Review Article

Topical lidocaine mediated plaster 5% and pregabalin for the treatment of post-herpetic neuralgia: A systematic review and meta-analysis.

Abstract:

Background and objectives: Post-herpetic neuralgia is common severe pain that leads to poor quality of life. Various topical and systemic drugs were in use including topical lidocaine mediated plaster 5% (05% LMP. This is the first meta-analysis to compare 5% lidocaine medicated plaster and pregabalin. Thus, this study aimed to assess the effectiveness of 5% LMP and pregabalin in PHN and compare these medications regarding the same.

Methods: We searched PubMed, MEDLINE, Google Scholar, EBSCO, and Cochrane Library for publications assessing 5% lidocaine medicated plaster and pregabalin drugs on post-herpetic neuralgia. We included articles published in English from inception up to February 2022. All types of studies were included except case reports, case series, studies on animals, and experimental studies. The terms used were: 5% lidocaine medicated plaster, pregabalin, post-herpetic neuralgia, pain relief, pain reduction, and pain scores. We identified 579 articles and the number stood at 435 after duplication removal, of them, 45 full texts were screened. Eight cohorts from seven studies were included in the final meta-analysis. The most recent RevMan system was used for data analysis.

Results: The pain score was significantly lower among patients receiving topical lidocaine compared to placebo or pre and post-intervention (odd ratio, -1.91, 95% *CI*, -3.77-0.04). Lidocaine Medicated Plaster 5% and pregabalin were effective for pain relief in PHN. However, 5% LMP was more effective (odd ratio, 2.11, 95% *CI*, 1.41-3.17).

Interpretation and Conclusion: Five % lidocaine medicated plaster was effective for the treatment of post-herpetic neuralgia. In addition, the drug was more beneficial than placebo and pregabalin. Further randomized controlled studies assessing the use of LMP 5% on acute herpes zoster and post-herpetic neuralgia are recommended.

Keywords: Lidocaine medicated plaster, Post-herpetic neuralgia, pain score, pain relief.

1. Introduction:

Post-herpetic neuralgia is defined as neuropathic pain that persisted after three months of herpes zoster. The pain is usually chronic and refractory to oral medications for neuropathic pain including anti-epileptic medications, antidepressants, and alpha-2 delta ligands. Oral medications are limited by their unwanted side effects and a combination of both systemic therapy and topical therapy is usually required [1]. Previous studies showed the effectiveness of 5% lidocaine-medicated plaster (5% LMP) in post-herpetic neuralgia treatment [2]. The American Academy of Neurology, the European Federation of Neurological Societies, and the Canadian Pain Society recommended 5% LMP and 1.8% LMP for the treatment of PHN. The American Food and Drug Administration approved both topical therapies in the year 1999 and 2018 respectively [3]. The annual incidence of herpes zoster varied between 3% and 6%, of the 9 to 34% will suffer from post-herpetic neuralgia. The cost-effectiveness of 5% LMP in the treatment of PHN had been previously documented [4]. Pregabalin is an alkylated analogue of γ-aminobutyric acid and structurally related to gabapentin [5]; the drug is widely used for neuropathic pain [6-8]. The United States Food and Drug Administration approved Pregabalin for various disorders including epilepsy, neuropathic pain, and post-herpetic neuralgia. In addition, the drug is in off-label use for others [9]. Results from previous meta-analysis found that pregabalin is effective for postherpatic neuralgia and sleep quality [10-12] Literature regarding the efficacy of 5% LMP and pregabalin for PHN is scarce. Therefore, the present meta-analysis aimed to assess the effectiveness of 5% LMP and pregabalin in PHN and compare the superiority of these medications regarding the same.

2. Subjects and Methods:

2.1. Inclusion criteria according to PICOS:

We systematically searched PubMed, MEDLINE, Google Scholar, EBSCO, and Cochrane Library for publications assessing 5% lidocaine medicated plaster and pregabalin drugs on post-herpetic neuralgia. In addition, articles comparing the effects of both drugs were included. All types of studies were included (prospective and retrospective cohorts, case-control, and randomized trials) except case reports, case series, studies on animals, and experimental studies.

2.2. Outcome measures:

The outcomes measures were:

The treatment responders (number of patients (with post-herpetic neuralgia) showing pain relief or meaningful reduction in pain scores).The reduction of neuropathic pain symptom inventory scores or allodynia severity ratings. Two points reduction on a six-point verbal rating scale. Maximum and minimum pain intensities and coanalgesic consumption. Brief Pain Inventory. The comparison between pain score after 5% LMP and pregabalin was reported.

2.2. Literature search:

The author searched PubMed, MEDLINE, Google Scholar, EBSCO, and Cochrane Library from the first published article up to February 22, 2022. The articles must be published in the English language. The terms used were: 5% lidocaine medicated plaster, pregabalin, post-herpetic neuralgia, pain relief, pain reduction, and pain scores. The titles and abstracts were screened. In addition, the references of the texts included were screened. We identified 579 articles and the number stand at 435 after duplication removal, of them, 45 full texts were screened. Eight cohorts from seven studies were included in the final meta-analysis. A pre-specified data sheet was used to collect the author's name, country of publication, year of publication, the number of patients who showed pain relief, and the pain scoring pre and post intervention. The Newcastle Ottawa Scale risk of bias and a modified Cochrane risk was used to assess the quality of the included studies [13, 14]. Figure 1, tables 1-4.

2.3. Statistical analysis:

The data were entered manually in the last version RevMan system (continuous for pain scores and dichotomous for patients with pain relief). The fixed effect was applied for the comparison of LMP 5% and pregabalin comparison and the random effect for LMP 5% effect due to the substantial heterogeneity. Funnel plot was included for figure 2.. A-P- the value of <0.05 was considered significant.

Figure 1. The effects of 5% lidocaine medicated plaster and pregabalin on post-herpetic neuralgia (The PRISMA Chart)

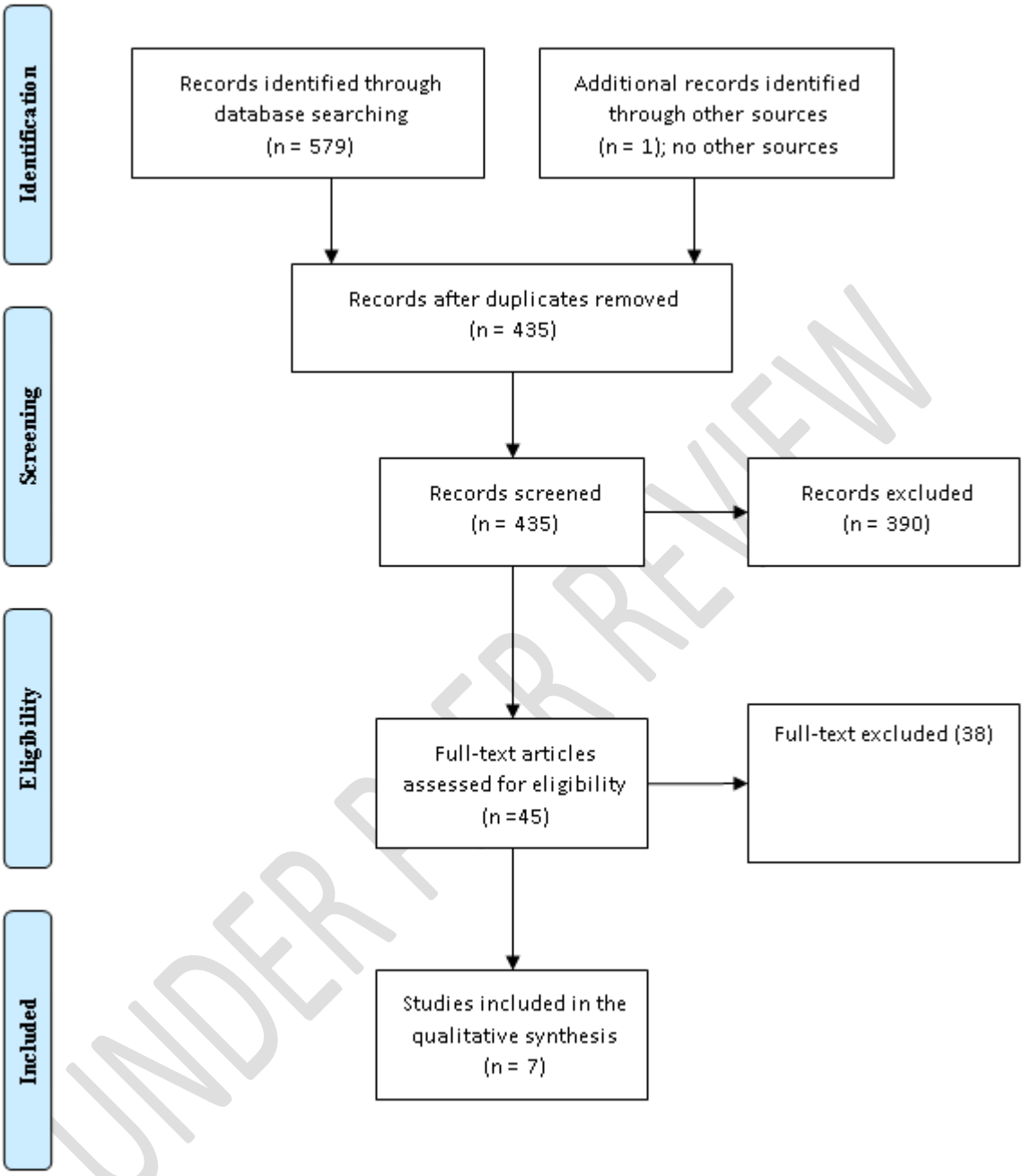


Table 1. Five% lidocaine-medicated plaster for the treatment of post-herpetic neuralgia

Author	Country	Intervention	Control	Methods
Baron et al. 2009 [15]	Germany	4.1±1.91	6.7±1.2	Randomized controlled trial, 28 patients
Binder et al. 2009 [16]	Germany	1.5±0.02	1.2±0.02	Randomized controlled trial,3/71 vs. 31/194
Delorme et al. 2011 [17]	France	4.1 ± 1.7	7.5 ± 1.4	Retrospective, four patients with PHN
Nalamachu et al. 2013 [18]	USA	3.03±3	5.13±2.5	A post hoc analysis of 203 patients
Wasner et al. 2005 [19]	Germany	48.6±32.1	58.6±27.4	A prospective cohort of 18 cohorts

Table 2. Five% lidocaine-medicated plaster versus pregabalin for the treatment of post-herpetic neuralgia

Author	Country	Lidocaine	Pregabalin	Methods
Baron et al. 2009 [15]	Germany	60/96	45/96	Randomized controlled trial
Baron et al. 2009 [20]	Germany	35/55	21/55	Randomized controlled trial 2/55 vs. 22/55
Baron et al. 2010 [21]	Germany	28/45	20/43	Randomized controlled trial

Table 3. Risk of bias of the included randomized trials

Author	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Baron et al. 2009 [15]	Unclear	Unclear	Low	Low	Low	Low	unclear
Binder et al. 2009 [16]	Low	Unclear	Low	Low	Low	High	Unclear
Baron et al. 2009 [20]	Unclear	Unclear	Low	Low	Low	Low	Unclear
Baron et al. 2010 [21]	Unclear	Unclear	Low	Low	Low	Low	Unclear

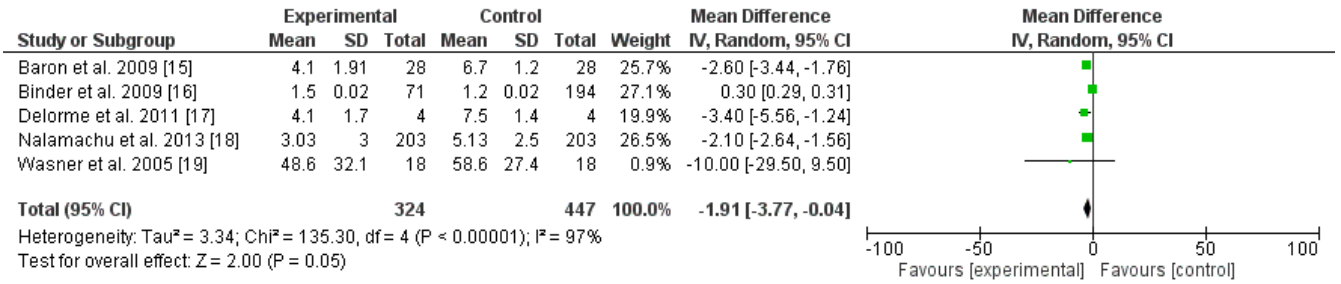
Table 4. Newcastle Ottawa scale risk of bias of the observational studies

Author	Country	Selection bias	Comparability bias	Outcome	Total score
Delorme et al. 2011 [17]	UK	4	1	3	8
Nalamachu et al. 2013 [18]	Australia	4	2	3	9
Wasner et al. 2005 [19]	Turkey	4	1	3	8

3. Results:

We included five studies [15-19] (four from Europe and one from the USA, four randomized controlled studies, one prospective cohort, a retrospective study, and a post hoc analysis of 203 patients). The studies included 771 patients. All the studies showed low pain score among patients who used 5% LMP, except Blinder et al. [16]. The pain score was significantly lower among patients receiving topical lidocaine compared to placebo or pre and post-intervention (odd ratio, -1.91, 95% *CI*, -3.77-0.04). The random effect was used due to the substantial heterogeneity, I^2=97%, P-value for heterogeneity <0.00001, Chi-square=135.30, mean difference=4. The P-value for the overall effect was 0.05. Figure 2. The three studies [15, 20, 21] comparing Lidocaine Medicated Plaster 5% and pregabalin (209 events among 390 patients) showed more pain relief among patients used LMP 5%,(odd ratio, 2.11, 95% *CI*, 1.41-3.17). No heterogeneity was found, I^2 =0.0%. The P-value for the overall effect was 0.0003. The mean difference=2, and the chi-square, 0.76. Figure 3.

Figure 2. Lidocaine 5% medicated plaster and post-herpetic neuralgia



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baron et al. 2009 [15]	4.1	1.91	28	6.7	1.2	28	25.7%	-2.60 [-3.44, -1.76]
Binder et al. 2009 [16]	1.5	0.02	71	1.2	0.02	194	27.1%	0.30 [0.29, 0.31]
Delorme et al. 2011 [17]	4.1	1.7	4	7.5	1.4	4	19.9%	-3.40 [-5.56, -1.24]
Nalamachu et al. 2013 [18]	3.03	3	203	5.13	2.5	203	26.5%	-2.10 [-2.64, -1.56]
Wasner et al. 2005 [19]	48.6	32.1	18	58.6	27.4	18	0.9%	-10.00 [-29.50, 9.50]
Total (95% CI)			**324**			**447**	**100.0%**	**-1.91 [-3.77, -0.04]**

Heterogeneity: Tau² = 3.34; Chi² = 135.30, df = 4 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.00 (P = 0.05)

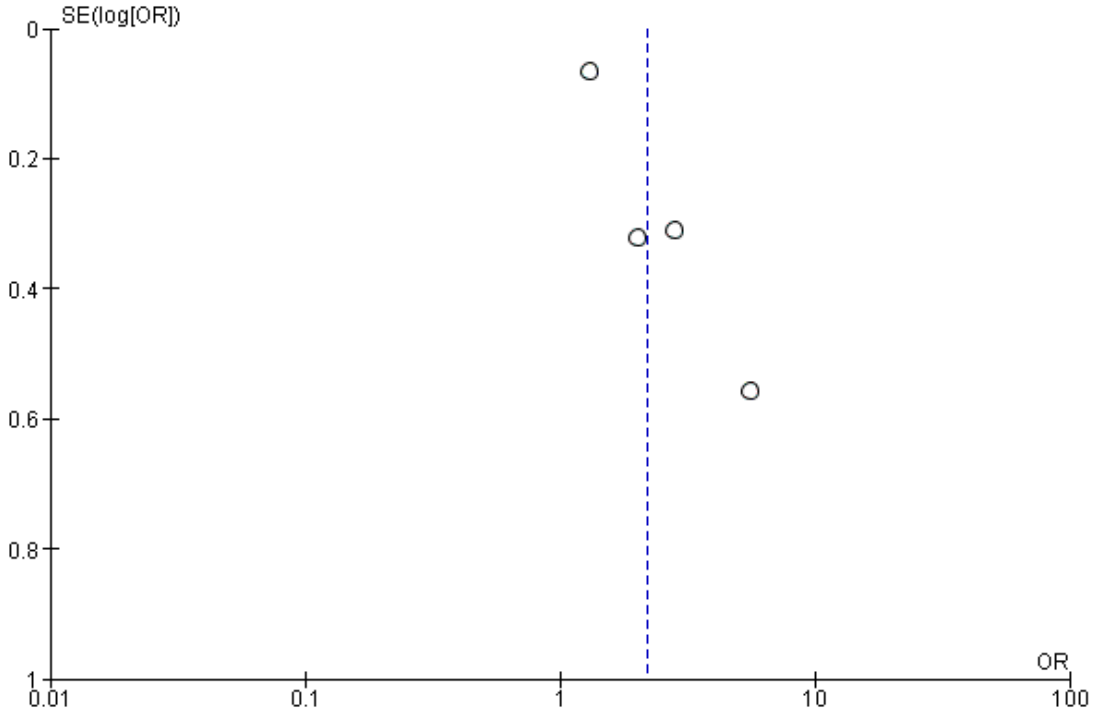
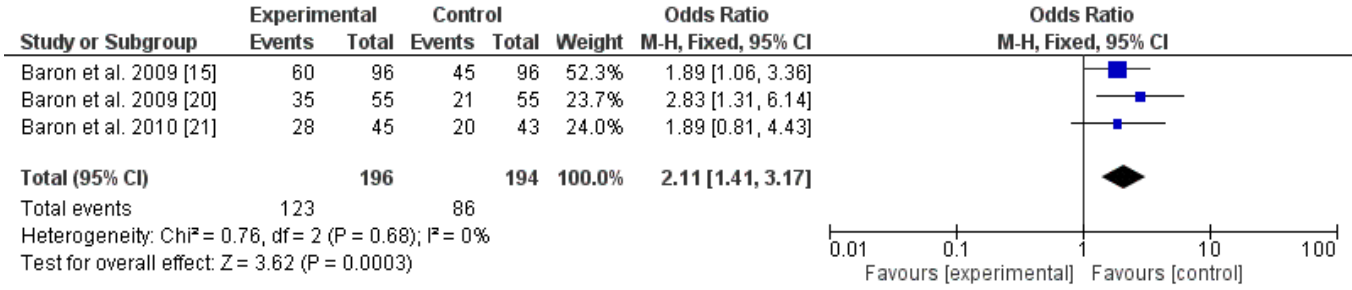


Figure 3. Lidocaine 5% medicated plaster versus pregabalin and post-herpetic neuralgia



4. Discussion:

In the current meta-analysis, 5% lidocaine medicated plaster was effective for the treatment of post-herpetic neuralgia. In addition, the drug was more effective than placebo and pregabalin (odd ratio, -1.91, 95% *CI*, -3.77-0.04, and 2.11, 95% *CI*, 1.41-3.17 respectively). A similar previous meta-analysis found that LMP 5% mediated plaster was superior to placebo and other topical remedies including capsaicin and nonsteroidal anti-inflammatory drugs [22]. However, the previous meta-analysis had several limitations including the small sample of the included studies and patients, a lack of face-to-face comparison, and different methodologies of the studies. Although previous meta-analysis found that pregabalin is effective for post-herpetic neuralgia pain [5, 10, 23]]. Our meta-analysis also is the first to compare LMP 5% and pregabalin. LMP 5% advantage is decreasing nociception without leading to complete nerve block and minimal absorption. Thus, low systemic side effects and lower drug interactions [3]. Another systematic review found no conclusive evidence of efficacy. However, the review included all types of neuropathic pain [24]. A systematic review conducted in the year 2011 found that LMP 5% was non-inferior to pregabalin, the study was limited by a lack of objective meta-analysis (only one study included) [25]. LMP 5% may be recommended as the first treatment for localized post-herpetic neuralgia due to its efficacy and minimal systemic effects [26], LMP 5% was shown to reduce pain, improve mood, cognition, and quality of life [27, 28]. This is the first meta-analysis to compare LMP 5% with pregabalin, we found that LMP 5% was more effective than pregabalin. Previous reviews showed that 5% LMP side effects are minimal including local erythema and blisters in contrast to the systemic effects of pregabalin (dizziness, weight gain, sedation, and peripheral edema) [29, 30]. The results of this analysis should viewed in the face of the following limitations: the same group of researchers from Germany published the three studies included in the comparison between 5% LMP and pregabalin. In addition, the small number of the included studies, the different measures for pain relief scoring, and the substantial heterogeneity limited the current review.

5. Conclusion: Five % lidocaine-mediated plaster was effective for the treatment of post-herpetic neuralgia. In addition, the drug was more effective than placebo and pregabalin. Further randomized controlled studies assessing the use of LMP 5% on acute herpes zoster and post-herpetic neuralgia are recommended.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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