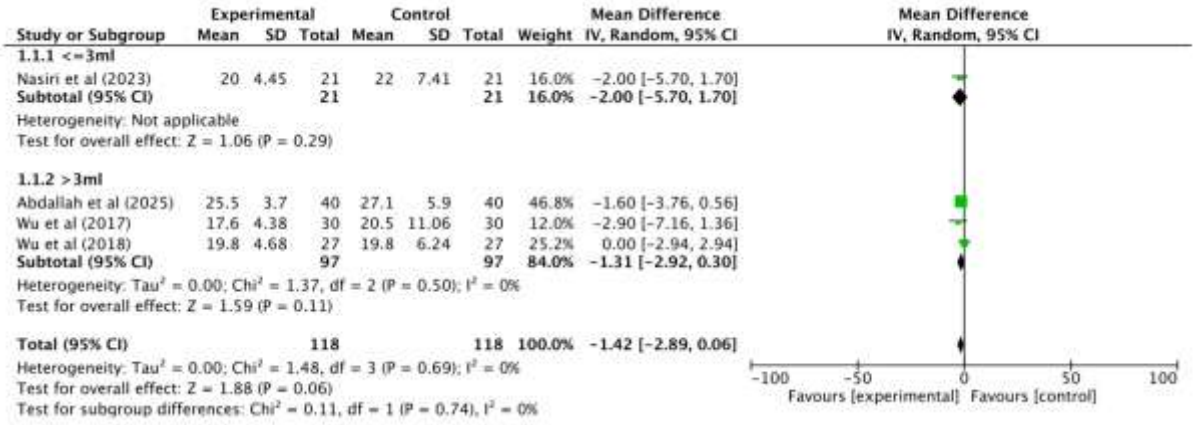

Figure 2. Symptom Severity Scale (≤3mL vs >3mL)

Functional Status Scale

Only one article assessed the effect of PIT with D5W at a dose of ≦3 ml on FSS assessment parameters. In that article, PIT with D5W at a dose of ≦3 ml did not have a significant effect on FSS compared to controls (p=0.58); however, PIT with D5W at a dose of >3 ml did have a significant effect on FSS compared to controls (p=0.009). Overall, PIT with D5W at either a dose of ≦3 ml or >3 ml had a significant effect on FSS compared to controls (MD = 0-2.82; 95% CI = -5.72 to -0.82, p=0.006) (Figure 3). There was mild subgroup heterogeneity (I^2=4.8%) in this analysis.

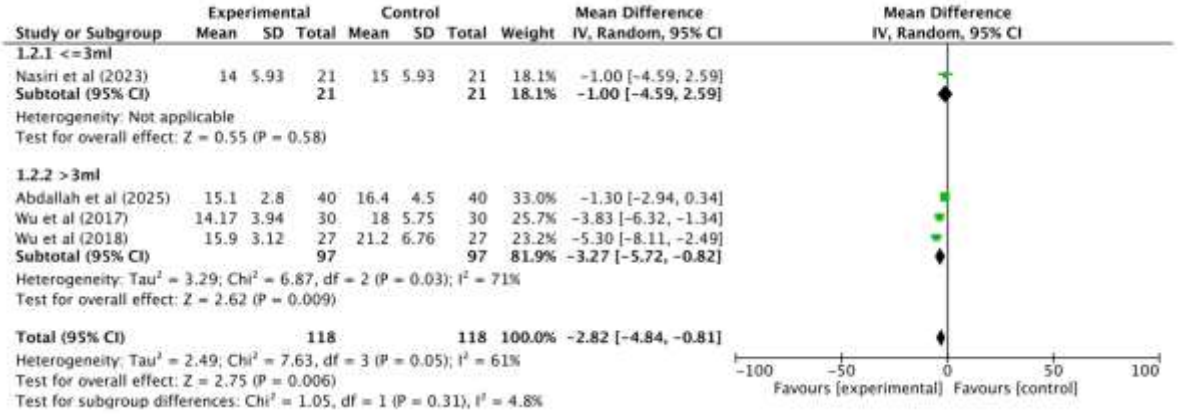

Figure 3. Functional Status Scale (≤3mL vs >3mL)

Visual Analog Scale

Only one article assessed the effect of PIT with D5W at a dose of ≦3 ml using VAS assessment parameters. In that article, PIT with D5W at a dose of ≦3 ml did not have a significant effect on VAS compared to the control (p = 0.33); on the other hand, PIT with D5W at a dose of >3 ml have a significant effect on VAS compared to the control (p <0.001). Overall, PIT with D5W at either a dose of ≦3 ml or >3 ml had a significant effect on VAS compared to the control (MD = -1.02; 95% CI = -1.42 to -0.63, p <0.00001) (Figure 4). There was no subgroup heterogeneity (I^2 = 0%) in this analysis.

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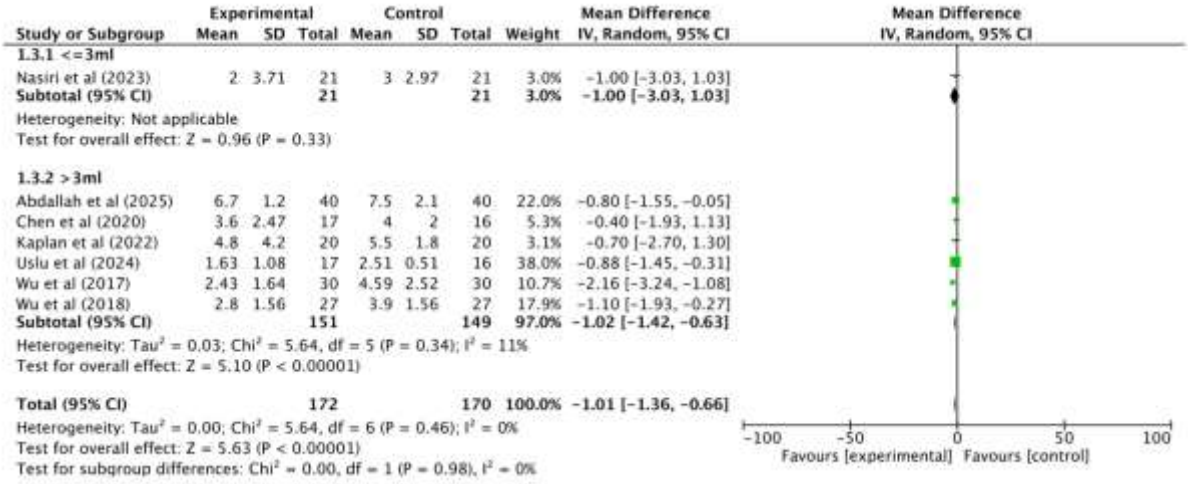

Figure 4. Visual Analog Scale (≤3mL vs >3mL)

***Sensory Nerve Conduction Velocity* (m/s)**

Only one article assessed the effect of PIT with D5W at a dose of ≦3 ml on SNCV assessment parameters. In that article, PIT with D5W at a dose of ≦3 ml did not significantly affect SNCV compared with controls (p=0.23); similarly, PIT with D5W at a dose of >3 ml did not significantly affect SNCV compared with controls (p=0.13). Overall, PIT with D5W at either a dose of ≦3 ml or >3 ml did not significantly affect SNCV compared with controls (MD = 0.71; 95% CI = -0.61 to 2.03, p=0.29) (Figure 5). There was moderate subgroup heterogeneity (I^2=40%) in this analysis.

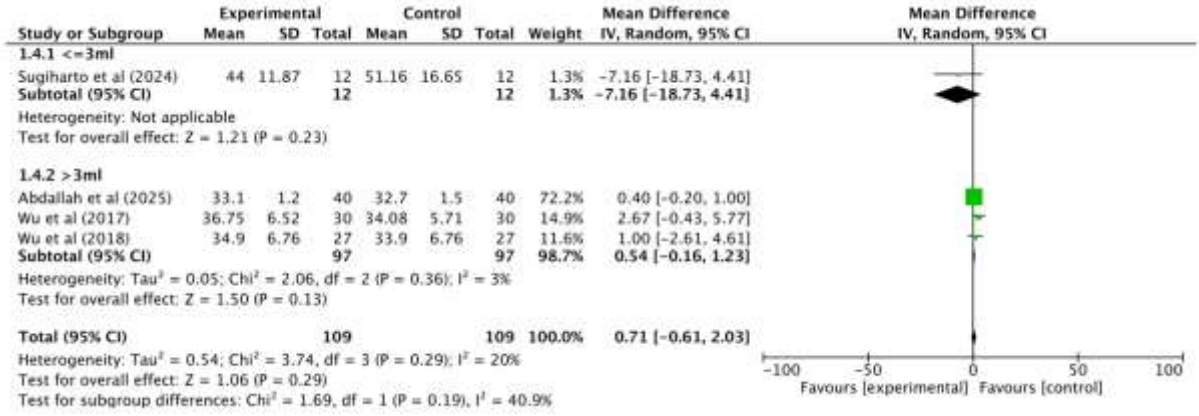

Figure 5. Sensory Nerve Conduction Velocity (≤3mL vs >3mL)

Distal Motor Latency

Only one article assessed the effect of PIT with D5W at a dose of ≥3 ml on DML assessment parameters. In that article, PIT with D5W at a dose of ≥3 ml did not have a significant effect on DML compared to controls (p=0.88); similarly, PIT with D5W at a dose of >3 ml also did not have a significant effect on DML compared to controls (p=0.06). Overall, PIT with D5W at either a dose of ≥3 ml or 3 ml did not have a significant effect on DML compared to controls (MD = -0.22; 95% CI = -0.45 to 0.01, p=0.07) (Figure 6). There was no subgroup heterogeneity (I^2=0%) in this analysis.

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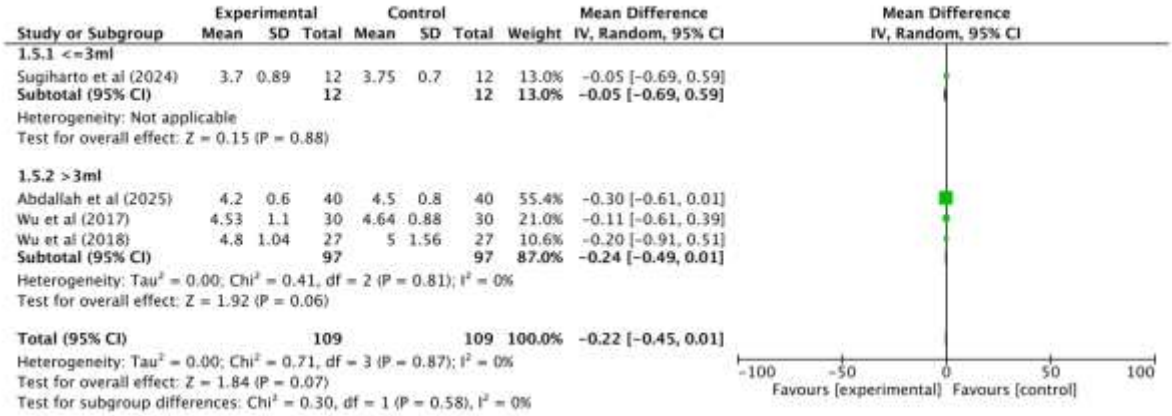

Figure 6. Distal Motor Latency (≤3mL vs >3mL)

Motoric Nerve Conduction Velocity

Only one article assessed the effect of PIT with D5W at a dose of ≥3 ml on MNCV assessment parameters. In that article, PIT with D5W at a dose of ≥3 ml did not have a significant effect on MNCV compared to controls (p=0.39); similarly, PIT with D5W at a dose of >3 ml also did not have a significant effect on MNCV compared to controls (p=0.51). Overall, PIT with D5W at either a dose of ≥3 ml or 3 ml did not have a significant effect on MNCV compared to controls (MD = 1.31; 95% CI = -1.58 to 4.20, p=0.38) (Figure 7). There was no subgroup heterogeneity (I^2=0%) in this analysis.

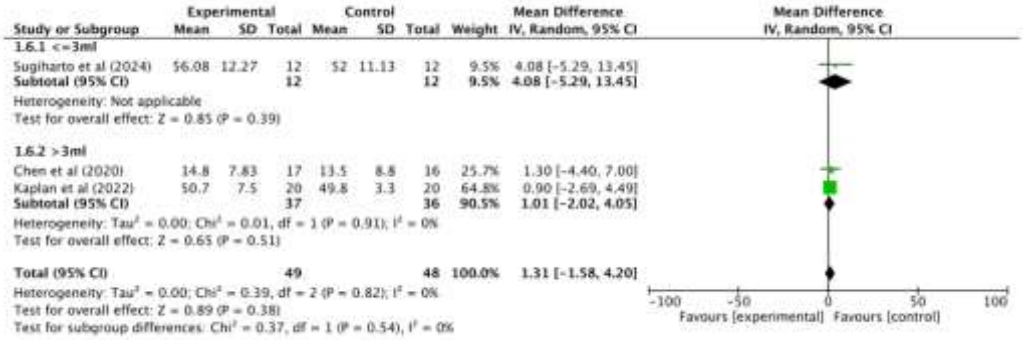

Figure 7. Motoric Nerve Conduction Velocity (≤3mL vs >3mL)

Quick-DASH

Only two articles assessed the effect of PIT with D5W doses >3 ml on the Quick-DASH assessment parameters. In these articles, PIT with D5W doses >3 ml did not significantly impact Quick-DASH compared to controls (MD = -1.89; 95% CI = -10.99 to 7.22, p = 0.68) (Figure 8). There was no subgroup heterogeneity (I^2 = 0%) in this analysis.

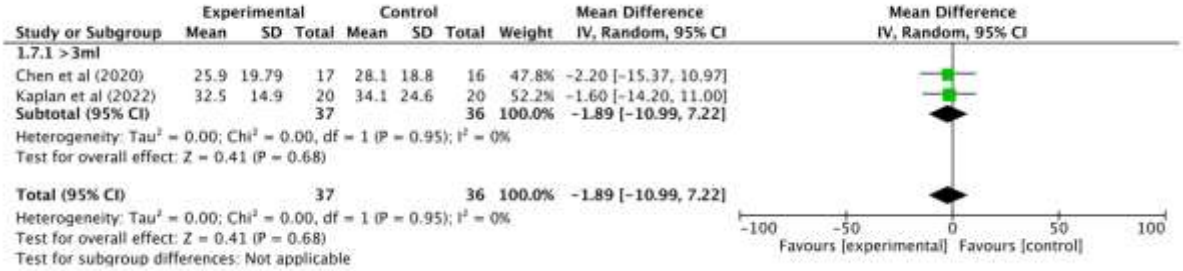

Figure 8. Quick-DASH (≤3mL vs >3mL)

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The effect of perineural injection treatment with D5W based on the length of follow up (≤3 months vs >3months)

Symptom Severity Scale

PIT with D5W had a significant effect on SSS for ≤3 months compared to controls (p=0.02); it even maintained a significant effect on SSS reduction for more than 3 months (p=0.03). Overall, PIT with D5W had a significant effect on SSS reduction compared to controls (MD = -4.58; 95% CI = -10.40 to -0.57, p=0.0004) (Figure 9). There was no subgroup heterogeneity (I^2=0%) in this analysis.

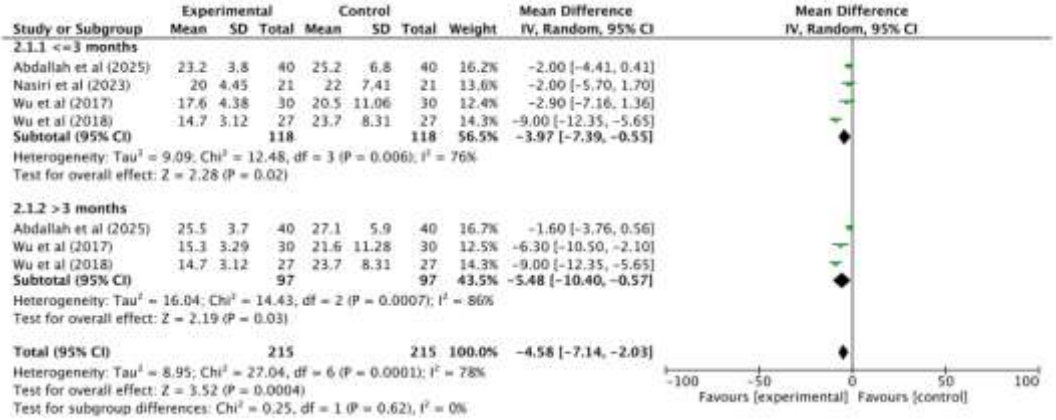

Figure 9. SSS (≤3 months vs >3 months)

Functional Status Scale

PIT with D5W had a significant effect on FSS for ≤3 months compared to controls (p=0.0003); it even maintained a significant effect on FSS improvement for more than 3 months (p=0.02). Overall, PIT with D5W had a significant effect on FSS improvement compared to controls (MD = -2.82; 95% CI = -4.35 to -1.30, p=0.0003) (Figure 10). There was a mild subgroup heterogeneity (I^2=4.4%) in this analysis.

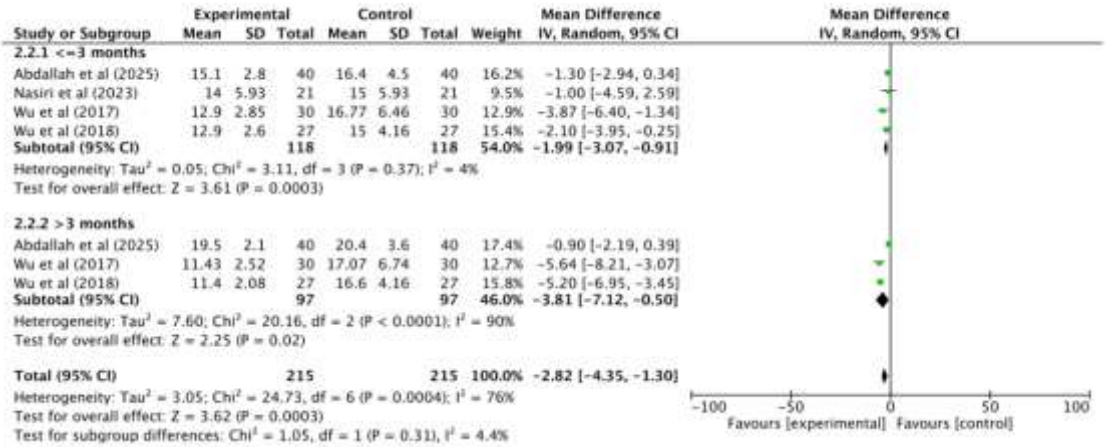

Figure 10. FSS (≤3 months vs >3 months)

Visual Analog Scale

PIT with D5W had a significant effect on VAS for ≤3 months compared to controls (p=0.003); it even maintained a significant effect on VAS reduction for more than 3 months (p=0.001). Overall, PIT with D5W had a significant effect on VAS reduction compared to controls (MD = -1.29; 95% CI = -1.88 to -0.69, p<0.0001) (Figure 11). There was no subgroup heterogeneity (I^2=0%) in this analysis.

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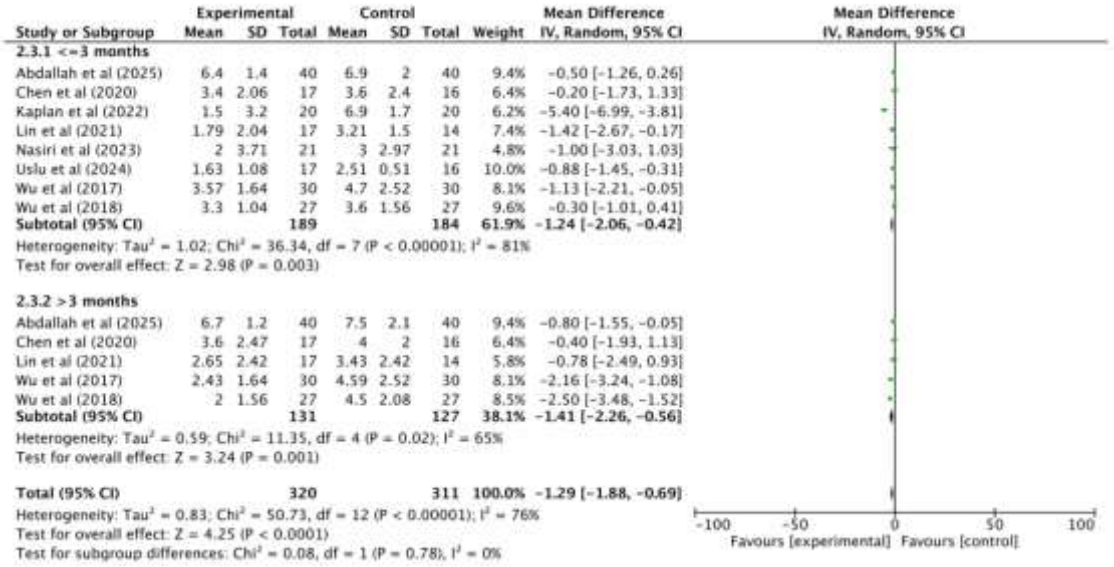

Figure 11. VAS (≤3 months vs >3 months)

***Sensory Nerve Conduction Velocity* (m/s)**

PIT with D5W did not have significant effect on SNCV for ≤3 months compared to controls (p=0.55); and also for more than 3 months (p=0.13). Overall, PIT with D5W did not have significant effect on SNCV compared to controls (MD = 0.46; 95% CI = -0.04 to 0.96, p=0.94) (Figure 12). There was no subgroup heterogeneity (I^2=0%) in this analysis.

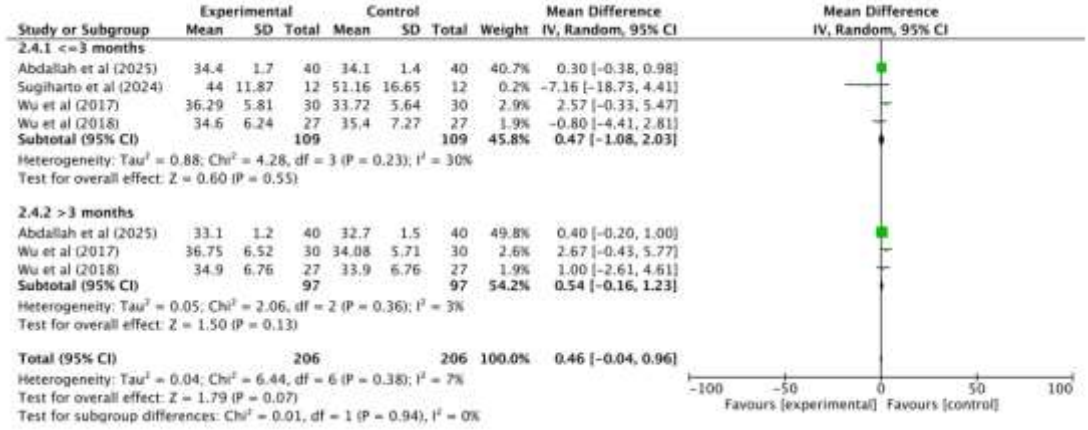

Figure 12. SNCV (≤3 months vs >3 months)

Distal Motor Latency

PIT with D5W did not have significant effect on DML for ≤3 months compared to controls (p=0.56); also for more than 3 months (p=0.06). Overall, PIT with D5W did not have significant effect on DML compared to controls (MD = -0.20; 95% CI = -0.40 to 0.01, p=0.06) (Figure 13). There was no subgroup heterogeneity (I^2=0%) in this analysis.

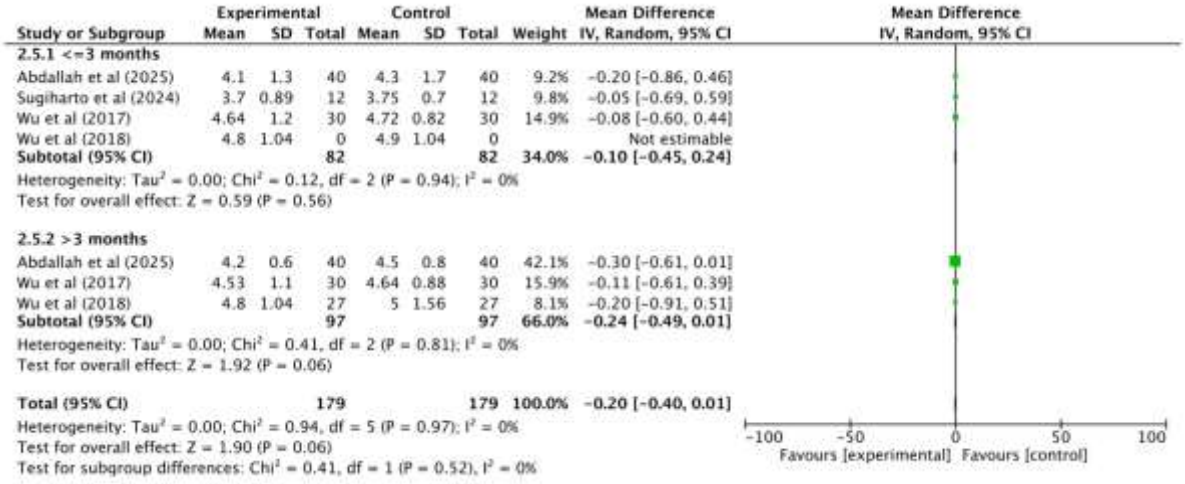

Figure 13. DML (≤3 months vs >3 months)

Motoric Nerve Conduction Velocity

PIT with D5W did not have significant effect on MNCV for ≤3 months compared to controls (p=0.67); also for more than 3 months (p=0.65). Overall, PIT with D5W did not have significant effect on MNCV compared to controls (MD = 0.77; 95% CI = -1.84 to 3.38, p=0.56) (Figure 14). There was no subgroup heterogeneity (I^2=0%) in this analysis.

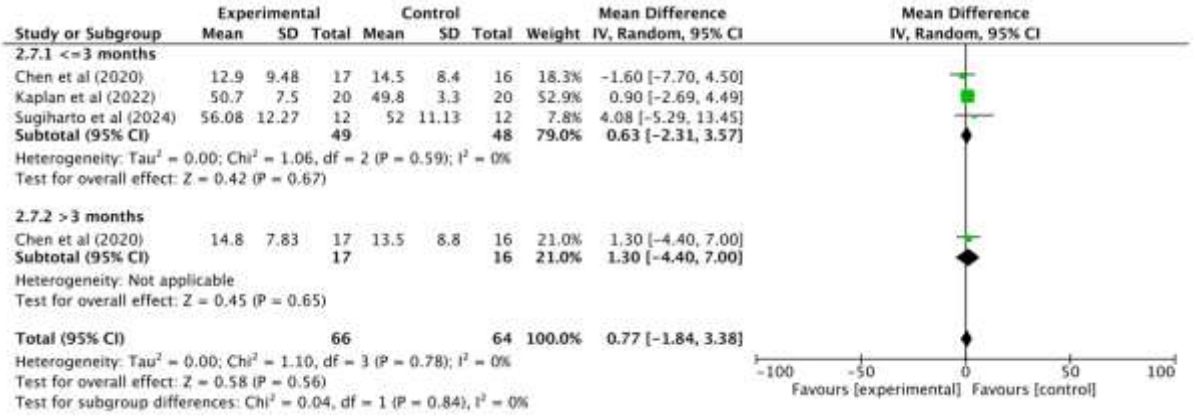

Figure 14. MNCV (≤3 months vs >3 months)

Quick-DASH

PIT with D5W did not have significant effect on quick-DASH for ≤3 months compared to controls (p=0.34); also for more than 3 months (p=0.65). Overall, PIT with D5W did not have significant effect on quick-DASH compared to controls (MD = -12.44; 95% CI = -37.19 to 12.30, p=0.32) (Figure 15). There was no subgroup heterogeneity (I^2=0%) in this analysis.

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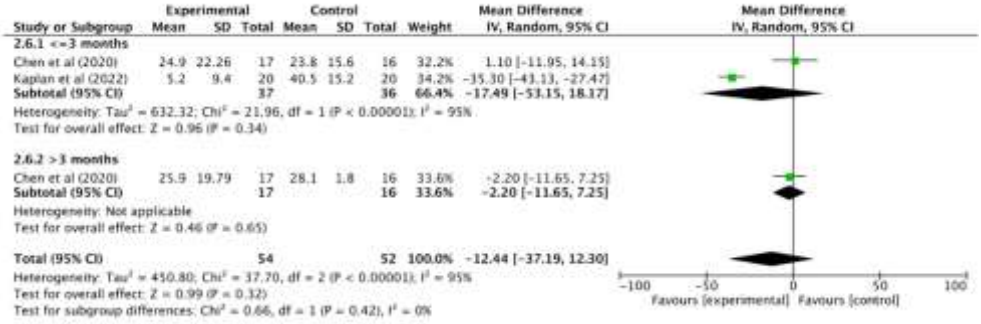

Figure 15. Quick-DASH (≤3 months vs >3 months)

Risk of Bias Assessment

All studies described the methods used to generate random allocation sequences. All studies reported how allocation blinding was performed. All studies blinded participants and personnel, including blinded outcome assessments, and none reported incomplete results. However, two articles remained unclear regarding reporting bias, and one article related to other bias. A summary of the risk of bias assessment is presented in Figure 16 and 17.

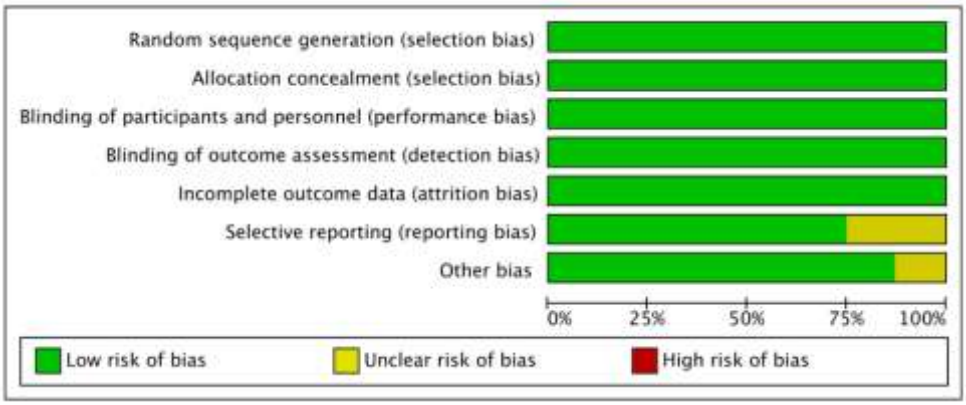

Figure 16. Bias Risk Level Chart in Review Manager 5.4.1

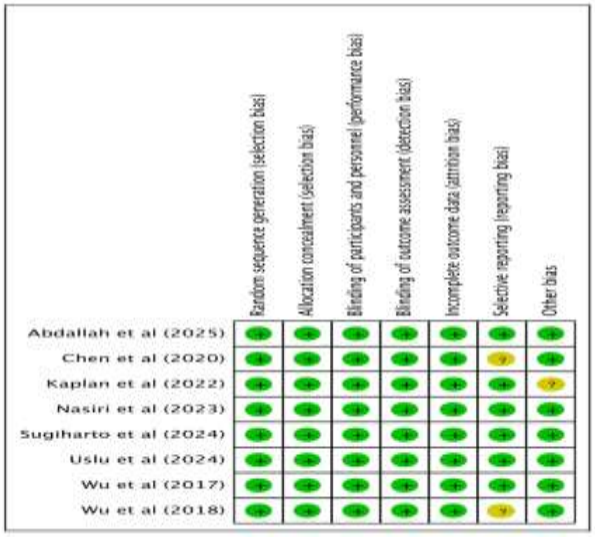

Figure 17. Summary of Bias Risk Levels in Review Manager 5.4.1

4. DISCUSSION

Approximately 2.4% of the human population is affected by peripheral neuropathy. Peripheral neuropathy can be a manifestation of various pathologies that require further evaluation or treatment. In addition, peripheral neuropathy must be treated before it causes complications, such as falls leading to fractures, or infections that can result in amputation.[9,16] The primary goal in evaluating neuropathy is to identify the etiology and, if possible, treat the underlying cause. However, even when neuropathy has a treatable etiology (such as diabetes mellitus, vitamin B12 deficiency, or toxic exposure), treatment is primarily aimed at preventing worsening of neuropathic symptoms. Symptoms that appear at the start of treatment or when the toxic agent is removed may improve and sometimes resolve. However, more often patients will experience residual symptoms due to neurogenic injury acquired prior to treatment. In cases where neuropathy is idiopathic or untreatable, management is symptomatic.[5]

Activation of non-nociceptive Aβ nerve fibers can cause excitation of dorsal spinal interneurons, which play an important role in processing and transmitting nociceptive signals. This excitation reduces the synaptic transmission efficiency of Aδ and C fiber release, which ultimately results in pain reduction. However, in peripheral neuropathy, there is a disruption in the interaction between non-painful Aβ fibers and the central pathway in the dorsal spinal horn, which increases the inhibition of wide dynamic range neurons (WDR) and results in pain.[16] Peripheral nerve compression causes nerve microcirculation disorders, ischemia, nerve conduction impairment, and changes in nerve dynamics due to adhesion and inflammation. This series of processes can gradually cause symptoms such as numbness, paresthesia, neuropathic pain, or muscle atrophy and weakness.[17]

PIT has been found to be useful in the management of peripheral neuropathy because previous studies have shown that PIT administration can alleviate neuropathic pain symptoms. However, the use of PIT to cure peripheral neuropathy is still unknown.[18] Neural prolotherapy or perineural therapy, first discovered and then significantly developed by Dr. John Lyftogt, consists of a series of small injections administered just under the skin that target areas of pain that feel sensitive using simple and natural substances.[4,19] The substance used by Dr. Lyftogt is 5% dextrose in sterile water (D5W) with a neutral pH of 7.4. The type of inflammation that occurs is called neurogenic inflammation (N-inflammation), which is produced by certain small sensory nerves that produce proteins (peptidergic). Buffered dextrose injections at low concentrations (5%) reduce N-inflammation. The main goal of this therapy is not to grow new tissue, but to reset the nerves to a healthy functional state.[20] PIT works by blocking Transient Receptor Potential Vanilloid-type 1 (TRPV1) receptors, thereby inhibiting the propagation of neuropathic pain signals, which produces an immediate analgesic effect. This therapy also inhibits neurogenic inflammation and stimulates the release of nerve growth factors that play a role in tissue repair and recovery. The use of PIT is supported by various publications that confirm its safety and effectiveness with positive outcomes, including in knee pain and sacroiliac pain.[19]

To date, there has been no specific research proving that PIT can cure peripheral neuropathy. In this meta-analysis, based on the dosage of PIT with D5W, the highest dose in this review article is 6ml of D5W. The results of the meta-analysis have shown that PIT with D5W provides a tendency to decrease SSS although not significant, but significantly increases FSS. PIT with D5W also significantly reduces peripheral neuropathy pain assessed by VAS. PIT with D5W also tends to provide a trend of improvement in SNCV and MNCV although not significant. PIT with D5W provides a trend of decreasing DML and quick-DASH although not significant. However, when we analyzed from the duration of the effect of significant changes after the intervention, PIT with D5W, regardless of the dose (1-6ml), provides a decrease in SSS, an increase in FSS, a decrease in VAS, both before 3 months after the intervention and even beyond 3 months (in this review article up to 6-12 months). PIT with D5W also shows a trend of improvement in SNCV and MNCV parameters both before 3 months after the intervention and after 3 months, although not significant. Likewise, the quick-DASH and DML parameters showed a downward trend after PIT with D5W before or after 3 months, although this was also not significant.

The mechanism of perineural injection treatment with a 5% dextrose solution in neuropathy caused by peripheral nerve compression can be divided into mechanical and pharmacological effects. Nerve release through the non-specific effects of fluid pressure can gradually reduce adhesions, increase blood flow, and restore nerve mobility to support the neuroregeneration process.[18,21,22] Glycopenia in perineural tissue can trigger progressive depolarization and increased hyperirritability of nociceptive nerve fibers, which is thought to occur due to reduced effectiveness of the ATPase pump that depends on the

availability of dextrose for ATP synthesis. The administration of dextrose injections plays a role in correcting this local glycopenia, thereby producing an analgesic effect.[23]

Several researchers have proposed that increased glucose, through potential sensorineural mechanisms, stabilizes neural activity or reduces neurogenic inflammation, thereby reducing neuropathic pain. When nerves are in a hypoglycemic environment, histopathological changes occur in the peripheral nerves, along with activation of nociceptive C fibers, with increased noxious signal transduction.[24] The mechanism of action of PIT with dextrose also involves binding to presynaptic calcium channels and inhibition of the release of neurodegenerative peptides, thereby reducing neurogenic inflammation. In addition, this therapy inhibits TRPV1 receptors that are sensitive to capsaicin, which are found in peripheral nerves, ligaments, tendons, and joints. Increased expression (upregulation) of TRPV1 is associated with neuropathic pain, while decreased expression (downregulation) of TRPV1 through D5W can inhibit the release of pro-nociceptive substances such as substance P and calcitonin gene-related peptide (CGRP).[6,25] The addition of glucose can normalize excessive activation in type C nociceptive nerve fibers. Increased extracellular glucose concentration can also cause hyperpolarization in C fibers, thereby stabilizing their activity. Although some cell types, such as chondrocytes or human monocytes, show a negative response to high glucose exposure (25 mM) by increasing the expression of proinflammatory cytokines and experiencing progressive dysfunction, neurons and neuronal stem cells appear to be more tolerant and even require higher glucose levels, up to 40 mM, and react worse to hypoglycemia than hypoxia.[26] PIT causes regression of soft tissue edema, reduction of chronic constriction at the insertion site, restoration of normal nerve growth factor, stimulation of nerve repair, and provides immediate analgesic effects that can last for several hours to several days (7–10).[6]

This study has several limitations. First, this meta-analysis included only a small number of articles because some articles that initially met the PICO criteria were excluded due to lack of clear outcome details. Second, there are no standard guidelines for the management of peripheral neuropathy that can be used as a reference in assessing the efficacy of peripheral neuropathy treatment. Nevertheless, this systematic review and meta-analysis concluded that PIT with dextrose can be considered an adjunct therapy for peripheral neuropathy, which has been shown to improve patients' clinical outcomes.

5. CONCLUSION

Administration of PIT with D5W with a dose of 1-6 ml can be a complementary treatment for peripheral neuropathy which has been proven to improve the clinical condition of patients assessed based on SSS, FSS, VAS, SNCV, MNCV, DML and quick-DASH since after the intervention even up to more than 3 months.

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None

AUTHOR CONTRIBUTIONS

Study conception and design: **GBR, YW**

Literature search, data extraction: **GBR, YW, WOS**

Analysis and interpretation of results: **GBR, NS**

Draft manuscript preparation: **GBR, YW, WOS**

Critical revision of the manuscript: **GBR, YW, WOS, NS**

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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