# Lidocaine iontophoresis for postmastectomy intercostobrachial neuralgia: single-blinded randomized controlled trial

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**Aim**
The aim was to investigate the efficacy of lidocaine iontophoresis for neuropathic pain management in intercostobrachial neuralgia after mastectomy.
**Design**
A single-blinded randomized controlled trial was conducted.
**Patients and methods**
A total of 40 patients with partial or radical mastectomy were randomly divided into two equal groups: group A (lidocaine iontophoresis) and group B (lidocaine patch). The methods of assessment included visual analog scale (VAS) and pain DETECT questionnaire. Group A received lidocaine iontophoresis day after day for 4 weeks. Group B received lidocaine 5% patch (LIDODERM) onto the painful area for 12 h daily. Treatment program extended for 1 month, whereas evaluation was done before and after treatment.
**Results**
There was no significant difference between both groups in VAS (0.14) and pain DETECT questionnaire (0.32), before treatment. Comparison between groups after treatment revealed a significant reduction in VAS and pain DETECT questionnaire of group A compared with that of group B ($P$=0.0001). The percent of reduction in VAS of groups A and B was 86.47 and 61.11%, respectively, whereas the percent of reduction in pain DETECT questionnaire was 76 and 49.57%, respectively.
**Conclusion**
It was concluded that lidocaine iontophoresis was safe and effective method for intercostobrachial neuralgia management after mastectomy in expression of decreasing pain intensity and quality.

**Keywords:**
lidocaine iontophoresis, mastectomy, pain DETECT questionnaire, visual analog scale

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## Introduction

Neuropathic pain (NP) can be demonstrated as a persistent or episodic pain associated with abnormal sensations called dysesthesia or pain from normally nonpainful stimuli like light touch. which is called allodynia [1]. NP is a chronic painful condition, always described as a shooting or burning pain which causes adverse effects on patients' quality of life including sleeping disorder, discomfort, restlessness, and depression [2,3].

Chronic NP after mastectomy was divided into four various categories: (a) phantom pain where there is aching sensation at the removed breast; (b) intercostobrachial neuralgia (ICN), [also known as postmastectomy pain syndrome (PMPS)] which is intense, sharp, shooting pain felt in the chest and present after mastectomy with or without axillary dissection; (c) neuroma pain, which is located at scar area in breast, chest, or arm and exaggerated by pressure; and (d) alternative nerve lesion, including medial or lateral pectoral, long thoracic and thoracodorsal nerve that may occur during surgical procedures [4].

PMPS can be caused by injury of intercostobracial nerve during surgical procedures. In 21 studies with different periods of follow-up (1–96 months), it was found that in all breast cancer surgeries, phantom breast pain represents 3–44% and ICN represents 16–39%, whereas in breast conserving surgeries, ICN represents 14–61% and neuroma pain represents 23–49% [4].

Several pharmacologic therapies including opioid analgesics, anticonvulsants, and tricyclic antidepressants are effective for chronic NP management [5]. However, oral medications have reported adverse effects and failed to obtain satisfying results in a higher proportion of patients [6]. Invasive therapies including frequent nerve blockages or corticoids injections are also an alternative therapies that can alleviate pain [7]. Localized treatments including lidocaine patches (LPs) and minimal dosage of capsaicin creams

(0.025–0.075%) have showed amelioration in chronic NP [8,9].

Regardless of new therapies, management of NP is still complicated, and there is no definite treatment that acts for all cases and their underlying mechanisms. So the rationale of this study was to evaluate the efficacy of lidocaine iontophoresis on intercostobrachial neuralgia after mastectomy, as this study may provide a new localized treatment method in NP management instead of oral medications with their systemic adverse effects.

It was hypothesized that there may be no significant difference between lidocaine iontophoresis and LP in management of NP.

## Patients and methods

### Patients

Outpatients with PMPS referred to our outpatient clinic from the National Institution of Oncology in Cairo, Egypt, were eligible for the study if they fulfilled the following requirements: (a) previous partial or radical mastectomy including axillary lymph node dissection for primary breast cancer, with no sign of disease recurrence at the moment of admission to the study; (b) moderate or severe pain of a tight, burning, or constricting nature, persisting for 3 months or more following the surgery, in the anterior chest wall, and/or axilla, and/or medial upper arm; (c) altered sensitivity of the skin (dysesthesia, allodynia, and hypohyperesthesia) in the painful area; (d) absence of other causes of arm pain (brachial plexus neuropathy owing to radiotherapy or to lymphedema entrapment, cervical radiculopathy, pericapsulitis of shoulder joint, and carcinomatous infiltration); (e) provided informed consent to participate to the study; (f) no topical agent used 7 days before trial onset; and (g) no new oral agent to be used during the trial.

Patients were excluded if (a) open skin lesions were present in the area of pain; (b) other skin conditions were present in the affected area; (c) severe depression with voiced suicidal intent was present; and (d) another unrelated significant pain problem existed.

### Sample size determination

Sample size calculation was performed before the study using G*POWER statistical software (version 3.1.9.2; Franz Faul, Universitat Kiel, Germany). Visual analog scale (VAS) was the primary outcome. The calculation revealed that the appropriate sample size for this study was $n$=40. Calculations were made using $\alpha$=0.05, $\beta$=0.2 and large effect size and allocation ratio N2/N1=1.

### Design

This study was a single-blinded randomized controlled trial and was approved by the ethical committee of the Faculty of Physical Therapy, Cairo University, NO:P.T.REC/012/001855. All patients were given an informed consent, and after inclusion, the patients were randomly divided into two equal groups.

Randomization process was applied using the envelope method. After patients agreed to participate in the study, cards with either 'lidocaine iontophoresis' or 'LP' written on them were sealed in envelopes; these envelopes were given to a staff physical therapist who was blinded to this study, and she/he picked one envelope. Depending on which card was selected, participants were allocated to their respective group. Group A comprised 20 patients who received lidocaine iontophoresis and group B comprised 20 patients who received LP.

The examining physical therapist was not involved in the randomization process and remained unaware of the treatment allocation. Patients were instructed not to reveal their treatment allocation to the physical therapists during assessment. Appointments for starting the treatment were arranged, and the treatment was started within one week of randomization.

### Treatment

A total of 40 female patients were randomized to either lidocaine iontophoresis (group A) or LP 5% (group B). Patients in group A received lidocaine iontophoresis (Phyaction 787; Uniphy BV, Netherland) day after day for 4 weeks. A cotton pad was soaked with 10 ml of 2% lidocaine with 0.9 sodium chloride, which acts as an indifferent solution. The cotton pad then was placed over the painful area and then electrode was placed over the pad and fixed with a thin, self-adhesive paper sheet. Iontophoresis current was 4 mA electrical current to the cathode for 10 min to deliver a dose of 40 mA/min.

Patients in group B were instructed to apply up to four lidocaine patch 5% (LIDODERM) onto the painful area for 12 h daily, always either during the day or at night. A maximum number of four patches could be applied to remain below 1/10 of the lidocaine blood levels that generate cardiac dysrhythmia. LP consisted of an adhesive material containing lidocaine 5% (700 mg/patch) applied to a non-woven polyester felt backing and covered with polyethylene terephthalate film-release liner and measures 10×14 cm.

Pain intensity was measured by a VAS and pain DETECT questionnaire. VAS is considered the 'gold standard' technique and is used particularly in pain-related research. It is consisted of a 10-cm line marked 'no pain' at one end and 'pain as bad as it could be' at the other. The patient marked the line according to the pain intensity experienced at that particular time [10].

The pain DETECT questionnaire consists of seven questions that address the quality of NP symptoms; it was completed by the patient, and no physical examination was required. The first seven questions ask about the gradation of pain, scored from 0 to 5 (never=0, hardly noticed=1, slightly=2; moderately=3, strongly=4, and very strongly=5). Question 8 asks about the pain course pattern, scored from −1 to 2, depending on which pain course pattern diagram is selected. Question 9 asks about radiating pain, answered as yes or no, and scored as 2 or 0, respectively.

The final score between −1 and 38 indicates the likelihood of a NP component. A score of less than or equal to 12 indicates that pain is unlikely to have a neuropathic component (<15%), whereas a score of greater than or equal to 19 suggests that pain is likely to have a neuropathic component (>90%). The Arabic version of this questionnaire is considered a simple validated and reliable assessment tool for NP components [11].

#### Statistical analysis

Descriptive statistics and *t*-test were conducted for comparison of participant characteristics between groups. Normal distribution of data was checked using the Shapiro–Wilk test for all variables. Levene's test for homogeneity of variances was conducted to test the homogeneity between groups. *t*-Test was conducted to compare mean values of VAS and pain DETECT questionnaire between both groups; and paired *t*-test was conducted to compare between pretreatment and post-treatment mean values of the measured variables in each group. The level of significance for all statistical tests was set at *P* less than 0.05. All statistical tests were performed through the statistical package for the social sciences (SPSS) version 19 for windows (IBM SPSS, Chicago, Illinois, USA).

## Results

A diagram of the patients' randomization in the study is shown in Fig. 1. A total of 52 female patients were admitted and assessed for eligibility, twelve of them were excluded as they did not meet the required criteria, whereas 40 patients were found to be eligible to participate in the study. All patients completed the treatment program without withdrawal.

#### Participant characteristics

Table 1 showed the participant characteristics of both groups. There was no significant difference between both groups in the mean age, weight, and height ($P>0.05$).

#### Within group comparison

There was a significant decrease in VAS and pain Detect after treatment in group A compared with that pretreatment ($P=0.0001$). The percent of decrease in VAS and pain DETECT questionnaire was 86.47 and 76%, respectively (Table 2, Figs 2 and 3).

Regarding group B, there was a significant decrease in VAS and pain Detect after treatment in group B compared with that before treatment ($P=0.0001$). The percent of decrease in VAS and pain DETECT questionnaire was 61.11 and 49.57%, respectively (Table 2, Figs 2 and 3).

#### Comparison between groups

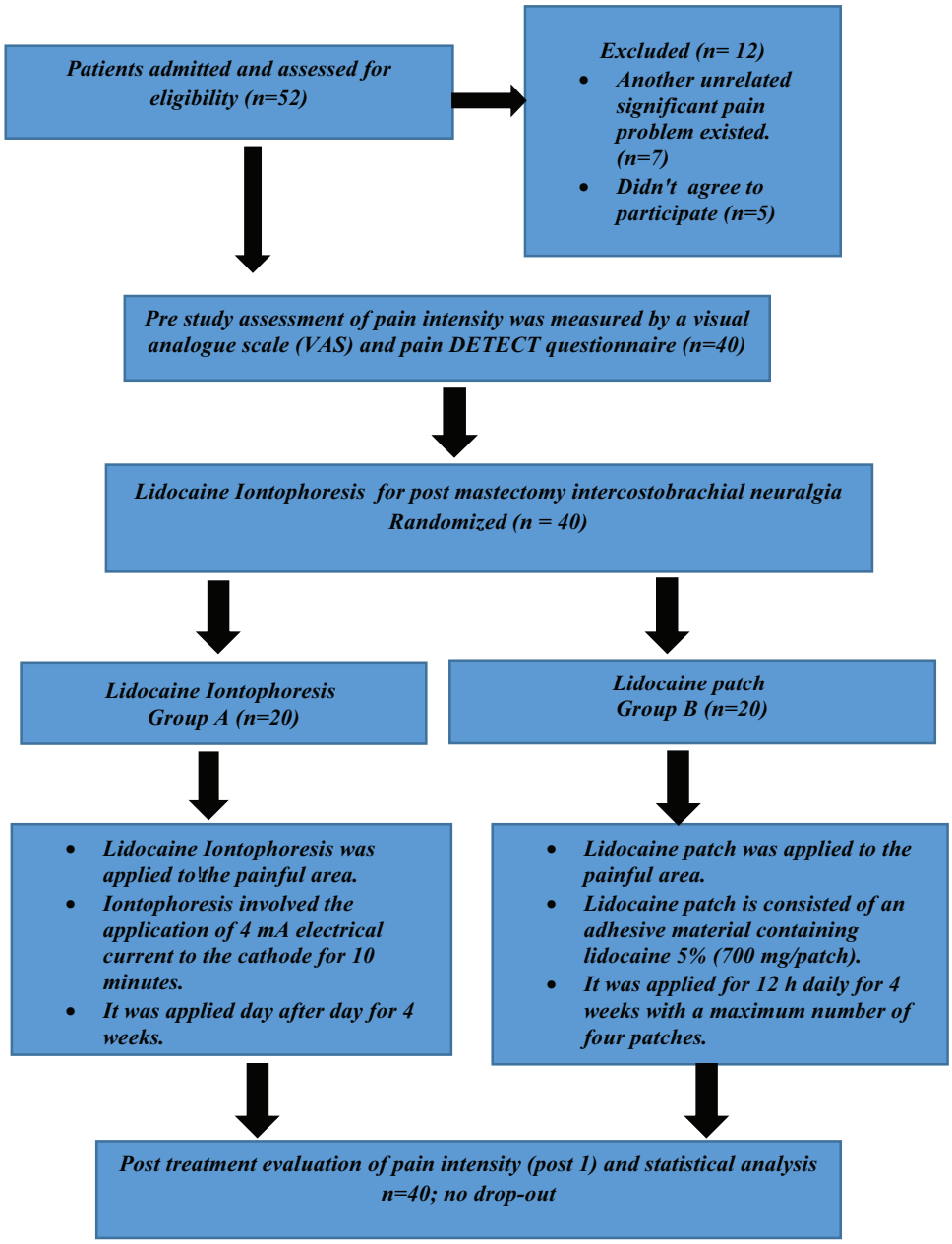
There was no significant difference between both groups in VAS and pain Detect before treatment ($P>0.05$). Comparison between groups after treatment revealed a significant decrease in VAS and pain DETECT questionnaire of group A compared with that of group B ($P=0.0001$) (Table 3, Figs 2 and 3).

## Discussion

Iontophoresis is a noninvasive therapeutic modality that allows permeation of ionized drug molecules through the skin by applying constant low-voltage electrical current. Many drugs can be transmitted via iontophoresis involving analgesics, anti inflammatory medications, and steroids [12]. Drug transmission via iontophoresis has many characteristics, as it is considered a safe, nonpainful and noninvasive modality. It eliminates systemic drug adverse effects and increases the therapeutic efficacy of the drug by bypassing hepatic first-pass metabolism. It introduces few amounts of drug in comparison with other drug delivery modalities and also reduces the dosage frequencies and improves patient compliance [13].

Dealing with and treating NP is a sophisticated process and usually needs different specializations. Various publications and clinical guidelines prompt topical lidocaine to be used as a first-line choice when

**Figure 1**




Participants' flow chart. Intercostobrachial neuralgia, visual analog scale, pain DETECT questionnaire, lidocaine iontophoresis, and lidocaine patch.

**Table 1 Comparison of participant characteristics between groups A and B**

| | Mean±SD | | MD | *t* Value | *P* value |
|---|---|---|---|---|---|
| | Group A | Group B | | | |
| Age (years) | 48.05±4.52 | 47.3±5.06 | 0.75 | 0.49 | 0.62 |
| Weight (kg) | 82.33±5.01 | 81.93±9.27 | 0.4 | 0.2 | 0.83 |
| Height (cm) | 172.16±5.76 | 171.83±9.69 | 0.33 | 0.16 | 0.87 |

treating localized NP [14–26]. Lidocaine iontophoresis is a substitutional procedure to deliver lidocaine through the skin by using a device which employs an electrical current to mobilize an ionized form of lidocaine toward the skin and subcutaneous tissue [27]. It was found that the permeation of the drug by using iontophoresis can be reinforced by 20–60 folds comparing with that of topical use [28].

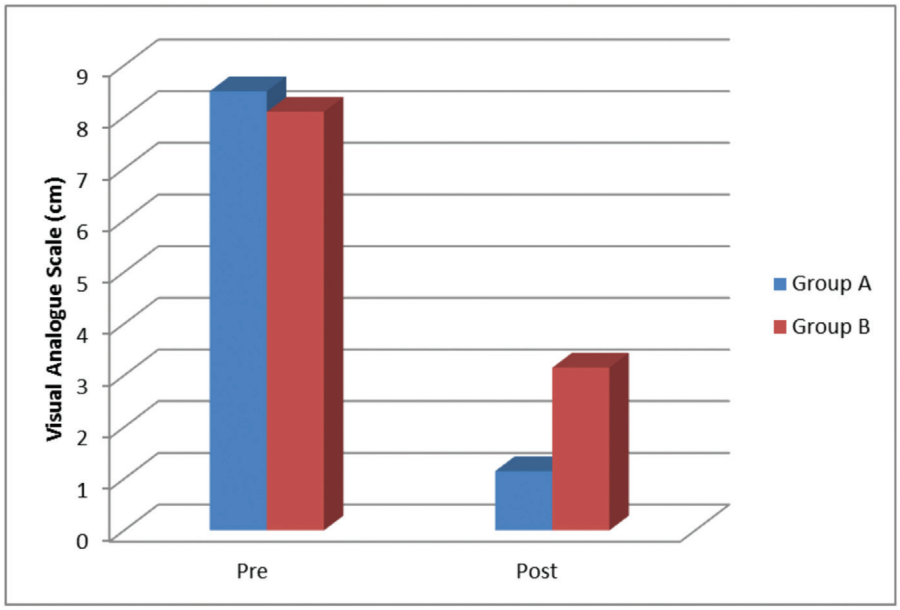
Lidocaine works via blocking of abnormally working (sensitive) sodium channels of nociceptors located in dermis [29], thus stabilizing the membrane potential of

**Table 2 Comparison of visual analog scale and pain detect between before and after treatment in groups A and B**

| | Mean±SD | | MD | % of change | *t* Value | *P* value |
|---|---|---|---|---|---|---|
| | Before treatment | After treatment | | | | |
| Group A | | | | | | |
| VAS | 8.5±0.88 | 1.15±0.36 | 7.35 | 86.47 | 40.44 | 0.0001* |
| Pain DETECT | 30±1.77 | 7.2±3.07 | 22.8 | 76 | 45.55 | 0.0001* |
| Group B | | | | | | |
| VAS | 8.1±0.78 | 3.15±0.67 | 4.95 | 61.11 | 24.95 | 0.0001* |
| Pain Detect | 29.45±1.7 | 14.85±1.95 | 14.6 | 49.57 | 31.27 | 0.0001* |

VAS, visual analog scale. *$P \leq 0.05$, statistically significant.

**Figure 2**



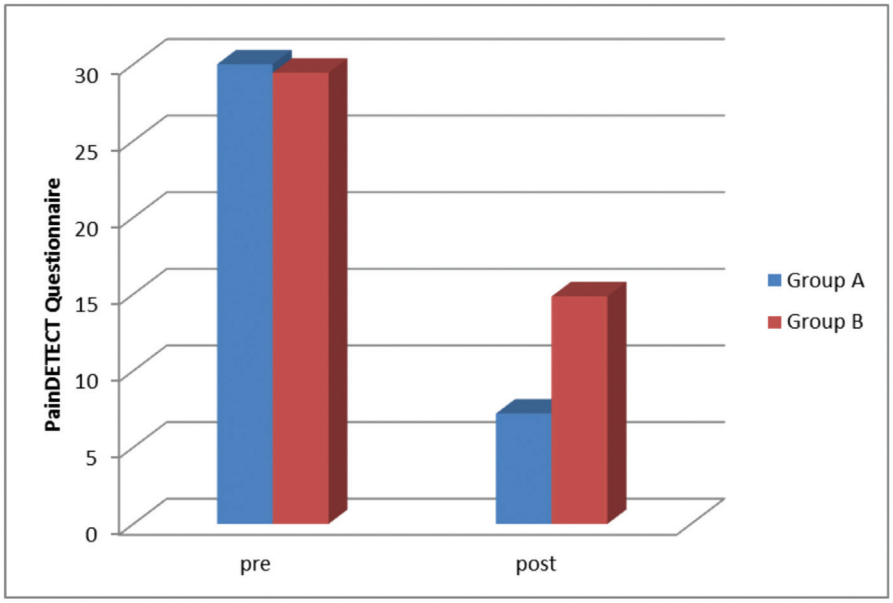

Mean values of visual analog scale before and after treatment in groups A and B.

abnormally excited Aδ and C fibers producing a decrease of their ectopic flow and subsidiary pain alleviation [29–32]. Lidocaine can be efficient in nociceptors-deprived skin [33,34], as the neighboring Aβ afferent to the affected nociceptors within the affected nerve can be targeted by lidocaine. This may cause blockage of sodium channels and thus decrease ectopic flow and decrease spontaneous pain and allodynia [29].

Sasao and Ozawa [35] investigated the effect of lidocaine iontophoresis in patients with postherpetic neuralgia (PHN). They carried out this study on more than 1000 patients with PHN (mean duration of PHN was 30.6 months). They found that after an average of 3.8 sessions of treatment, two-thirds of these patients were improved by 40–100%. Ozawa *et al.* [36] carried out a follow-up study to investigate clinical efficacy of lidocaine and methylprednisolone iontophoresis on PHN. Follow-up of 179 patients with PHN for 1–5 years after completion of treatment revealed that pain stayed without changing or decreasing comparing with pain scores recorded upon the end of treatment in 94.4% of patients. In spite of 42.6% of patients still keeping on some therapy, 90.9% were found to be able to take care of themselves. The authors concluded that iontophoresis has short-term and long-term effects and can be a beneficial clinical treatment option.

Several controlled clinical trials have demonstrated the efficacy and safety of the LP 5% for the treatment of NP. Hans *et al.* [37], conducted a prospective, open, nonrandomized study to investigate the effect of LP 5% on postoperative/post-traumatic neuropathic chronic cutaneous pain. A total of 40 patients were included, and the results showed that ~52.5% of the patients improved by lidocaine treatment, as the mean VAS score decreased from 7.225±1.209 at initial evaluation to 4.625±1.675 at the end of treatment (4 weeks). Garzón-Rodríguez *et al.* [38] used lidocaine 5% patches as a co-analgesic in cancer pain, and they concluded that lidocaine 5% patch has a beneficial short-term effect in the management of neuropathic cancer pain associated with allodynia whether the cause of pain was painful scar or chest wall tumor.

**Figure 3**




Mean values of pain DETECT questionnaire before and after treatment in groups A and B.

**Table 3 Comparison of visual analog scale and pain detect between groups A and B before and after treatment**

| | Mean±SD | | MD | *t* Value | *P* value |
|---|---|---|---|---|---|
| | Group A | Group B | | | |
| Before treatment | | | | | |
| VAS | 8.5±0.88 | 8.1±0.78 | 0.4 | 1.5 | 0.14 |
| Pain Detect | 30±1.77 | 29.45±1.7 | 0.55 | 1 | 0.32 |
| After treatment | | | | | |
| VAS | 1.15±0.36 | 3.15±0.67 | −2 | −11.7 | 0.0001* |
| Pain Detect | 7.2±3.07 | 14.85±1.95 | −7.65 | −9.39 | 0.0001* |

VAS, visual analog scale. *$P \leq 0.05$, statistically significant.

Delorme *et al.* [39] performed a retrospective, observational study to determine the efficacy and safety of using 5% lidocaine-medicated plaster in the management of refractory chronic NP by reviewing the medical record of 467 patients. There was more than one year between the time of onset and referral in two-thirds of cases. Approximately 78.1% of patients had a peripheral NP after surgery, whereas 23% had a post-traumatic pain. The results showed decrease in both pain intensity and analgesics consumption. The study demonstrated an excellent safety profile of 5% lidocaine-medicated plaster and supported its efficacy in management of chronic NP.

In a two-stage adaptive, open-label, randomized study comparing the effectiveness and safety of 5% lidocaine-medicated plaster with pregabalin in PHN and diabetic polyneuropathy (DPN), 300 patients were enrolled (96 with PHN and 204 with painful DPN). The results showed that there was an improvement in pain scores with 5% lidocaine-medicated plaster than with pregabalin in PHN (corresponding numbers for the per protocol set, PPS: 62.2 vs. 46.5%); both treatments were comparable in DPN (PPS: 66.7 vs. 69.1%). Moreover, 5% lidocaine-medicated plaster demonstrated greater quality of life improvement in patients with PHN; both treatments were comparable in patients with DPN. Both treatments decreased the severity of allodynia. It was concluded that in patients with PHN, 5% lidocaine-medicated plaster showed better effect in comparison with pregabalin, whereas in DPN, both treatments showed comparable effect supporting the use of 5% lidocaine-medicated plaster as a first-line choice in management of NP [30].

Galer *et al.* [40] enrolled 96 patients with PHN in a prospective, vehicle-controlled, double-blind, randomized study to evaluate the effectiveness of LP 5% in distinguished qualities of NP that are common in different neuropathic conditions by using NP scale. It was concluded that LP 5% improved all common pain qualities (i.e. 'sharp', 'hot', 'dull', and 'deep') which are believed to be nondermal and nonsuperficial in nature after the application of LP 5% for 3 weeks. Uzaraga *et al.*

[41] conducted a pilot study to evaluate the efficacy of topical amitriptyline, ketamine, and lidocaine (AKL) on NP caused by radiation dermatitis using Washington Neuropathic Pain Scale. The patients were instructed to apply AKL gel three times per day from the initial evaluation for 2 weeks after radiation. It was concluded that AKL decreased several measures of NP and can be considered as a safe and effective treatment option in treating NP following radiation dermatitis.

In our study, we reported a significant decrease in VAS and pain DETECT questionnaire of group A compared with that of group B ($P$=0.0001). The results showed that lidocaine iontophoresis is more effective than LP in intercostobrachial neuralgia management. However, this study is limited by small sample size and short duration of the treatment program, so more studies are required with larger sample to investigate and confirm the effectiveness of lidocaine iontophoresis in NP management considering the optimal dose and frequency. Follow-up study is also necessary to reveal the long-term effects of iontophoresis and recurrence of pain.

## Conclusion

Our observations are in agreement with the international guidelines that support topical lidocaine as a first-choice treatment for localized peripheral NP. The results of our study showed that topical lidocaine applied either by iontophoresis or patch has a clear and significant effect on NP in expression of decreasing pain intensity and quality, and also the results revealed that lidocaine iontophoresis is more effective and superior to LP, suggesting that lidocaine iontophoresis is recommended as a first-choice treatment in ICN.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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