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Effects of applying nerve blocks to prevent postherpetic neuralgia in patients with acute herpes zoster: a systematic review and meta-analysis

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Background: Postherpetic neuralgia (PHN) is a common and painful complication of acute herpes zoster. In some cases, it is refractory to medical treatment. Preventing its occurrence is an important issue. We hypothesized that applying nerve blocks during the acute phase of herpes zoster could reduce PHN incidence by attenuating central sensitization and minimizing nerve damage and the anti-inflammatory effects of local anesthetics and steroids.

Methods: This systematic review and meta-analysis evaluates the efficacy of using nerve blocks to prevent PHN. We searched the MEDLINE, EMBASE, Cochrane Library, ClinicalTrials.gov and KoreaMed databases without language restrictions on April, 30 2014. We included all randomized controlled trials performed within 3 weeks after the onset of herpes zoster in order to compare nerve blocks vs active placebo and standard therapy.

Results: Nine trials were included in this systematic review and meta-analysis. Nerve blocks reduced the duration of herpes zoster-related pain and PHN incidence of at 3, 6, and 12 months after final intervention. Stellate ganglion block and single epidural injection did not achieve positive outcomes, but administering paravertebral blockage and continuous/repeated epidural blocks reduced PHN incidence at 3 months. None of the included trials reported clinically meaningful serious adverse events.

Conclusions: Applying nerve blocks during the acute phase of the herpes zoster shortens the duration of zoster-related pain, and somatic blocks (including paravertebral and repeated/continuous epidural blocks) are recommended to prevent PHN. In future studies, consensus-based PHN definitions, clinical cutoff points that define successful treatment outcomes and standardized outcome-assessment tools will be needed. **(Korean J Pain 2017; 30: 3-17)**

Key Words: Epidural block; Herpes zoster; Nerve block; Paravertebral block; Postherpetic neuralgia; Stellate ganglion block.

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INTRODUCTION

Herpes zoster is an infectious disease caused by the reactivation of the varicella zoster virus. The virus usually lies dormant in the sensory ganglia of the cranial and spinal nerves following the resolution of chicken pox [1], but it can be reactivated in patients with decreased cell-mediated immunity due to advanced age or immunosuppressive medical conditions and malignancies [2]. Individuals affected by the reactivated herpes zoster develop characteristic dermatomally distributed vesicular skin lesions that usually heal within 2-3 weeks. Pain which often precedes or accompanies the herpes zoster rash is one of the most common and debilitating complications [3]. Although there is no unified or defined duration of pain, most clinicians define postherpetic neuralgia (PHN) as pain that lasts > 90 days from the onset of the skin rash [4-6].

PHN incidence varies from 5 percent to more than 50 percent depending on the study design, age distribution of the enrolled patients, and PHN definitions [5,7]. Although the intensity of postherpetic pain typically decreases over time, pain lasts more than 1 year in more than 30% of patients [5]. Pain severity ranges from mild to excruciating. In some individuals, intractable chronic pain can lead to depression, fatigue, and sleep disturbance [8,9]. The socioeconomic consequences secondary to prolonged severe pain include decreased socialization, daily activities, and quality of life [10]. Therefore, when treating patients with acute herpes zoster, it is important to prevent PHN at the same time in order to control acute viral infection and associated pain. Because of the complexity of the underlying pathophysiological mechanisms that contribute to the development of postherpetic neuralgia, various strategies for preventing PHN including corticosteroids, antidepressants and anticonvulsants, antiviral agents and vaccination have been proposed [6,10-13]. However, according to a recently published systematic review and meta-analysis, the effectiveness of these strategies toward preventing PHN is insufficient except among a limited and well-selected population (e.g., administering vaccines to adult ≥ 60 years) [7,14,15].

Applying sympathetic and somatic neural blocks via local anesthetics and/or corticosteroids has also been applied to control pain during the acute phase of herpes zoster and PHN, as well as reduce PHN incidence [16,17]. The rationale for applying neural blocks to treat herpes zoster is to attenuate central sensitization by interrupting the transmission of nociceptive afferent impulses to the central nervous system and minimize nerve damage by improving blood flow to the nervous tissue during deafferentation. Additionally, the anti-inflammatory effects of local anesthetics and corticosteroids within the territory of the affected nerve may play a role [18]. Some retrospective and observational studies fail to demonstrate the effectiveness of applying early neural blocks to prevent PHN [19] and only report short-term relief from acute pain [20]. Even though there is weak evidence that neural blocks can prevent PHN during the early phases of herpes zoster, several other studies suggest significant benefits [21,22].

This study investigated the efficacy of using neural blocks to prevent the development of PHN in patients with acute herpes zoster. We compared between-group differences in PHN incidence, as published in randomized controlled trials in which the enrolled patients received either standard therapy or standard therapy with additional nerve blocks.

MATERIALS AND METHODS

We searched several comprehensive databases in order to find published studies on applying neural blocks during the acute phase of herpes zoster to prevent PHN. This systematic review was designed according to the Cochrane Review Methods [23]. We report our findings in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [24].

1. Data and literature sources

The searches for this review were performed on April 30, 2014. We searched the MEDLINE, EMBASE, Cochrane Library, ClinicalTrials.gov, and KoreaMed databases. Both published and unpublished trials were included, and no language or date restrictions were applied to our electronic searches. Full-text searches were also performed using Google. All records were searched using the following terms: herpes zoster, nerve block, epidural, dorsal root ganglion, stellate ganglion, spinal nerve, sympathetic, postherpetic neuralgia. See **Appendices** for the comprehensive list. Search strategies were appropriately adapted for other databases according to the MEDLINE strategy. After the initial electronic search, the references of relevant studies were searched to identify additional studies.

Identified articles were individually assessed for inclusion.

2. Study selection

Potentially relevant articles were evaluated, and all data were extracted by two independent reviewers (Leem and Kim) according to the predefined selection criteria. Agreement was reached through discussion whenever differences arose. The two reviewers initially assessed the identified studies by the title and abstract. The full text of any potentially relevant articles was reviewed and assessed. Studies were included in our meta-analysis if they meet all of the four following conditions: (1) randomized controlled trials that enrolled patients with herpes zoster within 3 weeks after the onset of herpetic skin rash; (2) the treatment group received nerve blocks that consisted of local anesthetics and/or steroids in addition to standard medical therapy; (3) the control group received either nerve blocks with electrolyte solution and/or steroids or standard medical therapy without nerve blocks; and (4) outcome data were collected $>$ 12 weeks after the final intervention.

3. Data extraction

Data extraction was independently performed by at least two reviewers using a prespecified data-extraction form. Any discrepancies that remained unresolved following discussion were reviewed by a third author. Extracted data included study name, author, country, study year, inclusion and exclusion criteria, number of participants, duration of acute herpes zoster, characteristics of the administered neural blocks (e.g., route, frequency, dosage), number of withdrawals related to intervention, outcomes, and adverse events. The primary outcome was PHN incidence at 3, 6, and 12 months after the onset of herpetic skin rash. PHN was defined (according to clinical diagnostic criteria) as persistent pain at the affected site $\geq$ 3 months after the onset of the acute rash [25]. Secondary outcomes included duration of pain due to acute herpes zoster, pain severity measured using a validated visual analogue scale (VAS) or numerical rating scale (NRS) at 3, 6, and 12 months, and intervention-related adverse events. If the primary outcome variables were not mentioned, we estimated these data from the figures or requested the data by directly emailing the study authors.

4. Statistical analysis

The primary outcome of our review was the effect of the nerve blocks on PHN in patients with herpes zoster. Although PHN is generally defined as pain persisting $\geq$ 3 months after disease onset, it may last longer or recur. Therefore, in order to assess the long-term efficacy of intervention, we also evaluated outcomes at 6 and 12 months after final intervention. Secondary outcomes included duration of pain and adverse events caused by administering the nerve blocks. PHN was measured using pooled risk ratios (RR) and 95% confidence intervals (CI), which were calculated using the Mantel-Haenszel method according to the number of events and total number of patients included in the control and intervention groups of each study. Pain intensity was calculated using the weighted mean differences, 95% CIs, and mean and standard deviation values reported in each study using random effects modeling and inverse variance methods. Because all included studies used either VAS or NRS, which have different measurement scales, we used the standard mean differences to standardize the values from each scale. For studies that presented median and range values instead of mean and standard deviation values, we interpreted the median as the mean and calculated the standard deviation from the range using the equations included in the Cochrane Methods.

Heterogeneity was estimated using I^2 statistics, which measures the proportion of inconsistency between studies that arises from true differences rather than random errors or chance. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. We conducted subgroup analyses according to the type of nerve block performed on the intervention group (e.g., stellate ganglion, paravertebral, repeated/continuous epidural, single epidural blocks), frequency of administering the local anesthetics (e.g., single block, repeated/continuous block), and time after intervention (3, 6, 12 months). RevMan version 5.2 was used to perform these analyses.

RESULTS

1. Study identification

Database searches provided 930 articles (**Fig. 1**). Of these, 919 publications were excluded because it was clear from the title and abstract that they did not fullfil the selection criteria. We obtained the full manuscripts of the remaining 11 articles, but following additional scrutiny we only

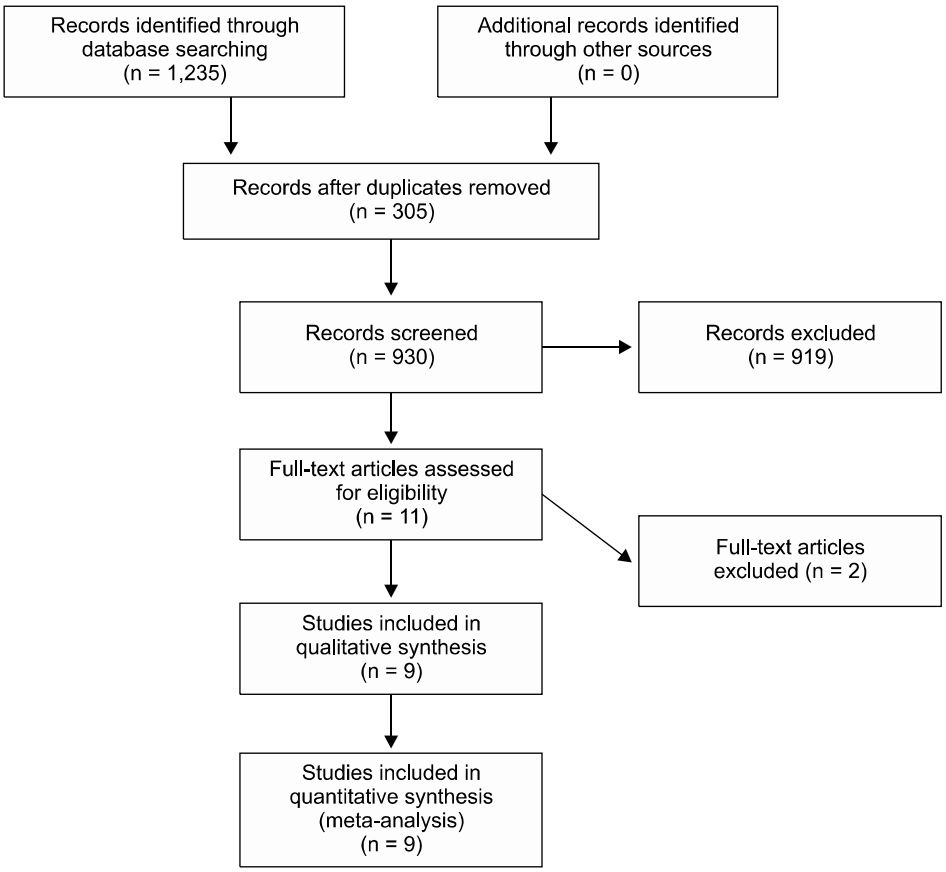

Fig. 1. Flow diagram demonstrating study search results.

identified 9 potentially relevant studies (**Fig. 1**). Two publications were excluded: 1 publication did not report PHN incidence and no reply was received from the authors [26], and 1 study utilized a cross-over design that used a bupivacaine and electrolyte solution [27].

2. Study characteristics and patient populations

Table 1 summarizes the country that conducted each relevant study, inclusion/exclusion criteria, interventions, outcome measures, and results of the included studies [28-36]. All included trials are randomized controlled parallel studies, except one [28]; however, we included this trial in this review because there were no differences in the demographic characteristics and the study participants were consecutively assigned. A total of 1,645 participants were enrolled in the 9 included studies. Sample sizes ranged between 20-598 patients. There were no differences in the sex ratios between the control and neural block groups mentioned in 8 trials [28-31,33-36]. Six trials [29,32-36] stated explicit age criteria for inclusion. Among these, 4 trials [29,33,34,36] included participants > 50 years old, 1 trial included patients > 55 years [35], and 1 trial included patients > 60 years [32]. Three trials [28,30,31] were conducted in Korea and did not state the age criteria, but the mean age of participants was > 56 years in all 3 trials. The inclusion criteria for the duration of acute herpes zoster in 7 trials [28,29,32-36] were within 2 weeks after the onset of the rash, and the remaining 2 trials extended duration to up to 3 weeks [30,31].

The types of administered neural blocks were determined according to the nerve affected with herpes zoster. Three trials administered stellate ganglion blocks to the facial, cervical, or upper thoracic segment [30,32,33]; 4 trials administered epidural blocks [28,31,35,36]; and 2 trials administered paravertebral blocks to the dermatome through the cervical to sacral spinal segments [29,34]. Two studies conducted by the same institution enrolled control groups that were administered electrolyte saline solution to the nerve [33,34], and 7 trials enrolled control groups that only received standard medical treatment without nerve blocks [28-32,35,36].

Injections varied in terms of frequency, volume, type

Table 1. Characteristics of Included Studies

Author, publication year	Category	Contents
Hwang et al. 1999 [28]	Inclusion criteria	65 patients HZ located in the cervical through the sacral dermatome within 14 days of onset of the disease.
	Exclusion criteria	Cranial nerve involvement, refusal, coagulopathy, cardiovascular disease.
	Intervention	Standard therapy plus continuous EB (initial bolus of 0.25% bupivacaine 5–7 ml and methylprednisolone 40mg, and then continuous infusion of 0.125% bupivacaine).
	Control	Standard therapy with antiviral agents (acyclovir 5 mg/kg 3 times a day for 7 days) and supplementary analgesics.
	Outcome	Changes of intensity of pain with a self-rating relief-of-pain scale. Calculated the days required for the relief of pain (DRP), duration of the late residual pain (DRLP) and the total duration of pain (TDP). Follow up to 6 months. Adverse events.
	Definition of PHN	Presence of pain at 4 weeks after skin eruption.
	Results	DRP, DRLP and TDP were significantly shorter in EB group. No serious adverse events.
	Comments	Adequacy of the EB was not mentioned. Omitted steroid in control group. Single center study. Allocation was consecutive, but there were no differences in demographic characteristics.
Ji et al. 2009 [29]	Inclusion criteria	132 HZ patients in dermatome below C6 within 7 days after onset of the rash. Older than 50 years.
	Exclusion criteria	Coagulopathy, psychiatric disease, allergy to methylprednisolone and bupivacaine, and immune disorder.
	Intervention	Standard treatment plus PVB with 10 ml 0.5% bupivacaine and 40 mg methylprednisolone, 4 injections every 48 hours for a week.
	Control	Standard treatment (oral acyclovir 800 mg, 5 times daily for 7 days, and analgesics as needed).
	Outcome	Presence (incidence) and severity [VAS as median (range) in patients with pain] of pain. Quality of life and adverse events. Followed up to 12 months.
	Definition of PHN	Burning and lancinating pain accompanied by allodynia, after 1, 3, 6 and 12 months.
	Results	Decreased incidence of PHN in PVB group, no difference in quality of life and severity of pain between groups.
	Comments	Nerve stimulator for PVB and verified adequacy of PVB with disappearance of pain. Single center study. Steroid not used in control group.
Lee et al. 1999 [30]	Inclusion criteria	20 HZ patients in cranial nerve, cervical and upper thoracic segments within 21 days of appearance of the skin lesion.
	Exclusion criteria	Other combined pain disorders.
	Intervention	Standard therapy plus SGB 2–12 times during hospital stay as needed with 0.8% mepivacaine.
	Control	Standard therapy with acyclovir, analgesics and antibiotics as needed.
	Outcome	VAS (mean ± SD), Incidence of PHN, adverse events. Followed up to 3 months.
	Definition of PHN	Longer than 6 weeks after skin eruption, NRS > 25/100.
	Results	Lowered pain intensity in SGB group, no significant difference in the incidence of PHN. No serious adverse events.
	Comments	Adequacy of the SGB was not mentioned. Omitted steroids in both two groups. Single center study.
Lee et al. 1999 [31]	Inclusion criteria	75 HZ patients located in the cervical through the sacral dermatome within 20 days of onset of the disease.
	Exclusion criteria	Cranial involvement.
	Intervention	Standard therapy plus repetitive epidural injection (initial 0.2% bupivacaine 5–7 ml with methylprednisolone 40–60 mg and then 0.2% bupivacaine 5–7 ml 2 times a day for 4–6 days.
	Control	Standard therapy with antiviral agents (acyclovir 5 mg/kg 3 times a day for 5–7 days) and supplementary analgesics.
	Outcome	Incidence of PHN and Kaplan-Meier analysis of the days to pain relief. Followed up to 3 months.
	Definition of PHN	Longer than 3 months, VAS > 10/100
	Results	No differences in the incidence of PHN and Kaplan Meier analysis of the days to pain relief curve.
	Comments	Adequacy of the EB was not mentioned. Omitted steroid in control group. Single center study.

Table 1. Continued

Author, publication year	Category	Contents
Lipton et al. 1987 [32]	Inclusion criteria	30 herpes zoster ophthalmicus patients within 2 weeks of onset of the rash. Over 60 years.
	Exclusion criteria	Not mentioned
	Intervention	Single SGB with 10 ml of a mixture of equal part of 1% lidocaine and 0.5% bupivacaine. Repeat as needed after 3 months.
	Control	Intravenous acyclovir (10 mg/kg) 3 times daily for 9 days plus intravenous prednisolone 60 mg/d for 8 days with a change to oral regimen and progressively tapered for 3 weeks.
	Outcome	Not mentioned.
	Definition of PHN	Presence or frequent pain at 6 months.
	Results	No difference in the incidence of PHN and healing time of the skin lesion.
	Comments	Adequacy of the SGB was verified by the miosis, hyperthermia, vasodilation and pain relief. Steroids not used in both groups. Single center study.
Makharita et al. 2012 [33]	Inclusion criteria	64 facial HZ patients less than 2 weeks after skin eruption, those under of received appropriate antiviral therapy, over 50 years.
	Exclusion criteria	Refusal, no antiviral therapy, neurological deficits, hepato-renal disease, coagulopathy, diabetes, malignancy.
	Intervention	Two times SGB 1 week apart with 6 ml of 0.125% bupivacaine and 8 mg dexamethasone.
	Control	Two times SGB 1 week apart with 6 ml saline.
	Outcome	VAS (all participants with mean ± SD), incidence of PHN, analgesic consumption, satisfaction, duration of pain and eruptive stage. Adverse events. Followed up to 6 months.
	Definition of PHN	Persistent herpetic pain after 3 and 6 months.
	Results	Shorter duration of pain and herpetic eruption, lower doses of analgesics in the active group. Lowered incidence of PHN at 6 months, and higher satisfaction at 3 and 6 months in the active group. No serious adverse events.
	Comments	Fluoroscopic guide. Single center study. Steroid not used in control group.
Makharita et al. 2015 [34]	Inclusion criteria	143 chest wall HZ patients less than 1 week after onset of the rash, over 50 years.
	Exclusion criteria	Refusal, no antiviral therapy, mild pain, coagulopathy, malignancy, hepato-renal disease, diabetes, steroid therapy.
	Intervention	Standard therapy plus continuous PVB (initial bolus of 0.25% bupivacaine 5–7 ml and methylprednisolone 40 mg, and then continuous infusion of 0.125% bupivacaine).
	Control	Antiviral therapy (acyclovir 800 mg 5 times daily for 7 days) plus single PVB with 10 ml of 0.5% bupivacaine and 8 mg dexamethasone.
	Outcome	VAS (all participants with mean ± SD), incidence of PHN, analgesic consumption, duration of pain and eruption, and adverse events. Followed up to 6 months.
	Definition of PHN	Persistent herpetic pain after 3 and 6 months.
	Results	Decreased pain intensity at 3 week, total analgesic consumption and incidence of PHN at 6 months, shorter duration of pain and eruption in active group. No serious adverse events.
	Comments	Fluoroscopic guide. Single center study. Steroid not used in control group.

of administered local anesthetics, and steroids. Two trials only administered a single injection [31,36], but multiple or continuous injections were administered in 7 studies [28–31,33–35]. Outcome measures differed widely between trials. All included trials reported PHN incidence, as defined as the presence of persistent pain and/or abnormal sensations relevant to the dermatome that were affected by herpes zoster. However, the duration and cutoff times for PHN pain ranged from 1 month through 1 year. Two trials stated that the pain intensity used to define PHN was VAS > 10/100 [31] or > 25/100 [30], respectively. The remaining 7 trials did not mention the pain intensity used to define PHN. In our present review, we used PHN incidence at 3 months after the onset of the rash in the meta analysis, and additionally PHN incidence at 6 and 12 months was used to assess the long-term effects.

Table 1. Continued

Author, publication year	Category	Contents
Pasqualucci et al. 2000 [35]	Inclusion criteria	569 HZ patients with skin rash of less than 7 days duration, and a pain score > 7 on a 10 cm VAS. Older than 55 years.
	Exclusion criteria	Kidney failure, liver damage, peptic ulcer, coagulopathy and previous systemic treatment with antiviral agents, steroids, local anesthetics, capsaicin or acetylsalicylic acid.
	Intervention	Intermittent bolus injection of 0.25% bupivacaine 6–12 ml via epidural catheter inserted at the relevant dermatome for 7 days plus 40 mg methylprednisolone through the catheter every 3–4 days for 7 consecutive days. The cycle was repeated for additional 7 days if pain persisted.
	Control	Intravenous acyclovir (10 mg/kg) 3 times daily for 9 days plus intravenous prednisolone 60 mg/d for 8 days with a change to oral regimen and progressively tapered for 3 weeks.
	Outcome	Presence of pain with VAS median (range) in patients with pain and abnormal sensation with VRS median (range) in patients with abnormal sensation. Ratio of complete recovery. Adverse events. Followed up to 1 year.
	Definition of PHN	Persistent pain or abnormal sensation at 1, 3, 6 and 12 months after the end of the treatment.
	Results	Lowered incidence of PHN throughout the observation periods in EB group, but no differences in severity of pain and abnormal sensation between two groups. No serious adverse events.
	Comments	Fluoroscopy used during epidural catheterization. Steroid used in both two groups. Two center study. The mean time from onset of rash to beginning of treatment was shorter in control group.
van Wijck et al. 2006 [36]	Inclusion criteria	598 HZ patients in dermatome below C6 within 7 days after onset of skin rash. Older than 50 years.
	Exclusion criteria	Coagulopathy, allergy to methylprednisolone and bupivacaine, and serious immune disorder.
	Intervention	Standard treatment plus single EB with a mixture of 80mg methylpredinisolone and 10 mg bupivacaine (0.25% weight/volume).
	Control	Standard treatment (either oral acyclovir 800 mg 5 times, famciclovir 500 mg 3 times, or valaciclovir 1,000 mg 3 times daily for 7 days, and analgesics as needed).
	Outcome	Presence (incidence) and severity [VAS as median (25th–75th percentile) in patients with pain] of pain. Adverse events related with EB. Followed up to 6 months.
	Definition of PHN	Persisted pain longer than 1 month after inclusion.
	Results	Incidence of PHN and severity of pain decreased only at 1 month in EB group. No significant differences in outcome at 3 and 6 months between two groups. No major adverse events.
	Comments	No radiological aids and verified adequacy of EB with sensory loss in the relevant dermatome. Multicenter study. Not used steroid in control group. Baseline pain intensity was slightly lower in control group.

HZ: herpes zoster, EB: epidural block, DRP: days required for the relief of pain, DRLP: duration of the late residual pain, TDP: total duration of pain, PVB: paravertebral block, VAS: visual analogue scale, PHN: postherpetic neuralgia, SGB: stellate ganglion block, NRS: numeric rating scale, VRS: verbal rating scale.

3. Quality of the included studies

The heterogeneity between the trials included in this review is high in terms of PHN incidence. However, when the outcomes of the subgroups were assessed according to the type of nerve block (stellate ganglion block, paravertebral block, or epidural block), heterogeneity was insignificant ($I^2 < 30\%$). Despite the poor quality of some trials, the paucity of high quality randomized controlled trials made us include those trials in the meta-analyses because there were no significant differences in the outcomes that are relevant to this review.

Risk of bias is summarized in **Fig. 2**. In 5 trials published after 2000 [29,33-39], participants were randomly assigned using a computer-generated algorithm or computer program with block generation. Although detailed methods for allocation were not mentioned in 4 trials published before 2000 [28,30-32], the demographic characteristics of the control and intervention groups are similar. It is virtually impossible to study patients who receive nerve blocks in a blind manner. Procedural pain and the symptoms and signs of sensory-motor and/or sympathetic blocks may induce placebo effects. Furthermore, ethical

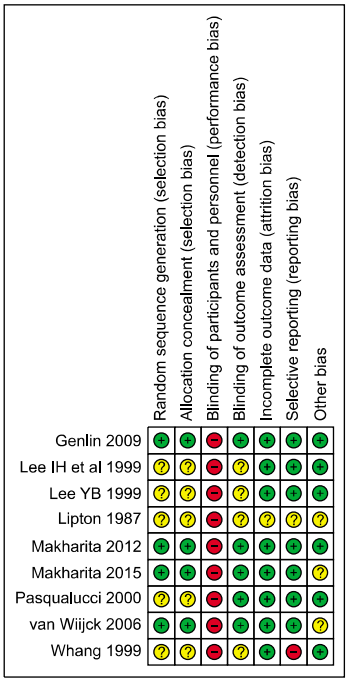

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Green = low risk of bias; yellow = unclear risk of bias, red = high risk of bias.

issues make it difficult to enroll active control groups. As a result, we assessed all 9 trials included in this review as "high" risk to the point of "blinding the participants and personnel". In 5 trials [29,33–36], the outcomes and adverse events were assessed by researchers who were unaware of the study protocol and graded as "low" risk for detection bias, but the other 4 trials did not present sufficient information to make a decision [28,30–32]. For selective reporting bias, PHN incidence was not the primary outcome in 1 trial [28], and another trial did not present any information about the 4 PHN cases in the control group [36]. The demographic characteristics of the participants were not similar between trials. Time from disease onset to the first block was not similar between groups [33], and the baseline pain intensity was slightly lower in the control group [36].

4. PHN at 3, 6, and 12 months after the Onset of the Herpes Zoster

We performed a meta-analysis in order to combine the relevant data obtained by the 9 included trials. The results show that PHN incidence following nerve block application was significantly reduced in comparison with standard treatment alone at 3, 6, and 12 months after the onset of herpes zoster (RR = 0.43, CI = 0.25–0.76, P = 0.004, I^2 = 74% at 3 months; RR = 0.41, CI = 0.2–0.83, P = 0.01, I^2 = 77% at 6 months; RR = 0.17, CI = 0.1–0.28, P = 0.00001, I^2 = 0% at 12 months) (**Fig. 3**). To reduce heterogeneity, we performed a subgroup analysis according to the type of nerve block administered at 3 months after herpes zoster was diagnosed. PHN incidence was not reduced by administering stellate ganglion block (RR = 0.50, CI = 0.22–1.17, P = 0.11, I^2 = 17%) or a single epidural block (RR = 0.89; CI = 0.65–1.22, P = 0.47). However, PHN incidence was significantly reduced by administering continuous/repeated epidural blocks (RR = 0.34, CI = 0.17–0.67, P = 0.002, I^2 = 11%) and paravertebral blocks (RR = 0.37, CI = 0.17–0.81, P = 0.01, I^2 = 32%) (**Fig. 4**). According to the subsequent meta-analysis of the differences between administering single or repeated/continuous blocks, PHN incidence was significantly reduced by administering repeated/continuous block (RR = 0.30, CI = 0.23–0.41, P = 0.000001, I^2 = 0%) but not a single block (RR = 0.84, CI = 0.63–1.11, P = 0.22, I^2 = 0%) in comparison with standard therapy alone (**Fig. 5**).

5. Secondary outcome measures

Most of the studies included in this review used VAS or NRS to measure intensity and/or changes in pain. One study used a self-rating relief-of-pain scale, where pain intensity was defined as 100 at the time of admission (or worst pain) and no pain was defined as 0 [28]. Three trials reported the duration of pain as measured by the complete resolution of herpetic pain and/or days required for pain intensity to decrease from 100 to 0 [28,33,34]. The meta analysis of these 3 trials indicated that pain duration after administering nerve blocks was significantly shorter than after standard therapy (pain duration with days, mean difference = −13.68, CI = −18.70 − −8.66, P < 0.00001, I^2 = 0%) (**Fig. 6**).

Eight trials [28–31,33–36] included in this review reported the pain intensity from baseline through the end of the study, but 4 trials did not [28,31,32,35]. To report the pain intensity during the observation periods, 3 trials used the mean and standard deviation values of all participants [29,33,34], but 3 trials described pain as the median (range) or median values (25–75 percentile) of only the patients with pain [29,35,36]. Two trials [28,31] reported pain

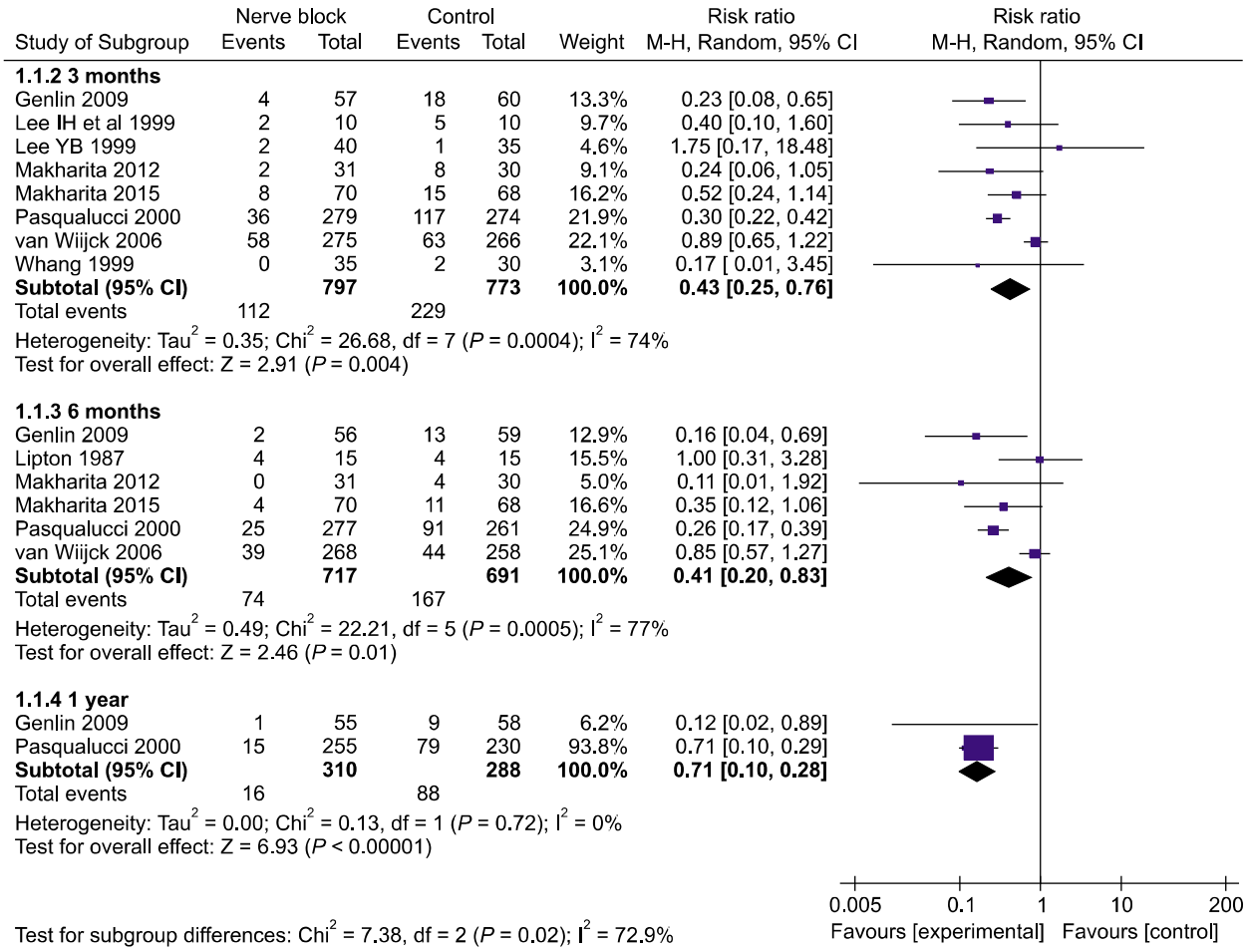

Fig. 3. Effects of nerve blocks on the incidence of postherpetic neuralgia. The incidence of postherpetic neuralgia was significantly lowered in nerve block treatment compared with control standard treatment at 3, 6 and 12 months after the onset of herpetic skin rash, but heterogeneity among trials was high.

duration, and 1 trial [32] reported the individual VAS scores of 4 PHN cases. Therefore, we did not combine these data in this meta-analysis. Pain severity significantly differed between stellate ganglion block and standard therapy at 3 and 6 months in only 1 trial [33], but there were no significant differences in pain severity between nerve block and standard therapy throughout the observation period (up to 12 months) in the other 4 trials [29,30,34,36].

All of the trials included in this review report the adverse events associated with the relevant neural blocks. The common adverse events reported by the 3 trials on epidural and paravertebral blocks include dizziness, headache, and backache. One trial [31] reported a 5.5% incidence (16 of 290 patients) of dura puncture while administering epidural blocks. Two trials on the effects of epidural block reported the absence of adverse events. Commonly observed adverse events related to stellate ganglion block included drowsiness, local pain, changes in voice, and dysphagia. Most of the minor adverse events fully recovered within 2 weeks. One trial [35] reported study withdrawal due to adverse events related to interventions. Adverse events that caused withdrawal included nausea/vomiting and gastralgia in the standard groups, and dizziness, flushes, headache, backache, sweating, fainting, neck pain, stiffness, and the catheter falling out of the patient. None of the included trials in this review reported clinically meaningful or serious adverse events.

DISCUSSION

The aim of this review was to investigate administering neural blocks in order to prevent the development of post-

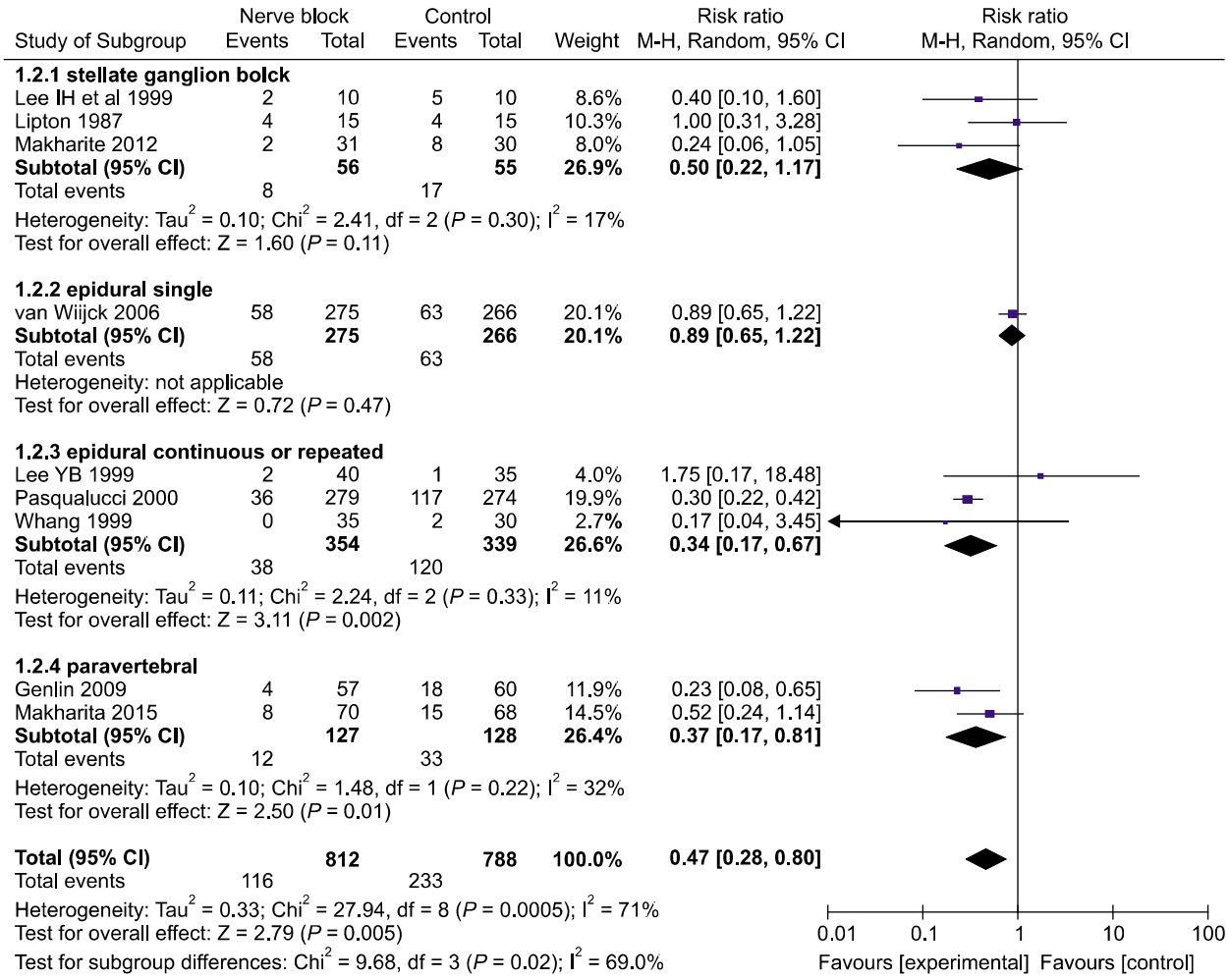

Fig. 4. Effects of nerve blocks on the incidence of postherpetic neuralgia according to the types of nerve block. The incidence of postherpetic neuralgia was lowered by repeated/continuous epidural block, but not by stellate ganglion block and single epidural block.

herpetic neuralgia in patients with acute herpes zoster. Here, we present the primary outcomes (i.e., PHN incidence) according to > 90 days of persistent pain after the onset of herpetic skin rash because 90 days is widely accepted and reported in the literature [5,6]. Despite different study designs, neural block methodologies, observation periods, and outcome measurements, we determine the PHN incidence at 3 months after the final intervention in the 9 included trials. Three of 9 trials compared standard medical therapies and/or placebo injection with stellate ganglion block [30,32,33], 4 of 10 trials performed comparisons with epidural block [28,31,35,36], and the other 2 trials performed comparisons with paravertebral block [29,34]. The results of the meta-analysis of these trials revealed significant differences between the control groups and intervention groups in terms of the PHN incidence at 3, 6, and 12 months after inclusion. Among the trials included in our meta analysis, the incidences of PHN in the control and placebo injection groups were 2.8% and 42.7% at 3 months, 13.3% and 33.9% at 6 months, and 16% and 34.4% at 12 months. These values, which are considered the natural PHN incidence, are similar to previously reported studies [5,7]; in contrast, PHN incidence in the groups treated with nerve blocks was 0–26.7% at 3 months, 0–26.7% at 6 months, and 2–5.9% at 12 months. Incidence was significantly lower in comparison to the control groups during each observation period, and the efficacy of administering neural blocks to prevent the development of PHN increased over time.

Thus, we conclude that administering neural blocks

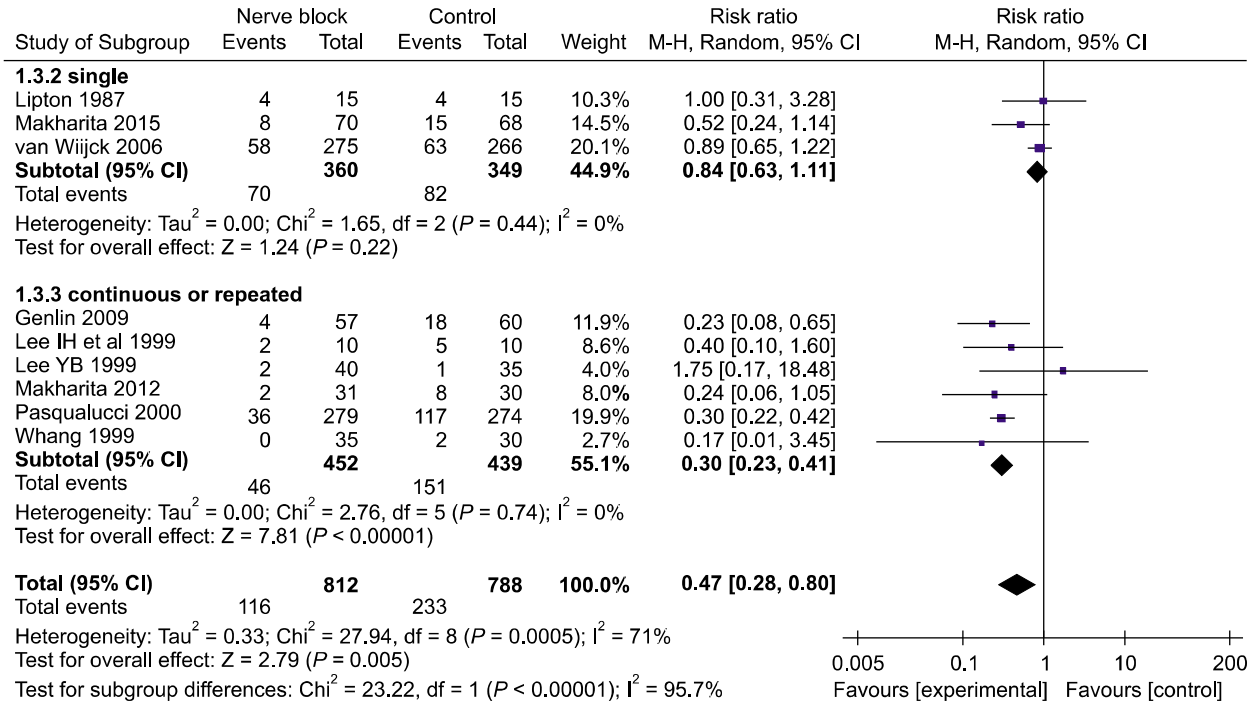

Fig. 5. Comparison of single block versus repeated/continuous blocks on the incidence of postherpetic neuralgia. The incidence of postherpetic neuralgia was lowered by repeated/continuous blocks, but not single block.

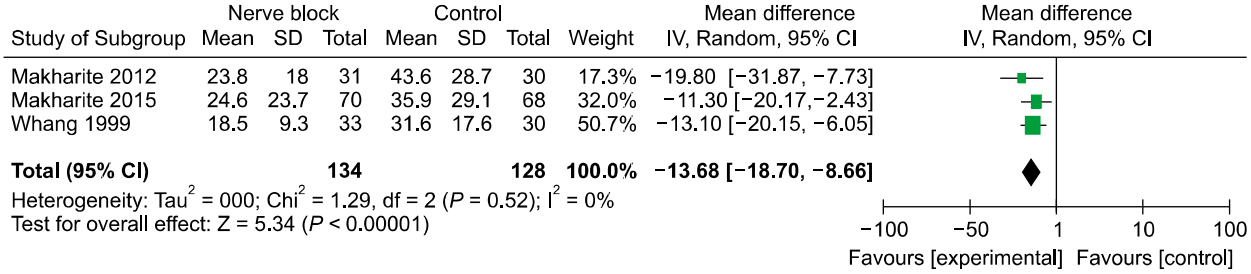

Fig. 6. Effects of nerve blocks on the duration of acute pain caused by herpes zoster.

during the acute phase of herpes zoster reduces PHN incidence, but significant heterogeneity between trials remains (P = 0.004, I^2 = 75%). In subsequent analyses, we found that this heterogeneity was due to the type of neural block that was administered. When we conducted a subgroup analysis according to the type of neural block administered at 3 months after the final intervention, PHN incidence among patients who received stellate ganglion block was not significantly reduced [29,32,33]. PHN incidence was 11% in the stellate ganglion block groups vs 31% in control groups (P = 0.12, I^2 = 42%). However, in the 2 studies in which stellate ganglion blocks were administered more than twice [24,29], incidence was significantly reduced in comparison with the control groups (P = 0.02). PHN incidence in the three trials that investigated the effects of continuous or repeated epidural blocks was significantly reduced (11% in epidural group vs 36% in the control group; P = 0.05, I^2 = 41%) [28,31,35]. However, the trial that investigated the effects of administering a single epidural block to 541 patients reported no differences in PHN incidence (21% in epidural group vs 24% in control group, P = 0.47) [36]. These results indicate that even when epidural blocks are administered to control pain during the acute phase of herpes zoster, the repetitive/continuous blocking of noxious stimuli from reaching the central nervous system is needed in order to more ef-

fectively prevent PHN. Finally, 2 trials investigated the effects of administering paravertebral block to 255 participants and reported significantly reduced PHN incidence (9% in the paravertebral group vs 26% in the control group; P = 0.01, I^2 = 37%) [29,34]. Unlike single paravertebral block [33], however, administering a single epidural block did not effectively prevent PHN [36]. There are several possible explanations for this difference. First, the demographic characteristics of the control and intervention groups in the single epidural trial are not similar. The baseline pain intensity of the participants in the single epidural block trial was higher than the control group. Next, participants with systemic diseases such as diabetes or hepatic and renal diseases were excluded from the paravertebral block trial. Additionally, the administering of more complete and unilateral somatic and sympathetic blocks could have contributed to the lower PHN incidence in the paravertebral block trial.

In addition to PHN incidence, we also analyzed pain duration and intensity at 3 months after final intervention. Three included trials recorded pain duration [28,33,34], and the results of the meta-analysis show that administering nerve blocks significantly reduced pain duration. Furthermore, in these trials, PHN incidence at 3 months was also significantly lower in the nerve block groups in comparison with groups that were administered standard therapy (7.3% vs 19.4%, P = 0.006). In the 5 included studies that evaluated pain intensity during the observation periods, only 1 study reported decreased pain intensity at 3 and 6 months in the nerve block group [33], but there was no significant difference in pain intensity at > 3 months in the remaining 4 studies [29,33,34,36]. However, we could not perform an additional meta-analysis because of the different data representations. These differences in pain evaluation methods may have resulted from the small sample sizes and low PHN incidences. Therefore, in order to investigate the efficacy of administering neural blocks to manage pain severity in patients with herpes zoster, a large, prospective, randomized trial is necessary in the future. Ideally, consensus-based multicenter studies are needed to compare outcomes.

Many studies investigate using neural blocks to manage pain due to herpes zoster. The results of randomized controlled trials on administering sympathetic nerve block reveal that applying nerve blocks shortens acute pain in herpes zoster [25,27], and these results are consistent with our current findings. Unfortunately, these studies were excluded from this review because they did not report PHN incidence. A few retrospective and observational studies also investigate the preventive effects of early nerve blocks on the development of the PHN. Although several studies report the beneficial effects of applying early nerve blocks on PHN incidence [21,22,36,37], many other studies fail to demonstrate efficacy [20,22,38]. Regardless of the results, most studies are weakened by the short-term follow-up period [27], lack of control groups [20-22,38,39], unclear identification of herpes zoster patients [22], small sample sizes [27,40], and the use of different clinical cutoff times to define PHN. All of the methodological concerns listed above make it difficult to interpret the results and draw conclusions. In a recent review conducted by the International Association for the Study of Pain Neuropathic Pain Special Interest Group (NeuPSIG), Dworkin et al. [42] reserved a conclusion regarding the preventive effects of neural blockade on the development of PHN due to the relative paucity of high-quality randomized controlled studies and different study results. However, there are no effective treatments that prevent PHN, and administering early nerve blocks may help prevent PHN in patients who require hospitalized care due to old age, severe acute pain, and rash [43-45].

Our present review warrants cautious interpretation due to several limitations. First, although the results of this meta-analysis demonstrate decreased PHN incidence following the application of nerve blocks (14%) in comparison with the control groups (30%), the overall PHN incidence in nerve block group at 3 months does not differ from the previously reported studies on populations > 50 years (6.2-43%) [5,35,46]. These results may originate from discrepancies in the inclusion criteria of the study populations, definitions of pain severity due to PHN, and possible overestimation. Second, due to the relative paucity of the high-quality randomized controlled trial, we only included 1 non-randomized trial [28]. In that trial, all admitted patients were consecutively allocated, and there were no differences in the demographic characteristics. Third, we cannot provide standard guidelines regarding nerve blocks, such as number, frequency, duration, or type of local anesthetics with or without steroids. However, a recent review on the use of epidural steroid injections—one of the most common practices in pain practice—concluded that minor variations in nerve block techniques are unlikely

to significantly affect outcomes [47]. Lastly, most of the included trials in this review were not designed to set placebo intervention. The therapeutic effects of placebo interventions, especially in pain medicine, remain debatable [48,49]. Injecting an inactive solution into the nerve tissue is unethical and is not a true placebo due to the lack of local anesthetic effects. In this review, 2 trials conducted by the same authors and institutions administered placebo interventions (electrolyte solutions) to control groups [17,34], but there were no differences in PHN incidence in comparison with other studies in which the control groups did not receive placebo injections (P = 0.96; data not shown).

In summary, applying nerve blocks during the acute phase of herpes zoster shortens the duration of zoster-related pain. Stellate ganglion blocks fail to decrease the incidence of postherpetic neuralgia, but multiple blocks may demonstrate beneficial effects. Somatic blocks, including repeated/continuous epidural blocks and paravertebral blocks, prevent PHN and reduce the likelihood of occurrence. The preventive effects of early nerve block may be more potent when performed with repetitive/continuos treatment modalities than single administration. For future studies, consensus-based definitions of PHN, successful clinical cutoff points that define treatment outcomes, and standardized outcome assessment tools, including physical and emotional functioning, will be required.

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Appendices

Appendix 1. MEDLINE search strategy

1. Zoster[tiab] OR Shingles[tiab] OR "Postherpetic Neuralgia"[tiab] 14433
2. ("Herpes Zoster"[Mesh]) OR "Neuralgia, Postherpetic"[Mesh] 9990
3. 1 OR 2 16960
4. ("Anesthesia, Epidural"[Mesh]) OR "Anesthesia, Local"[Mesh]) OR "Nerve Block"[Mesh]) OR "Stellate Ganglion"[Mesh]) OR "Superior Cervical Ganglion"[Mesh]) OR "Anesthetics, Local"[Mesh]) OR "Injections, Spinal"[Mesh]) NOT "Blood Patch, Epidural"[Mesh] 72500
5. "Epidural Anesthesia"[tiab] OR "Local Anesthesia"[tiab] OR "Nerve Block"[tiab] OR "Nerve Blocks"[tiab] OR "Nerve Blockade"[tiab] OR "Nerve Blockades"[tiab] OR "Stellate Ganglion"[tiab] OR "Stellate Ganglia"[tiab] OR "Stellate Ganglias"[tiab] OR "Superior Cervical Ganglia"[tiab] OR "Epidural Injections"[tiab] OR "Epidural Injection"[tiab] OR "Spinal Injections"[tiab] OR "Spinal Injection"[tiab] 26898
6. 4 OR 5 84853
7. 3 AND 6 359

Appendix 2. EMBASE search strategy

1. Zoster:ab,ti OR Shingles:ab,ti OR 'Postherpetic Neuralgia':ab,ti 17893
2. 'herpes zoster'/exp OR 'postherpetic neuralgia'/exp 20149
3. 1 OR 2 26758
4. 'epidural anesthesia'/exp OR 'local anesthesia'/de OR 'nerve block'/exp OR 'stellate ganglion'/exp OR 'cervical ganglion'/exp OR 'sympathetic ganglion'/exp OR 'local anesthetic agent'/de OR 'intraspinal drug administration'/de OR 'epidural drug administration'/exp OR 'intrathecal drug administration'/exp 112805
5. 'Epidural Anesthesia':ab,ti OR 'Local Anesthesia':ab,ti OR 'Nerve Block':ab,ti OR 'Nerve Blocks':ab,ti OR 'Nerve Blockade':ab,ti OR 'Nerve Blockades':ab,ti OR 'Stellate Ganglion':ab,ti OR 'Stellate Ganglia':ab,ti OR 'Stellate Ganglias':ab,ti OR 'Superior Cervical Ganglia':ab,ti OR 'Epidural Injections':ab,ti OR 'Epidural Injection':ab,ti OR 'Spinal Injections':ab,ti OR 'Spinal Injection':ab,ti 34046
6. 4 OR 5 122624
7. 3 AND 6 774

Appendix 3. Cochrane search strategy

1. MeSH descriptor: [Herpes Zoster] explode all trees 358
2. MeSH descriptor: [Neuralgia, Postherpetic] explode all trees 104
3. #1 or #2 436
4. Zoster or Shingles or "Postherpetic Neuralgia":ti,ab,kw (Word variations have been searched) 1081
5. #3 or #4 1097
6. MeSH descriptor: [Anesthesia, Epidural] explode all trees 1795
7. MeSH descriptor: [Anesthesia, Local] explode all trees 1752
8. MeSH descriptor: [Nerve Block] explode all trees 2647
9. MeSH descriptor: [Stellate Ganglion] explode all trees 34
10. MeSH descriptor: [Superior Cervical Ganglion] explode all trees 0
11. MeSH descriptor: [Anesthetics, Local] explode all trees 5981
12. MeSH descriptor: [Blood Patch, Epidural] explode all trees 23
13. #6-11/or 9335
14. #13 not #12 9325
15. "Epidural Anesthesia" or "Local Anesthesia" or "Nerve Block" or "Nerve Blocks" or "Nerve Blockade" or "Nerve Blockades" or "Stellate Ganglion" or "Stellate Ganglia" or "Stellate Ganglias" or "Superior Cervical Ganglia" or "Epidural Injections" or "Epidural Injection" or "Spinal Injections" or "Spinal Injection":ti,ab,kw (Word variations have been searched) 7945
16. #14 or #15 12803
17. #16 and #5 57
18. #17/Trials 50

Appendix 5. Koreamed search strategy

1. "Herpes Zoster"[ALL] OR "Neuralgia, Postherpetic"[ALL] OR "Shingles"[ALL] OR "Zoster"[ALL] 595
2. "Anesthesia, Epidural"[ALL] OR "Anesthesia, Local"[ALL] OR "Nerve Block"[ALL] OR "Stellate Ganglion"[ALL] OR "Anesthetics, Local"[ALL] OR "Injections, Spinal"[ALL] 2123
3. 1 AND 2 52