Systematic Review

The Treatment of Topical Drugs for Postherpetic Neuralgia: A Network Meta-Analysis

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Background: Postherpetic neuralgia (PHN) is a neuropathic pain that causes a reduction in patients' quality of life. There are many topical drugs for PHN, including topical lidocaine patch, topical application of capsaicin, and others.

Objectives: This study aims to compare the efficacy and safety of topical drugs for PHN.

Study Design: Relevant studies were found by systemically searching for terms including "topical" and "Postherpetic neuralgia" in PubMed, Cochrane library, MEDLINE, and EMBASE databases (inception through June 12, 2019). The primary outcome was the percentage of change in the Numeric Rating Scale or the Visual Analog Scale scores from baseline. The secondary outcome was the number of adverse events.

Methods: The efficacy and safety of topical drugs for PHN was investigated by the pairwise meta-analysis and Bayesian network meta-analysis, applying Revman 5.3, the Stata 14.0 software, and GeMTC 0.14.3.

Results: Twelve studies met the inclusion criteria, and eligible studies were selected for the ultimate meta-analysis. Our meta-analysis displayed 6 topical drugs for PHN. Lidocaine, high-concentration capsaicin, and aspirin/diethyl ether (ADE) had a higher possibility of bringing pain relief than placebo. Among them, lidocaine had the highest possibility of being the most effective drug for PHN and had the statistical significances compared with diclofenac, high-concentration capsaicin, indomethacin, low-concentration capsaicin, and placebo, and lidocaine was significantly preferable than other effective drugs in the aspect of safety.

Limitations: (1) The small number of included studies; (2) a small number of patients and short-term trials in progress, including lidocaine and ADE; (3) both randomized controlled trial and crossover randomized trial were included in our network meta-analysis; (4) only studies published in English were evaluated; (5) lack of head-to-head comparisons of some treatments; (6) different measurement methods were used in different trial, which may cause deviation; and (7) with the lack of cycles in the included trials, the inconsistency factors cannot be calculated, and node-splitting method cannot be performed in our network meta-analysis to check the inconsistency.

Conclusions: Compared with other topical drugs, lidocaine was the most effective and most tolerable drug to be recommended for PHN.

Key words: Topical agents, postherpetic neuralgia

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Postherpetic neuralgia (PHN), a neuropathic pain syndrome, is the persistent complication that follows an outbreak of acute herpes zoster and it typically begins after 1 to 6 months of lesion crusting. PHN occurs in approximately 10% to 20% of patients who are aged 50 years or older after the 3 months of zoster onset (1). Additionally, the number of patients with PHN greatly increases with age. The

incidence rate of PHN is up to 75% in patients who are aged 70 years or older after the acute episode of herpes zoster (2). The quality of life of patients is affected by this persistent symptom, which may even persist for years (3). The underlying mechanisms have been explored in these 2 aspects: (1) the persistent vesicular stomatitis virus exists after the acute episode of herpes zoster, and its level is higher than incubation, and as a result, it makes sustaining pain (4); and (2) the infection of acute zoster may cause neural damage, which changes pain perception and enhances neuronal excitability (5).

The first- and second-line drugs for PHN include pregabalin, gabapentin, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and others (6), however, systemic therapy for PHN is often limited by the problems of poor tolerance and safety (7). The limitations of these medicines have promoted the development of topical drugs, including topical lidocaine patch, topical application of capsaicin, and others (8,9). According to previous studies, lidocaine is usually recommended as the first-line drug, whereas capsaicin may be the second-line drug in case of adverse reactions for PHN (10,11).

However, these recommendations were tested by the direct comparison studies or traditional meta-analysis. To the best of our knowledge, the traditional meta-analysis evaluates the single intervention, which confuses clinicians in the choice of rational treatment. The network meta-analysis was designed to comprehensively evaluate the efficacy and safety of topical drugs for PHN.

Methods

Protocol and Registration

The detailed protocol was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO); registration number CRD42019145004. Our meta-analysis agreed with the PRISMA statement, and the network meta-analysis extension statement of PRISMA.

Literature Search

Relevant studies were found by systemically searching for terms including "topical" and "postherpetic neuralgia" in PubMed, Cochrane library, MEDLINE, and EMBASE databases (inception through June 12, 2019). Studies were limited to the randomized controlled trials (RCTs) and English language. The search strategies and details are displayed in Supplementary File 1.

Inclusion and Exclusion Criteria

The inclusive criteria used for selection of studies were as follows: (1) the patients were diagnosed with PHN; (2) interventions were topical drugs, including topical lidocaine patch, topical application of capsaicin, and others; (3) the primary outcome was the percentage of change in pain relief from the baseline, applying the Visual Analog Scale or the Numeric Rating Scale, and the subordinate outcome was adverse events (AEs) count; and (4) studies were limited to double-blind, RCTs, including crossover trials. Studies that met the following criteria were excluded: (1) cohort study, case–control study, case reports, case series, and narrative reviews; (2) animal experiments; (3) publications in non-English languages; (4) publications that did not provide sufficient data; (5) the comparation was not among the topical drugs; and (6) patients with nerve injury and other peripheral neuropathic pain. In cases of multiple publications from the overlapping cohorts, only the most recent comprehensive results with the largest sample size were included in this study for data analyses.

Selection of Studies

In the primary screening process, 2 reviewers (XL and JZ) independently examined the titles and abstracts of the potential studies. The full text of each study was individually retrieved and checked in the secondary screening. Subsequently, all relevant studies were obtained for independent assessment by the other 2 reviewers (QZ and KL) according to the inclusive and exclusive criteria. If there was any contradiction, the disagreement was resolved by the third author (LW).

Assessment of Study Quality and Data Extraction

The Cochrane risk of bias tool was adopted for assessing the risk of bias of the studies included (12). The scale consists of several domains, including random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data reporting, selective reporting, and other biases. Each domain was rated as "high risk," "unclear risk," or "low risk." Two authors (XL and JZ) independently assessed the quality of the studies and extracted the data from each study, including the information of first author's name, publication year, country of origin, population size, follow-up period, specific treatment, and pain scale. If there was any contradiction, the disagreement was resolved by the third author (LW).

Statistical Analysis

Meta-analysis was applied by Revman 5.3 (Cochrane Collaboration, Oxford, UK), the Stata 14.0 (StataCorp LP, College Station, TX, USA), and GeMTC 0.14.3 software (MRC Biostatistics Unit, Cambridge, UK). The network meta-analysis was implemented based on the Bayesian framework. Standardized mean difference (SMD), odds ratio (OR), and 95% confidence interval (CI) were calculated to investigate the efficacy and safety of competing interventions for PHN. Each intervention was performed by the traditional pairwise meta-analysis of random effects (13), and the secondary outcome, counts of AEs, was evaluated by the OR for competing interventions with random effects Poisson model. The inclusive drugs were ranked by the Bayesian models, using 4 chains, and running 100,000 iterations with the burn-in phase of 40,000 iterations. The surface under the cumulative ranking curve (SUCRA) was performed to evaluate the efficacy of the comparable drugs for PHN. Node-splitting was applied to check the existence of inconsistency (14). Funnel plots were performed to detect potential publication bias of the inclusive studies (15).

Results

Selection of Studies and Characteristics of Included Studies

After removal of duplications, 375 original studies were obtained from the initial online search. Twenty-eight studies were eligible, according to primary screening of titles and abstracts. After reviewing full text, 16 studies were excluded for the following reasons: (1) duplicate data publication (16-18); (2) no valid data (8,9,19-23); (3) publications in non-English languages (24-26); (4) observational trial (27); and (5) published as conference abstracts (17,28). Twelve studies were finally included in this network meta-analysis based on the inclusion and exclusion criteria (29-40). The flowchart of selection process is shown in Fig. 1. Characteristics of the selected studies are summarized in Table 1.

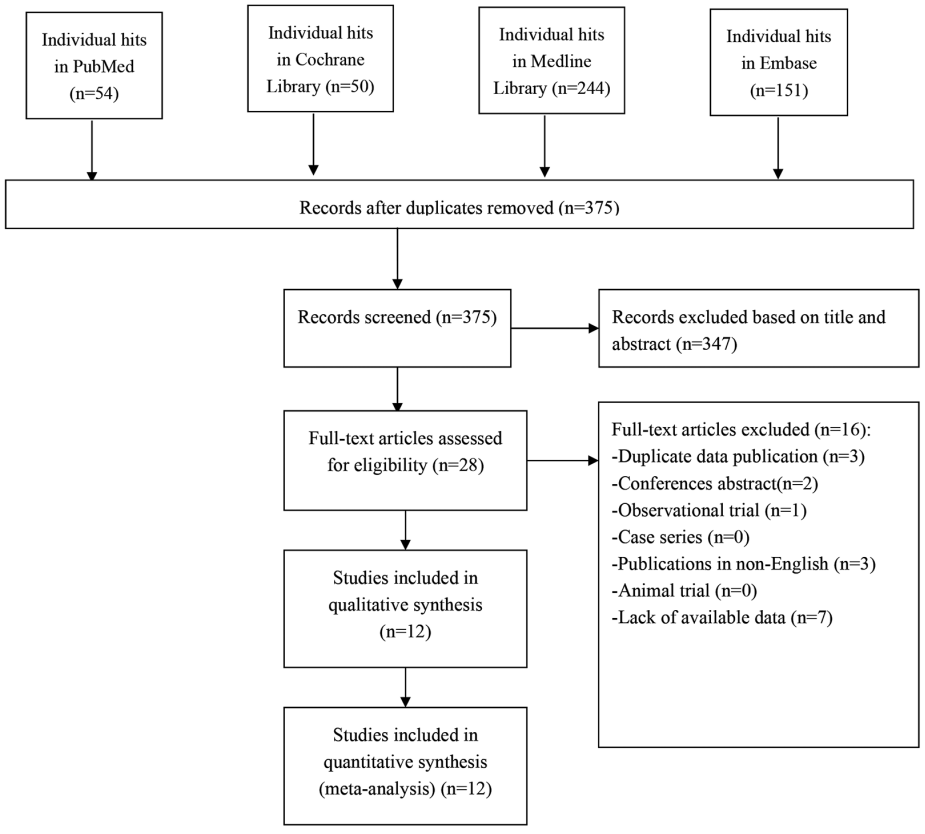

Fig. 1. *Flow diagram presenting the process of the study section.*

Table 1. *Characteristics of studies selected for meta-analyses.*

Study Description									Treatment/Pain Reduction			Control/Pain Reduction			Counts of Adverse Events (AES)		Jadad Scord
Reference	Type of study	Country	Intervention	n (total)	Primary Outcome	Method	Duration of PHN	Duration of Treatment	Percent Change (Mean)	Percent Change (SD)	n	Percent Change (Mean)	Percent Change (SD)	n	Treatment (n,%)	Control (n,%)	
Watson 1993	RCTs	Canada	low-concentration capsaicin VS placebo	143	VAPS	Cream	> 6 months	6 weeks	-15.0%	50.08%	74	-5.2%	16.73%	69	45 (61%)	23 (33%)	4
Webster 2010[a]	RCTs	USA	high-concentration capsaicin VS low-concentration capsaicin	299	NPRS	Patch	> 6 months	12 weeks	-25.0%	30.54%	222	-14.7%	30.80%	77	131 (59%)	43 (56%)	4
Webster 2010[b]	RCTs	USA	high-concentration capsaicin VS low-concentration capsaicin	155	NPRS	Patch	> 3 months	12 weeks	-36.6%	37.87%	102	-32.3%	37.93%	53	76 (75%)	28 (53%)	4
Backonja 2008	RCTs	USA	high-concentration capsaicin VS low-concentration capsaicin	402	NPRS	Patch	> 6 months	12 weeks	-29.9%	30.00%	206	-20.4%	29.96%	196	203 (99%)	174 (88%)	5
Irving 2011	RCTs	USA	high-concentration capsaicin VS low-concentration capsaicin	418	NPRS	Patch	> 6 months	12 weeks	-32.3%	31.01%	212	-25.0%	30.99%	204	208 (98%)	177 (87%)	4
Backonja 2010	RCTs	USA	high-concentration capsaicin VS low-concentration capsaicin	38	NPRS	Patch	> 6 months	4 weeks	-32.7%	29.60%	26	-4.4%	19.90%	12	11 (42%)	2 (17%)	5
Teixeira 2015	crossover randomized trial	Brazil	low-concentration capsaicin VS placebo	13	VAPS	Cream	> 6 months	6 weeks	-24.1%	29.55%	13	-6.0%	40.33%	13	87.50%	60.00%	4
Wasner 2005	crossover randomized trial	Germany	Lidocaine VS placebo	18	VAPS	Patch	N/A	1 week	-28.6%	41.37%	18	-8.6%	38.18%	18	N/A	N/A	4
Kanai 2010	crossover randomized trial	Japan	Lidocaine VS placebo	24	VAPS	eye drops	> 3 months	1 week	-84.8%	34.40%	24	-17.4%	42.26%	24	3 (12.5%)	1 (4.2%)	5
Kanai 2009	crossover randomized trial	Japan	Lidocaine VS placebo	24	VAPS	pump spray	> 3 months	1 week	-62.3%	36.25%	24	-6.6%	27.09%	24	0 (0%)	0 (0%)	4
Giuseppe 1992[a]	crossover randomized trial	Italy	ADE vs placebo	7	VAPS	ethyl ether	> 3 months	4 weeks	-63.0%	36.78%	7	-24.3%	38.89%	2	0 (0%)	0 (0%)	4
Giuseppe 1992[b]	crossover randomized trial	Italy	indomethacin	7	VAPS	ethyl ether	> 3 months	4 weeks	-59.2%	39.69%	7	-24.3%	38.89%	2	1 (14.3%)	0 (0%)	4
Giuseppe 1992[c]	crossover randomized trial	Italy	diclofenac	7	VAPS	ethyl ether	> 3 months	4 weeks	-60.1%	40.22%	7	-24.3%	38.89%	3	0 (0%)	0 (0%)	4

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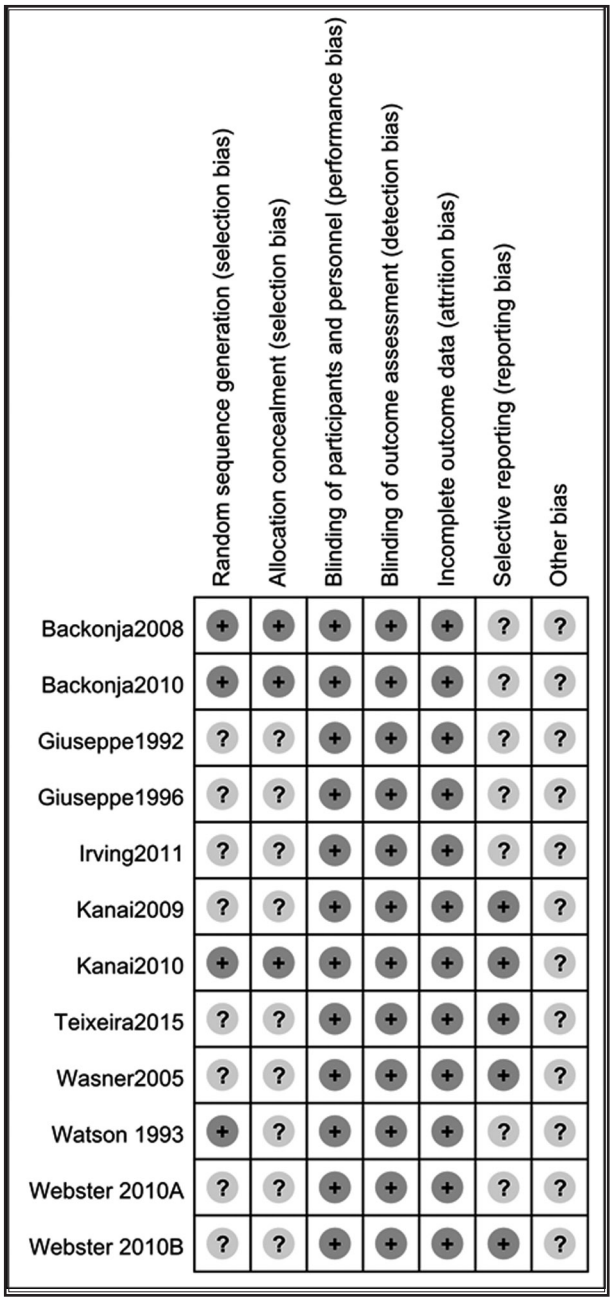
Study Description								Treatment/Pain Reduction			Control/Pain Reduction			Counts of Adverse Events (AES)		Jadad Scord
Reference	Type of study	Country	Intervention	n (total)	Primary Outcome	Method	Duration of PHN	Duration of Treatment	Percent Change (Mean)	Percent Change (SD)	n	Percent Change (Mean)	Percent Change (SD)	n	Treatment (n,%)	Control (n,%)	
Giuseppe 1996	crossover randomized trial	Italy	ADE vs placebo	22	VAPS	ethyl ether	> 3 months	4 weeks	-65.7%	30.49%	22	-34.1%	35.18%	7	0 (0%)	0 (0%)	4
Giuseppe 1996	crossover randomized trial	Italy	indomethacin	22	VAPS	ethyl ether	> 3 months	4 weeks	-47.1%	27.20%	22	-34.1%	35.18%	7	1 (4.5%)	0 (0%)	4
Giuseppe 1996	crossover randomized trial	Italy	diclofenac	22	VAPS	ethyl ether	> 3 months	4 weeks	-46.8%	27.67%	22	-34.1%	35.18%	8	1 (4.5%)	0 (0%)	4

Methodological Quality

According to the Cochrane risk of bias tool, none of the included studies were considered as high risk of bias. However, a large proportion of studies had an unclear risk of selection bias, including random sequence generation (67%) and allocation concealment (75%). Approximately 58% of the studies were considered as low risk of reporting bias. All studies have low risk of performance bias and detection bias. In aspect of the other bias, all studies have unclear risks. The final quality of studies is presented in Table 2, indicating low risk of bias in inclusive studies, and they provided strong evidence for the outcome of the meta-analysis.

Table 2. *The summary by the Cochrane risk of bias tool.*



Efficacy Comparison

All data from the 12 studies were analyzed, consisting of 1,563 patients with PHN and 7 interventions including placebo, low-concentration capsaicin, high-concentration capsaicin, lidocaine, aspirin/diethyl ether (ADE), indomethacin, and diclofenac. Statistical significance of traditional pairwise comparison was found in ADE of -0.95 (95%CI: -1.49, -0.40) versus placebo, high-concentration capsaicin of -0.92 (95%CI: -0.43, -0.15) versus low-concentration capsaicin, and lidocaine of -1.31 (95%CI: -2.11, -0.50) versus placebo, which is presented in Table 3. The weighted network is presented in Fig. 2A. The differences in the efficacy of interventions on pain relief were evaluated by the SMD, which is shown in Table 4, and the rank of the efficacy was based on the Bayesian framework, which is presented in Table 5. According to SUCRA shown in Table 6, the lidocaine ranked first, and was to be the best topical drug for pain relief in PHN. Comparison-adjusted funnel plot is presented in Fig. 3A, which showed possible low risk of publication bias in pain relief.

Safety Comparison of AEs

Eight out of 12 studies were analyzed, consisting of 1,490 patients with PHN and 4 interventions including placebo, low-concentration capsaicin, high-concentration capsaicin, and lidocaine. The major AEs were papules, swelling, pain exacerbation, and others. There were no serious AEs in all treatments. A total of 4 trials were excluded from the meta-analysis due to a lack of the number of AEs. The comparison of AEs was calculated OR and 95% confidence intervals. Statistical significance of traditional pairwise comparison was found in high-concentration capsaicin of 3.40 (95%CI: 1.44, 8.02) versus low-concentration capsaicin of 3.14 (95%CI: 1.65, 5.97), which is presented in Table 7. The weighted network of AEs are presented in Fig. 2B. The differences in safety of interventions on pain relief were evaluated by OR, which is shown in Table 8. High-concentration capsaicin was ranked the least tolerable therapy due to causing the highest number of AEs, and lidocaine was ranked the third tolerable therapy following the low-concentration capsaicin and placebo (PLA), which is presented in Table 9. Comparison-adjusted funnel plot is presented in Fig. 3B and showed possible low risk of publication bias in the AEs.

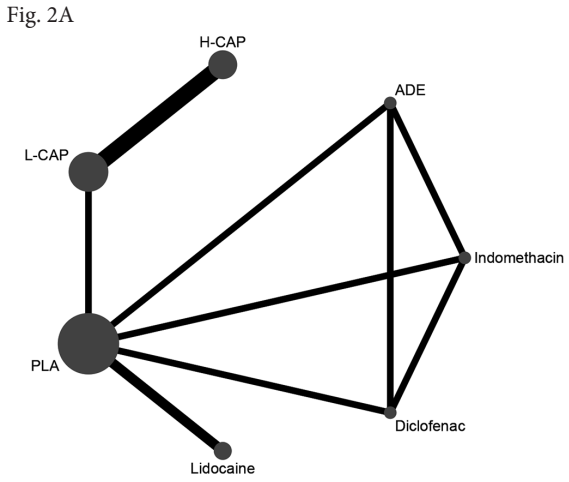
Table 3. *The direct efficacy comparisons of the different classes of treatments.*

Class 1 vs. Class 2	SMD	95%CI		*P* value
		Lower	Upper	
L-CAP VS PLA	-0.29	-0.6	0.01	0.06
H-CAP VS L-CAP	-0.29	-0.43	-0.15	< 0.0001
Lidocaine vs PLA	-1.31	-2.11	-0.5	0.001
Indomethacin VS PLA	-0.5	-1.03	0.02	0.06
Diclofenac VS PLA	-0.5	-1.02	0.03	0.06
ADE VS Diclofenac	-0.5	-1.02	0.03	0.06
ADE VS Indomethacin	-0.5	-1.02	0.03	0.06
Diclofenac VS Indomethacin	0	-0.51	0.52	0.99
ADE VS PLA	-0.95	-1.49	-0.4	0.0007

Discussion

To the best of our knowledge, our network meta-analysis is the most comprehensive data analyses of current topical drugs for PHN. In our network meta-analysis, the inclusive studies used the different measures of pain relief. The SMD was performed in evaluating the percentage of change of efficacy before and after the topical treatment. All the evidence regarding these contrasts comes from the trials that directly compare them. Both consistency model and inconsistency model had similar random effects standard deviation in our network meta-analysis (41). We considered the data of our network meta-analysis to have good consistency, and data can be pooled to perform the network meta-analysis. According to the SUCRAs and overall rank, lidocaine, ADE, and high-concentration capsaicin displayed effective pain relief for PHN. The result of our network meta-analysis is consistent with recommendation of PNH treatment (10,11).

Lidocaine, ADE, and high-concentration capsaicin have been used in neuropathic pain. The link of these 3 topical drugs may be associated with the pain transmission and pain response, which may be greatly important to the development of PHN (5,42-44). The capsaicin was well known as a selective ligand of TRPV1 receptor. Capsaicin has the function of binding with receptors. Repeated exposure of capsaicin leads to reversible desensitization and defunctionalization of TRPV1 receptor, and then the sensory axons containing TRPV1 receptors may enter into a long-term refractory period and have no response to pain stimulation. The



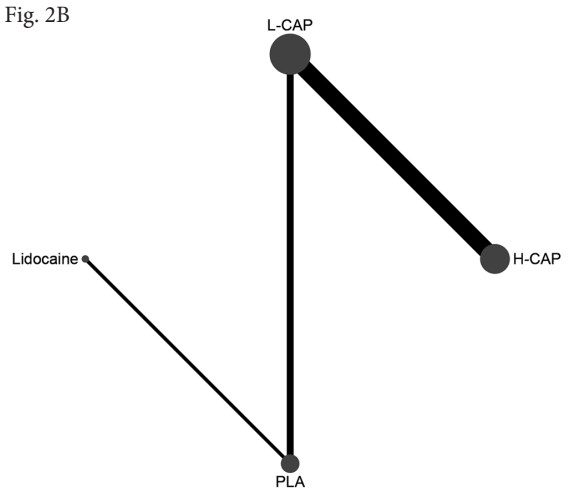


Fig. 2. *(A) A network of efficacy comparisons between the different classes of treatments in this network meta-analysis. (B) A network of AEs comparison between the different classes of treatments in this network meta-analysis.*

Table 4. *The network meta-analysis results of efficacy comparisons.*

ADE						
-16.07 (-34.47, 3.07)	**Diclofenac**					
-12.83 (-37.98, 17.05)	3.31 (-25.72, 31.69)	**HCAP**				
-15.34 (-36.58, 4.01)	0.77 (-18.31, 19.50)	-3.82 (-31.66, 27.36)	**Indomethacin**			
-22.41 (-47.66, 5.46)	-6.50 (-33.87, 20.03)	-9.64 (-18.50, -3.08)	-6.34 (-35.34, 20.60)	**LCAP**		
19.88 (-5.51, 44.79)	36.04 (7.19, 60.12)	32.53 (7.03, 52.86)	35.49 (5.29, 59.90)	42.44 (19.05, 61.84)	**Lidocaine**	
-33.49 (-55.19, -12.87)	-18.24 (-41.14, 2.28)	-21.05 (-40.46, -5.44)	-18.13 (-42.51, 2.18)	-11.16 (-27.86, 3.15)	-53.98 (-67.22, -38.32)	**PLA**

capsaicin also has the ability to degenerate the reversible nerve fiber. As a result, the capsaicin can prevent the pain transmission and reduce the pain response (42,43). The mechanism of aspirin to relieve pain may be its function, including inhibition of prostaglandin synthesis and preventing the sensitization of C polymodal nociceptors (45,46). The potential mechanism of lidocaine to relieve pain may be its sodium channel blocking effect, which directly leads to the dysfunction or damage of pain receptors (44). As mentioned earlier, these 3 topical drugs are able to affect the pain transmission and pain response, thus relieving the pain of PHN. Additionally, topical lidocaine can restrain inflammatory factors of damaged tissue, which also plays an important role in pain (47). It may affect persistent virus that exists in damaged tissue. Therefore lidocaine displayed the most effective pain relief for PHN.

In the aspect of AEs, the evaluation was performed in high-concentration capsaicin (HCAP), low-concentration capsaicin (LCAP), placebo (PLA), and lidocaine by sufficient evidence.

The evidence for ADE, indomethacin, and diclofenac was only found in 2 studies with 29 cases having inadequate data in AEs. ADE, indomethacin, and diclof-

Fig. 3A

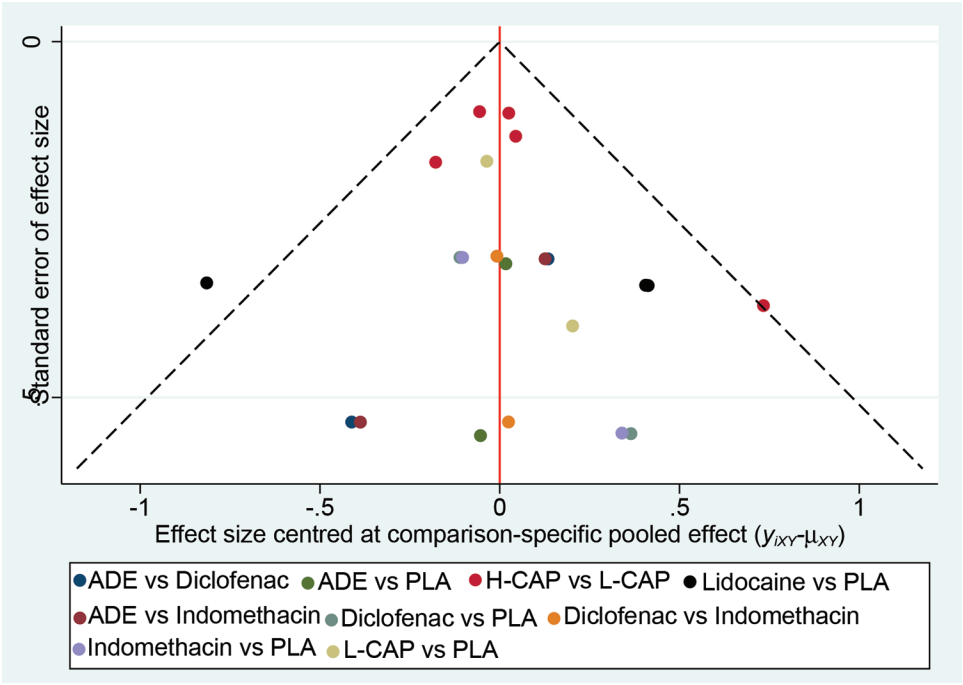


Fig. 3B

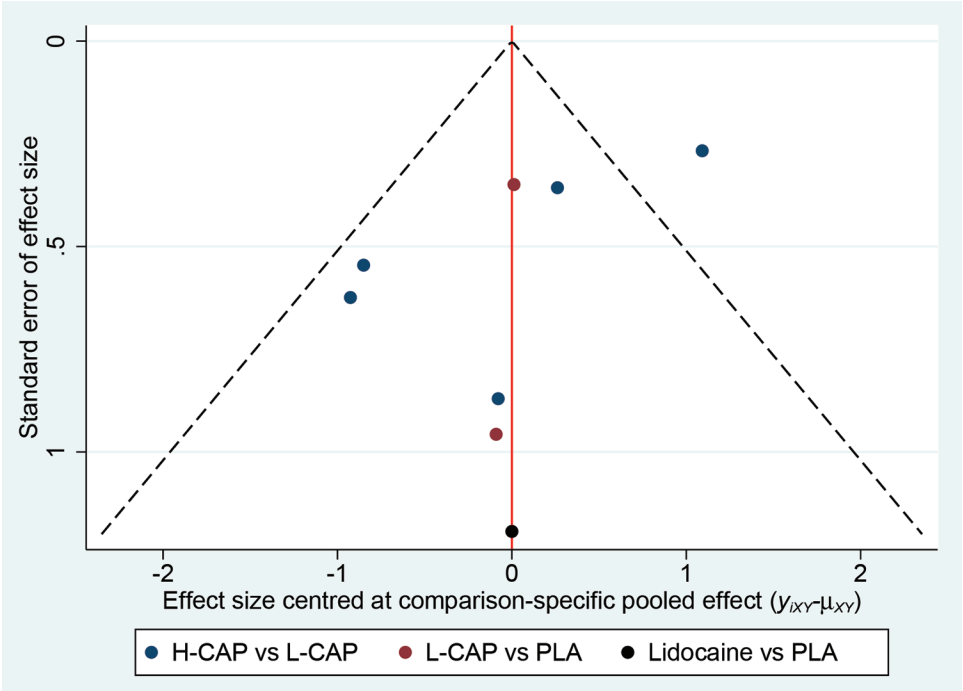


Fig. 3. *(A) Funnel plot for the detection of publication bias in efficacy comparisons. (B) Funnel plot for the detection of publication bias in AEs comparison.*

Table 5. *Diagrams of rank analysis of efficacy comparisons.*

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
ADE	0	0.01	0.02	0.06	0.16	0.7	0.06
Diclofenac	0.04	0.17	0.25	0.3	0.21	0.02	0
HCAP	0	0.01	0.28	0.21	0.33	0.16	0.01
Indo-methacin	0.03	0.18	0.24	0.25	0.25	0.05	0
LCAP	0.05	0.54	0.2	0.17	0.05	0	0
Lidocaine	0	0	0	0	0.01	0.06	0.93
PLA	0.88	0.1	0.02	0	0	0	0

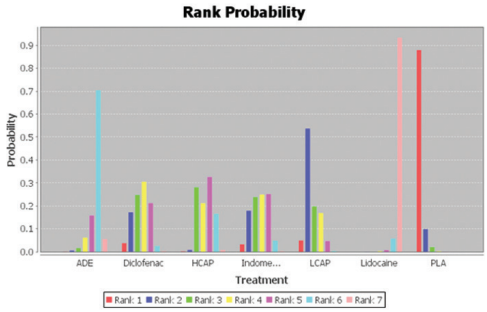


Table 6. *SUCRA.*

Treatment	SUCRA	PrBest	MeanRank
ADE	83.8	18.8	2.0
Diclofenac	45.4	0.2	4.3
H-CAP	53.6	0.2	3.8
Indomethacin	45.7	0.3	4.3
L-CAP	23.8	0.0	5.6
PLA	1.2	0.0	6.9

Table 8. *The network meta-analysis results of AEs comparison.*

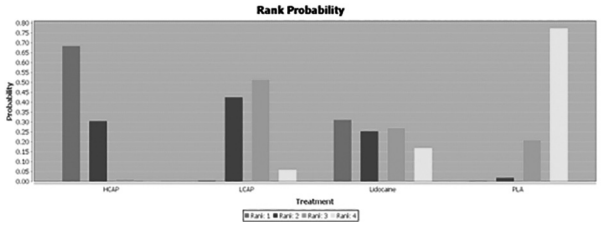
HCAP			
3.51 (1.32, 10.79)	LCAP		
2.63 (0.04, 126.52)	0.74 (0.01, 28.77)	Lidocaine	
11.74 (1.69, 97.93)	3.34 (0.62, 19.53)	4.46 (0.18, 217.68)	PLA

Table 7. *The direct AEs comparison of the different classes of treatments.*

Class 1 vs. Class 2	OR	95%CI		*P* value
		Lower	Upper	
L-CAP VS PLA	3.14	1.65	5.97	0.0005
H-CAP VS L-CAP	3.4	1.44	8.02	0.0005

Table 9. *Diagrams of rank analysis of AEs comparison.*

Drug	Rank 1	Rank 2	Rank 3	Rank 4
HCAP	0.68	0.3	0.01	0
LCAP	0	0.42	0.51	0.06
Lidocaine	0.31	0.25	0.27	0.17
PLA	0	0.02	0.21	0.77



enac were excluded from the AEs evaluation because of this limitation. Lidocaine may be the most beneficial topical drug for PHN because the clinical practice of high-concentration capsaicin could be restricted from its multiple AEs.

In comparison of the topical treatment, the outcome may be affected by several factors. The transdermal uptake of drugs was affected by the skin's factors, including the temperature, hydration, cutaneous vasoactivity, and specific variation, therefore the suitable delivery in the skin can enhance the increased absorption of the drugs to affect efficacy (48,49). The delivery systems of inclusive studies had 5 items, including patch, cream, ethyl ether, eye drops, and pump spray. However, different delivery systems of different topical drugs were performed in the comparison, which may lead to the biased results. Furthermore, the duration of the local drug may affect infiltration (50). The majority of duration of the lidocaine, ADE, indomethacin, and diclofenac is less than 4 weeks, whereas the capsaicin was used more than 4 weeks. This limitation may lead to the bias of the evaluation of the effective treatment, and the short-term duration may cover up the AEs of the lidocaine, ADE, indomethacin, and diclofenac. Apart

from these 2 aspects, there are still limitations that may exist in the evaluation.

The limitations of our network meta-analysis are listed as follows: (1) the small number of included studies; (2) a small number of patients and short-term trials in progress, including lidocaine and ADE; (3) both RCT and crossover randomized trial were included in our network meta-analysis; (4) only studies published in English were evaluated; (5) lack of head-to-head comparisons of some treatments; (6) different measurement methods were used in different trial, which may cause deviation; and (7) with the lack of cycles in the included trials, the inconsistency factors cannot be calculated, and node-splitting method cannot be performed in our network meta-analysis to check the inconsistency.

Conclusions

The topical lidocaine was preferable to other topical drugs for PHN. More hand-to-hand studies with larger sample size and longer trial period are warranted to support our findings and explore the efficacy and safety of the topical drugs.

Author Contributions

LW designed the study protocol, provided revision for intellectual content, and final approval of the manuscript; XL and JZ contributed to the literature search, data extraction, statistical analysis, and manuscript writing; QZ and KL also contributed to the literature search and data extraction. All of the authors have read and approved the final manuscript.

Supplemental material available at www.painphysicianjournal.com

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Supplemental File 1. S*earch strategies and details*.

Pubmed:

#1 "Administration, Topical"[Mesh]
#2 stick-on[Title/Abstract] OR cutaneous[Title/Abstract] OR dermal[Title/Abstract] OR transcutaneous[Title/Abstract] OR percutaneous[Title/Abstract] OR skin[Title/Abstract] OR massage[Title/Abstract] OR embrocation[Title/Abstract] OR gel[Title/Abstract] OR trigeminal ointment[Title/Abstract] OR aerosol[Title/Abstract] OR lotion[Title/Abstract] OR mousse[Title/Abstract] OR foam[Title/Abstract] OR liniment[Title/Abstract] OR spray[Title/Abstract] OR rub[Title/Abstract] OR balm[Title/Abstract] OR salve[Title/Abstract] OR emulsion[Title/Abstract] OR oil[Title/Abstract] OR patch[Title/Abstract] OR plaster[Title/Abstract]
#3 "Neuralgia, Postherpetic"[Mesh]
#4 Postherpetic Neuralgia[Title/Abstract] OR PHN[Title/Abstract] #5 "Randomized Controlled Trials as Topic"[Mesh]
#6 randomi*ed controlled trial[Title/Abstract] OR double- blind[Title/Abstract] OR blind*[Title/Abstract] OR mask*[Title/Abstract] OR clinical trial[Title/Abstract] OR trial[Title/Abstract]
#7 #1 or #2
#8 #3 or #4
#9 #5 or #6
#10 #7 and #8 and #9
#11 #10 Filters: Randomized Controlled Trial; Humans

Medline:

#1 MH=Randomized Controlled Trials as Topic/ #2 TS=(randomi*ed controlled trial)
#3 TS=(double-blind)
#4 TS=(blind*)
#5 TS=(mask*)
#6 TS=(clinical trial)
#7 TS=(trial)
#8 MH=Administration, Topical
#9 TS=(stick-on)
#10 TS=(cutaneous)
#11 TS=(dermal)
#12 TS=(transcutaneous)
#13 TS=(percutaneous)
#14 TS=(skin)
#15 TS=(massage)
#16 TS=(embrocation)
#17 TS=(gel)
#18 TS=(ointment)
#19 TS=(aerosol)
#20 TS=(cream)
#21 TS=(lotion)
#22 TS=(mousse)
#23 TS=(foam)
#24 TS=(liniment)
#25 TS=(rub)
#26 TS=(balm)
#27 TS=(salve)
#28 TS=(emulsion)
#29 TS=(oil)
#30 TS=(patch)

#31 TS=(plaster)
#32 MH=Neuralgia, Postherpetic
#33 TS=(plaster)
#34 TS=(Postherpetic Neuralgia)
#35 TS=(PHN)
#36 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#37 #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR
#23 OR # 22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15
OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8
#38 #35 OR #34 OR #33 OR #32
#39 #38 AND #37 AND #36
#40 #38 AND #37 AND #36 Refined by: PUBLICATION TYPES:
(RANDOMIZED CONTROLLED TRIAL) AND MeSH HEADINGS: (HUMANS)

EMBASE:

#1. 'randomized controlled trial'
#2. (randomi*ed controlled trial or double-blind or blind* or mask* or clinical trial or trial)
#3. 'topical drug administration'
#4. (stick-on or cutaneous or dermal or transcutaneous or percutaneous or skin or massage or embrocation or gel or ointment or aerosol or cream or lotion or mousse or foam or liniment or spray or rub or balm or salve or emulsion or oil or patch or plaster)
#5. 'Postherpetic Neuralgia'
#6. (Neuralgia, Postherpetic or PHN) #7. #1 or #2
#8. #3 or #4
#9. #5 or #6
#10. #7 and #8 and #9
#11. #10 AND 'human'/de AND 'randomized controlled trial'/de

Cochrane:

#1 Administration, Topical in Title Abstract Keyword - (Word variations have been searched)
#2 Neuralgia, Postherpetic in Title Abstract Keyword - (Word variations have been searched)
#3 Randomized Controlled Trials in Title Abstract Keyword - (Word variations have been searched)
#4 #1 and #2 and #3