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Systematic Review

Interventional Treatments for Postherpetic Neuralgia: A Systematic Review

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Background: Postherpetic neuralgia, a persistent pain condition often characterized by allodynia and hyperalgesia, is a deleterious consequence experienced by patients after an acute herpes zoster vesicular eruption has healed. The pain associated with postherpetic neuralgia can severely affect a patient's quality of life, quality of sleep, and ability to participate in activities of daily living. Currently, first-line treatments for this condition include the administration of medication therapies such as tricyclic antidepressants, pregabalin, gabapentin, and lidocaine patches, followed by the application of tramadol and capsaicin creams and patches as second- or third-line therapies. As not all patients respond to such conservative options, however, interventional therapies are valuable for those who continue to experience pain.

Objective: This review focuses on interventional therapies that have been subjected to randomized controlled trials for the treatment of postherpetic neuralgia, including transcutaneous electrical nerve stimulation; local botulinum toxin A, cobalamin, and triamcinolone injection; intrathecal methylprednisolone and midazolam injection; stellate ganglion block; dorsal root ganglion destruction; and pulsed radiofrequency therapy.

Study Design: Systematic review

Setting: Hospital department in Taiwan

Methods: Search of PubMed database for all randomized controlled trials regarding postherpetic neuralgia that were published before the end of May 2017.

Results: The current evidence is insufficient for determining the single best interventional treatment. Considering invasiveness, price, and safety, the subcutaneous injection of botulinum toxin A or triamcinolone, transcutaneous electrical nerve stimulation, peripheral nerve stimulation, and stellate ganglion block are recommended first, followed by paravertebral block and pulsed radiofrequency. If severe pain persists, spinal cord stimulation could be considered. Given the destructiveness of dorsal root ganglion and adverse events of intrathecal methylprednisolone injection, these interventions should be carried out with great care and only following comprehensive discussion.

Limitations: Although few adverse effects were reported, these procedures are invasive, and a careful assessment of the risk-benefit ratio should be conducted prior to administration.

Conclusion: With the exception of intrathecal methylprednisolone injection for postherpetic neuralgia, the evidence for most interventional procedures used to treat postherpetic neuralgia is Level 2, according to "The Oxford Levels of Evidence 2". Therefore, these modalities have received only grade B recommendations. Despite the lack of a high level of evidence, spinal cord stimulation and peripheral nerve stimulation are possibly useful for the treatment of postherpetic neuralgia.

Key words: Interventional treatment, postherpetic neuralgia, botulinum toxin, steroid, stellate ganglion block, peripheral nerve stimulation, paravertebral block, radiofrequency, spinal cord stimulation

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Postherpetic neuralgia is defined as the occurrence of chronic, persistent, debilitating pain with dermatomal distribution in patients who have recovered from shingles. The pain associated with this condition may be described as aching, itchy, lancinating, or sharp. Additionally, patients with postherpetic neuralgia frequently experience allodynia, hyperalgesia, areas of anesthesia, and deficits in thermal, tactile, pinprick, or vibration sensations within or extending beyond the margins of the affected dermatomes. Generally, the risk of developing persistent severe pain is fairly low among primary care patients who have recovered from a herpes zoster infection. At 3months after the onset of shingles, patients aged < 60 years have a 1.8% risk of postherpetic neuralgia, whereas patients aged > 60 years have risks of 3.3% after 12 months (1). Despite the low probability, however, severe postherpetic neuralgia is considered intolerable by the affected patients.

Currently, postherpetic neuralgia is initially treated with medication. The European Federation of Neurological Societies presents Level A evidence for both first- and second-line medication therapies, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, pregabalin, gabapentin, tramadol, capsaicin (8%) patches, and lidocaine patches, and the number needed to treat (NNT) of these medication therapies range from 11-25 (2,3). However, patients who experience persistent pain despite conservative treatment may benefit greatly from interventional therapies. Despite the perceived benefits, to our knowledge, no previous review has focused on the efficacies of interventional procedures for the treatment of postherpetic neuralgia.

To address this paucity of information, the present review aims to briefly describe the interventional procedures currently available for the treatment of postherpetic neuralgia.

Methods

This systematic review followed the recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (4).

Eligibility Criteria

Eligibility criteria are described according to the PICOS (patients, interventions, controls, outcomes, and studies) framework.

Patients

Patients who had postherpetic neuralgia were included.

Interventions

Patients with postherpetic neuralgia received one of the following interventional treatments: injection (such as local injection, peripheral nerve block, neuraxial block and stellate ganglion block), nerve stimulation (such as transcutaneous electrical nerve stimulation, peripheral nerve stimulation and pulsed radiofrequency), spinal cord stimulation and destructiveness of dorsal root ganglion.

Controls

Basic drug treatment without any interventional treatment was considered.

Outcomes

The studies enrolled should include basic information: author, published journals, year of publication, number of cases in each group, study design, and duration of follow-up; and also outcome evaluation with pain status, sleep condition, medication use, and quality-of-life assessment or functional evaluation.

Studies

For each intervention, systematic reviews and meta-analysis were considered first, followed by randomized controlled trials (RCTs), observational studies, and then case series and case reports, if no better evidence was available.

Literature Search

A comprehensive literature search for studies that evaluated the interventional treatments of postherpetic neuralgia was conducted in the PubMed database using the keyword "postherpetic neuralgia." The search was limited to English language studies and clinical trials published before May 2017. Identified studies included those that focused on interventional treatment of postherpetic neuralgia. Relevant studies in review articles, including systematic reviews and meta-analysis, were manually included.

Studies were excluded if 1) they were conducted in healthy volunteers or in patients with a diagnosis other than postherpetic neuralgia; 2) they only evaluated pharmacologic, surgical, or noninterventional treatments; 3) the study methods were not adequately described with regard to study design, intervention, and outcomes; 4) the study results reported for postherpetic neuralgia were combined with those for other pain conditions; or 5) the study results for the primary outcome were only presented graphically and specific pain scores and *P* values were not reported.

Study Selection

After the search, 2 reviewers screened the titles and abstracts of the potentially eligible studies independently and then read the full text of the remaining articles. Any disagreements during the process were resolved by consensus.

Quality Assessment

For RCTs, the internal validity of the included trials was assessed according to the 7 criteria set by the Cochrane Handbook (5): random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias (adequate description of sample size calculation and detailed disclosure of sources of funding). The judgments of bias were expressed as "high risk," "low risk," or "unclear risk" via RevMan 5.3 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark). For case series and case reports, the Joanna Briggs Institute Critical Appraisal Tools were used (6). All disagreements were resolved by consensus.

Results

Study and Patient Characteristics of Included Trials

A total of 219 clinical trials and 65 review articles were identified in the PubMed database using their search criteria. Manual searching identified another 22 trials. After excluding the irrelevant articles defined by our exclusion criteria, 33 studies were included in the review (Fig. 1). The included studies were published between 1999 and 2017 and are summarized in Tables 1-13 (7-39). The risk of bias graph and summary are pre-

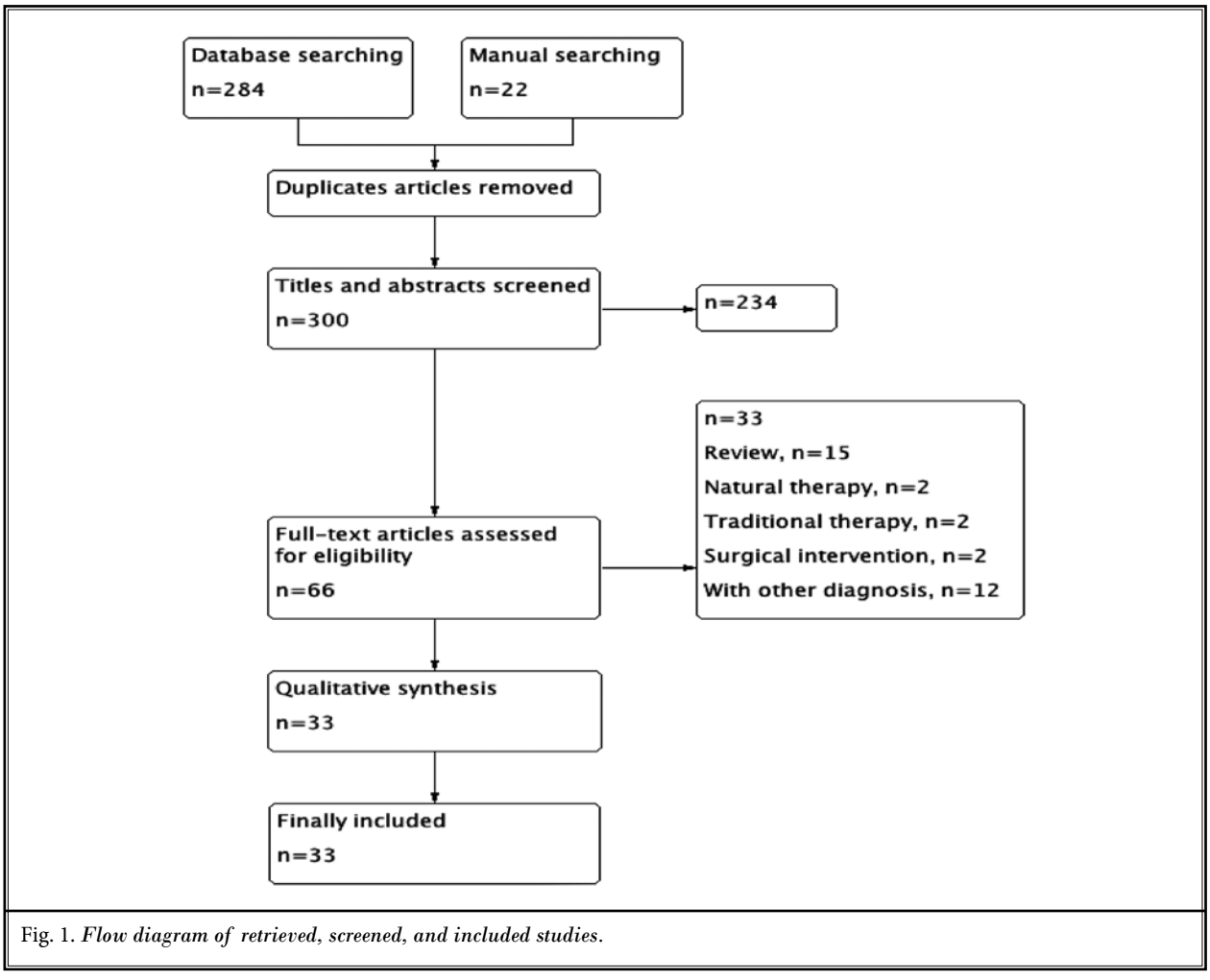

Fig. 1. *Flow diagram of retrieved, screened, and included studies.*

Table 1. *Designs of studies exploring the treatment of postherpetic neuralgia with botulinum toxin A.*

	Study Design	Inclusion Criteria	Groups	n	Route of Administration	Dose of Botox	Outcome	Level of Evidence
Xiao et al (7)	Double-blind placebo RCT	Pain > 3 mos with a VAS score ≥ 5; failure or adverse side effects from nonopioid pharmacotherapy	Botox A, lidocaine, saline solution (placebo)	20, 20, 20	SC	5 U/mL, max 200 IU	VAS: more significant improvement in the Botox group (onset: 3-5 days; peak: 7 days; duration: 3 mos). Sleep time: significantly greater improvement in Botox group. Opioid usage: lower rate in Botox group.	1b
Apalla et al (8)	Parallel, double-blind, and single-dose placebo RCT	Pain > 3 mos, VAS score ≥ 7	Botox A, saline solution (placebo)	15, 15	SC	5 U/route, total 100 IU, diluted with 4 mL of 0.9% saline solution	VAS: 87% of patients have a ≥ 50% reduction in the median time of 7.44 days, with maintenance for 16 wks. Sleep score: significant improvement by wk 2, persists at 4 wks.	1b

Abbreviations: SC, subcutaneous.

Table 2. *Designs of studies exploring the treatment of postherpetic neuralgia with combinations including transcutaneous electrical nerve stimulation.*

	Study Design	Inclusion Criteria	Groups	n	Route of Administration	Dose	Outcome	Level of Evidence
Barbarisi et al (9)	RCT	Patients age: 50-80 yrs, pain > 3 mos, VAS score ≥ 6, SF-MPQ > 20	Pregabalin plus TENS, Pregabalin plus placebo	15, 15	PO pregabalin	TENS: 100 Hz, 125 μs, 30 minutes/day, for 4 wks. Pregabalin: 75-300 mg BID.	VAS: 30%-40% VAS reduction in TENS group (baseline VAS: 40). SF-MPQ: baseline, 20; endpoint, 10-14 (P < 0.00). Sleep interference: baseline, 5.3-5.5; endpoint, 2.3-2.7 (*P* < 0.02).	1b
Xu et al (10)	RCT	Patients age ≥ 50 yrs; pain > 3 mos, VAS score ≥ 4, T6-T10 dermatomes	TENS plus cobalamin, lidocaine, or both cobalamin and lidocaine	30, 30, 30	SC methylcobalamin with or without lidocaine	TENS: 100 Hz, 40-60 mA, 30 minutes/day, 6 day/wk, for 8 wks. Methylcobalamin: 1,000 mcg 1% lidocaine 40 mg	VAS: 63% and 30% of patients had ≥ 30% and ≥ 50% reductions in methylcobalamin groups (OR: 56 vs. lidocaine group). Significant differences in continuous pain, paroxysmal pain, and allodynia scores in methylcobalamin group (*P* < 0.05). Lower ADL and QOL scores and higher EQ-VAS scores in methylcobalamin group (*P* < 0.05).	1b
Ing et al (11)	RCT	Refractory postherpetic neuralgia	TENS or sham group	10, 10	Not mentioned	TENS-TBM: 15 minutes/day, 3-7 day intervals.	NPSS: 39.9% reduction in average (*P* < 0.001).	1b

Abbreviations: ADL, activities of daily living; BID, twice a day; EQ-VAS, EuroQoL visual analog scale; OR, odds ratio; PO, orally; QOL, quality of life; SC, subcutaneous; SF-MPQ, short-form McGill Pain Questionnaire; TBM, Tennant Biomodulator; TENS, transcutaneous electrical nerve stimulation.

Table 3. *Designs of a study of transcutaneous electrical nerve stimulation as a preventive measure against postherpetic neuralgia.*

	Study Design	Inclusion Criteria	Groups	n	Route of Administration	Dose	Outcome	Level of Evidence
Stepanovic et al (12)	Multicenter prospective RCT	New onset of herpes zoster	TENS, antivirus, TENS plus antivirus, and control	36, 71, 77, 38	Brivudine 125 mg QD for 7 days (n = 141), Valacyclovir 1 g TID for 7 days (n = 7)	TENS: 20-40 Hz, 0.02 ms, 3-30 mA, 30 minutes/day, 10-15 sessions	Pain: lower with treatment than with control (OR: 0.89, P = 0.001).	1b

Abbreviations: OR, odds ratio; QD, once per day; TENS, transcutaneous electrical nerve stimulation; TID, 3 times per day.

Table 4. *Design of a study of local triamcinolone injection for the treatment of postherpetic neuralgia.*

	Study Design	Inclusion Criteria	Groups	n	Route	Dose	Outcome	Level of Evidence
Amjad and Mashhood (31)	RCT	Patient age: 40-80 yrs, pain > 1 mo	Triamcinolone-lidocaine, or lidocaine alone	30, 30	SC	(QOW*3)	63.3% and 83.3% of patients have > 50% reduction in pain at 6 and 12 wks (P < 0.001).	1b

Abbreviations: QOW*3, once every 2 weeks for 3 times; SC, subcutaneous.

Table 5. *Designs of studies using intrathecal injection to treat postherpetic neuralgia.*

	Study Design	Inclusion Criteria	Groups	n	Route	Dose	Outcome	Level of Evidence
Kikuchi et al (14)	RCT	Intractable PHN (pain > 1 yr)	IT MP, epidural MP	14, 15	IT, epidural	IT: 3 mL of 2% lidocaine and 60-mg MP; epidural: 5 mL of 2% lidocaine and 60-mg MP (QW*4)	≥ 50% global pain relief: IT 92.3% vs. epidural 16.7% (P < 0.01). Persistent reductions in pain, lancinating pain, and allodynia for 24 wks in IT group (P < 0.005). Reduced areas of maximum pain and allodynia in IT group (P < 0.005).	1b
Kotani et al (13)	RCT, blinded	Intractable PHN (pain > 1 yr)	MP-lidocaine, lidocaine, and no treatment	89, 91, 90	IT	3 mL of 3% lidocaine, 60 mg of MP (QW*4)	≥ 50% global pain relief, with 91% reduction in MP-lidocaine group for 2 yrs (P < 0.001). Greater improvement in the severity of burning and lancinating pain, allodynia, and areas of maximal pain and allodynia in the MP-lidocaine group for 2 yrs (P < 0.001).	1b
Dureja et al (16)	RCT	PHN with lumbar dermatomes of 3-6 mos duration	Epidural MP, IT midazolam, epidural MP-IT midazolam	50, 50, 50	Epidural, IT	Epidural: 60-mg MP in 10 mL of NS; IT: 2-mg midazolam in 2 mL of preservative-free solvent	VAS for pain and allodynia: ~ 50% pain relief in both IT midazolam groups for 3 wks; persistent relief only in MP-midazolam group for 12 wks. ≥ 50% global pain relief persists for 12 wks in MP-midazolam group (P < 0.05). Significant reduction in analgesic use and better quality of sleep in MP-midazolam group.	1b
Rijsdijk et al (15)	RCT	Intractable PHN (pain > 6 mos), VAS score ≥ 4	MP-lidocaine and lidocaine alone	6, 4	IT	MP 60 mg and lidocaine 60 mg or lidocaine 60 mg only (QW*4)	VAS scores for global pain and lancinating pain decreased significantly in lidocaine group. Analgesic use unchanged. *The trial was stopped because of safety concerns and futility of IT MP.	1b

Abbreviations: IT, intrathecal; MP, methylprednisolone; NS: normal saline solution; PHN, postherpetic neuralgia; QOW*4, once every 2 weeks for 4 times.

Table 6. *Design of a study using stellate ganglion block to treat an acute facial herpetic eruption.*

	Study Design	Inclusion Criteria	Groups	n	Route of Administration	Dose	Outcome	Level of Evidence
Makharita et al (17)	RCT, double-blind trial	Facial herpetic eruption of < 2 wks duration, antiviral therapy, patient age > 50 yrs	8-mL saline solution or bupivacaine-dexamethasone	30, 31	Fluoroscopy-guided stellate ganglion injection	6-mL bupivacaine 0.125% plus 8-mg dexamethasone (total: 8 mL)	Reduced VAS ($P < 0.05$), pregabalin dose ($P < 0.01$), and acetaminophen dose ($P < 0.05$) in the treatment group for 6 mos.	1b

Table 7. *Design of a study of the use of dorsal root ganglion destruction to treat postherpetic neuralgia.*

	Study Design	Inclusion Criteria	Groups	n	Route of Administration	Dose	Outcome	Level of Evidence
Chun-jing et al (32)	RCT, parallel group	PHN > 12 wks, VAS score ≥ 4	Dexamethasone or Adriamycin plus dexamethasone	36, 36	Fluoroscopy-guided injection of 3-5 DRG segments	2.5-mg dexamethasone, 1-mL 0.25% Adriamycin	Lower VAS and SF-MPQ in Adriamycin group for 6 mos ($P < 0.05$).	1b

Abbreviations: PHN, postherpetic neuralgia; DRG, dorsal root ganglion; SF-MPQ, short-form McGill Pain Questionnaire.

Table 8. *Design of a study of pulsed radiofrequency for the treatment of postherpetic neuralgia.*

	Study Design	Inclusion Criteria	Groups	n	Route of Administration	Dose	Outcome	Level of Evidence
Ke et al (18)	Double-blinded RCT	Refractory PHN > 6 mos, VAS score > 3	PRF, or sham group	48, 48	Fluoroscopy-guided, the lesion of one segment and the nearby DRG	42°C, 120 seconds, twice for the same level (frequency-only sensory mode 50 Hz was mentioned) (QW*3)	Greater improvement of VAS for 6 mos ($P < 0.0001$) and SF-36 score ($P < 0.05$), and lesser analgesic dosage ($P < 0.001$) in PRF group.	1b
Pi et al (19)	RCT	PHN, VAS score > 5, lower back	PRF plus PO medication or PO medication only	64, 64	Ultrasound-guided paravertebral puncture	42°C, 240 seconds, 3-4 times, 2 Hz, pulse width: 20 Ms, 26-56 V (frequencies: sensory mode, 50 Hz, 0.4 V; sport mode, 2 Hz, 0.8 V) (once only)	Greater improvements in VAS and PSQI scores and reduced morphine consumption for 2 mos in PRF group ($P < 0.05$). Higher efficacy rate in PRF group ($P < 0.015$).	1b
Saxena et al (20)	Double-blinded RCT	PHN, VAS score ≥ 3, T3-T11	PRF plus PO pregabalin or PO pregabalin	30, 30	Fluoroscopy-guided in 3 consecutive intercostal spaces	42°C, 180 seconds, QOW (frequency and voltage were only mentioned for sensory and motor threshold at 50 Hz, 0.8 V and 2 Hz, 2 V, respectively)	Higher efficacy rate in PRF group at 1 wk, persisted for 4 wks ($P < 0.001$). Greater improvements in VAS, NRS sleep, and GPE scores at 2 wks in PRF group.	1b
Wang et al (21)	Single-blinded RCT	PHN > 3 mos, VAS score > 5, thoracic to lumbar	PRF plus PO medication or PO medication only	30, 30	Ultrasound-guided; lesion in one segment and adjacent DRG	42°C, 180 seconds, twice (frequency and voltage not mentioned)	Greater pain relief and lower SF-MPQ and NRSSIS scores in PRF group at 2 days ($P = 0.001$).	1b

Abbreviations: DRG, dorsal root ganglion; GPE, global perceived effect; NRS, numeric rating scale; NRSSIS, Numeric Rating Scale Sleep Interference Score; PHN, postherpetic neuralgia; PO, orally; PRF, pulsed radiofrequency; PSQI score, Pittsburgh Sleep Quality Index; QW*3, weekly for 3 times; QOW, once every 2 weeks; SF-MPQ, short-form McGill Pain Questionnaire. {

Table 9. *Characteristics of studies in which postherpetic neuralgia was treated with spinal cord stimulation.*

	n	Type of Study	Localization	Setting of Stimulation	Outcome	Level of Evidence
Harke et al (23)	28	Case series (patients with preserved sensory function)	Range from C2-S1	Pulse width: 90-450 ms; frequency: 50-130 Hz; current: 1-6 V (9 generators needed to be changed because of flat batteries after 2 yrs continuous stimulation)	Before: VAS scores, 7-10/10. After: Long-term responders: VAS, 1/10 until 29-mo follow-up (23/28), normalized PDI scores, completely removed/significantly reduced analgesic, corticosteroid, and anticonvulsant use. Short-term responders: average VAS 1 → 7 after 8 mos (5/28).	4
Moriyama (24)	14	Case series (refractory even to CEB)	Range from T3-T10	Initial: pulse width, 210 μs; frequency, 50 Hz; current, 3.8-8.2 V. Adjustment: pulse width, 450 μs; frequency, 20-80 Hz; current, 3.8-8.2 V. (Lead placement: stimulus sensation sites overlapped pain areas at the second to fourth corpus vertebra on the cranial side of herpes zoster dermatomes)	Before: VAS scores 60-100 (mean = 89). After CEB: VAS 34-100 (mean = 68). After SCS: VAS 0-48 (mean = 14), opioid cessation. Adverse effects: hypotension (3/14), ischuria (7/14).	4
Iseki et al (22)	2	Case series (subacute herpes zoster, 2 mos)	T3 (responsive to CEB, barbiturate, and ketamine; refractory to lidocaine and morphine) → spinal cord to central nerve level	Pulse width: 210 ms; frequency: 15 Hz; current: 3 V (Lead placement: tip at T1, end at T3)	Before: VAS scores 8/10, gabapentin 600 mg/day, amitriptyline 10 mg/day with drowsiness. After 1-wk treatment: VAS 1-2/10 (discharge with gabapentin 300 mg/day and amitriptyline 10 mg/day; gabapentin 300 mg/day 1 y later).	4
			T3-4	Pulse width: 210 ms; frequency: 5 Hz; current: 6 V (Lead placement: tip at lower edge of C7, end at upper edge of T2)	Before: VAS score 8/10, gabapentin 600 mg/day with dizziness and drowsiness. After 10-day treatment: VAS 1-2/10 (discharge with gabapentin 300 mg/day), duration of up to 1 yr.	
Baek et al (33)	11	Case series	Range from C5-L2 (those with permanent SCS: C5-L1)	— Those with > 50% reduction in pain receive permanent SCS (4/11)	Before: VAS score 8/10. After permanent SCS: VAS 1.5-2.9/10.	4
Yanamoto and Murakawa (34)	33	Case series	— (cervical: 5; thoracic: 28)	—	Before: average VAS score of 6.8. After: average VAS 3.8 (63.3% persisted > 6 mos).	4
Liu et al (35)	6	Case series*	Range from T6-T12	DREZotomy after confirmed SCS for 1 wk. SCS settings: 50-150 Hz, 2.8-5.4 V, 150-500 μs.	Before: average VAS score 8.4. After: average VAS 2.4 (persists for 1 y).	4

Abbreviations: CEB, continuous epidural blocks; DREZotomy, dorsal root entry zone lesion; PDI, pain disability index; SCS, spinal cord stimulation.
**Patients ultimately underwent DREZotomy guided by spinal cord stimulation.*
—No details were mentioned in the study.

Table 10. *Characteristics of cases using peripheral nerve stimulation to treat intractable postherpetic neuralgia.*

	n	Target Sites	Setting of Stimulation	Outcome	Level of Evidence
Dunteman (36)	2	Ophthalmic division of the trigeminal nerve	Pulse width: 390 μs; frequency: 50 Hz; amplitude: off-3 V (adjusted by the patient)	Before: VAS score 6-8/10. After: VAS 4/10, decreased medication requirement (hydrocodone 1-2 tablets every 2-3 days, complete topical agent cessation), improved sleep and mood.	4
		Ophthalmic division of the trigeminal nerve	Pulse width: 420 μs; frequency: < 55 Hz; amplitude: 1-5 V	Before: methadone 15 mg/day, oxycodone 15-20 mg/day, and daily ice packs. After: cessation of daily ice packs and methadone, reduction in oxycodone use by > 50%.	
Johnson and Burchiel (26)	4	Supraorbital region	—*	After: 50% of patients experience > 50% decrease in pain and decrease in medication use.	4
Yakovlev and Peterson (37)	1	Right subscapular and right paraspinal area of the upper thoracic region	Pulse width: 450 μs; frequency: 60 Hz; amplitude: 3 mA	Before: gabapentin 600 mg Q8H, morphine SR# 15 mg Q12H, and lidocaine topical 5% patch (3 patches worn on affected areas 12 hours on or 12 hours off). After: complete pain relief, cessation of all pain medications (at 6-mo follow-up), and improved sleep and functional status.	5
Kouroukli et al (38)	2	Lateral thoracic region	Pulse width: 180 μs; frequency: 60 Hz; amplitude: 1.9 V	Before: gabapentin 600 mg TID, venlafaxine 75 mg QD, mexiletine 200 mg TID, codeine 30 mg QID, and lidocaine 5% patch (worn on affected areas for 12 hours on or 12 hours off). After: pregabalin 75 mg BID and significant improvements in sleep and functional status at a 3-mo follow-up; cessation of all pain medications at 6-mo follow-up.	4
		Lateral thoracic region	Pulse width: 150 μs; frequency: 60 Hz; amplitude 2 V	Before: gabapentin 800 mg TID, venlafaxine 75 mg QD, and pregabalin 150 mg BID with no significant pain relief. After: complete pain relief, pregabalin 75 mg BID, and improvements in sleep and QOL at 3-mo follow-up.	
Surjya Prasad et al (39)	1	Supraorbital nerve	—*	Persistent 100% pain relief from the first day. Drugs were gradually tapered off within 2 wks. The patient is currently at 8 wks poststimulation with 100% pain relief.	5
Lerman et al (25)	1	Left supraorbital and supratrochlear nerve	Pulse width: 130 μs; frequency: 100-1200 Hz; amplitude: 6.2 mA	Before: VAS score 8/10. After: VAS 1/10 at 9-mo follow-up.	5

Abbreviations: BID, twice a day; Q8H, every 8 hours; Q12H, every 12 hours; QD, once per day; QOL, quality of life; SR, sustained release; TID, 3 times per day.
*No setting details mentioned in the study.

sented in Figs. 2 and 3, respectively. Of the 33 included studies, 20 were RCTs, of which 2 had a parallel design. The majority of the remaining 13 nonrandomized studies were case series.

Of the 20 included RCTs, 17 focused on interventional treatments, such as botulinum toxin A injection (n = 2), cobalamin injection combined with transcutaneous electrical nerve stimulation (n = 1), transcutaneous electrical nerve stimulation (n = 2), local triamcinolone injection (n = 1), intrathecal methylprednisolone injection (n = 4), stellate ganglion block (n = 1), dorsal root ganglion destruction (n = 1), pulsed radiofrequency (n = 4), and peripheral nerve stimulation (n = 1), and interventional prevention methods, such as transcutaneous electrical nerve stimulation (n = 1) and paravertebral blocks (n = 2). The remaining 13 studies included case series of spinal cord stimulation (n = 6) and peripheral nerve stimulation (n = 3), and case reports of peripheral nerve stimulation (n = 3) and paravertebral blocks (n = 1) for interventional treatments.

Table 11. *Design of a study in which postherpetic neuralgia was treated with peripheral nerve adjustment.*

	Study Design	Inclusion Criteria	Groups	n	Technique of Nerve Adjustment	Frequency of Treatment	Outcome	Level of Evidence
Ma et al (27)	Prospective, single-blind RCT	Refractory condition for > 6 mos, VAS score > 3	Blank control group, peripheral nerve adjustment, or positive control	33, 31, 31	Four cannular needles each rotated clockwise and counterclockwise at one 45-degree cycle/s for 2 minutes; cannula remained in place for 24 hours	Twice weekly for 3 wks	In the treatment group: Greater VAS improvement and decreased rescue drug dosage for 1 wk ($P < 0.0001$). Greater improvement in QOL for 2 mos and in SF-36 scores ($P < 0.0001$).	1b

Abbreviations: QOL, quality of life.

Table 12. *Characteristics of a case in which postherpetic neuralgia was treated with repetitive paravertebral block.*

	n	Affected Area	Target Site	Dose	Outcome	Level of Evidence
Naja et al (28)	1	Mainly T1, extending to T4	Single injection at T1-T2 levels under nerve stimulator guidance; paravertebral catheter placement at T3 level	Single injection of bupivacaine 0.5% (19 mL) and clonidine 150 µg/mL (1 mL); repeated injection of same solution QOD for 3 wks.	Before: VAS 7-8/10 with mood changes and sleep disturbance even while using ACT, NSAIDS, tramadol, carbamazepine 1200 mg/day, amitriptyline 30 mg/day, and gabapentin 3600 mg/day. After: pain free during an 8-mo follow-up period.	5

Abbreviations: ACT, acetaminophen; QOD, once every 2 days.

Table 13. *Designs of studies in which paravertebral block was used to prevent postherpetic neuralgia in patients with acute herpes zoster.*

	Study Design	Inclusion Criteria	Groups	n	Dose	Outcome	Level of Evidence
Ji et al (30)	RCT	Herpes zoster-associated pain diagnosed 1-7 days after the onset of rash	Standard group: acyclovir, diclofenac; PVB group: standard treatment plus repeated paravertebral injections	68, 64	PO acyclovir 4000 mg/day for 7 days, PO diclofenac max 200 mg/day, paravertebral 0.25% bupivacaine 10 mL and MP 40 mg QOD*4 injections	Reduced pain and allodynia in PVB group for 1 yr ($P < 0.02$). Reduced diclofenac usage in PVB group ($P < 0.001$). Similar QOL improvement in both groups.	1b
Makharita et al (29)	Double-blind RCT	Herpetic eruption of < 1 wk duration with moderate-to-severe pain	Placebo or single injection of PVB with bupivacaine and dexamethasone	68, 70	PVB with 10-mL saline solution or 25-mg bupivacaine 0.25% plus 8-mg dexamethasone; PO pregabalin 150 mg BID in all patients	Shorter durations of pain ($P = 0.013$), herpetic eruption, and skin healing ($P < 0.001$), reduced PHN after 6 mos ($P < 0.05$), and reduced pregabalin and acetaminophen consumption for 3 wks in PVB group	1b

Abbreviations: BID, twice a day; MP, methylprednisolone; PHN, postherpetic neuralgia; PO, orally; PVB, paravertebral block; QOD*4, once every 2 days for 4 times; ; QOL, quality of life.{

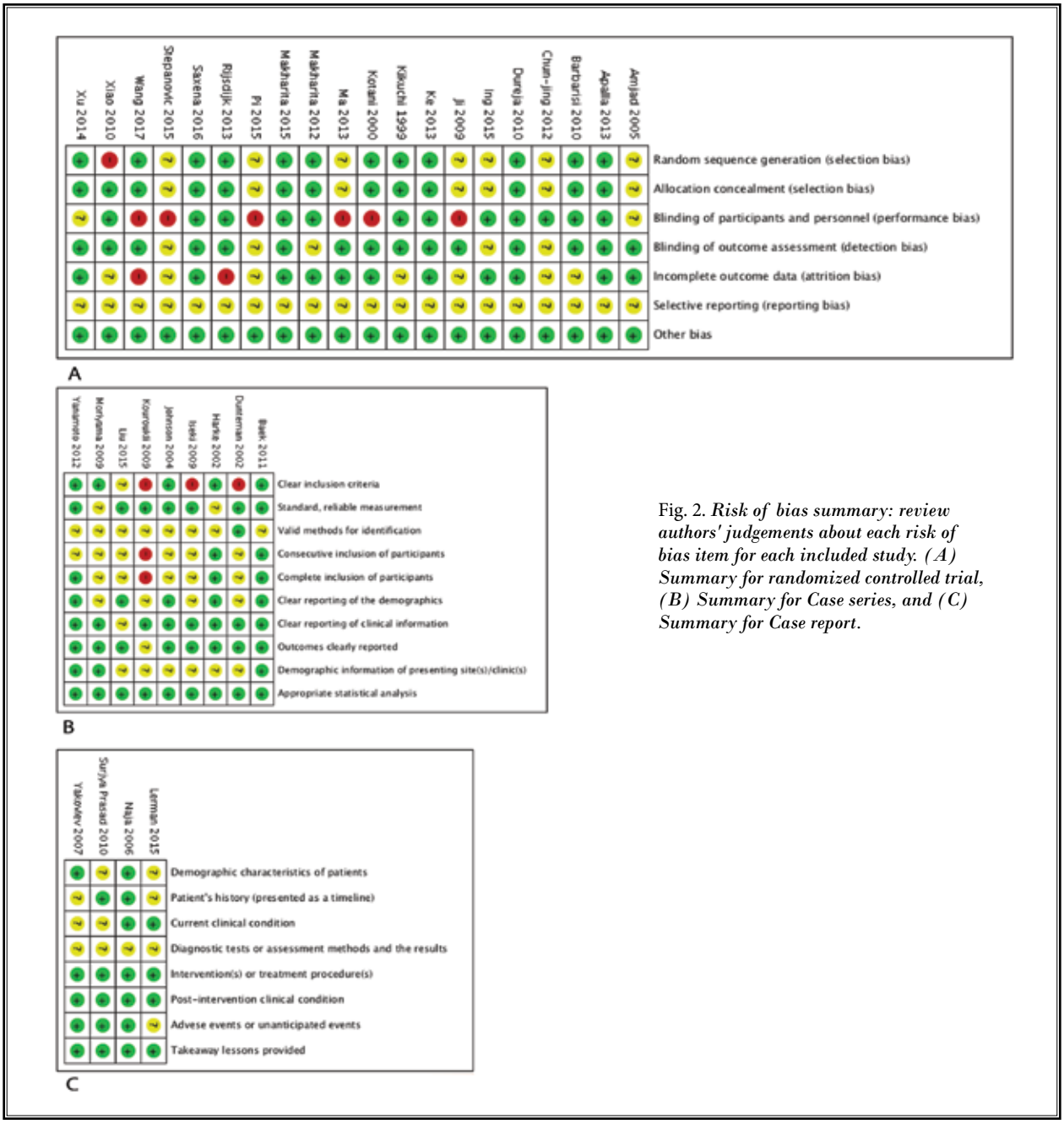

Fig. 2. *Risk of bias summary: review authors' judgements about each risk of bias item for each included study. (A) Summary for randomized controlled trial, (B) Summary for Case series, and (C) Summary for Case report.*

Outcomes Evaluated

Although the included studies evaluated various outcomes, they can be broadly categorized into 5 aspects: pain status (n = 33), medication usage (n = 18), sleep condition (n = 11), function (n = 7), and quality of life (n = 4). The majority of studies evaluated change in pain score as the primary outcome, most of which used a visual analog scale (VAS) or percentage of pain reduction to display the results. The remaining studies used a pain questionnaire (like short-form McGill Pain Questionnaire) or a neuropathic pain scale score (NPSS) as a pain evaluation tool. Medication usage—including opioids, other analgesics, and adjuvant agents—was mentioned in greater detail in case series and case reports. Of the 9 RCTs report-

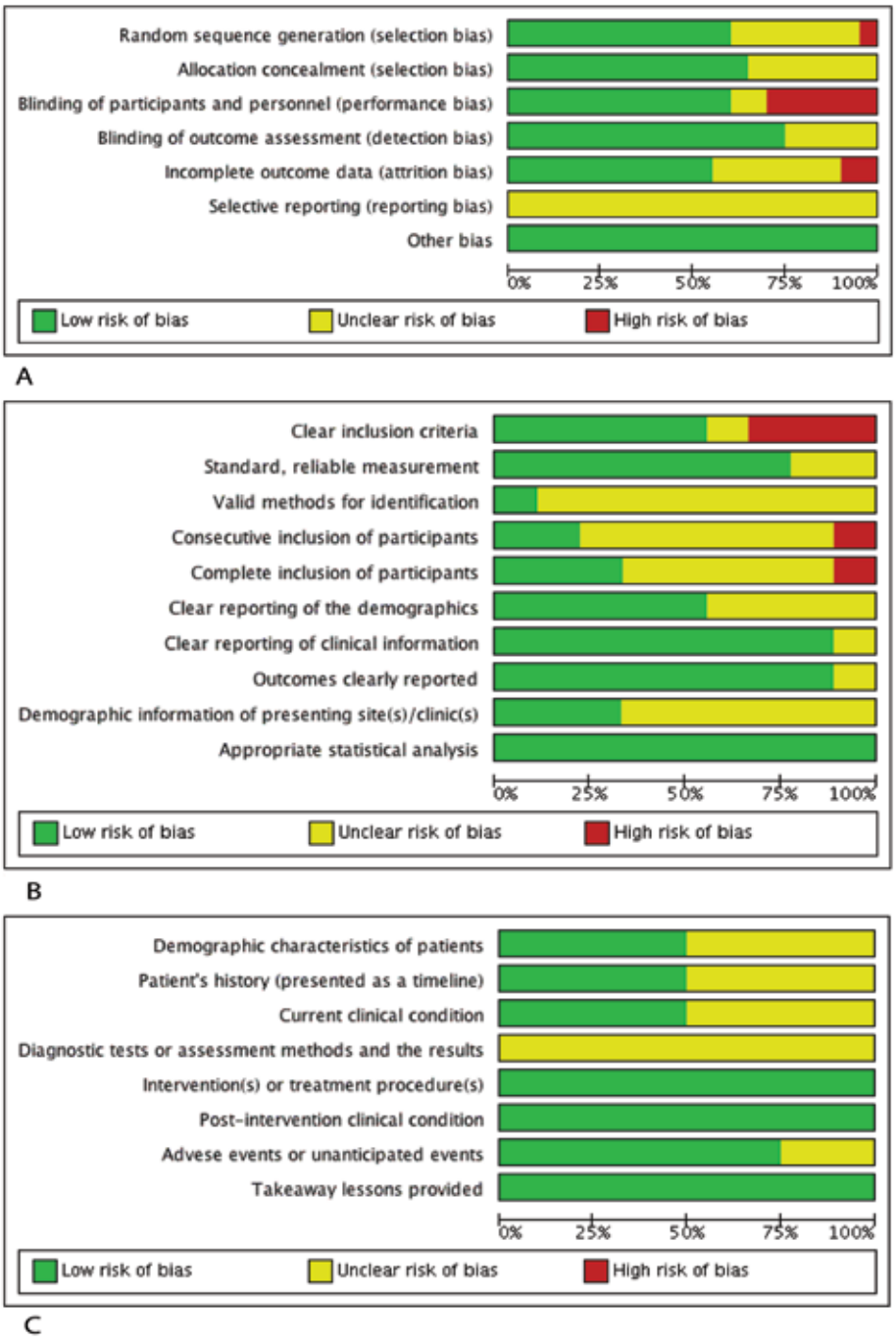

Fig. 3. *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (A) Graph for randomized controlled trial, (B) Graph for Case series, and (C) Graph for Case report.*

ing medication usage, only the average dosage of morphine (n = 1), tramadol (n = 2), nonsteroidal anti-inflammatory drugs (NSAIDs) (n = 2), acetaminophen (n = 4), and pregabalin (n = 2) were noted. Among the studies that evaluated sleep condition, sleep quality, sleep interference, and sleep score were used. Finally, 2 studies used the 36-Item Short Form Health Survey (SF-36) scores for functional evaluation, whereas the other studies that evaluated function or quality of life each used a different evaluation tool.

Subcutaneous Botulinum Toxin A Injection

Botulinum toxin is a neurotoxic protein purified from the bacterium Clostridium botulinum (40). The L chain, which exhibits Zn2+-dependent protease activity, selectively cleaves synaptosomal nerve-associated protein 25 to inhibit the release of neurotransmitters (41), including acetylcholine and substance P from motor and sensory neurons, respectively (42,43). Additionally, botulinum toxin reduces peripheral nociceptive input by inhibiting the release of glutamate (44), a peripheral neurotransmitter involved in neurogenic inflammation.

Two randomized, double-blind, placebo-controlled trials have evaluated the effectiveness of subcutaneous botulinum toxin A injection for persistent moderate-to-severe postherpetic neuralgia (Table 1) (7,8). In these studies, botulinum toxin was injected subcutaneously within a 1- to 2-cm radius over the painful region, and the maximum doses did not exceed 200 and 100 IU in studies by Xiao et al (7) and Apalla et al (8), respectively. The observed benefits in both studies included improved VAS scores and sleep durations and reduced numbers of patients using opioids. These effects emerged at 7 days after injection and persisted for 3 months. Apalla et al (8) reported an NNT of 1.2 for a 50% reduction in the VAS score, which was much smaller than the corresponding values for conservative medical treatments.

Transcutaneous Electrical Nerve Stimulation

The American Physical Therapy Association defines transcutaneous electrical nerve stimulation as the noninvasive and safe application of electrical stimulation to the skin for pain control (45). This therapy produces segmental inhibition in the dorsal horn (46), as well as descending inhibition (47), and stimulates the release of endogenous opioids to relieve pain at both low and high frequencies (48,49).

Previously, 2 RCTs have evaluated the efficacy of transcutaneous electrical nerve stimulation in combination with medication therapies for the treatment of postherpetic neuralgia outside of the facial area. Both studies applied high-frequency transcutaneous electrical nerve stimulation for 30 minutes per day during total periods of 4 to 8 weeks (Table 2). One trial demonstrated that the combination of transcutaneous electrical nerve stimulation with oral pregabalin yielded improvements in VAS scores, sleep interference, short-form McGill Pain Questionnaire total scores, and persistent pain intensity scores after 4 weeks (9). The results of the other trial suggested that transcutaneous electrical nerve stimulation plus the subcutaneous injection of either cobalamin alone or in combination with lidocaine yielded significant improvements in the average reported worst pain intensity, means intensities of continuous and paroxysmal pain, mean allodynia and paresthesia scores, ability to perform activities of daily living, and the health-related quality of life (10). Although the NNTs were 3.3 in the transcutaneous electrical nerve stimulation plus cobalamin group and 4.3 in the transcutaneous electrical nerve stimulation plus cobalamin and lidocaine, no statistically significant difference was observed between the 2 groups.

Yet another RCT evaluated the use of transcutaneous electrical nerve stimulation for the treatment of postherpetic neuralgia (11). In contrast to the 2 aforementioned studies, however, the third study used the Tennant Biomodulator (Biohealth, Germany), a type of self-controlled electronic neuroadaptive regulation device. Notably, the authors documented a significant reduction in the NPSS after 1 week (Table 2). As a combination therapy component, transcutaneous electrical nerve stimulation has also been used to prevent postherpetic neuralgia in patients with acute-stage herpes zoster (12). No articles related to this modality have reported complications (Table 3).

Local Triamcinolone Injection

Peripheral sensitization (50), which involves neural damage and inflammation with subsequent edema consequent to varicella zoster virus reactivation, is among the mechanisms underlying the development of postherpetic neuralgia. In this process, the injured tissue releases inflammatory mediators that reduce the nociception threshold, and thus activate peripheral nociceptors (51). Corticosteroids may ameliorate postherpetic neuralgia by modulating this inflammatory process.

One RCT reported a pain relief rate of 100% among patients with postherpetic neuralgia who were treated with a local (i.e., intralesional) injection of triamcinolone plus lidocaine (Table 4). All patients received 3 injections at 2-week intervals and reported pain relief at weeks 6 and 12; these time points corresponded to significant improvements in pain, as indicated by respective NNT values of 2.1 and 1.3, respectively. However, this extremely high relief rate might be attributable to the exclusion of patients with refractory conditions. Additionally, as the trial was conducted at a military hospital, it remains to be proven whether these improvements are reproducible in other populations.

Intrathecal Injection of Methylprednisolone with Local Anesthetics or Midazolam

Histopathologic studies of patients with postherpetic neuralgia have revealed subacute or chronic inflammatory processes involving the infiltration and accumulation of lymphocytes around the spinal cord (52), suggesting that inflammation may play a role in the development of postherpetic neuralgia. Furthermore, patients with postherpetic neuralgia have relatively higher interleukin-8 (IL-8) concentrations in the cerebrospinal fluid, a factor that was shown to correlate inversely with the duration of postherpetic neuralgia. A possible anti-inflammatory role for methylprednisolone is further supported by the ability of intrathecal methylprednisolone administration to reduce the IL-8 concentration (13).

Three RCTs have investigated the effectiveness of intrathecal methylprednisolone for intractable postherpetic neuralgia (Table 5) (13-15), which is defined as persistent pain regardless of the use of antidepressants, anticonvulsants, NSAIDs, epidural local anesthetics, topical agents, and physical therapy. The earliest RCT that was published by Kikuchi et al (14) compared the intrathecal versus epidural injection of methylprednisolone and found that the former reduced pain by > 50% in most patients at either 4 or 24 weeks after injection. The largest RCT, published in 2000, also reported promising outcomes (13); here, although intrathecal lidocaine significantly relieved pain by > 50% at the end of treatment, intrathecal methylprednisolone yielded superior pain relief both at the end of the treatment and after 2 years. In both studies, the injections were administered once weekly for 4 weeks, and the NNT for intrathecal methylprednisolone was 2. By contrast, the most recent RCT of this modality was terminated because of safety concerns and futility by the sixth patient in the treatment group (15), and differences in baseline characteristics (e.g., VAS score and age) between the 2 groups were evident because of the small sample size and may have confounded the results.

Preservatives are of considerable concern in all drug treatment studies. In the study by Kikuchi et al (14), the 60-mg methylprednisolone dose contained 43.5 mg of polyethylene glycol and 0.3 mg of myristyl-gamma-picolinium chloride, whereas only 0.039 mg (0.01 mg/mL) of myristyl-gamma-picolinium chloride remained after processing in the study by Rijsdijk et al (15). Kotani et al (13) did not emphasize the amounts of preservatives but did discuss the safety of methylprednisolone and the potential risks of adhesive arachnoiditis. Given the lack of evidence of a causal relationship between these preservatives and neurotoxicity, intrathecal methylprednisolone should be administrated after a careful assessment of the risk-benefit ratio.

Interestingly, another study demonstrated that the intrathecal administration of midazolam was associated with meaningful improvements in pain, allodynia, sleep quality, and changes in the area of allodynia (16). However, general pain relief was only observed during week 1 in patients receiving intrathecal midazolam alone, whereas administration in combination with epidural methylprednisolone yielded good pain relief for 12 weeks. In contrast to other protocols, this study administered only a single injection.

Stellate Ganglion Block

The sympathetic nervous system is believed to be an important mediator of pain (53). After nerve injury or tissue inflammation, collateral sprouting in the peripheral and dorsal root ganglia and the upregulation of functional adrenoceptors may lead to the formation of anatomic and chemical couplings between sympathetic postganglionic and afferent neurons. Sympathetic terminals also contribute to the sensitization of nociceptive afferents (54). However, the mechanisms by which the sympathetic nervous system affects postherpetic neuralgia remain uncertain.

Unlike other mentioned studies, the patients selected for a trial of stellate ganglion block had not yet developed postherpetic neuralgia; accordingly, the incidence of this condition was assessed as an outcome. Additionally, whereas most studies excluded patients with facial postherpetic neuralgia, the stellate ganglion block study selected only patients with herpetic eruptions involving the face. Following the stellate ganglion block injection, all patients received 150-mg pregabalin twice daily, in contrast to other studies in which analgesics were only administered as rescue therapy. Notably, the authors observed a significantly reduced incidence of postherpetic neuralgia and higher satisfaction scores among patients who received the stellate ganglion block. Furthermore, these patients reported a significant decrease in VAS scores from the first follow-up to the last follow-up (i.e., from the first week until 6 months postinjection). The groups receiving and not receiving the stellate ganglion block also exhibited significant differences in the required dosages of acetaminophen and pregabalin, beginning at the first and second weeks of follow-up. Those receiving the block stopped using pregabalin and acetaminophen after 2

and 6 months, respectively. No significant differences in adverse events were observed between the 2 groups (Table 6) (17).

Dorsal Root Ganglion Destruction

Histopathologic studies have identified the loss of cells, axons, and myelin and concomitant fibrosis in the sensory ganglia of patients with severe postherpetic neuralgia (52). Accordingly, the pain sensation may be caused by an ectopic discharge in the nociceptors and low-threshold afferents at the dorsal root ganglion (55). Adriamycin (Pfizer, Australia), also known as doxorubicin, is an anthracycline topoisomerase II inhibitor (56) associated with cytotoxic effects such as apoptosis, autophagy, and necrosis (57). Adriamycin is not a specific anti-tumor drug and can thus be used to affect the growth of cells in the body. Potentially, it could be used to destroy the dorsal root ganglion, and thus relieve pain by disrupting the related signaling pathway. Of note, the US Food and Drug Administration has only approved the use of Adriamycin for certain malignancies (56,58); accordingly, the use of this drug for dorsal root ganglion destruction is an off-label use. A clear understanding and thorough discussion should be completed before any such treatment is attempted.

Patients treated with Adriamycin plus dexamethasone reported improved VAS scores and short-form McGill Pain Questionnaire scores relative to both the baseline and the control group. These effects began after 1 week of treatment and persisted for 6 months. Although patients treated with dexamethasone alone also reported reduced pain and improved sensory and psychological function relative to the baseline, these improvements did not persist beyond 3 months (Table 7) (32).

Pulsed Radiofrequency

Radiofrequency is a minimally invasive, target-selective technique that can be used to reduce chronic postherpetic neuralgia-related pain (59). The underlying mechanism is attributed to the effects of a rapidly changing electrical field on neuronal membranes (60), which results in electrolyte conduction and subsequent depolarization (61). The first case series of the dorsal root ganglion as an interventional site was conducted in 2008; in a cohort of 49 patients, the authors reported a significant reduction in pain ratings during a 12-week follow-up (62). Subsequent case studies involving the anterior ethmoidal nerve (63), infraorbital nerve (64), mental nerve (65), and caudal epidural (66) also reported satisfactory pain relief that persisted for 6 months.

Four RCTs have specifically addressed the use of pulsed radiofrequency for postherpetic neuralgia (Table 8) (18-21). Two RCTs targeted areas near the dorsal root ganglion via the angulus costae (18) and paravertebral puncture (19), whereas the other 2 trials targeted the intercostal nerves but provided no further descriptions (20,21). All study outcomes, including VAS, average rescue medication dosage, most SF-36 index scores (e.g., general health perceptions, social function, emotional role, mental health index, bodily pain index, physical function, and physical role), and the Pittsburgh Sleep Quality Index scale, favored pulsed radiofrequency. The observed effects began on Day 2 or 3 after treatment and persisted for 2-6 months (i.e., study endpoint). No side effects such as pneumothorax, infection, nerve injury, postoperative paresthesia, pain exacerbation, or any other serious adverse effects were observed in all studies. A recent meta-analysis similarly demonstrated the effectiveness of pulsed radiofrequency, including significant pain improvement after 1 day, 1 week, and 1 and 3 months, with only minor adverse events (e.g., local symptoms and transient bradycardia) (67).

Spinal Cord Stimulation

Currently, the mechanism of spinal cord stimulation remains uncertain. The "gate control theory of pain" suggests that neural signal transmission is regulated by the dorsal horn of the spinal cord (46), where A-beta fibers inhibit the transmission of pain signals carried by C-fibers (68). This suggests that electrical spinal cord stimulation could reasonably modulate pain. Spinal cord stimulation may also affect the levels of γ-aminobutyric acid and adenosine in the dorsal horn and consequently reduce neuropathic pain (p.s. γ-aminobutyric acid = gamma-aminobutyric acid)and adenosine in the dorsal horn and consequently reduce neuropathic pain (69).

Preparation for spinal cord stimulation involves the placement of leads percutaneously into the epidural space and the connection of these leads to pulse generators. The first human trial of electrical spinal cord stimulation as a neuromodulatory method for treating nociceptive pain was conducted in 1967 (70,71). Currently, this modality is applied for analgesia (chronic pain syndromes, Lyme disease-related pain, irritable bowel syndrome, complex regional pain syndrome, radicular pain, cancer pain, Raynaud disease, pudendal neuralgia, neuropathic pain, refractory angina pectoris, chronic limb ischemia-related pain, and cluster

headache), movement adjustments (Parkinson disease [tremor], static balance, and gait), anti-arrhythmia (atrial fibrillation, ventricular arrhythmia), sphincter tone modulation (fecal incontinence), and minimally conscious state.

Previous studies have used spinal cord stimulation to treat unendurable herpes zoster-related pain in patients both in the subacute and chronic stages of postherpetic neuralgia. For subacute herpes zoster-related pain (~2 months after herpes zoster), temporary stimulation provided for a period of 7-10 days to a median of 2.5 months yielded immediate pain relief that persisted for > 1 year (22,23). For patients with chronic postherpetic neuralgia, permanent device placement is always conducted following a successful temporary trial. Here, quarterly spinal cord stimulation inactivation tests can be used to indicate the need for persistent spinal cord stimulation or for device explantation. In one study, most patients experienced the recurrence of pain within 1-46 hours, some (2 of 28 patients) regained pain after 2-6 months, and the remainder (8 of 28) discontinued spinal cord stimulation permanently after 3-66 months; of these, 2 eventually explanted the devices (23). Only one study mentioned adverse effects related to spinal cord stimulation, including hypotension (21%) and ischuria (50%) (24). However, another study reported the need to change generators after 2 years of continuous stimulation (Table 9) (23).

Different methods have been used to identify patients who would most likely benefit from spinal cord stimulation. One study selected patients with no or little sensory loss in the affected dermatomes (23), whereas another study enrolled only patients with persistent pain, regardless of continuous epidural infusion (24). Another study used responses to the continuous epidural infusion of barbiturates and ketamine as an indicator of central nerve-level pain from the spinal cord (22). All 3 studies reported significant reductions in postherpetic neuralgia following spinal cord stimulation. These findings might indicate that patients suffering from pain and allodynia caused by central sensitization and those with preserved neuronal and dorsal column function would respond well to spinal cord stimulation (23). By contrast, patients with marked sensory loss and those experiencing constant pain without allodynia would not benefit from spinal cord stimulation, as deafferentation and degeneration of the dorsal column might be the dominant mechanism (72). It is therefore important to select patients who are mechanistically more likely to respond to spinal cord stimulation to achieve better pain relief.

Peripheral Nerve Stimulation

The central mechanisms underlying postherpetic neuralgia include the necrosis and scaring of neurons in the dorsal root ganglion and inflammation involving both the anterior and posterior horns of the spinal cord. However, the pathophysiology of postherpetic neuralgia also involves a peripheral mechanism (73). According to the gate control theory of pain (36), postherpetic neuralgia may be a type of deafferentation pain, and therefore, the peripheral nerve may be possible treatment target.

Peripheral nerve stimulation may be solution for patients with intractable postherpetic neuralgia, especially those experiencing neuralgias of cranial nerve origin, which precludes the use of spinal cord stimulation. Case reports (Table 10) have revealed the successful use of peripheral nerve stimulation for pain reduction in patients suffering from postherpetic neuralgia of the supraorbital and thoracic regions. Initially, the patients received a diagnostic block to identify the segment in which temporary electrodes would be placed, and a permanent pacemaker was implanted subcutaneously after successful trials. The stimulation settings included pulse widths of 150-450 μs, frequencies of 50-60 pulses per second, and amplitudes of off to 5 V (or 3 mA) in the continuous or intermittent mode. One patient was subjected to treatment with a novel high-frequency peripheral nerve stimulator, which used a pulse width of 130 μs, frequency of 100-1200 Hz, and amplitude of 6.2 mA (25). Only one of the 11 cases experienced a complication, resulting from a short extension cable and required a reoperation for adjustment (26). The 9 of the 11 patients benefited from the treatment, as indicated by a reduction or complete relief of pain and minimal or no use of medication; additionally, some reported improvements in sleep and functional status. However, no RCT of peripheral nerve stimulation for intractable postherpetic neuralgia has been conducted, and uniform outcome measurements have not yet been established.

Of note, one RCT used a technique called peripheral nerve adjustment (Table 11) (27), which was originally performed using the "Fu's subcutaneous needle," (74) to target the peripheral nerve. This technique does not use electrode placement or electrical stimulation; rather, the peripheral nerve adjustment involves the subcutaneous insertion and rotation of 4 cannular

needles twice weekly for 3 weeks. In that study, the treatment group experienced significant reductions in VAS scores and rescue drug dosages and an improved quality of life. However, only the latter result persisted for 90 days; the former 2 effects were no longer observed at 28 days postprocedure. No side effects were reported except minor bleeding at the needle insertion sites.

Paravertebral Block

Paravertebral block, a common alternative to epidural injection, might provide short-term relief of intractable postherpetic neuralgia (14). A case report described successful pain reduction after a single injection in a patient with refractory postherpetic neuralgia who was administered a repetitive paravertebral block comprising bupivacaine and clonidine via a T3-level catheter for 3 weeks. The patient remained pain free during an 8-month follow-up (28). This longer treatment effect duration, compared with a previous study of epidural analgesia, might be attributable to a more condensed treatment course involving a total of 10 injections in 3 weeks versus 4 injections in 4 weeks. Studies with larger sample sizes are needed to further determine the effectiveness of a paravertebral block for postherpetic neuralgia (Table 12).

A paravertebral block was also used to prevent postherpetic neuralgia in patients with acute herpes zoster-related pain (Table 13). In one study, a lower VAS score and reduced doses of pregabalin and acetaminophen were observed during the first 4 weeks after a single paravertebral block injection, although the effects did not persist beyond that point (29). By contrast, the beneficial effects of repeated paravertebral block injections persisted for 12 months in another study, and this protocol was also associated with significant reductions in the duration of herpetic eruption and the time required for skin healing (30). All the earlier-mentioned studies used a nerve stimulator to identify the correct paravertebral space, and none reported any complications.

Discussion

There is a paucity of RCTs for each intervention, which might be the reason for the lack of systematic review and meta-analysis of single treatments. Subcutaneous botulinum toxin A injection (75) and pulsed radiofrequency were the only 2 interventional treatments with meta-analysis for postherpetic neuralgia. The meta-analysis for subcutaneous botulinum toxin A injection included 6 double-blinded RCTs; however, as patients with a diagnosis of postherpetic neuralgia or trigeminal neuralgia were enrolled, we rejected the conclusions of the meta-analysis and included the 2 RCTs specific to postherpetic neuralgia. The risks of bias for these 2 trials were low. Although the baseline VAS and maximal injected dosage differed in these 2 trials, they demonstrated a significant reduction of pain. Considering that the meta-analysis for pulsed radiofrequency analyzed the effects of neuropathic pain and did not subgroup the different etiologies of pain, the conclusion is not directly applicable to postherpetic neuralgia. We included 4 RCTs specific to postherpetic neuralgia in our meta-analysis, of which 2 focused on refractory postherpetic neuralgia. However, as the baseline VAS and treatment protocols were inconsistent across those 4 trials, they were not analyzed as a whole. Nevertheless, they all demonstrated a significant reduction of pain. A few treatments had more than 3 RCTs, such as transcutaneous electrical nerve stimulation and intrathecal injection, but they were not analyzed due to clear inconsistencies in baseline VAS, interventional protocols, and outcome evaluation methods. Of note, the most recent intrathecal methylprednisolone injection trial was terminated early due to adverse effects. As the reason for the different outcomes could not be determined as related to medication preparation or random effects, more reliable studies are required before this treatment can be evaluated. Only one RCT was available for each of the remaining treatments; as the risk of bias was mostly unclear, more evidence is needed to make recommendations. Spinal cord stimulation was presented only in one case series for intractable postherpetic neuralgia and it used a different entity of pain reduction. Compared with other interventions included in this article, spinal cord stimulation is more invasive, more expensive, and had ethical issues among the positive control group, which may be the reason for the lack of an RCT.

Conclusion

In conclusion, the current evidence is insufficient for determining the single best interventional treatment. Considering invasiveness, price, and safety, the subcutaneous injection of botulinum toxin A or triamcinolone, transcutaneous electrical nerve stimulation, peripheral nerve stimulation, and stellate ganglion block are recommended first, followed by paravertebral block and pulsed radiofrequency. If severe pain persists, spinal cord stimulation could be considered.

Table 14. *Summary of interventional treatments for postherpetic neuralgia.*

	Interventions	Possible Mechanisms	Studies	NNT	Complications
Central	IT injection of methylprednisolone	Modulation of inflammatory processes	Kikuchi et al (14)	1.3[b,f]	—l
			Kotani et al (13)	1.2[b]	NS
			Rijsdijk et al (15)	—[h]	NS
	Epidural injection of methylprednisolone	Modulation of inflammatory processes	Dureja et al (16)	4.8[b,g]	NS
	Spinal cord stimulation	Regulation of neural signals and neurotransmitter levels	Case series only	—[a]	Lead migration due to postural fluctuation; insulation coats of the wires snapped from the lead (69)
Peripheral	Subcutaneous botulinum toxin A injection	Inhibition of inflammatory mediator release	Xiao et al (7)	—[a]	NS
			Apalla et al (8)	1.2[b]	NS
	Local triamcinolone injection	Modulation of inflammatory processes	Amjad and Mashhood (31)	1.3[e]	Local skin atrophy (26.7%)
	TENS	Release of endogenous opioids; segmental inhibition in the dorsal horn	Barbarisi et al (9)	—[a]	—l
			Xu et al (10)	1.7[c]	Local bleeding and bruising (46.7%-53.3% in all groups)
			Ing et al (11)	1.4[d]	—l
	Peripheral nerve adjustment	Modulation of deafferentation pain	Ma et al (27)	—[a]	Minor bleeding at the puncture site
	Stellate ganglion block	Prevention of inflammation-related sprouting	Makharita et al (17)	5[i]	Vocal changes, dysphagia (2-6 hours), local pain, drowsiness (1 wk; 54.8% vs. control group, 66.7%)
	Paravertebral block	Modulation of inflammatory processes	Ji et al (30)	4.3[i,j] 5.6[i,k]	NS
			Makharita et al (29)	9.3[i,j] 9.5[i,k]	Drowsiness (1 wk; 47.1% vs. placebo group, 41.4%)
			Two combined studies (29,30)	6[i,j] 5.5[i,k]	—l
	DRG destruction	Disruption of pain transduction	Chun-jing et al (32)	—[a]	Local numbness, hypoesthesia
	Pulsed radiofrequency (DRG)	Alterations in electrolyte conduction and depolarization	Ke et al (18)	—[a]	Bradycardia (2.2%), intercostal artery injury (2.2%)m
			Pi et al (19)	6.4[n] 3.6[o]	NS
	Pulsed radiofrequency (intercostal nerves)		Saxena et al (20)	1.3[q]	Local redness (6.7%)p, somnolence (46.7%)p, dizziness (46.7%)p, nausea and vomiting (13.3%)p
			Wang et al (21)	—[a]	NS

Abbreviations: DRG, dorsal root ganglion; IT, intrathecal; NS, no significant complications reported; TENS, transcutaneous electrical nerve stimulation.

[a]Unable to count according to the article; [b]The NNT is counted if the VAS decreased by > 50% after treatment; [c]The NNT is counted according to patients with a VAS ≤ 3 in a comparison of TENS plus methylcobalamin versus TENS plus lidocaine; [d]The NNT is counted for patients with a ≥ 15% reduction in the NPSS; [e]100% pain relief at wk 12; [f]The NNT compares IT with epidural administration; [g]The NNT compares epidural methylprednisolone plus IT midazolam with IT midazolam alone; [h]Negative result; [i]NNT for the prevention of postherpetic neuralgia.

[j]Follow-up after 3 mos; [k]Follow-up after 6 mos; [l]Not mentioned in the article; [m]In sham group; [n]Decrease in VAS score > 1; [o]Decrease in VAS score > 3; [p]Insignificant difference when compared with control group; [q]VAS score ≤ 3 during wk 4.

Given the destructiveness of dorsal root ganglion and adverse events of intrathecal methylprednisolone injection, these interventions should be carried out with great care and only following comprehensive discussion

Finally, this review is subject to several limitations. First, we limited the search to studies written and or published in English only, which may lead to a language bias. Second, there were scarce articles for each

treatment, which may be caused by reporting bias and lead to publication bias. Third, most articles had an unclear risk of bias, hindering the ability to make any conclusions.

Conclusions

The interventional therapies administered for postherpetic neuralgia are summarized in Table 14. With the exception of intrathecal methylprednisolone injection for postherpetic neuralgia (American Academy of Neurology Level A) (76), the evidence for most interventional procedures used to treat postherpetic neuralgia is Level 2, according to "The Oxford Levels of Evidence 2" (77); therefore, these modalities have received only grade B recommendations. Despite the lack of a high level of evidence, spinal cord stimulation and peripheral nerve stimulation are possibly useful for the treatment of postherpetic neuralgia. Although few adverse effects were reported, these procedures are invasive, and a careful assessment of the risk-benefit ratio should be conducted prior to administration. Despite the lack of conclusive evidence, these interventional therapies remain valuable, especially for patients with postherpetic neuralgia refractory to standard conservative treatments and those who have experienced intolerable side effects from standard medications.

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