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Ultrasound-Guided Nerve Hydrodissection for the Management of Carpal Tunnel Syndrome: A Systematic Review and Network Meta-Analysis

KunWook Lee[1*], Jong Mi Park[2*], Seo Yeon Yoon[1], Min Seo Kim[3,4], Yong Wook Kim[1], Jae Il Shin[5,6,7], and Sang Chul Lee[1]

[1]Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, Korea;
[2]Department of Physical Medicine and Rehabilitation, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea;
[3]Cardiovascular Disease Initiative, Broad Institute of Harvard and MIT, Cambridge, MA, USA;
[4]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA;
[5]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea;
[6]The Center for Medical Education Training and Professional Development in Yonsei-Donggok Medical Education Institute, Seoul, Korea;
[7]Severance Underwood Meta-Research Center, Institute of Convergence Science, Yonsei University, Seoul, Korea.

Purpose: Ultrasound-guided nerve hydrodissection has emerged as a potential non-surgical treatment for carpal tunnel syndrome (CTS). The objective of this research was to offer suggestions for optimizing injectables utilized in hydrodissection for the treatment of CTS through a systematic review and network meta-analysis.

Materials and Methods: PubMed, MEDLINE, EMBASE, Cochrane, Scopus, and Web of Science were searched through April 25, 2024. Effect sizes were quantified using standard mean differences within a random-effects model. Effectiveness ranking for each treatment was expressed as the surface under the cumulative ranking curve (SUCRA).

Results: Nine studies with 458 patients with CTS were included. According to SUCRA, 5% dextrose (DW) was the most effective option for the Boston Carpal Tunnel Questionnaire (BCTQ) function at 99.9, 89.8, and 88.8 at 4, 12, and 24 weeks, respectively; for BCTQ symptoms, 5% DW was the most effective option at 99.9 at 4 weeks and platelet-rich plasma at 95.7 and 93.9 at 12 and 24 weeks, respectively. In terms of both BCTQ symptoms and BCTQ function, the 5 cc injection was the most effective, with SUCRA values of 99.5 for both categories. However, the effectiveness of the electrodiagnostic assessment and ultrasound variables was dependent on the type and dose of medication.

Conclusion: Administration of 5% DW showed better results in terms of initial symptom relief and long-term functional recovery compared to other agents, while platelet-rich plasma showed greater long-term symptom improvement; an injection dose of 5 cc showed the greatest benefit. However, additional research is required to establish precise protocols based on disease severity.

Key Words: Carpal tunnel syndrome, ultrasonography interventional, median nerve, treatment outcome

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Co-corresponding authors: Sang Chul Lee, MD, PhD, Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: bettertomo@yuhs.ac and
Jae Il Shin, MD, PhD, Department of Pediatrics, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 00372, Korea.
E-mail: shinji@yuhs.ac

*KunWook Lee and Jong Mi Park contributed equally to this work.
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INTRODUCTION

Carpal tunnel syndrome (CTS) is characterized by compression of the median nerve within the carpal tunnel. It is considered the most prevalent peripheral entrapment neuropathy, with a prevalence ranging from 3.5% to 10.5%.[1] Multiple factors such as edema, tendon inflammation, hormonal changes, and manual activity may contribute to increased compression of the median nerve, leading to symptoms such as hand numbness, pain, paresthesia, or neurological deficits. CTS typically begins with intermittent episodes of paresthesia and hand pain, primarily occurring at night, which gradually become more frequent and may also occur during the day. In later stages of the disorder, gradual loss of sensation and muscle weakness are observed, followed by atrophy of the thenar muscles.[2]

Local steroid injections and similar injectable therapies are widely used for the treatment of CTS. Previously, landmark-guided injections were performed; however, ultrasound-guided injections have recently been recognized to be more effective.[3,4] In addition, a new technique called hydrodissection is emerging as an increasingly popular treatment strategy, as it allows injectable agents to be administered and separated from the surrounding retinaculum and connective tissue under dynamic ultrasound visualization of the median nerve.[5] Typically, a thin 27-gauge needle is inserted into the wrist crease of a patient with CTS in a direction perpendicular or parallel to the median nerve, taking care to avoid major blood vessels or tendons in the carpal tunnel and not to inject directly into the median nerve. The solution is then injected into both the superior and inferior sides of the median nerve to separate it from the flexor retinaculum above and the subsynovial connective tissue below.[5] The decompression and adhesiolysis performed within the carpal tunnel can relieve pressure on the nervi nervorum and vasa nervorum of the median nerve. This process disrupts the nerve injury cycle and promotes healing; consequently, symptoms typically ameliorate in patients with CTS.[6]

Hydrodissection has gained attention as a potential therapeutic option in patients with CTS. Several injectable agents are available, including normal saline (NS), local anesthetics (LAs), corticosteroids, 5% dextrose (DW), and platelet-rich plasma (PRP). However, there is no consensus on the optimal type and volume of solution for hydrodissection. Therefore, this study aimed to perform a systematic review and network meta-analysis of existing randomized clinical trials to provide recommendations for effective injectables used in hydrodissection.

MATERIALS AND METHODS

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[7,8] for conducting and reporting the study. The PRISMA NMA checklist, which outlines the essential components of this study, is provided in Supplementary Material 1 (only online). This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on May 22, 2023 (registration number CRD42023425729). Institutional review board approval was not required.

Search strategy

We systematically searched several databases including PubMed, MEDLINE, EMBASE, Cochrane, Scopus, and Web of Science. Searches were conducted from the launch of the databases until March 16, 2023. An updated search was conducted on April 25, 2024. To obtain additional articles, the reference lists of included studies and review articles were searched. The search strategy was as follows: ("Carpal tunnel syndrome" OR "Wrist pain" OR "Median nerve neuropathy" OR "Median neuropathy" OR "Median mononeuropathy" OR "Median entrapment" OR "Median nerve entrapment" OR "Median nerve neuralgia") AND (hydrodissection OR "Hydro dissection" OR "Hydro Dissections" OR hydrodissections) (Supplementary Material 2, only online).

Inclusion and exclusion criteria

The study followed the Population, Intervention, Comparison, Outcomes, and Study (PICOS) framework to determine the inclusion criteria. Our study consisted of patients diagnosed with CTS, based on clinical symptoms, ultrasound, or electrodiagnostic testing, who underwent treatment with ultrasound-guided perineural injection or hydrodissection. Intervention included an ultrasound-guided perineural injection or hydrodissection using substances such as NS, 5% DW, various steroids (triamcinolone acetonide, betamethasone, and methylprednisolone), PRP, and hyaluronidase. The control group used a different type of injectable than the experimental group, and used ultrasound-guided perineural injection or hydrodissection. Outcomes included the clinical effectiveness of treatment, assessed through measures such as the Visual Analogue Scale and Boston Carpal Tunnel Questionnaire (BCTQ), which includes the Symptom Severity Scale and Functional Status Scale. Additionally, electromyography results, including the distal moter latency (DML) and sensory nerve conduction velocity (SNCV), were examined. Ultrasound scan results measuring the cross-sectional area (CSA) of the median nerve at the carpal tunnel inlet were also considered. The study design included only randomized controlled trials that reported baseline and post-intervention data, or changes in baseline data. Non-human studies, cohort studies, case reports, and studies that did not adhere to the PICOS framework were excluded.

Data extraction and quality assessment

Two reviewers, JMP and KWL, independently extracted the relevant information from the literature using a data extraction table based on the predefined inclusion criteria. Discrepancies were resolved by a third reviewer, SCL, through discussion.

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The components extracted from the included studies were the name of the author, year of publication, study design, sample size, population characteristics (mean age and sex), details of the intervention and control protocols, information on random sequence generation, allocation concealment, blinding, data withdrawals, and primary and secondary outcomes. In situations where the data provided in the studies were unclear or missing, attempts were made to contact the authors to obtain unpublished data that may be available. The revised Cochrane risk of bias tool for randomized trials (RoB2) were used to assess the quality of the included studies. RoB2 evaluates the risk of bias across five domains: the randomization process, deviations from the intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each domain was assessed as having a low risk of bias, intermediate risk of bias, high risk of bias, or no information.[9]

Statistical analysis

Inter-rater agreement analysis using Cohen's kappa was used to examine the consistency of the literature selected by the two reviewers. Statistical analyses were performed using IBM SPSS 25 (IBM Corp., Armonk, NY, USA). The mean and standard deviation (SD) of the change from baseline for the treatment and control groups was calculated. Chapter 6 of the Cochrane Handbook (version 6.4)[10] was consulted to calculate the mean and SD for studies with insufficient data. Effect sizes were measured using standard mean differences and 95% confidence intervals (CIs) in a random-effects model. To assess the inconsistency of treatments in the network, node-splitting analysis was employed. The ranking of the efficacy of each treatment was determined according to the surface under the cumulative ranking curve (SUCRA). Publication bias was evaluated using funnel plot symmetry. Egger's test *p*-value below 0.05 indicated significant publication bias. Network meta-analysis of each outcome was performed using the network package[11,12] in STATA software (version 18.0; Stata Corp LP, College Station, TX, USA), which uses a frequentist approach.

RESULTS

Study identification and characteristics

A flowchart depicting the selection of studies is presented in Fig. 1. Out of 783 studies initially screened, 221 duplicate studies were excluded from the meta-analysis. After considering the titles and abstracts, 344 and 185 papers were excluded, respectively; additionally, 24 out of the 33 remaining studies were excluded for various reasons. In the selection process, two studies were excluded as they were review articles, while one retrospective study was also excluded. Additionally, a study written in a language other than English was excluded. Furthermore, 16 studies were not relevant to hydrodissection and were therefore excluded. Three studies lacked appropriate controls, leading to their exclusion from the analysis. Finally, one additional study was excluded as the report was not retrieved. As a result, nine studies met the criteria and were eventually in-

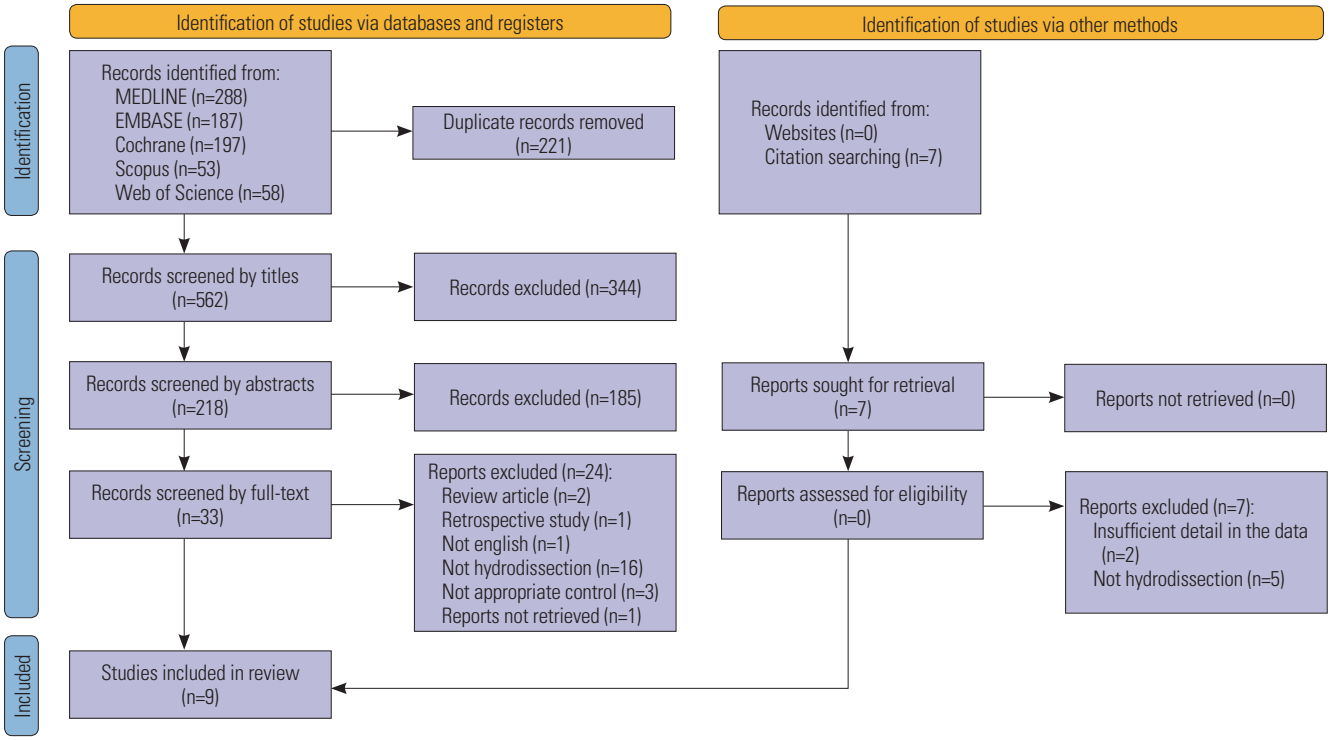

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for screening and selecting the studies.

cluded in the meta-analysis. The degree of agreement in the full-text review was measured using the kappa score, which yielded a value of 0.855, with a standard error of 0.098, indicating an almost perfect agreement between reviewers, and a high level of consensus during the selection process. Our meta-analysis included nine studies and 458 patients with CTS, while the number of participants in each study ranged from 20[13] to 64[14]. The average age of participants ranged from 38.3 years[15] to 60.3 years.[16] All studies included both male and female participants. The follow-up period of the studies ranged from 1 week[15-18] to 6 months.[13-21] Interventions included four studies with steroid injections,[13,14,17,20] five with 5% DW injections,[16,18-21] two with saline injections,[15,20] two with hyaluronidase injections,[15,17] and one with PRP injection.[19] Injectable doses included solutions of 1 cc,[16,18] 2 cc,[16,18] 3 cc,[19] 4 cc,[16,18] 5 cc,[13-15,17,20] or 10 cc.[14,15] Table 1 summarizes the specific characteristics of the included studies.

Risk of bias and publication bias assessment

All nine studies were randomized trials and described the randomization method. Except for one study,[19] most studies were double-blinded to the intervention and placebo groups, thereby reducing the risk of bias away from the intended intervention. Missing outcome bias was reported in two studies[13,19] and was determined as low risk in the remaining seven studies. Four studies[13,15,19,20] were assessed as being at risk of bias in their outcome measures since they included subjective outcome assessments, such as pain and functional disability questionnaires. All but one study[17] were conducted according to a pre-randomized study protocol, thus the bias in the selection of reported results was low. Fig. 2 presents a traffic light diagram illustrating the evaluation of each study included in the assessment. Funnel plots were used to evaluate the publication bias. The funnel plots and Egger's test did not show any significant signs of publication bias (Supplementary Fig. 1, only online). Therefore, the network meta-analysis did not reveal any significant evidence of publication bias.

Evaluation of inconsistency

Except for a few items, we found no statistical inconsistency in most node-splitting analyses (Supplementary Table 1, only online). Owing to these inconsistencies, the network meta-analysis should be interpreted carefully.

Effects by drug type

A network plot of ultrasound-guided nerve hydrodissection by drug type is shown in Fig. 3A, and Supplementary Table 2 (1)–(5) (only online) show the league tables for the network estimates for all comparisons. For the BCTQ symptom, DW had the highest SUCRA value (99.9 at week 4), while PRP had the highest SUCRA values of 95.7 and 93.9 at weeks 12 and 24, respectively, as shown in Fig. 4A. For the BCTQ function, DW was the best, with SUCRA values of 99.9, 89.8, and 88.8, at weeks 4, 12, and 24, respectively, as shown in Fig. 4B. For CSA, NS was the best with a SUCRA value of 80.9; DW was the best with a SUCRA value of 98.3 for SNCV evaluation; PRP was the best with a SUCRA value of 94.8 for DML evaluation, as shown in Table 2 (1).

Effects of injection volume

A network plot of ultrasound-guided nerve hydrodissection versus injection volume is shown in Fig. 3B, and Supplementary Table 2 (6) (only online) shows the league tables for the network estimates for all comparisons. For both BCTQ symptoms and function, 5 cc injections showed the most favorable results, with SUCRA levels of 99.5 and 99.5, respectively (Fig. 4C, Table 2 (2)).

Subgroup analysis: effects by drug type and injection volume

As the types of injectables and dosing protocols differed between the included studies, we performed subgroup analyses that considered both the type of injectables and the dose to examine the heterogeneity between studies. We defined an injection volume of 4 cc or more as a "large" volume and 2 cc or less as a "small volume." A network plot of ultrasound-guided nerve hydrodissection by injection volume is shown in Fig. 3C, and Supplementary Table 2 (7)–(9) (only online) show the league tables for the network estimates of all comparisons. In the BCTQ symptom and DML assessments, large steroids were the most effective, with SUCRA values of 99.9 and 91.8, respectively. In the BCTQ function and SNCV evaluations, small DW showed the best performance, with SUCRA values of 99.8 and 71.7, respectively. In the CSA evaluation, large NS performed the best, with a SUCRA value of 76.2 (Table 2 (3)).

Safety/adverse events

Six studies[13,16,17,19-21] reported no adverse effects. One study reported that 3.1% of participants experienced mild pain after injection, which resolved spontaneously without treatment.[14] Two of the included studies[15,18] did not mention side effects at all, making it impossible to know if they were present.

DISCUSSION

CTS can be addressed using both nonsurgical and surgical methods. Over time, a considerable percentage of patients (57%–66%) choose to undergo surgery after 1–3 years of nonsurgical treatment.[22] Surgical intervention for CTS yields positive outcomes in 75% of the patients; however, there are potential risks of symptom escalation and revision surgery (12%). Ultrasound-guided injections have emerged as a promising option for the treatment of CTS, showing significant clinical benefits and statistical significance, as they accurately and safely deliver medication to block nerves and reduce the risk of nerve trauma.[23,24] Compared with standard landmark-based peri-

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Table 1. Main Outcomes of the Studies Included in This Systematic Review and Meta-Analysis

Author	Study design	Experimental group (n)	Control group (n)	Age (mean±SD) (experimental/ control groups)	Female (%)	Follow-up duration	Outcome measures	Main findings	Adverse effects
Shen, et al.[19]	Single-blind RCT	3-cc PRP (n=26)	3-cc 5% DW (n=26)	56.8±1.7/ 58.5±2.1	90.4	1, 3, 6 Mo	1. BCTQ (SSS, FSS) 2. SNCV 3. DML 4. CSA	Injection of PRP reduced CSA more effectively compared to injection of 5% DW at 3 and 6 months post-injection for patients with moderate CTS	None
Wu, et al.[20]	Double-blind RCT	5 cc 5% DW (n=27)	3-cc Triamcinolone (10 mg/mL) +2-cc NS (n=27)	58.6±2.2/ 54.3±2.0	79.6	1, 3, 4, 6 Mo	1. VAS 2. BCTQ (SSS, FSS) 3. SNCV 4. DML 5. CSA	The effect of 5% DW injections was greater than that of corticosteroids, and the effect lasts longer	None
Wu, et al.[21]	Double-blind RCT	5 cc 5% DW (n=30)	5 cc NS (n=30)	58.47±2.33/ 58.10±1.93	83.3	1, 3, 6 Mo	1. VAS 2. BCTQ (SSS, FSS) 3. SNCV 4. DML 5. CSA	The 5% DW group showed improvement in all aspects compared to the NS group	None
Schrier, et al.[13]	Double-blind RCT	1-cc Betamethasone (6 mg)+1-cc 1% Lidocaine+3-cc NS (n=11)	1-cc Betamethasone (6mg)+1-cc 1% Lidocaine (n=9)	48.49±20.99/ 60.10±9.33	84.2	1, 6 Mo	1. VAS 2. BCTQ (SSS, FSS) 3. CSA 4. Displacement with finger flexion, and hand flexion	The 5 cc steroid hydrodissection group was not significantly different from the 2-cc steroid group	None
Alsaeid, et al.[17]	Double-blind RCT	3-cc 0.5% Bupivacaine+2-cc Dexamethasone (8 mg) (n=20)	3-cc 0.5% Bupivacaine+2-cc NS+300 units Hyaluronidase (n=20)	40.18±10.5/ 42.76±8.3	52.5	1 wk 1, 3, 6 Mo	1. BCTQ (SSS, FSS) 2. SNCV 3. DML 4. CSA	The hyaluronidase group significantly improved patients with mild to moderate CTS compared to the steroid group	None
Lin, et al.[18]	Double-blind RCT	4-cc 5% DW (n=17) 2-cc 5% DW (n=14)	1-cc 5% DW (n=14)	59.2±8.1/ 52.9±10.1/ 56.9±9.1	88.9	1 wk 1, 3, 6 Mo	1. VAS 2. BCTQ (SSS, FSS) 3. CSA 4. Elasticity 5. Mobility	The high-dose 5% DW group had improved nerve mobility and reduced CSA, but no change in elasticity	Not reported
Lin, et al.[16]	Double-blind RCT	4-cc 5% DW (n=21) 2-cc 5% DW (n=21)	1-cc 5% DW (n=21)	58.4±9.6/ 55.2±10.7/ 60.3±8.6	85.7	1 wk 1, 3, 6 Mo	1. VAS 2. BCTQ (SSS, FSS) 3. SNCV 4. DML 5. CSA 6. Q-DASH	The high-dose 5% DW group showed improvement over the low-dose group in all aspects	None
Wang, et al.[14]	Double-blind RCT	1-cc Triamcinolone acetonide (10 mg) +1-cc 2% Lidocaine+8-cc NS (n=32)	1-cc Triamcinolone acetonide (10 mg) +1-cc 2% Lidocaine (n=32)	52.87±10.19/ 53.28±9.67	81.25	1.5, 3 Mo	1. BCTQ (SSS, FSS) 1. SNCV	The 10-cc group did not show a significant difference in effectiveness compared to the 2-cc group	Two patients reported mild post-injection pain, which resolved spontaneously.
Elawamy, et al.[15]	Double-blind RCT	10-cc NS+1500 units Hyaluronidase (n=30)	10-cc NS (n=30)	40.7±6.5/ 38.3±5.4	56.7	1 wk 1, 3, 6 Mo	1. VAS 2. BCTQ (SSS, FSS) 3. CSA	The hyalase group showed better outcomes in CTS over 6 months of follow-up	Not reported

RCT, randomized controlled trial; PRP, platelet-rich plasma; VAS, Visual Analogue Scale; DW, dextrose; BCTQ, The Boston Carpal Tunnel Syndrome Questionnaire; SSS, symptom severity scale; FSS, functional status scale; SNCV, sensory nerve conduction velocity; DML, distal motor latency; CSA, cross-sectional area; CTS, carpal tunnel syndrome; NS, normal saline.

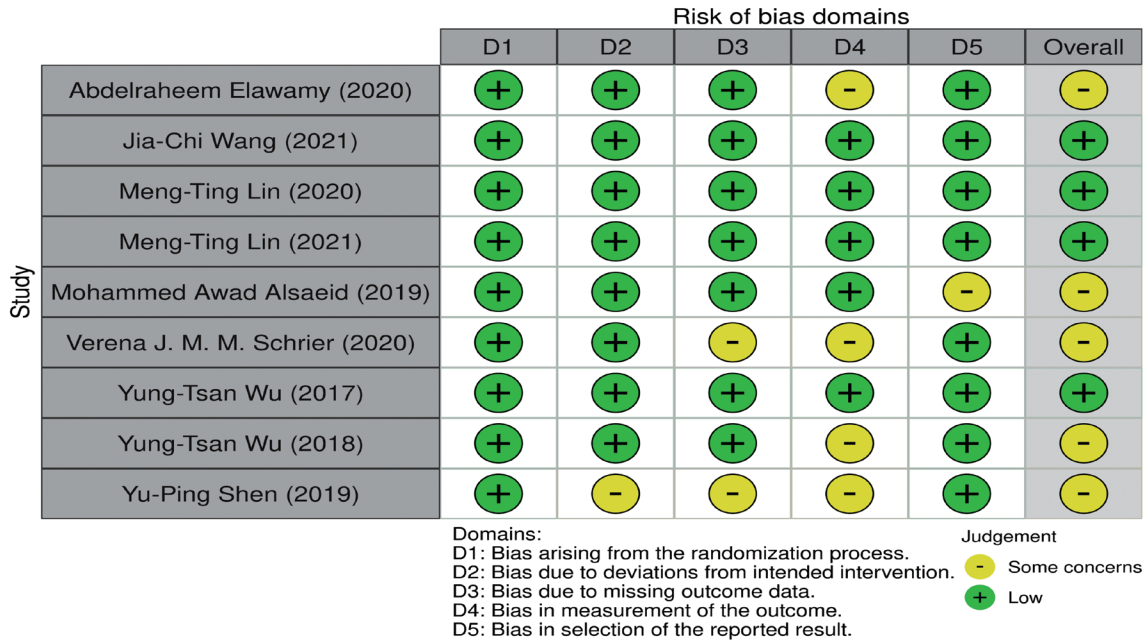

Fig. 2. Risk of bias in the included studies assessed using the Cochrane risk of bias 2.0 tool.

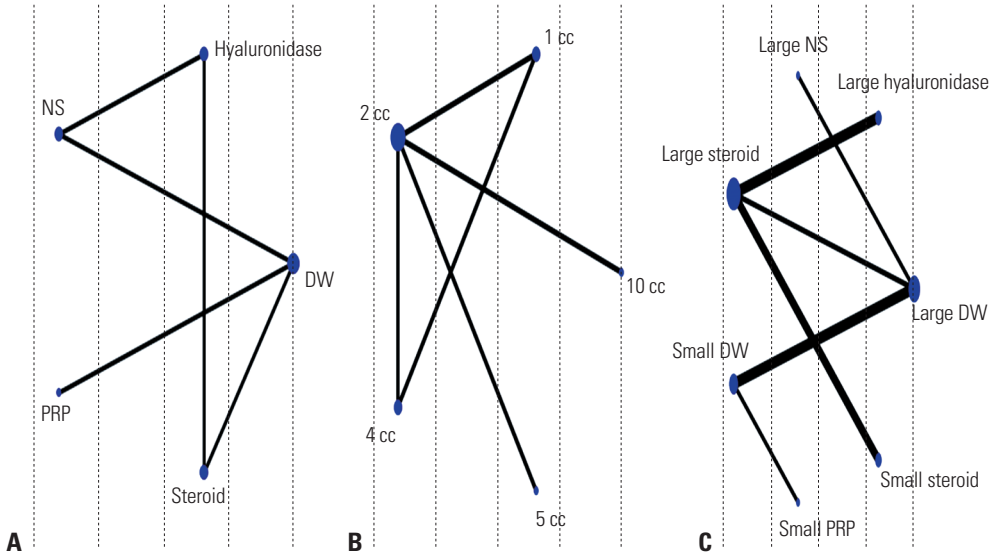

Fig. 3. Network plots of ultrasound-guided nerve hydrodissection treatment of carpal tunnel syndrome (CTS). (A) By drug type. (B) By injection volume. (C) By drug type and injection volume. NS, normal saline; DW, dextrose; PRP, platelet-rich plasma.

neural injections, nerve hydrodissection is considered an advanced technique that should be performed under ultrasound guidance.[25-27] A variety of injectables can be used for ultrasound-guided nerve hydrodissection in patients with CTS, with injection volumes ranging from 1 cc to 10 cc. This treatment is known to improve symptoms through mechanical decompression and the pharmacological effects of injected agent.

Looking first at the mechanical decompression aspect, a small injection into the perineural nerve under ultrasound guidance may theoretically separate the median nerve from the surrounding connective tissue. However, there is no consensus on the dose required to achieve sufficient nerve hydrodissection. Most of the included studies chose an injection volume of 5 cc for carpal tunnel injection, likely stemming from previous cadaveric studies that achieved complete intracarpal median nerve hydrodissection with the same volume.[28] Our analysis of these studies showed that 5 cc was the most effective dose for improving symptoms and function. In contrast, higher doses of 10 cc were less effective in improving symptoms and function, suggesting that increased carpal tunnel pressure is a factor in the pathogenesis of CTS and the 10 cc dose may offset the benefits of nerve hydrodissection by increasing intracarpal

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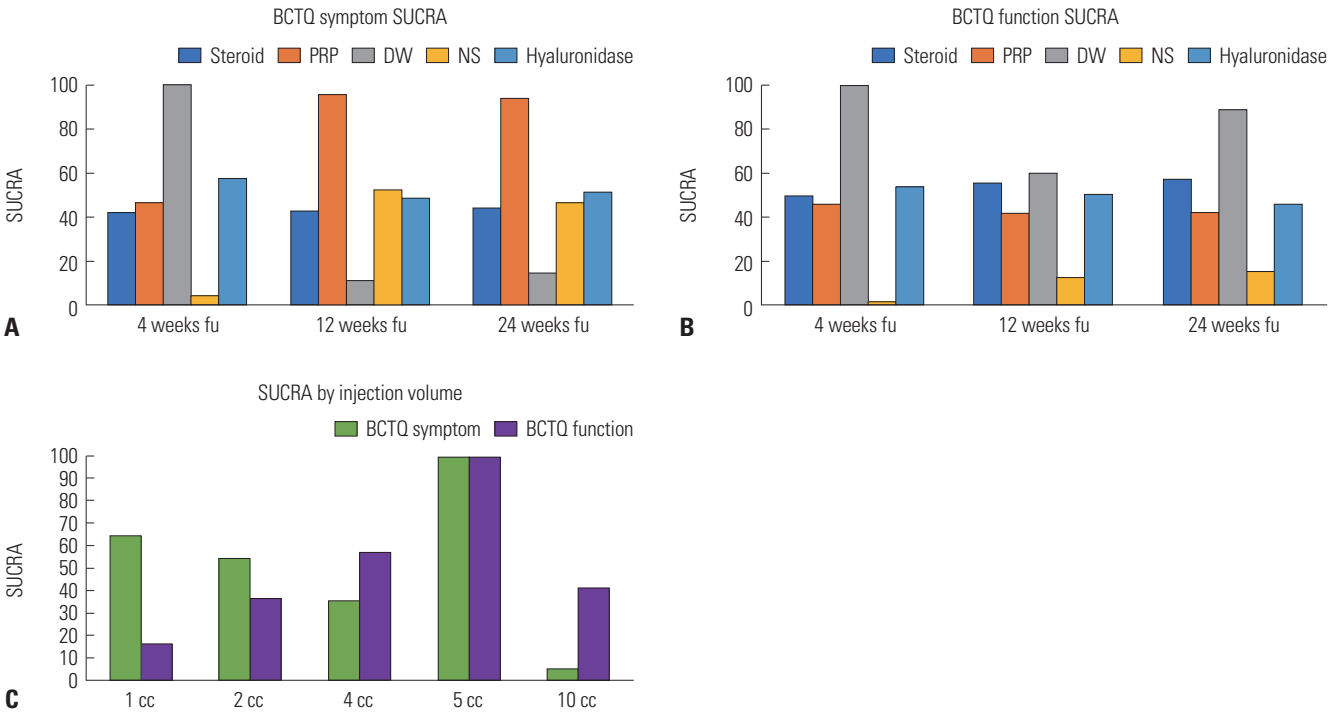

Fig. 4. Surface under the cumulative ranking curve (SUCRA) of ultrasound-guided nerve hydrodissection treatment of CTS. (A) Boston Carpal Tunnel Questionnaire (BCTQ) symptom SUCRA change by drug and follow-up period. (B) BCTQ function SUCRA change by drug and follow-up period. (C) BCTQ symptom and function SUCRA changes by injection volume. NS, normal saline; DW, dextrose; PRP, platelet-rich plasma; CTS, carpal tunnel syndrome.

Table 2. SUCRA Value of Ultrasound-Guided Nerve Hydrodissection Treatment of CTS

(1) SUCRA value by drug

	BCTQ symptom			BCTQ function			CSA	SNCV	DML
	4 weeks	12 weeks	24 weeks	4 weeks	12 weeks	24 weeks			
Steroid	42.1	42.5	43.9	49.4	55.6	57.4	50.2	43.8	51.8
PRP	46.5	95.7	93.9	45.8	42.0	42.5	40.6	60.4	94.8
DW	99.9	11.1	14.5	99.9	89.8	88.8	17.6	98.3	5.1
NS	4.3	52.2	46.7	1.5	12.5	15.5	80.9	29.4	75.1
Hyaluronidase	57.3	48.5	51.1	53.4	50.0	45.8	60.7	18.2	23.2

(2) SUCRA value by injection volume

	BCTQ symptom	BCTQ function
1 cc	64.6	16.3
2 cc	45.4	36.5
4 cc	35.5	56.8
5 cc	99.5	99.5
10 cc	4.9	41.0

(3) SUCRA value by drug type and injection volume

	BCTQ symptom	BCTQ function	CSA	SNCV	DML
Small steroid	61.0	50.8	38.0	41.7	42.8
Large steroid	99.9	63.7	62.5	39.6	91.8
Small DW	30.2	99.8	6.5	71.7	6.4
Large DW	40.5	25.5	67.0	41.3	17.6
Small PRP	19.5	23.1	45.6	62.0	67.7
Large NS	33.3	31.0	76.2	50.9	84.6
Large hyaluronidase	65.7	56.1	54.3	42.9	39.2

SUCRA, surface under the cumulative ranking curve; BTCQ, Boston Carpal Tunnel Questionnaire; NS, normal saline; DW, dextrose; PRP, platelet-rich plasma; CTS, carpal tunnel syndrome; CAS, cross-sectional area; SNCV, sensory nerve conduction velocity; DML, Distal Moter Latency.

tunnel pressure.

The pharmacological effects of each injection are described below.

Five percent DW is an isotonic solution containing 5% DW, specifically D-glucose, at a concentration of 278 mmol/L. However, the exact mechanism by which DW relieves neuropathic pain is not yet fully understood.[20] One hypothesis is that DW may relieve pain by modulating the transient receptor potential vanilloid receptor 1 (TRPV-1), which is often upregulated during chronic neuropathic pain.[29] Another mechanism involves the reversal of the hypoglycemic state that causes excessive C-fiber activation.[30] Consequently, the 20th edition of Harrison's Principles of Internal Medicine officially included this method as an alternative treatment against CTS.[31] In this study, DW resulted in early (4 weeks) symptomatic and long-term (4, 12, and 24 weeks) functional improvement.

PRP is a component of autologous blood with a high concentration of platelets compared to baseline before centrifugation. When activated, platelets release various mediators, including growth factors and cytokines.[32] Growth factors, such as the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF-1) are crucial for promoting axonal nerve regrowth and angiogenesis.[33] In this study, PRP resulted in long-term symptom improvement after 12 and 24 weeks, suggesting that the regenerative mechanism of PRP contributes to long-term symptom improvement rather than initial symptom improvement. However, PRP is generally more expensive than other injectables for several reasons. The cost of PRP involves drawing blood from the patient, centrifuging it to concentrate the platelets, and then preparing it for injection. This process requires specialized equipment and trained personnel, which increases the cost. On the other hand, 5% DW is a simpler and less expensive solution to prepare and administer. Although the high cost may be a barrier to the use of PRP, previous studies have reported that PRP is more cost-effective than methylprednisolone/triamcinolone injections due to its long-term effects.[34] Therefore, a full cost-effectiveness analysis of PRP versus 5% DW should be performed to guide the choice in future clinical practice.

Corticosteroids and LAs are commonly administered via ultrasound-guided injections for CTS due to their strong anti-inflammatory properties. They relieve pain by inhibiting cytokines, reducing inflammatory mediators, and preventing the recruitment and activation of inflammatory cells.[35] Particulate forms, such as triamcinolone acetonide, may have a longer duration of action although they may also cause longer post-injection pain.[36,37] Possible adverse effects of corticosteroids include axonal and myelin degeneration, skin thinning, tendon rupture, soft tissue atrophy, steroid flares, crystal-induced synovitis, and hot flushing.

LAs are frequently combined with steroids as primary pain-relieving agents during procedures.[38] LAs block voltage-gated sodium channels in axons, specifically those involved in pain perception, such as Aδ-fibers and C-fibers. Lidocaine, with a low pKa of 7.9, acts quickly, has moderate hydrophilicity, and provides pain relief for approximately 1 to 2 hours. In contrast, bupivacaine, has a higher pKa (8.1), a slower onset, a longer duration of action, and greater potency.[39,40]

Hyaluronidase is an enzyme isolated from mammalian tissues or produced as a recombinant protein. It acts as a mucolytic agent by reducing the viscosity of hyaluronan, a component of the extracellular matrix. This increased tissue permeability renders it useful in hydrodissection procedures as it helps the release of entrapped nerves by acting as an adhesiolytic agent.[41]

NS is unlikely to have a pharmacologic effect, a previous meta-analysis showed that patients with low back and lower extremity pain who received saline injection into the epidural space experienced pain relief and improved functional status.[42] This is thought to be due to high doses of saline removing or diluting chemical irritants that are locally concentrated around spinal nerve roots.[43] Therefore, in patients with CTS, saline injections are thought to have a pharmacologic effect in combination with physical nerve hydrodissection.

The main strength of this study is that it is the first quantitative network meta-analysis to identify the effects of various ultrasound-guided nerve hydrodissection treatments on symptoms, function, electromyographic variables, and ultrasound variables in patients with CTS. Until now, most studies on peripheral nerve entrapment have been narrative reviews,[40,44-46] making it difficult to compare treatments. A network meta-analysis published in 2020 found 5% DW and PRP to be superior, but there was no analysis of dose.[47] This study provides an analysis of effectiveness and dose by treatment type to help clinicians make better CTS treatment choices.

The first limitation of this study was the small number of studies included in the analysis and the small number of studies in one arm of each network plot. We were unable to perform additional statistical analyses, Egger's test, and meta-regression, due to having fewer than 10 included studies.[10] The second limitation was the inclusion of two papers each from research groups led by Wu, et al.[20,21] and Lin, et al.,[16,18] which limited the generalizability of the results. The third limitation was that CTS can be categorized as mild, moderate, or severe based on electrodiagnostic test results,[48] and treatment effects may differ for each stage; however, this network meta-analysis did not consider disease severity.

To address these limitations, future studies should include larger sample sizes and divide patients by symptom severity to determine the effect of nerve hydrodissection on a variety of variables, including symptoms and function, as well as the length of surgical delay by meta-regression methods as well as subgroup analysis. In addition, since different injectables have different costs, cost-effectiveness analyses of long-term treatment should be performed to establish protocols that allow clinicians to adapt treatment options based on patient char-

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acteristics.

This systematic review found that ultrasound-guided nerve hydrodissection with various injectable agents is effective and has fewer side effects. The use of 5% DW showed superior results in terms of initial symptom relief and sustained functional recovery compared to other substances. In addition, an injection dose of 5 cc produced the greatest effect. However, there was still heterogeneity in the effects of injectable type and dose on electrodiagnostic assessment and ultrasound variables. Therefore, further research is needed to establish precise treatment protocols based on disease severity.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: Jong Mi Park and Sang Chul Lee. Data curation: KunWook Lee and Jong Mi Park. Formal analysis: KunWook Lee and Jong Mi Park. Investigation: KunWook Lee and Jong Mi Park. Methodology: KunWook Lee and Jong Mi Park. Project administration: KunWook Lee and Jong Mi Park. Resources: KunWook Lee and Jong Mi Park. Software: KunWook Lee and Jong Mi Park. Supervision: Sang Chul Lee and Jae Il Shin. Validation: KunWook Lee and Jong Mi Park. Visualization: KunWook Lee and Jong Mi Park. Writing—original draft: KunWook Lee and Jong Mi Park. Writing—review & editing: all authors. Approval of final manuscript: all authors.

ORCID iDs

KunWook Lee https://orcid.org/0009-0003-7247-2496
Jong Mi Park https://orcid.org/0000-0003-4272-7489
Seo Yeon Yoon https://orcid.org/0000-0002-0365-2923
Min Seo Kim https://orcid.org/0000-0003-2115-7835
Yong Wook Kim https://orcid.org/0000-0002-5234-2454
Jae Il Shin https://orcid.org/0000-0003-2326-1820
Sang Chul Lee https://orcid.org/0000-0002-6241-7392

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