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Pharmacological and non-pharmacological strategies for preventing postherpetic neuralgia: a systematic review and network meta-analysis

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Background: Postherpetic neuralgia (PHN) is a refractory complication of herpes zoster (HZ). To prevent PHN, various strategies have been aggressively adopted. However, the efficacy of these strategies remains controversial. Therefore, we aimed to estimate the relative efficacy of various strategies used in clinical practice for preventing PHN using a network meta-analysis (NMA).
Methods: We performed a systematic and comprehensive search to identify all randomized controlled trials. The primary outcome was the incidence of PHN at 3 months after acute HZ. We performed both frequentist and Bayesian NMA and used the surface under the cumulative ranking curve (SUCRA) values to rank the interventions evaluated.
Results: In total, 39 studies were included in the systematic review and NMA. According to the SUCRA value, the incidence of PHN was lower in the order of continuous epidural block with local anesthetics and steroids (EPI-LSE), antiviral agents with subcutaneous injection of local anesthetics and steroids (AV + sLS), antiviral agents with intracutaenous injection of local anesthetics and steroids (AV + iLS) at 3 months after acute HZ. EPI-LSE, AV + sLS and AV + iLS were also effective in preventing PHN at 1 month after acute HZ. And paravertebral block combined with antiviral and antiepileptic agents was effective in preventing PHN at 1, 3, and 6 months.
Conclusions: The continuous epidural block with local anesthetics and steroid, antiviral agents with intracutaneous or subcutaneous injection of local anesthetics and a steroid, and paravertebral block combined with antiviral and antiepileptic agents are effective in preventing PHN.

Key Words: Anesthesia, Local; Anticonvulsants; Autonomic Nerve Block; Bayes Theorem; Injections, Epidural; Nerve Block; Network Meta-Analysis; Neuralgia, Postherpetic; Stellate Ganglion; Steroids; Systematic Review; Therapeutics.

INTRODUCTION

Postherpetic neuralgia (PHN), a persistent neuropathic pain that develops after acute herpes zoster (HZ), is the most frequent chronic complication of HZ [1]. HZ is caused by the reactivation of the varicella zoster virus (VZV), a highly contagious double-stranded DNA virus that causes chickenpox. The reactivation of VZV is associated with

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age-related decrease in cellular immunity to VZV and impaired cellular immune function [2]. The estimated overall incidence of HZ is 3.4-4.82/1,000 person-year and increases up to 11/1,000 person-year in patients aged 80 years and older. The lifetime risk ranges between 25% and 30% but is up to 50% for individuals older than 80 years [3]. HZ has recently been linked to an increased risk of cerebrovascular and cardiac events in the days following an acute infection [4], and is considered as a major public health problem because of its increasing incidence and because it is common in the aging population [1].

The risk of developing PHN in individuals with HZ is between 5% and 30%. Prodromal pain, older age, greater acute pain, a more widespread rash, and ophthalmic involvement are major risk factors for PHN [5]. The pain characteristics of PHN have been described as burning, aching, throbbing, stabbing, or shooting, and it may be continuous or intermittent. Allodynia, hyperalgesia, and dysesthesia were also observed. The pain severity varies from mild to excruciating; in some patients, the pain is intractable and leads to depression, fatigue, and sleep disturbance [6,7]. This severe chronic pain also leads to various socioeconomic consequences, including decreased socialization, daily activities, and quality of life [8,9]. Therefore, the prevention of PHN is a major objective in the treatment of HZ, along with treatment of the acute viral infection and acute pain. As the pathophysiological mechanisms of PHN are complex, various preventive strategies, including antiviral agents, vaccination, corticosteroids, antidepressants, anticonvulsants, and nerve blocks have been introduced. However, it remains unclear which strategies are more effective in preventing PHN.

Recently, a few systematic reviews and meta-analyses have investigated the preventive effects of various strategies [10-13]. However, each of systematic reviews and meta-analyses was only performed using a pair-wise approach; thus, only two strategies were compared. No previous network meta-analysis (NMA) has compared the effectiveness of all available strategies to prevent PHN. Furthermore, these meta-analyses only included studies conducted before 2014.

NMA, an extension of traditional pair-wise meta-analysis, is a research method that can compare and analyze comparative studies simultaneously by combining direct and indirect evidence in the network of the existing randomized controlled trials (RCT); it provides a relative efficacy and a hierachy of various treatments based on the corresponding surface under the cumulative ranking curve (SUCRA) value [14].

Thus, we reviewed all articles that investigated the effects of various strategies employed to prevent PHN and quantified the rank order of the efficacy of various strategies for preventing PHN using NMA.

MATERIALS AND METHODS

1. Protocol and registration

We developed the protocol for this systematic review and NMA in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [15]. The review protocol was registered at the International Prospective Register of Systematic Reviews (registration number: CRD42021225666; accessible at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=225666) on October 1, 2020.

This systematic review and NMA of pharmacological and non-pharmacological strategies for preventing PHN was performed according to the protocol recommended by the Cochrane Collaboration [16] and reported according to the PRISMA extension for NMA guidelines [17].

2. Search strategy

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from database establishment (MEDLINE; 1,946, EMBASE; 1,966) to December 2020 using search terms related to the pharmacological and non-pharmacological strategies for preventing PHN and updated it in June 2021. The search terms used for MEDLINE and EMBASE are presented in the **Appendix**. Two investigators (JHK and GJC) screened the titles and abstracts of the retrieved articles. The reference lists were imported to Endnote software 9.1 (Clarivate, London, UK), and duplicate articles were removed. Additional relevant articles were identified by scanning the reference lists of the articles obtained from the original search.

3. Inclusion criteria and exclusion criteria

We only included prospective RCTs that compared two or more pharmacological and non-pharmacological strategies for preventing PHN.

The PICO-SD information is as follows:

1. Patients (P): all patients with acute HZ
2. Intervention (I): pharmacological and non-pharmacological strategies employed to prevent PHN
3. Comparison (C): other pharmacological and non-pharmacological strategies employed to prevent PHN, placebo, or no treatment
4. Outcome measurements (O): The primary outcome

of this NMA was the incidence of PHN at 3 months after acute HZ. The secondary outcomes of this NMA were the incidence of PHN at 1 and 6 months after acute HZ, and severity of pain measured at 1, 3, and 6 months after acute HZ was also analyzed.

When the data for 1, 3, and 6 months was not presented, we included the data from the nearest time point, if possible.

5. Study design (SD): RCTs

The following types of studies were excluded:

1. Review articles, case reports, case series, letters to the editor, commentaries, proceedings, laboratory science studies, and all other non-relevant studies
2. Studies that failed to report the outcomes of interest

No language or date restrictions were applied in our study.

4. Study selection

Two investigators (JHK and GJC) independently screened the titles and abstracts of the searched studies to identify trials that met the inclusion criteria outlined above. For articles determined to be eligible for the analysis based on their titles and/or abstracts, the full paper was retrieved. Potentially relevant studies chosen by at least one investigator were retrieved, and the full text was evaluated. Full-text articles were assessed separately by two investigators (JHK and GJC), and any disagreements were resolved through discussion. In cases where agreement could not be reached, the dispute was resolved with the help of a third investigator (HK). To minimize data duplication because of multiple reports, articles from the same author, organization, or country were compared.

The degree of agreement for study selection between the two independent investigators was computed using kappa statistics to measure the difference between the observed and expected agreements, that is, whether they were random or by chance. Kappa values were interpreted as follows: 1) less than 0: less than chance agreement; 2) 0.01-0.20: slight agreement; 3) 0.21-0.40: fair agreement; 4) 0.41-0.60: moderate agreement; 5) 0.61-0.80: substantial agreement; and 6) 0.8-0.99: almost perfect agreement [18].

5. Data extraction

Using a standardized extraction form, the following data were extracted independently by two investigators (JHK and MKK): 1) title; 2) name of the first author; 3) name of the journal; 4) year of publication; 5) study design; 6) type of pharmacological and non-pharmacological strategies; 7) dose of pharmacological agents; 8) country; 9) risk of bias; 10) inclusion criteria; 11) exclusion criteria; 12) age; 13) sex; 14) number of subjects; 15) incidence of PHN at 1, 3, and 6 months after acute HZ; and 16) pain score measured at 1, 3, and 6 months after acute HZ.

If the information were inadequate, attempts were made to contact the study authors, and additional information was requested. If unsuccessful, missing information was calculated from the available data, if possible, or was extracted from the figure using the open source software Plot Digitizer (version 2.6.8; http://plotdigitizer.sourceforge.net).

The reference lists were divided into two portions. Two investigators (HYS and MKK) completed the data extraction, one for each half of the reference list. Data extraction forms were cross-checked to verify the accuracy and consistency of the extracted data.

6. Risk of bias

Risk of bias was assessed using the revised Cochrane risk of bias tool for randomized trials (RoB 2.0 version) (August 22, 2019) by two independent authors (BGK and HK) [19]. The RoB 2.0 is structured into five domains: D1) bias arising from the randomization process, D2) bias due to deviations from the intended interventions, D3) bias due to missing outcome data, D4) bias in outcome measurements, D5) bias in the selection of reported results. The overall risk of bias was evaluated. It was judged as low risk when the risk of bias in all domains was low, high when the risk of bias in at least one domain was high or the risk of bias in multiple domains was of some concern, and some concern if the overall judgement neither low nor high.

7. Statistical analyses

Ad-hoc tables were created to summarize the data from the included studies by showing their key characteristics and any important questions related to the review objectives. After extracting the data, the investigators determined the feasibility of the meta-analysis.

A multiple treatment comparison NMA is a meta-analysis generalization method that includes both direct and indirect comparisons of treatments. Both frequentist and Bayesian random-effects NMAs were conducted. A frequentist random-effects NMA was performed using the STATA software (version 15; StataCorp LP, College Station, TX) based on *mvmeta* with NMA graphical tools developed by Chaimani et al. [20].

Before conducting the NMA, we evaluated the transitivity assumption by examining the comparability of demographic data (age and sex), type of strategies for preventing PHN, and the risk of bias (low *vs.* removing low risk of bias

from the overall risk of bias) as potential treatment-effect modifiers across comparisons.

A network plot linking the included pharmacological and non-pharmacological strategies for preventing PHN and their combination with other pharmacological and non-pharmacological strategies was constructed to indicate the types of pharmacological and non-pharmacological strategies, number of patients on different strategies, and the level of pair-wise comparisons. The nodes show the pharmacological and non-pharmacological strategies compared, and the edges show the available direct comparisons among the pharmacological and non-pharmacological strategies. The nodes and edges are weighed on the basis of the number of patients and the inverse of standard error of the effect.

We evaluated the consistency assumption within the entire network using the design-by-treatment interaction model. We also evaluated each closed loop in the network to evaluate the local inconsistencies between the direct and indirect effect estimates for the same comparison. For each loop, we estimated the inconsistency factor (IF) as the absolute difference between the direct and indirect estimates and the corresponding 95% confidence interval (CI) for each paired comparison in the loop [21]. When the IF value with 95% CI started at 0, it indicated that the direct and indirect evidence were consistent.

In the predictive interval (PrI) plot, the mean summary effects with CI were presented together with their PrIs to facilitate interpretation of the results, considering the magnitude of heterogeneity. PrIs provide an interval that is expected to encompass the estimate of a future study. A rankogram and cumulative ranking curve were drawn for each pharmacological and non-pharmacological strategy. Rankograms are the probabilities for treatments to assume a possible rank. We used the SUCRA values to present the hierarchy of pharmacological and non-pharmacological strategies for preventing PHN. SUCRA is a relative ranking measure that accounts for the uncertainty in the treatment order; it accounts for both the location and variance of all relative treatment effects. A higher SUCRA value indicates that the individual interventions have more positive results [22]. A comparison-adjusted funnel plot was used to assess the presence of small-study effects [23].

To test the robustness of the results from frequentist random NMA, we also conducted a Bayesian NMA using the fixed and random-effects models as well as Markov Chain Monte Carlo (MCMC) methods with the R statistical package *gemtc* [24]. Due to a lack of understanding on PHN, we used uninformative prior distributions automatically provided by the *gemtc* package. MCMC simulations were run using four chains with different initial values for an inferential 100,000 iterations after 50,000 burn-ins and thinning of 100. The convergence of fixed and random models derived from MCMC simulations was assessed using trace and density plots, and Gelman-Rubin-Brooks methods with a potential scale reduction factor (PSRF) of up to 1. And the comparing of the fit for fixed and random models was assessed using Dbar (posterior mean of the deviance), PD (adequate number of parameters), and DIC (deviance information criterion, the sum of Dbar and PD) statistics. We also calculated the SUCRA values from the Bayesian model and compared them with those in the frequentist model. We also performed a meta-regression analysis considering the potential influences of the risk of bias (low risk *vs.* some concern or high risk), sex, and mean age on each outcome.

8. Quality of evidence

The evidence grade was determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, which involves a sequential assessment of the evidence quality, an assessment of the risk-benefit balance, and a subsequent judgment on the strength of the recommendations [25].

RESULTS

1. Study selection

A total of 1,090 studies were found after searching MEDLINE, EMBASE, CENTRAL, and Google Scholar, with an additional 77 studies discovered after conducting a manual search, such as looking at references from included studies/reviews, and additional searching of related/cited articles in PubMed and Google Scholar. A total of 1,070 studies were retained after removing duplicates. After reviewing the titles and abstracts, 972 studies were excluded. In the first stage of the study selection process, the kappa value between two investigators was 0.764.

The remaining 98 studies were thoroughly examined, and 59 were eliminated for the following reasons: Meta-analysis [10,13,26-33], were irrelevant to outcomes of the study [34-55], unavailable outcomes [56-67], non-original data [68-71], grouping [72-77], and were nonrandomized studies [78-82]. As a result, 39 studies met the criteria for inclusion in this systematic review and meta-analysis (**Fig. 1**). In the second stage of the study selection process, the kappa value between two investigators was 0.834.

2. Study characteristics

Table 1 summarizes the characteristics of the 39 stud-

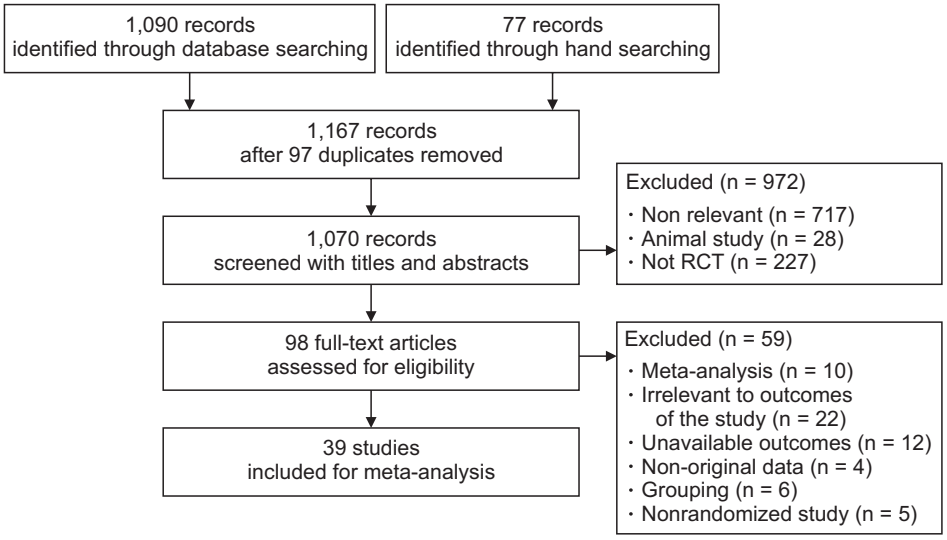

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flowchart of included and excluded trials. RCT: randomized controlled trial.

ies that met the inclusion criteria. The pharmacological and non-pharmacological strategies used to prevent PHN consisted of antiviral agents (AV) [83-109]; a combination of antiviral agents and antiepileptics (AV + AE) [93,98-101,104,107-109]; electric nerve stimulation (ENS) [93,103]; a combination of antiviral agents and electric nerve stimulation (AV-ENS) [103]; a combination of antiviral agents, antiepileptics, and paravertebral block using local anesthetics and steroids (AV + AE-pv) [97,102]; a combination of antiviral agents and epidural block using local anesthetics and steroids (AV-eLS) [96]; a combination of antiviral agents and steroids (AV + SR) [88,110,111]; continuous epidural block using local anesthetics, steroids and epinepherine (EPI-LSE) [110]; steroids (SR) [92,112-115]; antiepileptics (AE) [92,93,115]; a combination of antiviral agents and intracutaneous injection using local anesthetics and steroids (AV + iLS) [105]; a combination of antiviral agents and subcutaneous injection using local anesthetics and steroids (AV + sLS) [106]; varicella zoster vaccine immunoglobulin (VZVIG) [116]; adrenocorticotropic hormone (ACTH) [112]; a combination of antivial agents and intracutaneous injection using methylene blue and local anesthetics (AV-iLM) [117]; a combination of antiviral agents and intracutaneous injection using local anesthetics (AV-iL) [105]; a combination of antiviral agents and continuous & intermittent epidural block using local anesthetics (AV-ecL) [118]; a combination of antiviral agents and intermittent epidural block using local anesthetics (AV-eiL) [118]; radiotherapy (RTx) [92]; a combination of antiviral agents, antiepileptics and stellate ganglion block using local anesthetics and steroids (AV + AE-sgLS) [101]; a combination of antiviral agents and stellate ganglion block using local anesthetics (AV-sgL) [95]; a combination of antiviral agents, antiepileptics, and intracutaneous injection using local anesthetics and steroids (AV + AE-iLS) [107]; a combination of antiviral agents, antiepileptics and cervical nerve root block using local anesthetics, steroids, and cobalamide (AV + AE-cLSC) [109]; stellate ganglion block using local anesthetics (sgL) [119]; and pulsed radiofrequency on the Gasserian ganglion (pRF) [120].

3. Risk of bias assessment

The risk of bias assessment is described in **Table 2**.

4. Synthesis of results

With regard to the outcomes of each specific datum, we generated a network plot (**Fig. 2**), inconsistency plot (**Fig. 3**), a predictive interval plot compared with the control (**Fig. 4**), expected mean ranking and the SUCRA values for each strategy (**Fig. 5**), the comparison-adjusted funnel plot (**Fig. 6**), and the SUCRA values from the Bayesian model compared with the SUCRA values from the frequentist model (**Fig. 7**). **Figs. 2-7** present a summary of the results (A, B, C, D, E, and F in each figure correspond to the incidence of PHN at 3 months, incidence of PHN at 1 month, incidence of PHN at 6 months, pain score at 3 months, pain score at 1 month, and pain score at 6 months, respectively).

5. Incidence of PHN at 3 months after acute HZ

A total of 27 studies (3,136 patients) measured the incidence of PHN at 3 months after acute HZ. Of these, one study was separated from the loops [117]. NMA was performed excluding the abovementioned study. Thus, only 26 studies (3,072 patients) were analyzed. The network plot of all eligible comparisons for this endpoint is shown in **Fig. 2A**. Although all 17 management modalities (nodes) were connected to the network, two comparisons (AV and

Table 1. Characteristics of the trials included in the systematic review and network meta-analysis

Author, year	Management	Number of patients	Age, yr	Sex, M/F	Pain assessment tool	Outcomes of interest					
						Incidence of PHN at 1 month	Incidence of PHN at 3 months	Incidence of PHN at 6 months	Mean pain score at 1 month	Mean pain score at 3 months	Mean pain score at 6 months
Bulilete et al., 2019 [108]	Valaciclovir + gabapentin	50	65.1	20/28	10-point VAS	•	•		•	•	
	Valaciclovir + placebo	48	66.0	18/30							
Lee et al., 2016 [104]	Valaciclovir + gabapentin	60	62.58	18/42	10-point Likert scale	•	•		•	•	
	Valaciclovir	60	61.83	25/35							
Stepanović et al., 2015 [103]	TENS	36	57.3	14/22	VAS	•	•	•			
	Symptomatic care	38	59.9	16/22							
	Antiviral agent	71	70.6	32/39							
	Antiviral + TENS	77	65.6	27/50							
Makharita et al., 2015 [102]	Acyclovir + pregabalin + saline (paravertebral)	70	56.2	31/37	VAS		•	•	•	•	•
	Acyclovir + pregabalin + bupivacaine + dexamethasone (paravertebral)	73	56.8	34/36							
Makharita et al., 2012 [101]	Antiviral + pregabalin + saline (SGB)	30	59.6	14/16	VAS		•	•	•	•	•
	Antiviral + pregabalin + bupivacaine + dexamethasone (SGB)	30	60.6	13/18							
Krcevski Skvarc and Kamenik, 2010 [98]	Antiviral + placebo	15	63	4/11	10 point Likert scale		•	•	•		
	Antiviral + pregabalin	14	67	6/8							
Ji et al., 2009 [97]	Acyclovir	64	68	28/36	VAS	•	•	•	•	•	•
	Acyclovir + bupivacaine + methylprednisolone (paravertebral)	68	66	30/38							
van Wijck et al., 2006 [96]	Acyclovir	297	66	116/181	VAS	•			•	•	•
	Acyclovir + bupivacaine + methylprednisolone (epidural)	301	66	118/183							
Pasqualucci et al., 2000 [110]	Acyclovir + prednisolone	279	66.9	125/154	VAS	•	•	•	•	•	•
	Bupivacaine + epinephrine + methylprednisolone via epidural catheter	290	68.7	131/159							
Ahmed et al., 1998 [94]	Famciclovir	25	53	11/14	VAS 100 mm		•	•	•	•	•
	PENS	25	56	12/13							
Bowsher, 1997 [93]	Acyclovir + amitriptyline	9	71.3	14/24	NR	•	•	•			
	Amitriptyline	29									
	Acyclovir + placebo	17	72.7	14/20							
	Placebo	17									
Harding and Porter, 1991 [114]	Acyclovir	24	62.1	6/17	VAS 100 mm				•	•	•
	Placebo	22	70.6	9/19							
Benoldi et al., 1991 [92]	Prednisolone	9	68.5	4/5	NR		•	•			
	RTx	9	67.2	3/6							
	Acyclovir	9	67.1	6/3							
	Carbamazepine	9	63	3/6							
Esmann et al., 1987 [88]	Acyclovir + prednisolone	41	72.8	17/24	Slight, moderate, sever, attacks per day, highest grading	•	•				
	Acyclovir + placebo	37	71.4	8/29							
Cobo et al., 1986 [87]	Acyclovir	36	NR	13/23	None, mild, moderate, severe		•				
	Placebo	35		21/14							
Balfour et al., 1983 [85]	Acyclovir	52	NR	29/23	NR	•	•				
	Placebo	42		25/17							
Esmann et al., 1982 [84]	Acyclovir	27	65.7	10/17	NR	•	•				
	Placebo	29	68.6	10/19							
Bean et al., 1982 [83]	Acyclovir	19	53.2	6/13	NR	•	•				
	Placebo	10	50.5	7/3							
Keczkes and Basheer, 1980 [115]	Prednisolone	20	66.4	14/6	NR	•					
	Carbamazepine	20	68.5	14/6							
Cui et al., 2018 [107]	Acyclovir + pregabalin + ropivacaine + methylprednisolone (intracutaneous)	51	61.7	21/28	VAS	•	•	•	•	•	•
	Acyclovir + pregabalin + saline (intracutaneous)	51	61.8	20/28							
Cui et al., 2017 [105]	Acyclovir + ropivacaine + methylprednisolone (intracutaneous)	48	63.7	21/26	VAS	•	•	•	•	•	•
	Acyclovir	48	63.0	19/27							
Ni et al., 2017 [106]	Acyclovir + triamcinolone + lidocaine (subcutaneous)	50	63.84	23/27	NRS	•	•	•			
	Acyclovir	50	65.86	24/26							
Zheng et al., 2019 [109]	Famciclovir + pregabalin + placebo (cervical root block)	70	63.41	31/39	11 point scale		•	•	•	•	•
	Famciclovir + pregabalin + lidocaine + triamcinolone + cobalamine (cervical root block)	70	65.84	29/41							

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Table 1. Continued

Author, year	Management	Number of patients	Age, yr	Sex, M/F	Pain assessment tool	Outcomes of interest					
						Incidence of PHN at 1 month	Incidence of PHN at 3 months	Incidence of PHN at 6 months	Mean pain score at 1 month	Mean pain score at 3 months	Mean pain score at 6 months
Hwang et al., 1999 [79]	Acyclovir + bupivacaine + methylprednisolone (continuous epidural infusion)	40	60.8	18/22	VRS 0-100		•				
	Acyclovir	35	56.1	9/26							
Wan et al., 2019 [120]	Sham	48	64.87	20/28	VAS				•	•	•
	PRF on gasserian ganglion	48	66.01	23/25							
Hügler et al., 2002 [116]	Human albumin (placebo)	20	67.65	NR	VAS	•					
	VZVIG	20	71.6								
Cui et al., 2016 [117]	Valacyclovir + methylene blue + lidocaine (intradermal)	32	69.5	13/19	VAS 100 mm	•	•		•		
	Valacyclovir + lidocaine (intradermal)	32	72.5	11/21							
Payne et al., 1989 [91]	Placebo	17	70	10/7	NR	•	•	•			
	Isoprinosine	21	70	10/11							
Wood et al., 1994 [111]	Acyclovir 7 days	101	58	39/62	0-5; non-noticeable to excruciating	•					
	Acyclovir 7 days + prednisoone 21 days	99	59	37/62							
	Acyclovir 21 days	101	59	38/63							
	Acyclovir 21 days + prednisolone 21 days	99	60	39/60							
McGill et al., 1983 [86]	Placebo	20	68.8	7/13	0-3		•				
	Acyclovir	17	70.4	3/14							
Wassilew et al., 1987 [89]	Acyclovir	29	62.5	9/20	0-5	•	•	•			
	Placebo	31	63.4	6/25							
Mandal et al., 1988 [90]	Acyclovir	26	67.4	11/15	0-4	•					
	Placebo	30	68.4	9/21							
Lee et al., 1999 [95]	Acyclovir + mepivacaine (stellate ganglion block)	10	65.0	3/7	VAS 0-100 mm				•		•
	Acyclovir	10	67.2	5/5							
Harding et al., 1986 [119]	1% lignocaine & 0.5% marcaine (stellate ganglion block)	NR	71.5	NR	VAS 0-100 mm				•	•	
	Placebo		72.2								
Kanodia and Singhal, 2011 [99]	Acyclovir + pregabalin	23	46	19/4	VAS 100 mm				•		
	Acyclovir + placebo	22	47	17/5							
Kanodia et al., 2012 [100]	Acyclovir + gabapentin 300 mg/day	15	64	11/4	VAS 100 mm				•		
	Acyclovir + gabapentin 600 mg/day	14	65	9/5							
	Acyclovir + gabapentin 900 mg/day	13	65	10/3							
	Placebo	14	63	11/3							
Manabe et al., 2004 [118]	Acyclovir + bupivacaine (continous epidural infusion, intermittent epidural bolus)	29	67	9/20	VAS	•					
	Acyclovir + normal saline (continous epidural infusion) + bupivacaine (intermittent epidural bolus)	27	65	13/14							
Clemmensen and Andersen, 1984 [112]	ACTH	17	55	10/7	0-4	•					
	Prednisolone	19	56	13/6							
	Placebo	19	56	10/9							
Eaglstein et al., 1970 [113]	Triamcinolone	15	NR	NR	NR		•				
	Placebo	19									

PHN: postherpetic neuralgia, TENS: transcutaneous electrical nerve stimulation, SGB: stellate ganglion block, PENS: percutaneous electrical nerve stimulation, RTx: radiotherapy, PRF: pulsed radiofrequency, VZVIG: varicella zoster vaccine immunoglobulin, ACTH: adrenocorticotropic hormone, NR: not reported, VAS: visual analogue scale, NRS: numerical rating scale.

control [CTR]) were more directly compared with the other 15 nodes. No network inconsistency was observed [χ^2 (7) = 8.94, P = 0.257].

Ten closed loops were identified in the network after compariing the incidence of PHN at 3 months after acute HZ, but four loops (CTR/AV + AE/AE [93], CTR/ENS/AV-ENS [103], AV/SR/RTx [92], and SR/RTx/AE [92]) were formed only by multi-arm trials. Of the six closed loops, inconsistencies were observed in 1/10/12 (CTR/SR/AE) (**Fig. 3A**). EPI-LSE showed a lower incidence of PHN at 3 months after acute HZ than CTR in terms of 95% CI and PrI; moreover, AV + iLS and AV + AE-pv showed a lower incidence of PHN at 3 months after acute HZ than CTR, but only in terms of 95% CI (**Fig. 4A, Supplementary Fig. 1A, Supplementary Table 1A**). The insignificances in the 95% PrIs suggests that any future RCTs could change the significance of the efficacy of these comparisons. The rankograms and cumulative ranking curve showed that EPI-LSE followed by AV + sLS and AV + iLS had the lowest incidence of PHN at 3 months after acute HZ (**Supplementary Figs. 1B, 1C**). The expected mean rankings and SUCRA values of each intervention are presented in **Fig. 5A**. According to the SUCRA value, the incidence of PHN at 3 months after acute HZ was lower in the order of the EPI-LSE (97.0%), followed by AV + sLS (79.5%), AV + iLS (79.2%), and AV + AE-sgLS (76.7%).

The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, which

Table 2. Risk of bias assessment

Study, year	Randomization process		Intended interventions		Missing outcome data		Measurement of the outcome		Selection of the reported result		Overall result
Bulilete et al., 2019 [108]	Some concern	No statement for allocation concealment	Low risk	Both blinded	Low risk	1/98 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Lee et al., 2016 [104]	Some concern	No statement for allocation concealment	Some concern	No specific information	Some concern	No specific information	Some concern	No specific information	Low risk	Predefined outcomes	Some concern
Stepanović et al., 2015 [103]	Some concern	No statement for allocation concealment	Some concern	Blinded only in assesor	Some concern	No specific information	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Makharita et al., 2015 [102]	Some concern	No statement for allocation concealment	Low risk	Both blinded	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Makharita et al., 2012 [101]	Some concern	No statement for allocation concealment	Low risk	Both blinded	Low risk	3/64 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Krcevski Skvarc and Kamenik, 2010 [98]	High risk	No specific information	Some concern	No specific information	Low risk	No exclusion	Some concern	No specific information	Low risk	Predefined outcomes	High risk
Ji et al., 2009 [97]	Some concern	No statement for allocation concealment	Some concern	Blinded only in assesor	Low risk	19/132 dropped, propotions existed	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
van Wijck et al., 2006 [96]	Some concern	No statement for allocation concealment	Some concern	Blinded only in assesor	Low risk	33/598 dropped, propotions existed	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Pasqualucci et al., 2000 [110]	Some concern	No statement for allocation concealment	Some concern	Blinded only in assesor	Low risk	31/600 dropped, protocol violation	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Ahmed et al., 1998 [94]	Some concern	No statement for allocation concealment	Some concern	Blinded only in assesor	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Bowsher, 1997 [93]	Low risk	Sealed envelop	Low risk	Both blinded	Low risk	6/80 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	Low risk
Harding and Porter, 1991 [114]	High risk	No statement for allocation concealment, randomization sequence	Some concern	Both blinded	Some concern	8/46 dropped, no specific propotion revealed	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Benoldi et al., 1991 [92]	High risk	No statement for allocation concealment, randomization sequence	Some concern	Different procedure	Low risk	1/36 dropped, unrelated to the outcome	Some concern	No specific information	Low risk	Predefined outcomes	High risk
Esmann et al., 1987 [88]	High risk	No statement for allocation concealment, randomization sequence	Some concern	Both blinded	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Cobo et al., 1986 [87]	High risk	No statement for allocation concealment, randomization sequence, basement difference existed	Low risk	Both blinded	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Balfour et al., 1983 [85]	Some concern	No statement for allocation concealment, randomization sequence	Low risk	Both blinded	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Esmann et al., 1982 [84]	Some concern	No statement for allocation concealment, randomization sequence	Low risk	Both blinded	Low risk	1/56 dropped	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Bean et al., 1982 [83]	High risk	No statement for allocation concealment	Some concern	Both blinded	Some concern	2/31 dropped	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Keczkes and Basheer, 1980 [115]	Some concern	No statement for allocation concealment, randomization sequence	Low risk	Both blinded	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Cui et al., 2018 [107]	Some concern	No statement for allocation concealment	Low risk	Both blinded	Low risk	5/102 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Cui et al., 2017 [105]	Some concern	No statement for allocation concealment, randomization sequence	Some concern	Both blinded	Low risk	2/96 dropped	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Ni et al., 2017 [106]	Some concern	No statement for allocation concealment	Some concern	No specific information	Low risk	5/100 dropped, unrelated to the outcome	Some concern	No specific information	Low risk	Predefined outcomes	Some concern

Table 2. Continued

Study, year	Randomization process		Intended interventions		Missing outcome data		Measurement of the outcome		Selection of the reported result		Overall result
Zheng et al., 2019 [109]	Some concern	No statement for allocation concealment	Low risk	Both blinded	Low risk	13/153 dropped	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Hwang et al., 1999 [79]	High risk	No statement for allocation concealment, randomization sequence	Some concern	No specific information	Low risk	No exclusion	Some concern	No specific information	Low risk	Predefined outcomes	High risk
Wan et al., 2019 [120]	Some concern	No statement for allocation concealment	Some concern	Both blinded	Low risk	2/96 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Hügler et al., 2002 [116]	High risk	No statement for allocation concealment, randomization sequence	Some concern	Both blinded	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Cui et al., 2016 [117]	Some concern	No statement for allocation concealment, randomization sequence	Some concern	No specific information	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Payne et al., 1989 [91]	Some concern	No statement for allocation concealment	Low risk	Both blinded	Low risk	3/41 dropped	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Wood et al., 1994 [111]	Some concern	No statement for allocation concealment	Low risk	Both blinded	Low risk	51/400 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
McGill et al., 1983 [86]	Some concern	No statement for allocation concealment	Low risk	Both blinded	Low risk	3/40 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Wassilew et al., 1987 [89]	Some concern	No statement for allocation concealment, randomization sequence	Low risk	Both blinded	Low risk	2/60 dropped	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Mandal et al., 1988 [90]	High risk	No statement for allocation concealment, randomization sequence, basement difference existed	Low risk	Both blinded	Low risk	8/64 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Lee et al., 1999 [95]	High risk	No statement for allocation concealment, randomization sequence, basement difference existed	Some concern	No specific information	Low risk	No exclusion	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Harding et al., 1986 [119]	Some concern	No statement for allocation concealment	Some concern	No specific information	Some concern	No specific information	Some concern	No specific information	Low risk	Predefined outcomes	Some concern
Kanodia and Singhal, 2011 [99]	Some concern	No statement for allocation concealment, randomization sequence	Low risk	Both blinded	Some concern	No specific information	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Kanodia et al., 2012 [100]	Some concern	No statement for allocation concealment, randomization sequence	Low risk	Both blinded	Some concern	No specific information	Low risk	Blinded	Low risk	Predefined outcomes	Some concern
Manabe et al., 2004 [118]	High risk	No statement for allocation concealment, randomization sequence, basement difference existed	Low risk	Both blinded	Low risk	3/59 dropped, unrelated to the outcome	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Clemmensen and Andersen, 1984 [112]	High risk	No statement for allocation concealment, randomization sequence, basement difference existed	Low risk	Both blinded	Low risk	5/60 dropped, unrelated to outcome	Low risk	Blinded	Low risk	Predefined outcomes	High risk
Eaglstein et al., 1970 [113]	High risk	No statement for allocation concealment, randomization sequence	Low risk	Both blinded	Some concern	1/35 dropped	Low risk	Blinded	Low risk	Predefined outcomes	High risk

suggested a less likely publication bias (**Fig. 6A**). The network diagnostics, using trace and density plots, showed that model convergence was valid in both fixed and random-effects models (**Supplementary Figs. 1D, 1E**). However, the Gelman-Rubin-Brooks methods with PSRF and DIC showed that the random-effects model is a slightly

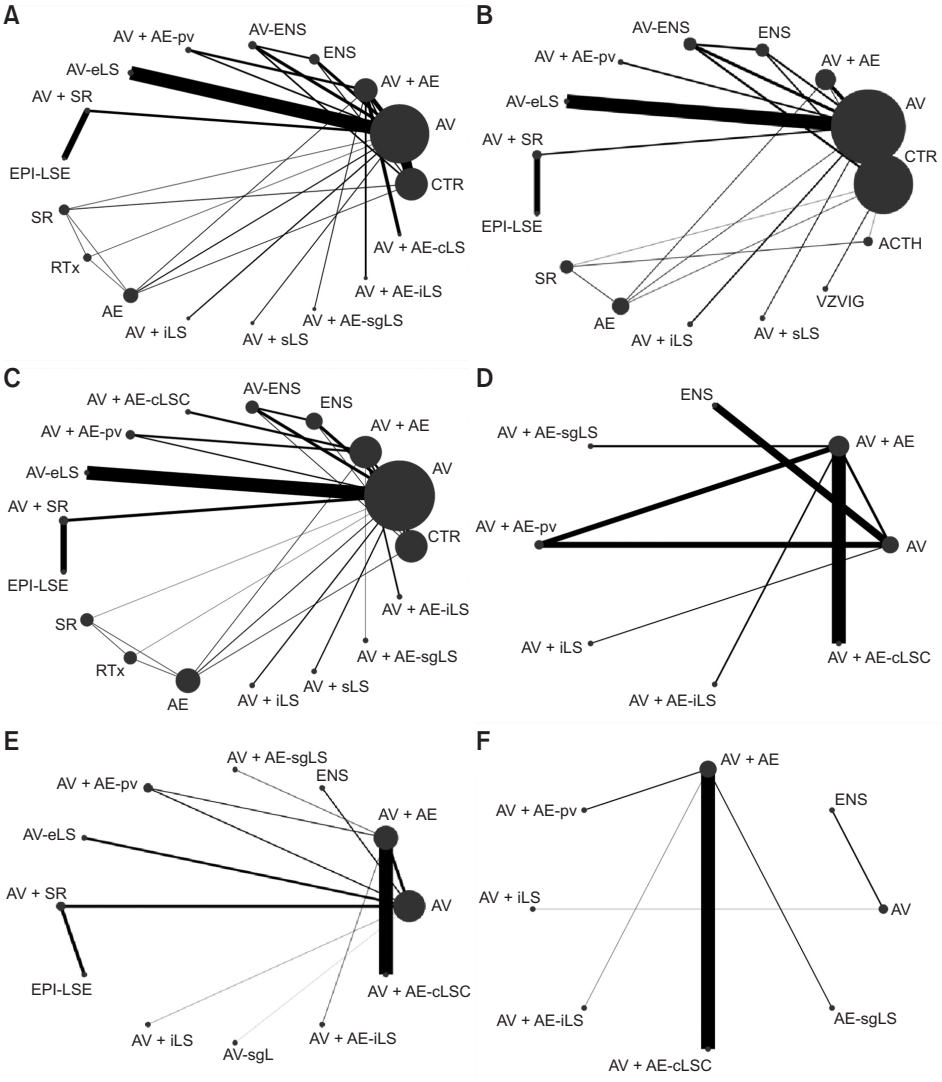

Fig. 2. Network plot of included studies. The nodes show each strategy and the edges show the available direct comparisons among the strategies. The nodes and edges are weighed based on the number of included patients and inverse of standard error of effect. (A) The incidence of postherpetic neuralgia at 3 months after acute herpes zoster, (B) the incidence of postherpetic neuralgia at 1 month after acute herpes zoster, (C) the incidence of postherpetic neuralgia at 6 months after acute herpes zoster, (D) pain score measured at 3 months after acute herpes zoster, (E) pain score measured at 1 month after acute herpes zoster, and (F) pain score measured at 6 months after acute herpes zoster. CTR: control, RTx: radiotherapy, VZVIG: varicella zoster vaccine immunoglobulin, ACTH: adrenocorticotrophic hormone.

better fit for the data (**Supplementary Figs. 1F, 1G, Supplementary Table 1**). Heterogeneity was also decreased in random-effects model compared with fixed-effects model (**Supplementary Table 1**). Thus, we analyzed the data using a random-effects model.

The SUCRA values from the Bayesian model were similar to those from the frequentist model (**Fig. 7A**). When performing a meta-regression analysis using the risk of bias (low risk *vs.* some concern or high risk), age and sex did not improve the model fit or substantially decrease the heterogeneity, and were not considered statistically significant (**Supplementary Table 3**).

6. Incidence of PHN at 1 month after acute HZ

A total of 21 studies (2,612 patients) measured the incidence of PHN at 1 month after acute HZ. Of these, two studies were separated from the loops [117,118]. We performed an NMA excluding those studies. Thus, a total of 19 studies (2,492 patients) were analyzed. The network plot of all eligible comparisons for this endpoint is shown in **Fig. 2B**. Although all 15 management modalities (nodes) were connected to the network, two comparisons (AV and CTR) were more directly comparable than the other 13 nodes. No network inconsistencies were observed [χ^2 (4) = 7.97, P = 0.093].

Ten closed loops were identified in the network after comparing the incidence of PHN at 1 month after acute HZ. Four loops (CTR/AV + AE/AE [93], CTR/ENS/AV-ENS [103], CTR/SR/ACTH [112], and AV/ENS/AV-ENS [103]) were formed only by multi-arm trials. Of the six closed loops, inconsistencies were observed in 1/10/11 (CTR/SR/AE), and 1/2/3 (CTR/AV/AV + AE) (**Fig. 3B**). EPI-LSE, AV + iLS, AV + AE-pV, AV + sLS, and AV + SR showed a lower incidence of PHN at 1 month than CTR, only in terms of 95% CI not in PrI (**Fig. 4B, Supplementary Fig. 2A, Supplementary Table 1B**). The rankograms showed that EPI-LSE followed by AV + AE-pV had the lowest incidence of PHN at 1 month after

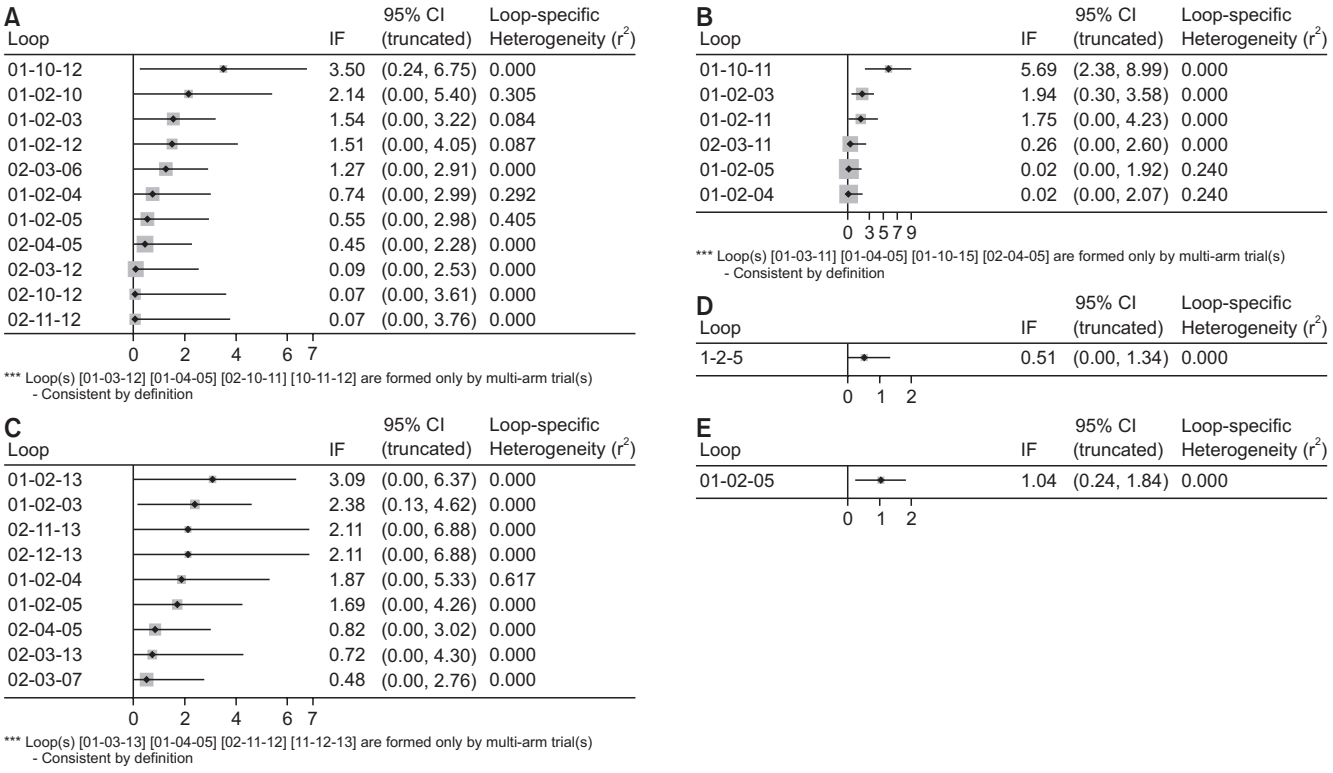

Fig. 3. Inconsistency plot between the direct and indirect effect estimates for the same comparison. Inconsistency factor (IF) as the absolute difference with 95% confidence interval (CI) between the direct and indirect estimates for each paired comparison is presented. IF values close to 0 indicate that the two sources are in agreement. (A) The incidence of postherpetic neuralgia at 3 months after acute herpes zoster, (B) the incidence of postherpetic neuralgia at 1 month after acute herpes zoster, (C) the incidence of postherpetic neuralgia at 6 months after acute herpes zoster, (D) pain score measured at 3 months after acute herpes zoster, and (E) pain score measured at 1 month after acute herpes zoster.

acute HZ (**Supplementary Fig. 2B**). A cumulative ranking plot was drawn, and the SUCRA probabilities of the different interventions for PHN at 1 month after acute HZ were calculated (**Supplementary Fig. 2C**).

According to the SUCRA values, the incidence of PHN at 1 month after acute HZ was lower in the order of the EPI-LSE (98.7%), followed by AV + AE-pV (81.4%), AV + iLS (80.9%), and AV + sLS (77.0%) (**Fig. 5B**). The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, suggesting a lesser probability for publication bias (**Fig. 6B**).

The network diagnostics using trace and density plots showed that model convergence was valid in both fixed-effects and random-effects models (**Supplementary Figs. 2D, 2E**). However, the Gelman-Rubin-Brooks method with the PSRF and DIC showed that the random-effects model is a slightly better fit for the data (**Supplementary Figs. 2F, 2G, Supplementary Table 2**). Thus, we analyzed the data using a random-effects model. The SUCRA values from the Bayesian model were similar to those from the frequentist model, demonstrating the robustness of our analysis (**Fig. 7B**). When performing a meta-regression analysis using the risk of bias (low risk *vs.* some concern or high risk), age and sex did not improve the model fit or substantially decrease the heterogeneity, and were not considered statistically significant (**Supplementary Table 3**).

7. Incidence of PHN at 6 months after acute HZ

A total of 17 studies (2,502 patients) measured the incidence of PHN at 6 months after acute HZ. Although all 17 management modalities (nodes) were connected to the network, three comparisons (AV, AV + AE and CTR) were more directly comparable than the other 14 nodes (**Fig. 2C**). There was no evidence of network inconsistency [χ^2 (6) = 8.72, P = 0.190]. Thirteen closed loops were identified in the network after comparing the incidence of PHN at 6 months after acute HZ, but four loops (CTR/AV + AE/AE [93], CTR/ENS/AV-ENS [103], AV/SR/RTx [92], and SR/RTx/AE [92]) were formed only by multi-arm trials. Of the six closed loops, inconsistencies were observed in the 1/2/3 loop (CTR/AV/AV + AE) (**Fig. 3C**). AV + AE-pv showed a lower incidence of PHN at 6 months after acute HZ than CTR, only in terms of 95% CI (**Fig. 4C, Supplementary Fig. 3A, Supplementary Table 1C**). The AV + AE-cLSC showed marginal significance.

The rankograms and cumulative ranking plot showed that AV + AE-sgLS, AV + AE-cLSC, AV + AE-pv, and AV +

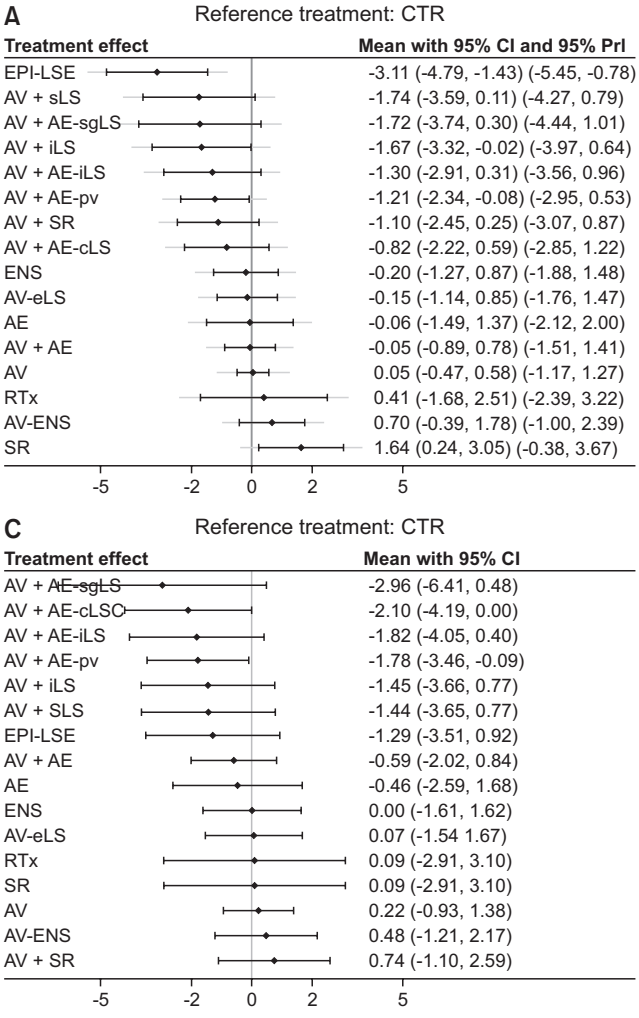

Fig. 4. Predictive interval plots (PrIs) compared with control. A diamond shape represents the mean summary effects. The black line represents the 95% confidence interval (CI), and the red line represents the PrI. PrIs provide an interval that is expected to encompass the estimate of a future study. (A) The incidence of postherpetic neuralgia at 3 months after acute herpes zoster, (B) the incidence of postherpetic neuralgia at 1 month after acute herpes zoster, and (C) the incidence of postherpetic neuralgia at 6 months after acute herpes zoster. CTR: control, RTx: radiotherapy, VZVIG: varicella zoster vaccine immunoglobulin, ACTH: adrenocorticotrophic hormone.

AE-iLS had the lowest incidence of PHN at 6 months after acute HZ (**Supplementary Figs. 3B, 3C**).

According to the SUCRA value, the incidence of PHN at 6 months after acute HZ was lower in the order of the AV + AE-sgLS (87.8%), followed by AV + AE-cLSC (81.7%), AV + AE-pv (77.9%), and AV + AE-iLS (76.0%) (**Fig. 5C**). The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, suggesting a lesser probability for publication bias (**Fig. 6C**). The network diagnostics, using trace and density plots, showed that model convergence was valid in both fixed-effects and random-effects models (**Supplementary Figs. 3D, 3E**). However, the Gelman-Rubin-Brooks methods with PSRF and DIC showed that the random-effects model is a slightly better fit for the data (**Supplementary Figs. 3F, 3G, Supplementary Table 2**). Thus, we analyzed the data using a random-effects model.

The SUCRA values from the Bayesian model were similar to those from the frequentist model, demonstrating the robustness of our analysis (**Fig. 7C**). When performing a meta-regression analysis using the risk of bias (low risk *vs.* some concern or high risk), age and sex did not improve the model fit or substantially decrease the heterogeneity, and were not considered statistically significant (**Supplementary Table 3**).

8. Pain score measured at 3 months after acute HZ

A total of 14 studies (2,047 patients) measured the pain score at 3 months after acute HZ. Of these, three studies [104,114,119] did not report any information on the degree of scattering. Thus, we attempted to contact the study authors but could not obtain information on the degree of scattering. As two studies were separated from the loops [110,120], we performed an NMA, excluding those studies. Thus, only nine studies (1,225 patients) were analyzed. The network plot of all eligible comparisons for this endpoint is shown in (**Fig. 2D**). Eight management modalities (nodes) were connected to the network. One closed loop (the 1/2/5 loop) (AV/AV + AE/AV + AE-pv) was identified in the network after comparing the pain score at 3 months after acute HZ, which shows no evidence of inconsistency

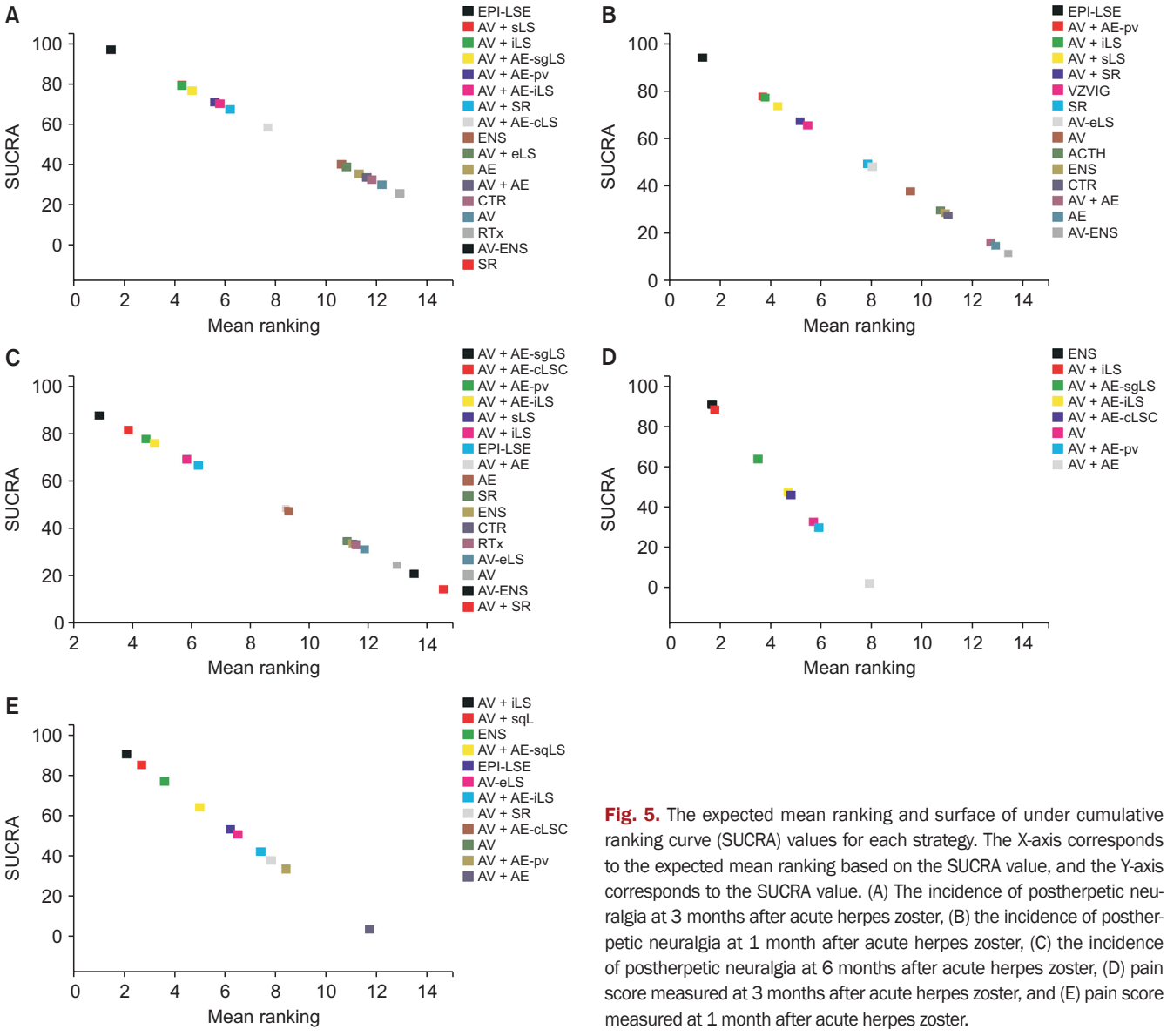

Fig. 5. The expected mean ranking and surface of under cumulative ranking curve (SUCRA) values for each strategy. The X-axis corresponds to the expected mean ranking based on the SUCRA value, and the Y-axis corresponds to the SUCRA value. (A) The incidence of postherpetic neuralgia at 3 months after acute herpes zoster, (B) the incidence of postherpetic neuralgia at 1 month after acute herpes zoster, (C) the incidence of postherpetic neuralgia at 6 months after acute herpes zoster, (D) pain score measured at 3 months after acute herpes zoster, and (E) pain score measured at 1 month after acute herpes zoster.

(**Fig. 3D**).

A PrI plot and league table comparing all groups were drawn (**Supplementary Fig. 4A, Supplementary Table 1D**). The rankograms and cumulative ranking plot showed that AV + iLS and ENS had the lowest pain score at 3 months (**Supplementary Figs. 4B, 4C**). According to the SUCRA values, the pain score at 3 months was lower in the order of the ENS (93.0%) followed by AV + iLS (91.0%), followed by AV + AE-sgLS (65.9%) (**Fig. 4E**). The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, which suggested a lesser probability for publication bias (**Fig. 6D**). The network diagnostics using trace and density plots showed that model convergence was valid in both fixed-effects and random-effects models (**Supplementary Figs. 4D, 4E**). However, the Gelman-Rubin-Brooks methods with PSRF and DIC showed that the random-effects model is a slightly better fit for the data (**Supplementary Figs. 4F, 4G, Supplementary Table 2**). Thus, we analyzed data using random-effects model.

The SUCRA values from the Bayesian model were similar to those from the frequentist model, demonstrating the robustness of our analysis (**Fig. 7D**). When performing a meta-regression analysis using the risk of bias (low risk *vs.* some concern or high risk), age and sex did not improve the model fit or substantially decrease the heterogeneity, and were not considered statistically significant (**Supplementary Table 3**).

9. Pain score measured at 1 month after acute HZ

A total of 21 studies (2,758 patients) measured the pain

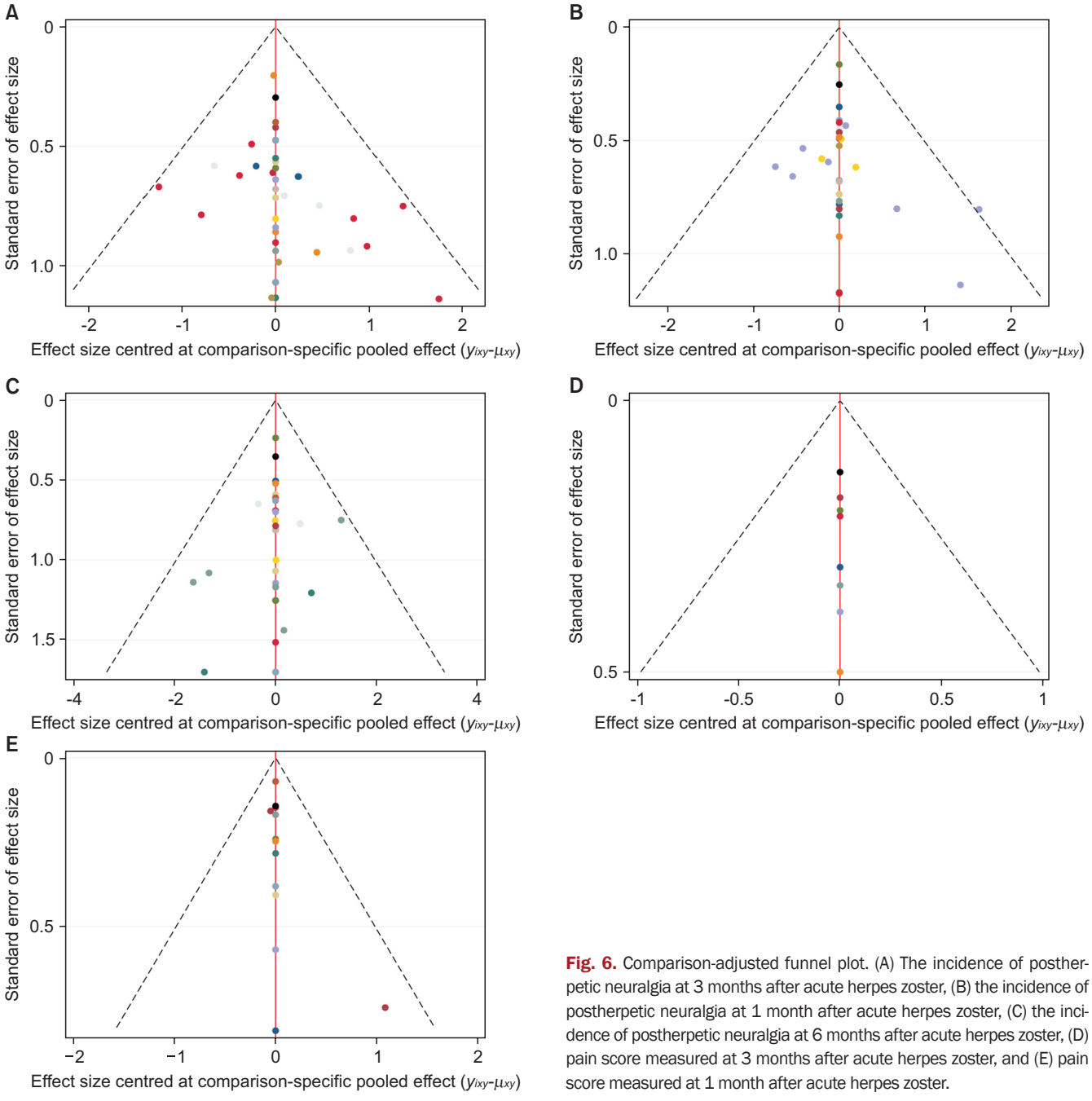

Fig. 6. Comparison-adjusted funnel plot. (A) The incidence of postherpetic neuralgia at 3 months after acute herpes zoster, (B) the incidence of postherpetic neuralgia at 1 month after acute herpes zoster, (C) the incidence of postherpetic neuralgia at 6 months after acute herpes zoster, (D) pain score measured at 3 months after acute herpes zoster, and (E) pain score measured at 1 month after acute herpes zoster.

score at 1 month after acute HZ. Of these, three studies [104,114,119] did not report any information on the degree of scattering. Thus, we attempted to contact the study authors, but could not obtain information on the degree of scattering. As three studies were separated from the loops [116,117,120], we performed NMA excluding those studies. Thus, only 15 studies (2,385 patients) were analyzed. The network plot of all eligible comparisons for this endpoint is shown in (**Fig. 2E**). Although all 12 management modalities (nodes) were connected to the network, two comparisons (AV and AV + RE) were more directly comparable than the other 10 nodes.

There was no evidence of network inconsistency [χ^2 (1) = 0.14, P = 0.713]. One closed loop (the 1/2/5 loop) (AV/AV + AE/AV + AE-pv) was identified in the network after comparing the pain scores at 1 month after acute HZ, which showed inconsistencies in this loop (**Fig. 3E**).

A PrI plot and league table, comparing all groups, were drawn (**Supplementary Figs. 5A, Supplemeantary Table 1E**).

The rankograms and cumulative ranking plot showed that AV + iLS and AV + AE-sqLS had the lowest pain score at 1 month (**Supplementary Figs. 5B, 5C**). According to the SUCRA values, the pain score at 1 month was lower in the

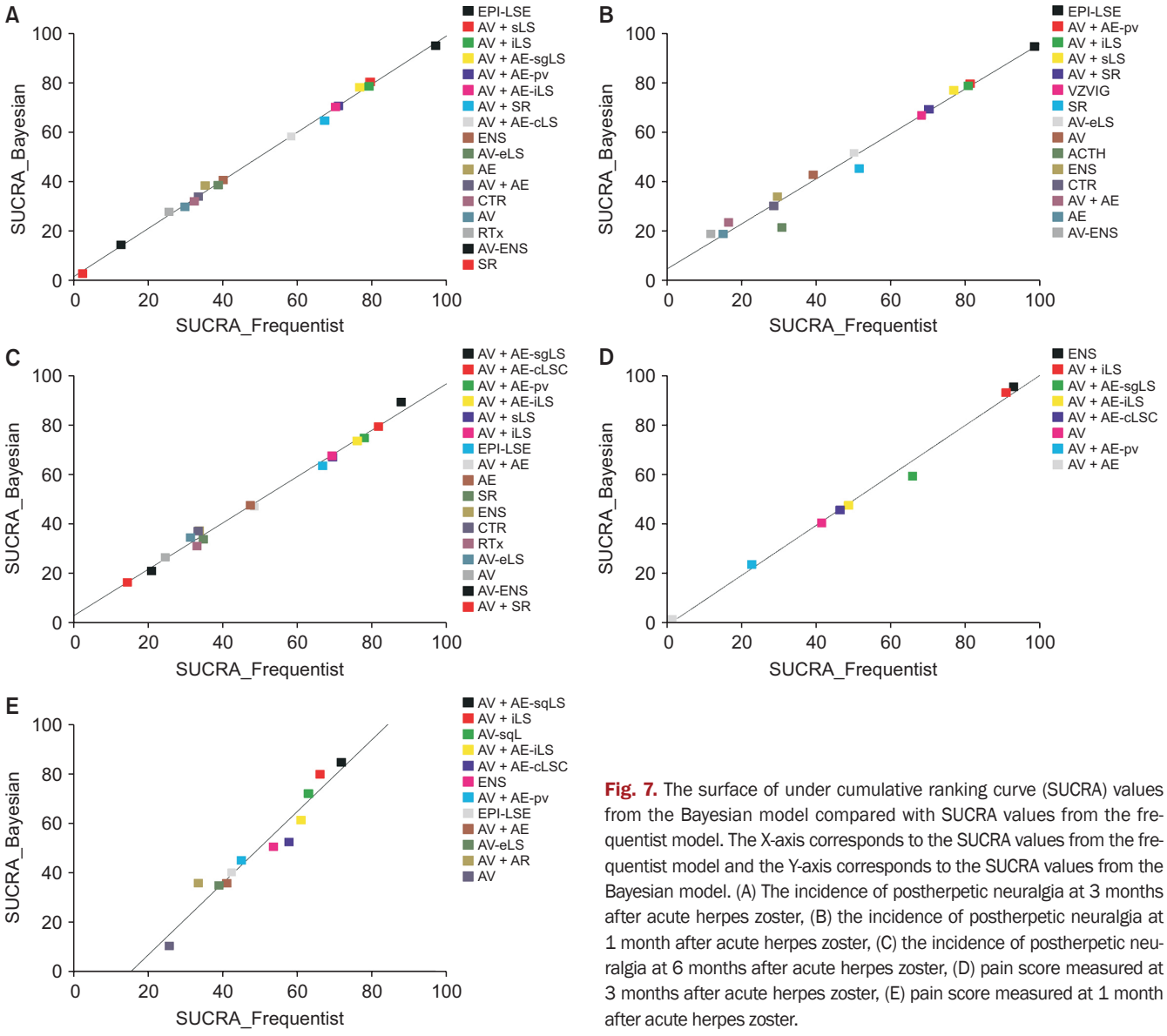

Fig. 7. The surface of under cumulative ranking curve (SUCRA) values from the Bayesian model compared with SUCRA values from the frequentist model. The X-axis corresponds to the SUCRA values from the frequentist model and the Y-axis corresponds to the SUCRA values from the Bayesian model. (A) The incidence of postherpetic neuralgia at 3 months after acute herpes zoster, (B) the incidence of postherpetic neuralgia at 1 month after acute herpes zoster, (C) the incidence of postherpetic neuralgia at 6 months after acute herpes zoster, (D) pain score measured at 3 months after acute herpes zoster, (E) pain score measured at 1 month after acute herpes zoster.

order of the AV + AE-sgLS (71.8%), followed by AV + iLSL (66.1%), AV-sgL (63.0%), and AV + AE-iLS (61.0%) (**Fig. 5E**). The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, suggesting a lesser probability for publication bias (**Fig. 6E**).

The network diagnostics, using trace and density plots, showed that model convergence was valid in both fixed-effects and random-effects model (**Supplementary Figs. 5D, 5E**). However, the Gelman-Rubin-Brooks methods with PSRF and DIC showed that the random-effects model is a slightly better fit for the data (**Supplementary Figs. 5F, 5G, Supplementary Table 2**). Thus, we analyzed data using the random-effects model.

The SUCRA values from the Bayesian model were similar to those from the frequentist model, demonstrating the robustness of our analysis (**Fig. 7E**).

When performing a meta-regression analysis using the risk of bias (low risk *vs.* some concern or high risk), age and sex did not improve the model fit or substantially decrease the heterogeneity, and were not considered statistically significant (**Supplementary Table 3**).

10. Pain score measured at 6 months after acute HZ

A total of 10 studies (1,407 patients) measured the pain score at 6 months after acute HZ. Of these, two studies [97,114] did not report any information on the degree of scattering. Thus, we attempted to contact the study authors but could not obtain information for the degree of scattering. As two studies were separated from the loops [110,120], we performed an NMA excluding those studies. However, as the ENS/AV/AV + iLS loop and AV + AE-pV/AV

Table 3. The GRADE evidence quality for each outcome

	Number of studies	Number of patients	Quality assessment					Quality
			ROB	Inconsistency	Indirectness	Imprecision	Publication bias	
Incidence of postherpetic neuralgia at 3 mo after acute herpes zoster	26	3,072	Not serious	Not serious	Serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Incidence of postherpetic neuralgia at 1 mo after acute herpes zoster	19	2,492	Not serious	Not serious	Serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Incidence of postherpetic neuralgia at 6 mo after acute herpes zoster	17	2,502	Not serious	Not serious	Serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Pain score measured at 3 mo after acute herpes zoster	9	1,225	Not serious	Not serious	Serious	Serious	Not serious	⊕⊕◯◯ Low
Pain score measured at 1 mo after acute herpes zoster	15	2,385	Not serious	Not serious	Serious	Not serious	Not serious	⊕⊕⊕◯ Moderate

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation, ROB: risk of bias.

+ AE/AV + AE-iLS/AV + AE-cLSC/AE-sgLS were separated, an NMA was not performed (**Fig. 2F**).

11. Quality of the evidence

Five outcomes were evaluated using the GRADE system. The evidence quality was moderate for the incidence of postherpetic neuralgia at 1, 3, and 6 months after acute HZ and the pain score measured at 1 month after acute HZ, whereas the evidence quality was low for pain score measured at 3 months after acute HZ (**Table 3**).

DISCUSSION

The present NMA demonstrated that decreasing the incidence of PHN at 3 months after acute HZ in the order of EPI-LSE, AV + sLS, AV + iLS, AV + AE-sgLS, and AV + AE-pV.

After the initial infection, VZV remains in a latent state inside the dorsal root ganglion. A decrease in cell-mediated immunity due to various reasons reactivates latent VZV, thus inducing inflammatory reactions, finally leading to central and peripheral nerve damage. During these processes, unilateral and painful skin eruptions develop along the dermatome of the damaged nerve. Damaged central and peripheral nerves induce repetitive stimuli, an increase in neuronal excitability, an alteration in pain perception, and central sensitization in the nociceptive system, which subsequently leads to the development of PHN [121-123].

Our study showed that EPI-LSE was most effective in preventing PHN at 1 and 3 months after acute HZ; this finding is consistent with that of a previous systematic review, which reported that continuous epidural block is effective in preventing PHN at 3 months after acute HZ [13]. Epidural local anesthetics, steroids, and epinephrine reduce local inflammation in the dorsal root ganglia and attenuate central sensitization, thus showing the preventive effects of EPI-LSE. Epidural analgesia also has the theoretical benefit of reducing the systemic toxicity of pharmacologic agents, because the amount of pharmacologic agent used in epidural analgesia is reduced compared with that used for systemic administration. Although many studies suggest significant benefits from epidural analgesia [79,110], some studies only showed the short-term effects of this strategy in acute pain [124].

Many clinicians prescribed antiviral agents immediately after the appearance of cutaneous rash. Because viral replication induces nerve inflammation and the adjuvant tissue damage, blocking the viral replication through the administration of antiviral agents is thought to play an important role in the treatment of acute HZ and prevention of PHN. A previous systematic review showed that antiviral agents administered within 72 hours after the onset of skin rash may decrease the incidence or duration of PHN [12]. However, another systematic review reported that antiviral agents have no effect in reducing the incidence of PHN [125]. These differences may be because prevention of PHN can only be achieved when nerve damage and inflammatory reactions caused by viral proliferation are reduced, and central sensitization is attenuated by inhibiting the transmission of nociceptive afferent signals caused by previous damage.

In our study, the antiviral agents alone did not show a preventive effect compared with a placebo. However, antiviral agents combined with subcutaneous or intracutaneous injection of local anesthetics and steroids have shown beneficial effects. The effects of subcutaneous [106,126] and intracutaneous injections [105,107] have also been demonstrated in several previous studies when combined with antiviral agents. Local anesthetics injected in subcutaneous or intracutaneous lesions may block the

C-nociceptors and the afferent transmission of painful signals. Furthermore, a steroid in the injectate decreased the neural inflammation and had a neuroprotective effect [127]. These mechanisms act synergistically to reduce pain and prevent PHN. These interventions combined with antiviral agents can be useful strategies to prevent PHN in clinical practice, because subcutaneous or intracutaneous injection is a safe, convenient, and time-efficient interventional technique.

The paravertebral block is one of the most commonly used interventions for reducing pain in patients with acute HZ. A paravertebral block is characterized by direct penetration of local anesthetics into the spinal nerve, including the dorsal ramus, rami communicants, and sympathetic chain. In our study, a paravertebral block combind with antiviral and antiepileptic agents was effective in preventing PHN at 1, 3, and 6 months; this findings is consistent with that of a previous meta-analysis, which reported the favorable impact of the paravertebral block on the prevention of PHN [13]. Although paravertebral block and epidural analgesia showed an equivalent analgesic effect for thoracotomy pain [128,129], the preventive effect of PHN in AV + AE-pV was longer (at 1, 3, and 6 months) than that in EPI-LSE (at 1 and 3 months). This difference may be because sympathetic blockade in the paravertebral block induces the interruption of vasospasm of endoneural arterioles and prevention of re-spasm, thereby providing a longer blocking effect and a more beneficial effect on attenuating the central sensitization [48,102]. However, although theoretical benefits through various mechanisms were expected, no additional benefit was shown for paravertebral blocks repeated more than twice [130]. Therefore, additional well-designed RCTs related to the time and number of trials for effective prevention are needed. Adding antiepileptic and antiviral agents to the paravertebral block also extends the duration of preventive effects by inhibiting viral proliferation at an early stage of the neuropathic component of pain.

The present study has several limitations. First, as with all systematic reviews and meta-analyses, there was demographic, clinical, and methodological heterogeneity. However, we evaluated the transitivity assumption and performed a meta-regression analysis, which suggested the presence of heterogeneity; however, the heterogeneity had less impact on the outcomes. Second, the estimates through the NMA might be affected by inconsistencies in the NMA that compared more than two arms [131,132]. When we carefully reviewed the inconsistency in the entire network and loop to enhance the reliability of the results, overall inconsistency was less likely. The strategies determined in the current NMA were effective in a limited number of clinical trials. As our NMA was based on various single-center small-scale trials, the risk of overestimation or underestimation of the true treatment effects or lack of power to discriminate the effectiveness of strategies to prevent PHN may be present. Thus, more data from well-designed and high-quality RCTs, according to the consensus-based definition of PHN and standardized outcome assessment, are needed to verify our results.

Despite these limitations, the current NMA has several strengths compared with previous meta-analyses. First, this is the first NMA to compare and quantify the rank order of the relative effects of various strategies for preventing PHN, which may help patients, clinicians, and policy makers make evidence-based decisions when selecting strategies for preventing PHN. Second, a rigorous methodology based on a published, pre-planned protocol with a sensitive and systematic search was used. Third, inconsistencies among the enrolled studies were not significant, and the publication bias among the enrolled studies was minimal.

In summary, the continuous epidural block with local anesthetics, antiviral agents with intracutaneous or subcutaneous injection with local anesthetics and steroid, and paravertebral block combind with antiviral and antiepileptic agents are effective strategies for preventing PHN.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3344/kjp.2021.34.4.509.

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Appendix. Search term

MEDLINE

1. randomized controlled trial.pt
2. randomized controlled trial$.mp
3. controlled clinical trial.pt
4. controlled clinical trial$.mp
5. random allocation.mp
6. exp double-blind method/
7. double-blind.mp
8. exp single-blind method/
9. single-blind.mp
10. or/1-9
11. clinical trial.pt
12. clinical trial$.mp
13. exp clinical trial/
14. (clin$ adj25 trial$).mp
15. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).mp
16. random$.mp
17. exp research design/
18. research design.mp
19. or/11-18
20. 10 or 19
21. Case report.tw.
22. Letter.pt.
23. Historical article.pt.
24. Review.pt.
25. or/21-24
26. 20 not 25
27. Exp Neuralgia, Postherpetic/
28. Zoster-associated pain.mp
29. Herpetic pain.mp
30. Herpetic Neuralgia.mp
31. Postherpetic neuralgia.mp
32. PHN.mp
33. or/27-32
34. Herpes zoster.mp
35. Herpes$.mp
36. herpetic$.mp
37. HHV.mp
38. Zona.mp
39. Zoster.mp
40. Shingles.mp
41. Varicella.mp
42. Chickenpox.mp
43. post-herpetic.mp
44. VZV.mp
45. Or 34-44/
46. neuralgi$.mp
47. pain.mp
48. or 46-47/
49. 45 and 48

50. 33 or 49
51. 26 and 50
52. Exp Antidepressive agents/
53. Amitriptyline.mp
54. (Damilen or Domical or Tryptine or Tryptizol or Tryptanol or Elavil or Amineurin or Amitrip or Laroxyl or Endep or Lentizol or Novoprotect or Saroten or Syneudon or Triptafen or Amitrol or Anapsique or Amitriptylin$).ti,ab,hw.
55. Norttriptyline.mp
56. (Allegron or Aventyl or Noritren or Norpress or Nortrilen or Norventyl or Norzepine or Pamelor or Sensoval) .ti,ab,hw.
57. Imipramine.mp
58. (Tofranil orTofranil-PM or Imiprami$ or imizine).ti,ab,hw.
59. Milnacipran.mp
60. (Ixel or Toledomin or Dalcipran or savella or impulsor).ti,ab,hw.
61. Or 52-60/
62. Exp anticonvulsants/
63. Gabapentin.mp
64. (Gabapentin or Neurontin).ti,ab,hw.
65. Pregabalin.mp
66. (Pregabalin or Lyrica).ti,ab,hw.
67. Carbamazepine.mp
68. (Carbamazepin$ or Neurotol or Tegretol or Amizepine or Epitol or Carbazepin or Finlepsin).ti,ab,hw.
69. Oxycarbamazepine.mp
70. (oxycarbazep$ or OCBZ or Oxtellar or Trileptal).ti,ab,hw
71. OR 62-70/
72. Exp Capsaicin/
73. (Capsaicin$ or Nonenamide or Axsain or Zacin or Capsicum or Capsidol or Zostrix or Capzasin or Gelcen or Katrum or Capsin).ti,ab,hw.
74. Exp Botulinum Toxins/
75. (Jeuveau or Botox or Xeomin or Myobloc or Neuronox or BTX or Neurobloc).ti,ab,hw.
76. Exp analgesics/
77. Exp analgesics, opioid/
78. (Morphine or Fentanyl or Alfentanil or Sufentanil or Remifentanil or Buprenorphine or Meperidine or Pethidine or Nalbuphine or pentazocin or butophanol or nalorphine or oxycodone or hydromorphone or oxynorm or methadone).ti,ab,hw.
79. Exp Anti-Inflammatory Agents, Non-Steroidal/
80. (aspirin or diclofenac or Cambia or Cataflam or Voltaren-XR or Zipsor or Zorvolex or diflunisal or Dolobid or etodolac or ibuprofen or Motrin or Advil or indomethacin or Indocin or ketoprofen or Active-Ketoprofen or Orudis or ketorolac or Toradol or nabumetone or Relafen or naproxen or Aleve or Anaprox or Naprelan or Naprosyn or oxaprozin or Daypro or piroxicam or Feldene or salsalate or Disalsate or Amigesic or sulindac or Clinoril or tolmetin or Tolectin).ti,ab,hw.
81. Exp Cyclooxygenase 2 Inhibitors/
82. (cox 2 or Celecoxib or Consensi or valdecoxib or Bextra or Rofecoxib or Vioxx or Celebrex or Etoricoxib).ti,ab,hw.
83. Exp acetaminophen/
84. (Paracetamol or APAP or acetyl-para-aminophenol or Actamin or Anacin AF or Apra or Bromo Seltzer or Children's Tylenol or Elixsure Fever/Pain or Mapap or Medi-Tabs or Q-Pap or Silapap Childrens or Tactinal or Tempra Quicklets or Tycolene or Tylenol or Vitapap).ti,ab,hw.
85. Exp Lidocaine/
86. (Lidocaine or Lignocaine or Xyloneural or Octocaine or Xylesthesin or Xylocaine or Xylocitin or Dalcaine or Versatis).ti,ab,hw.
87. Exp Ketamine/
88. (Ketamin or Ketamina or Ketamine or Ketaminol or Ketanest or Ketaset or Tekam or Vetalar or Ketalar or Calipsol or Kalipsol or Calypsol).ti,ab,hw.

89. Exp clonidine/
90. (Klofenil or Clofenil or Chlophazolin or ST-155 or ST 155 or ST155 or Gemiton or Hemiton or Isoglaucon or Klofelin or Clofelin or Clopheline or M-5041T or M 5041T or M5041T or Catapres or Catapresan or Catapressan or Dixarit).ti,ab,hw.
91. Exp Dexmedetomidine/
92. (Dexmedetomidin$ or MPV-1440 or MPV 1440 or MPV1440 or Precedex or MPV 785).ti,ab,hw.
93. Exp Vitamin B 12/
94. (Vitamin B12 or Cyanocobalamin or Cobalamins or Cobalamin or Eritron).ti,ab,hw.
95. Or 52-94/
96. Exp Nerve Block/
97. Nerve.mp
98. Block$.mp
99. 97 and 98
100. Chemical.mp
101. Neurolys$.mp
102. 100 and 101
103. Chemodenervation$.mp
104. 96 or 99 or 102 or 103
105. Neuraxial block.mp
106. Exp Anesthesia, Epidural/
107. Epidural block.mp
108. Paravertebral block.mp
109. stellate ganglion block.mp
110. local injection.mp
111. Exp Transcutaneous Electric Nerve Stimulation/
112. Nerve stimulation.mp
113. Exp Pulsed Radiofrequency Treatment/
114. Heat RF.mp
115. Exp spinal cord stimulation/
116. Exp Electroacupuncture/
117. Destruction and (dorsal root ganglion or drg).mp
118. Nerve destruction.mp
119. Exp Acupuncture/
120. (acupuncture or needle or needling or electro-acupuncture or cupping or moxibustion or pricking or pyonex or bloodletting).mp
121. Exp Anesthesia, Local/
122. OR 96-121/
123. 95 OR 122
124. 51 AND 123