Randomized Controlled Trial

Lidocaine Infusion Versus Duloxetine for Prevention and Management of Taxane-Induced Peripheral Neuropathy among Breast Cancer Patients-A Randomized Controlled Study

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Background: Taxane-induced peripheral neuropathy (TIPN) among breast cancer patients is considered one of the most devastating side effects affecting compliance to chemotherapy protocol and patients' quality of life (QOL).

Objectives: This trial aimed to evaluate the effect of lidocaine infusion vs oral duloxetine on the incidence and severity of TIPN and QOL in patients with breast cancer scheduled for neoadjuvant taxane therapy (TT).

Study Design: Prospective, randomized, single-blinded, controlled trial.

Setting: This study was carried out on 60 patients with breast cancer scheduled for 12 weeks of TT at the Medical Research Institute Hospital, Alexandria University after obtaining local Ethics Committee approval (IORG008812) and getting a written informed consent from each patient. It was registered in the "clinical trials library for protocol registration and results system" with the number NCT04732455.

Methods: Sixty women scheduled for TT weekly for 12 weeks, were randomly allocated to receive intravenous saline infusion in the control group (GC), or lidocaine 2mg/kg with saline infusion in the lidocaine group (GL), or saline infusion and 30 mg duloxetine in the duloxetine group (GD). All infusions were administered over 40 minutes before each TT. Oral duloxetine was prescribed once daily starting from the night before commencing TT and continued for 12 weeks. Douleur Neuropathique en 4 Questions (DN4) questionnaire was filled weekly to detect the incidence of neuropathic pain (NP). The nerve conduction study (NCS) aimed to detect and measure the degree of neuropathy before starting the chemotherapy protocol and post-12 weeks of Taxol Therapy. NP Scale was measured weekly to assess the severity of NP symptoms. Patients' QOL was evaluated by the European Organization for Research and Treatment of Cancer QOL Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale.

Results: Thirty-five percent of patients reported DN4 > 4 points in GC after 6 weeks of TT in comparison to 5% in GL and 0% in GD ($P = .005$). Moreover, the incidence rose to 75% in GC compared to 20% in GL and 25% GD at the end of TT ($P < 0.001$). The severity of symptoms, global pain intensity, and patients' unpleasantness were significantly more in GC than GL and GD in the last 4 weeks of TT ($P < 0.05$). NCS showed that 55% and 25% of patients developed mild and moderate axonal neuropathy, respectively, in GC. In contrast, mild neuropathy was developed in 20% and 25% of patients in GL and GD, respectively, and moderate neuropathy in 5% in both groups. The negative impact of TT on QOL was more significant in GC than GL and GD at weeks 8 and 12 of TT ($P < 0.001$).

Limitations: Limited reference data for all treatment regimens to include in the Discussion section.

Conclusions: Lidocaine and duloxetine have a comparable effect to decrease the incidence and severity of TIPN. Moreover, patients' QOL was significantly better in both groups.

Key words: Lidocaine infusion, duloxetine, taxane-induced peripheral neuropathy, breast cancer, DN4

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Chemotherapy-induced peripheral neuropathy (CIPN) is considered the most debilitating side effect of chemotherapy, occurring in 20% to 85% of patients with cancer undergoing chemotherapy. It occurs due to injury or degeneration of the peripheral nerve fibers (1). The CIPN is predominantly a sensory phenomenon starting in the toes and fingers and spreads proximally in a glove and stock distribution (2). The most neurotoxic classes of anticancer drugs are platinum-based drugs, taxanes, ixabepilone, and thalidomide and its analogs (3). Taxane therapy (TT) is commonly used in patients with breast cancer. Taxane-induced peripheral neuropathy (TIPN) may persist up to 3 years after chemotherapy completion, making challenges for cancer survivors as a major cause of ongoing pain with a negative influence on function and quality of life (QOL) (4,5). Also, it can limit the therapeutic opportunities for patients leading to a reduction of chemotherapeutic dose or complete cessation of chemotherapy, which may reduce treatment effectiveness and negatively affect the overall survival (6).

The pathophysiology of CIPN is multifactorial involving microtubule disruption, oxidative stress, mitochondrial damage, altered ion channel activity, myelin sheath damage. and DNA damage of the peripheral nerve fibers, as well as immunological processes and neuroinflammation (7,8). Chemotherapeutic agents also affect peripheral and central neuronal satellite glial cells, astrocytes, and microglia leading to neuroinflammation and the development of CIPN (9). Early detection of CIPN in breast cancer patients undergoing TT is the key for adequate management. Frequent patient assessment and nerve conduction studies help in locating sensory deficits and early therapeutic interventions (10,11).

Several drugs are used for the management of CIPN, including duloxetine, a selective serotonin and norepinephrine reuptake inhibitor approved by the US Food and Drug Administration (FDA) as an effective drug against CIPN (12). Lidocaine is a valuable drug used for the management of neuropathic pain (NP) as it blocks the sodium channels in the neuronal cell membrane that may play a vital role in the pathogenesis and maintenance of both inflammatory and neuroplasticity (13). Lidocaine has been shown to have an antihyperalgesic and antiallodynic effect both in the peripheral and central nervous systems (14).

Objectives

The aim of the study was to evaluate the effect of lidocaine vs duloxetine on reducing the incidence and severity of TIPN and QOL of patients with breast cancer.

Methods

Study Design and Setting

The present prospective randomized, single-blinded controlled study was carried out on 60 patients with breast cancer scheduled for 12 weeks of TT at the Medical Research Institute Hospital, Alexandria University after obtaining local Ethics Committee approval (IORG 000812), (IRB 00010526) and getting a written informed consent from each patient. The recruitment period started in March 2021 and finished in November 2022. It was registered in the "clinical trials library for protocol registration and results system" with the number NCT04732455. The current study meets the Consolidated Standards of Reporting Trials 2010 statement (15).

Randomization and Allocation Concealment

The allocation sequence was computer-generated using the permuted block randomization technique and the block size was variable. The allocation sequence/code was concealed from the person allocating the patients to the intervention arms using sealed opaque envelopes and a blinded nurse determined the group assignments. Investigators were unaware of the medications and their doses.

After obtaining local Ethics Committee approval (IORG008812) and getting a written informed consent from each patient, patients were randomly allocated into 3 equal groups to receive intravenous (1V) saline infusion in the control group (GC) or lidocaine 2 mg/kg with saline infusion in the lidocaine group (GL) or saline infusion and 30 mg duloxetine in the duloxetine group

(GD). The infusion was administered over 40 minutes before each TT and duloxetine 30 mg taken orally once at night before commencing TT then daily for 12 weeks. In GL, if Douleur Neuropathique en 4 Questions (DN4) ≥ 4 was reported by the patients at any time throughout the 12 weeks of TT, lidocaine (2 mg/kg) was reinfused after each TT session. If lidocaine side effects, such as circumoral numbness, twitches, and metal test in mouth, were recorded at any time, lidocaine infusions were reduced to 1 mg/kg. If lidocaine side effects persisted, lidocaine infusion stopped and the patient was managed accordingly, and excluded from the study. In GD, if any selected patient reported DN4 ≥ 4 during the course of TT, the duloxetine dose was raised to 60 mg daily till the end of the study. History was taken properly from each patient and all patients were trained to use all questionnaires in the study.

Eligibility Criteria

Women (18-65 years old) with breast cancer, at any stage, indicated for taxane chemotherapy for 12 weeks were eligible for the study.

Exclusion Criteria

Patients with earlier documented history of gloves and stock neuropathy due to any medical condition, such as diabetes mellitus, pregnant women, alcohol abusers, or patients with abnormal renal or liver function. Also, patients reporting allergy to local anesthetics, myocardial infarction within 6 months, or profound high-grade arrhythmias were excluded from the study. Any neurological or psychological problem, and history of earlier chemotherapy treatment were considered other causes for exclusion.

Study Outcomes

The primary outcome measure was the severity of TIPN among the studied groups. Secondary outcomes were the incidence of TIPN among the patients, degree of neuropathy, QOL of the selected patients, and complications induced by the studied drugs.

Measurements

Demographic Features of the Patients

Age (years), Weight (kg).

NP Characters and Severity

Severity and characters of NP were measured by the NP Scale (NPS) (0-10 cm) (16,17) after each TT session for 12 weeks. The NPS includes an introduction describing how people may experience pain sensations differently and how unpleasantness differs from intensity. The scale presents 10 domains of pain, including 2 items that assess global pain, pain intensity, and pain unpleasantness, and 8 items that assess the specific qualities of NP: sharp, hot, dull, cold, sensitive, itchy, deep, and surface (18). NPS was categorized into: 1) NPS 0-29 cm = not in pain, 2) NPS 30-40 cm = mild, 3) NPS 41-70 cm = moderate, and lastly NPS 71-100 cm = severe.

Incidence of NP Among Patients

It was measured by the DN4 questionnaire after each TT session for 12 weeks. The DN4 questionnaire is a clinician-administered questionnaire consisting of 10 items. Seven items related to pain quality (i.e., sensory and pain descriptors) and 3 items based on the clinical examination (19).

Severity and Degree of Peripheral Neuropathy

A nerve conduction study was performed to detect peripheral neuropathy before commencing TT protocol and after 12 weeks of TT. Amplitude (AMP) reduction change (mv-μv), which represents axonal damage and nerve conduction velocity (NCV) slowing change (m/s) that shows demyelination of the nerve, was measured based on the following equation:

- AMP reduction (mv-μv) change % = (AMP before TT - AMP after TT) /AMP before TT
- NCV slowing (m/s) change % = (NCV before TT - NCV after TT) /NCV before TT

The degree of neural damage depends on the progression in nerve conduction abnormalities. Mild affection represents sensory nerve affection in lower limbs, moderate nerve affection is when involvement includes sensory and motor fibers in both lower limbs and severe affection is when involvement includes sensory and motor nerves in both lower and upper limbs (20,21).

Patients' QOL

The European Organization of Research and Treatment of Cancer QOL Questionnaire-CIPN 20-Item Scale (EORTC QLQ-CIPN20) is a 20-item questionnaire with a 4-point Likert scale (1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much) that assesses the severity of neuropathy symptoms and its impact on QOL of patients (22). It was measured for each patient before

starting TT protocol, at week 8 and at week 12 of TT. QLQ-CIPN20 was categorized: 1) up to 18 = not at all, 2) 19-36 = a little, 3) 37-54 = quite a bit, and lastly 55-72 = very much.

Complications

Any complication that occurred during or after the treatment with lidocaine or duloxetine were reported and managed accordingly.

Statistical Analysis

Data were analyzed using IBM SPSS Software Package Version 20.0 (IBM Corporation, Armonk, NY). Qualitative data were described using number and percentages. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using mean and SD, and median and IQR. The significance of the obtained results was judged at the 5% level. Chi-square test or Monte Carlo test (when > 20% of the cells have expected count < 5) was used for categorical variables, to compare between different groups. F test (analysis of variance) was used for normally distributed quantitative variables, to compare between more than 2 groups, and post hoc test (Tukey) for pairwise comparisons. The Kruskal-Wallis test was used for abnormally distributed quantitative variables, to compare between more than 2 studied groups, and post hoc (Dunn's multiple comparisons test) for pairwise comparisons.

Sample Size

The sample size was calculated using G* Power Version 3.1.9.2. (Heinrich-Heine-Universität, Düsseldorf, Germany). The sample size was calculated based on a previous study (23) aimed to find out the safety and efficacy of duloxetine for the treatment of NP. The minimum required sample size was found to be 18 patients per group (number of groups = 3) (total sample size = 54 women) (24), sample was increased to 20 patients per group (total sample size = 60) to control for attrition (withdrawal) bias.

Results

Eighty patients were assessed for eligibility. Twenty patients were excluded (18 did not meet the inclusion criteria and 2 declined to participate). The selected 60 patients were randomized into 3 equal groups, 20 patients each. Attrition ratio was 0% as shown in the consort flow diagram (Fig. 1).

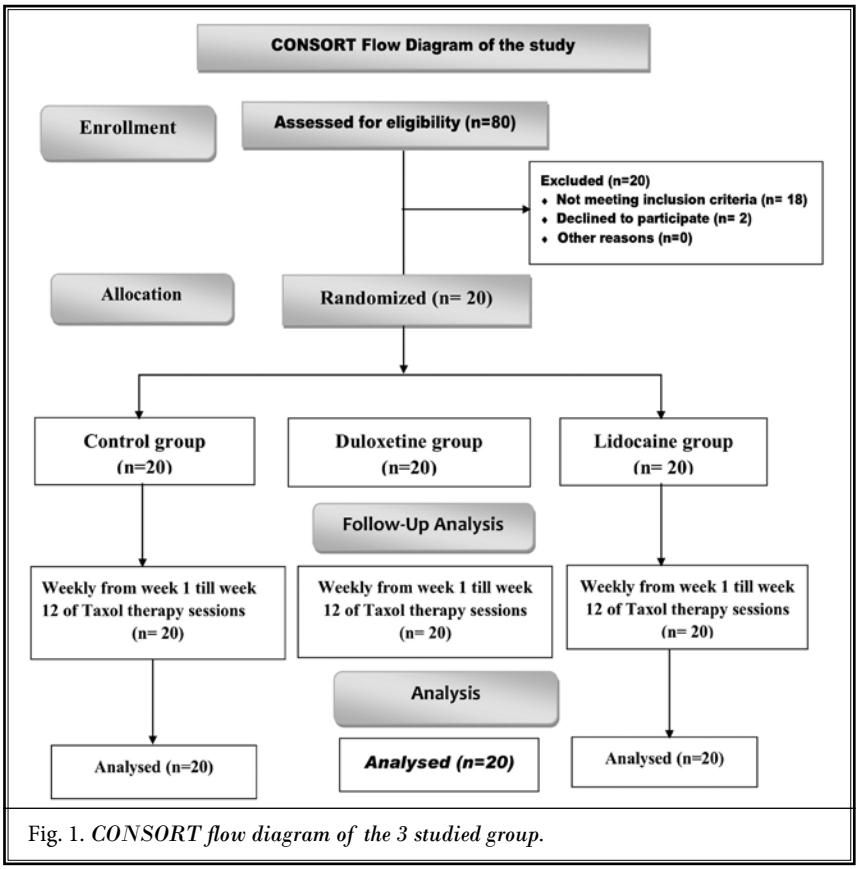

Fig. 1. *CONSORT flow diagram of the 3 studied group.*

General Characteristics of the Studied Patients

Demographic data were comparable in the 3 studied groups (Table 1).

Detection of Taxane-Induced NP Measured by DN4 Score

None of the patients reported NP (DN4 ≥ 4) during the first 4 weeks of TT. Fifteen percent of patients in GC got NP early in week 5 of TT. The incidence of NP was higher in GC. It was reported by 35% of patients in comparison to 5% in GL and 0% in GD after 6 weeks of TT (P = 0.005). This incidence rose to 75% of patients in GC compared to 20% and 25% in

GL and GD, respectively, after completion of TT ($P < 0.001$) (Table 2).

Categorization and Severity of TT-Induced NPS (0-100 cm)

Mild NP (30-40 cm) was reported by more patients in GC in comparison to GL and GD at weeks 6 and 7 and throughout the last 3 weeks of TT ($P < 0.05$). Moderate NP (41-70 cm) was not reported by any patient in GL or GD, while it was shown in 20% to 30% in GC throughout the last 3 weeks of TT (Fig. 2). The global pain intensity, unpleasantness, and most of NPSs symptoms (except cold, and dull pain sensation, which was not reported by any patients in the studied group) were significantly more intense in GC in comparison to GL and GD in the last 4 weeks of TT ($P < 0.05$) (Table 3).

Detection of TIPN by Nerve Conduction Study

The nerve conduction study (NCS) showed a significant reduction change in AMP (mv-μv) of motor branches of ulnar and tibial nerves and sensory branch of the sural nerve in GC than GL and GD ($P < 0.05$). Slowing velocity of conduction of radial, ulnar, sural, and tibial nerves was detected in GC than GL and GD ($P < 0.05$) (Table 4). The NCS showed a higher number of patients in GC 55% who developed mild axonal neuropathy and 25% developed moderate neuropathy in comparison to 20% and 25% of patients who had mild neuropathy in GL and GD, respectively, and 5% got moderate neuropathy as shown in Fig. 3.

Categorization of EORTC QLQ-CIPN20

The EORTC QLQ-CIPN categories showed that 70% and 80% of patients in GC reported quite a bit affection of QOL at weeks 8 and 12 of TT, respectively, compared to 5% and 15% of patients in GL and 10% and 20% of patients in GD ($P < 0.001$) (Fig. 4).

Complications

Apart from slight dizziness and headiness, which were reported in 5% of patients in GL and dry mouth reported in 5% of patients in GD, no one reported major complications. No deaths or life-threatening toxicity was recorded.

Discussion

The current study successfully addressed that lidocaine and duloxetine reduced significantly the incidence of NP in comparison to the saline placebo group after 6 weeks and after completion of TT. The analysis of NPS items showed that the global pain intensity, unpleasantness, and most of NPS items (except cold and dull pain, which were not reported by any patients in the studied group) were significantly less in GL and GD than GC at the last 3 weeks of TT. No patient reported moderate NP symptoms in GL and GD in comparison to 25% of patients in GC after completion of TT.

The efficacy of duloxetine for treatment of CIPN was shown in recently published reviewed articles that clearly supported the use of duloxetine as the first-line

Table 1. *Demographic data in the 3 studied groups.*

	GC (n = 20)	GL (n = 20)	GD (n = 20)	FP
Age (y)	44.0 ± 7.94	44.50 ± 11.02	47.75 ± 9.69	0.415
Weight (kg)	78.85 ± 14.68	76.45 ± 12.43	78.15 ± 11.74	0.836

Data was expressed using Mean ± SD. F: F for one-way ANOVA test.
P: *P* value for comparing between the 3 studied groups.

Table 2. *Percent of patients reporting DN4 ≥ 4 (0-10 points) in the studied groups.*

DN4 Neuropathy (≥ 4)	GC (n = 20)	GL (n = 20)	GD (n = 20)	χ^2P
Week 1	0 (0%)	0 (0%)	0 (0%)	–
Week 2	0 (0%)	0 (0%)	0 (0%)	–
Week 3	0 (0%)	0 (0%)	0 (0%)	–
Week 4	0 (0%)	0 (0%)	0 (0%)	–
Week 5	3 (15%)	0 (0%)	0 (0%)	MCP = 0.097
Week 6	7 (35%)	1 (5%)*	0 (0%)**	MCP = 0.005
	FEP* = 0.044, FEP** = 0.008, FEP*" = 1.000			
Week 7	10 (50%)	3 (15%)*	2 (10%)**	0.006
	*P** = 0.018, *P*** = 0.006, FEP*" = 1.000			
Week 8	11 (55%)	5 (25%)	7 (35%)	0.139
Week 9	11 (55%)	6 (30%)	5 (25%)	0.108
Week 10	14 (70%)	5 (25%)*	6 (30%)**	0.007
	*P** = 0.004, *P*** = 0.011, *P*" = 0.723			
Week 11	15 (75%)	4 (20%)*	5 (25%)**	< 0.001
	*P** < 0.001, *P*** = 0.002, FEP*" = 1.000			
Week 12	15 (75%)	4 (20%)*	5 (25%)**	< 0.001
	*P** < 0.001, *P*** = 0.002, FEP*" = 1.000			

Data was expressed by using number (%).
χ^2: Chi-square test; FE: Fisher Exact ; MC: Monte Carlo
P: *P* value for comparing between the 3 studied groups.
P*: *P* value for comparing between Control and Lidocaine.
P**: *P* value for comparing between Control and Duloxetine.
P*": *P* value for comparing between Lidocaine and Duloxetine.

Fig. 2. *Percent of patients reported NPS categories throughout the taxane therapy protocol in the 3 studied groups.*

therapeutic treatment against CIPN (25,26). Duloxetine is a serotonin-noradrenaline reuptake inhibitor, and its analgesic effects are approved by the FDA. It increased serotonin and noradrenaline in the central nervous system and between nerve synapses. Therefore, it enhances the descending pain inhibitory processing and suppresses hyperalgesia and allodynia. In consistence with the present study, Hirayama et al (27) conducted a randomized controlled study (RCT) on 34 Japanese CIPN patients, crossover was used between duloxetine and Vitamin B12 (VB12) placebo. Significant differences were observed between the GD and the VB12 groups with respect to numbness (P = 0.03) and pain (P = 0.04) at 4 weeks after administration. These findings suggested that duloxetine had a beneficial effect on CIPN caused by oxaliplatin, paclitaxel, vincristine, or bortezomib in Japanese patients. Similar findings were reported by Otake et al (28) as they evaluated the ef-

Table 3. *Items of NPS (0-10 cm) among the 3 studied groups during TT.*

Items of NPS	Time of Assessment	GC (n = 20)	GL (n = 20)	GD (n = 20)	HP	*P**	*P***	*P*''
Intense Pain	Week 5	3 (2-3.5)	2.5 (1-4)	2 (0.5-3)	0.109	> 0.05	> 0.05	> 0.05
	Week 6	3 (3-4)	2* (1-3)	2.5** (2-3)	0.023	0.009	0.042	0.563
	Week 7	4 (3-4)	2* (0-3.5)	3** (2-3)	0.006	0.002	0.016	0.527
	Week 8	4 (3-5)	3* (2-4)	3** (2-3)	0.001	0.011	< 0.001	0.229
	Week 9	4 (4-5)	2* (1-3)	3** (1.5-3)	< 0.001	< 0.001	< 0.001	0.825
	Week 10	4.5 (4-5)	2* (0-3)	3** (1.5-3)	< 0.001	< 0.001	< 0.001	0.243
	Week 11	5 (4-5.5)	2* (1-3)	1** (1-3)	< 0.001	< 0.001	< 0.001	0.930
	Week 12	5 (3-6)	2* (1-3)	2.5** (1-3)	< 0.001	< 0.001	< 0.001	0.503
Sharp Pain Sensation	Week 5	2 (2-3)	1.5 (0-3.5)	2 (0.5-2)	0.120	> 0.05	> 0.05	> 0.05
	Week 6	2 (2-3)	1* (0-1)	2 (1-2)	0.001	< 0.001	0.084	0.051
	Week 7	3 (2-3)	1* (0-2.5)	1.5** (1-2.5)	0.001	0.001	0.002	0.889
	Week 8	3 (3-4)	2* (1-3)	2.5** (1-3)	0.020	0.011	0.024	0.761
	Week 9	3 (3-4)	1* (0-3)	2** (1-3)	0.001	0.001	0.002	0.731
	Week 10	3.5 (2.5-4)	1.5* (1-3)	2** (1-3)	0.004	0.001	0.047	0.103
	Week 11	3.5 (2-5)	2* (1-3)	1.5** (1-3)	0.002	0.001	0.005	0.606
	Week 12	4 (3-5)	2* (1-3)	2** (1-3)	< 0.001	< 0.001	< 0.001	0.794
Hot Pain Sensation	Week 5	2 (2-3.5)	1* (0-2.5)	1** (0.5-2)	0.001	0.001	0.005	0.561
	Week 6	3 (2-3)	1* (0-1.5)	1** (0-2)	< 0.001	< 0.001	< 0.001	0.852
	Week 7	3 (2.5-4)	0.5* (0-2.5)	1** (0-3)	< 0.001	< 0.001	0.001	0.408
	Week 8	3 (3-4)	2.5* (1-3)	2.5** (1-3)	0.010	0.005	0.016	0.680
	Week 9	3 (3-4)	1.5* (0-3)	2** (1-3)	0.002	0.001	0.005	0.592
	Week 10	3 (3-4.5)	2* (0.5-3.5)	2** (1-3)	0.001	0.003	< 0.001	0.586
	Week 11	4 (3-6)	2* (1-3)	2.5** (1-3)	< 0.001	0.001	< 0.001	0.752
	Week 12	4 (3-6)	2* (1-2.5)	2** (1-3)	< 0.001	< 0.001	< 0.001	0.816

Table 3 cont. *Items of NPS (0-10 cm) among the 3 studied groups during TT.*

Items of NPS	Time of Assessment	GC (n = 20)	GL (n = 20)	GD (n = 20)	HP	*P**	*P***	*P*"*
Sensitivity to Touch	Week 5	2 (0.5-2)	0 (0-1)	0 (0-2)	0.053	> 0.05	> 0.05	> 0.05
	Week 6	3 (2-3)	0* (0-0.5)	0** (0-1)	< 0.001	< 0.001	< 0.001	0.768
	Week 7	2.5 (1.5-3)	0* (0-2.5)	1** (0.5-2)	0.006	0.002	0.027	0.350
	Week 8	3 (2-4)	1.5* (1-2.5)	2.5 (1.5-3.5)	0.032	0.012	0.527	0.058
	Week 9	3 (2.5-3.5)	2* (1-3)	2** (1-2)	0.010	> 0.05	0.003	0.289
	Week 10	3 (2.5-4)	1* (0-3)	1.5** (0-2.5)	0.008	0.009	0.006	0.893
	Week 11	3 (2-3.5)	2* (1-3)	2** (1-3)	0.025	0.011	0.036	0.654
	Week 12	3 (2-5)	2* (1-3)	1.5** (1-3)	0.002	0.002	0.002	0.923
Itchy Pain Sensation	Week 5	2 (1-3)	0* (0-2)	1 (0-2.5)	0.011	0.003	0.128	0.135
	Week 6	3 (2-4)	0* (0-2.5)	2** (0-2)	0.001	0.001	0.003	0.589
	Week 7	3 (2-4)	1* (0-3)	1.5** (0-3)	0.002	0.003	0.001	0.799
	Week 8	2 (2-3)	1 (0-4)	2 (1-3)	0.500	> 0.05	> 0.05	> 0.05
	Week 9	3 (2-4)	2* (1-3)	2** (1-2.5)	0.017	0.020	0.010	0.798
	Week 10	3 (2.5-4)	1.5* (1-3)	2** (0.5-3)	0.003	0.005	0.003	0.871
	Week 11	3 (2-5.5)	2* (1-3)	2.5** (1-3)	0.010	0.007	0.011	0.852
	Week 12	3.5 (3-5)	2* (1-3)	2** (2-3)	0.001	< 0.001	0.003	0.574
Unpleasant Sensation	Week 5	3.5 (2.5-4)	2* (1-3)	3** (1-3)	0.017	0.009	0.020	0.792
	Week 6	3 (2-4)	1.5 (1-4)	3 (2-3)	0.200	> 0.05	> 0.05	> 0.05
	Week 7	4 (3.5-5)	2* (1-3.5)	3** (2-4)	0.003	0.001	0.016	0.372
	Week 8	3 (3-4)	3.5 (1-4)	3 (2-4)	0.583	> 0.05	> 0.05	> 0.05
	Week 9	4 (3-5)	3* (2-4.5)	2** (1-3)	0.001	0.045	< 0.001	0.084
	Week 10	4 (3.5-5)	2.5* (1-3)	3** (2-4)	< 0.001	< 0.001	0.011	0.094
	Week 11	5 (3-6)	2* (1-2.5)	2** (2-3)	< 0.001	< 0.001	0.001	0.219
	Week 12	4 (3-6)	2* (1-3.5)	3** (2-3)	0.002	0.001	0.011	0.363
Intense of Superficial Pain	Week 5	3.5 (1-4.5)	0.5* (0-2)	0.5** (0-2)	< 0.001	< 0.001	0.001	0.944
	Week 6	3 (2-4)	1* (0-2.5)	1.5** (0-2.5)	0.003	0.002	0.005	0.767
	Week 7	3.5 (2-4)	0* (0-1.5)	1** (1-2)	< 0.001	< 0.001	0.010	0.110
	Week 8	3 (2-5)	2* (0-2.5)	2 (1-4.5)	0.004	0.001	0.107	0.090
	Week 9	4 (2-5)	1.5* (1-3)	1.5** (1-3)	0.004	0.003	0.008	0.712
	Week 10	4 (2.5-5)	1.5* (0.5-3)	3** (1-3)	0.001	0.001	0.003	0.640
	Week 11	4 (2-6)	2* (1.5-3)	2** (2-3)	0.001	0.001	0.003	0.739
	Week 12	4 (2-5)	1* (0-2)	2** (1-3.5)	< 0.001	< 0.001	0.039	0.063

Data was expressed by using Median (IQR).
P: *P* value for Kruskal-Wallis test for comparing between the 3 studied groups, pairwise comparison between each 2 groups were done using post hoc test (Dunn's for multiple comparisons test); *P*: *P* value for comparing between the 3 studied groups; *P**: *P* value for comparing between Control and Lidocaine; *P***: *P* value for comparing between Control and Duloxetine; *P*"*: *P* value for comparing between Lidocaine and Duloxetine

fectiveness of duloxetine in gynecological cancer CIPN cases. Smith et al (29) conducted a multicenter RCT on 231 cancer patients receiving chemotherapy investigating duloxetine efficacy against CIPN. The observed mean difference in the average pain score between duloxetine and placebo was 0.73 (95% CI, 0.26-1.20). Of those initially receiving duloxetine, 59% reported decreased pain of any amount compared to 38% of those initially receiving placebo.

The present study added important information to the previously mentioned studies that recommended the use of duloxetine for CIPN, as it showed that lidocaine was comparable to duloxetine against TIPN. IV lidocaine infusion is a newer treatment possibility

Table 4. *Reduction AMP (mv-μv)% and slowing in NCV (m/s) % after 12 weeks of TT in the 3 studied groups.*

AMP Reduction and NCV Slowing Change %	GC (n = 20)	GL (n = 20)	GD (n = 20)	HP	P*	P**	P*''
Sural AMP (μv)	55.3 (41.7-81.4)	23.9* (8.6-40.2)	31.0** (19.2-39.3)	< 0.001	< 0.001	< 0.001	0.486
Radial AMP (μv)	20.8 (16.2-36.9)	11.86 (7.29-26.1)	22.8 (-0.29-33.8)	0.257	> 0.05	> 0.05	> 0.05
Sural NCV (m/s)	24.5 (11.8-36.9)	-0.7* (-3.8-4.2)	4.4** (3.0-6.0)	< 0.001	< 0.001	0.003	0.092
Radial NCV (m/s)	20.3 (9.9-24)	-1.1* (-11.3-4.3)	-0.7** (-12-2.7)	< 0.001	< 0.001	< 0.001	0.800
Ulnar AMP (mv)	25.6 (16.6-36.4)	7.1* (4.7-11.8)	7.9** (4.8-12.8)	< 0.001	< 0.001	< 0.001	0.881
Tibial AMP (mv)	40.1 (24.6-49.2)	6.1* (1.3-16.6)	8.6** (4.9-27.4)	< 0.001	< 0.001	0.003	0.296
Ulnar NCV (m/s)	14.1 (9.3-16.2)	4.5* (-3.1-6.7)	5.2** (-1.3-7.1)	< 0.001	< 0.001	0.001	0.835
Tibia NCV (m/s)	24.8 (15.9-37.2)	2.1* (-2.0-4.95)	4.8** (2.3-7.2)	< 0.001	< 0.001	< 0.001	0.176

Data was expressed by using Median (IQR).
H: H for Kruskal-Wallis test, pairwise comparison between each 2 groups was done using post hoc test (Dunn's for multiple comparisons test).
P: *P* value for comparing between the 3 studied groups. *P**: *P* value for comparing between Control and Lidocaine. *P***: *P* value for comparing between Control and Duloxetine. *P*'': *P* value for comparing between Lidocaine and Duloxetine.

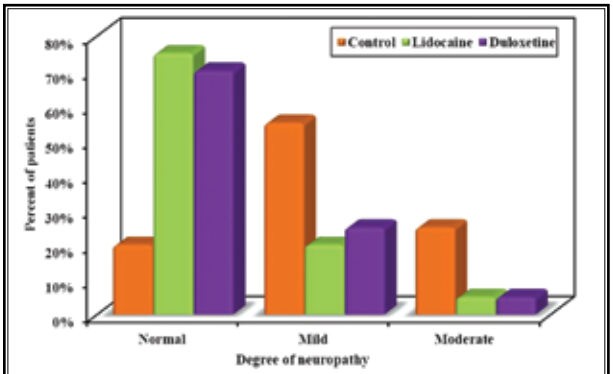

Fig. 3. *Percent of patients reported EORTC QLQ-CIPN20 categories in the 3 studied groups (18-72) throughout taxane therapy protocol.*

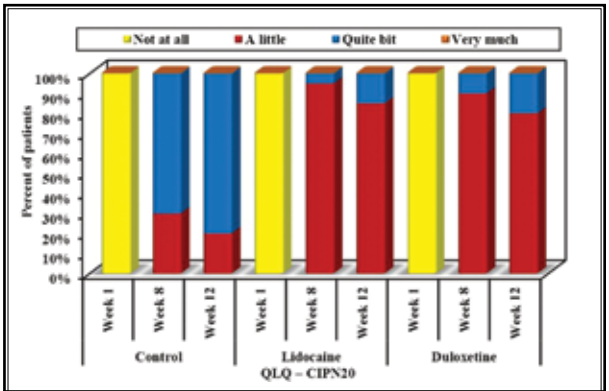

Fig. 4. *Percent of patients with different degree of neural damage measured by NCS in the 3 studied groups after completion taxane therapy protocol*

for different causes of NP, including CIPN (30). It is a sodium channel blocker that prevents the passage of sodium ions through the channel pore. It has analgesic and anti-inflammatory effects with a minimal side-effect profile. Current information showed its efficacy on NP for weeks after administration. But till now there is not enough data to support its use for prevention or treatment of CIPN.

One observational cohort design study evaluated the use of IV lidocaine (1.5 mg/kg in 10 minutes followed by 1.5 mg/kg/h over 5 hours) on 9 patients with CIPN, performed by van den Heuvel et al (30) in 2017. The authors reported that lidocaine minimized the intensity of NP in 8 out of 9 patients (> 30% pain intensity difference). The result was promising, but their study was performed on a limited number of patients and the efficacy of lidocaine was evaluated for 25 days only (30).

Lidocaine was previously investigated for treatment of different causes of peripheral NP other than CIPN and showed good evidence. A systematic review and meta-analysis and Cochrane Database of Systematic Review were done by Tremont-Lukats et al (31), and Challapalli et al (32), respectively, to figure out the efficacy and safety of systemically administered local anesthetics compared with placebo or active drugs. The authors concluded that lidocaine and oral analogs were safe drugs in controlled clinical trials for NP and central pain, were better than placebo, and were as effective as other analgesics (31,32).

Lidocaine used for management of diabetic neuropathy, postherpetic neuralgia (PHN), and failed back pain syndrome showed contrary results to the present study. In one RCT (33), 183 patients with PHN received either 5 mg/kg IV lidocaine infusion or placebo. No sig-

nificant difference was found between the GL and placebo groups. However, lidocaine infusion significantly improved the anxiety and depression status, physical and emotional functionality, and mental health. Another randomized double-blind, crossover trial (34) compared IV lidocaine infusion (5 mg/kg) with active placebo infusion having diphenhydramine (50 mg). The study included 34 patients with chronic diabetic neuropathy or PHN. The authors concluded that no significant long-term analgesic or QOL benefit from IV lidocaine relative to control infusion for chronic peripheral NP (34). Moreover, a randomized, double-blinded, prospective, crossover research on 18 patients was performed by Park et al (35) to assess the effectiveness of 1 mg/kg lidocaine, or 5 mg/kg lidocaine IV infusion vs a 0.9% normal saline placebo on failed back surgery syndrome. The study showed that except for acute, cold, dull, and deep pain, the NPS score revealed no statistically significant difference in pain across the 3 therapies (35). We should note that the type of pain in the previous 2 mentioned studies was mostly a mixed type of pain.

To explain the difference between the result of the current study, which showed the beneficial effect of lidocaine on TIPN and other earlier studies, we should focus on the different tools used for assessment of NP in the present study. DN4, NPS, and NCS all were used for detection and assessment of NP characteristics and severity. However, in the earlier studies, they used DN4 only for diagnosis of NP. A recent study (10) supported the use of combined methods for assessing CIPN for obtaining better results. They divided the assessment techniques into objective and subjective approaches. The NCS is one of the objective methods that helps in assessing CIPN, while subjective tests include patient-reported assessments of their neuropathy, NPS, and others. A limitation of the combined assessment was that they were time-consuming methods for assessment.

In the current study, NCS showed that the incidence of mild and moderate neuropathy was less in GL and GD than GC. Axonal and nerve demyelination were significantly less in GL and GD than GC. The role of neurophysiological study in the diagnosis of CIPN was clarified in Argyriou et al (36). They concluded that NCS was extremely useful in detecting subclinical, initial symptomatic stages of NP, and the extent and severity of large nerve fiber damage. It was used to monitor long-term nerve lesions. Indeed, neurotoxic chemotherapy agents lead to impaired large myelinated nerve fibers and hence standard NCS can provide useful prognostic and diagnostic information (36). Similarly, Wang et al (37) conducted a cohorts study on 84 patients on chemotherapy using 160 NCS assessments. The results confirmed that damage of sensory and motor nerves was profound in patients at various stages of neurotoxic chemotherapy that were detected by NCS (37).

Finally, the result of the current study showed that the negative impact of TT on QLQ-CIPN20 was less significantly measured in GL and GD than GC at weeks 8 and 12 of TT. In agreement of the present study, a previous trial (38) reported that lidocaine plaster was an excellent drug for improving the QOL in patients with NP whose pain was sensitive to topical lidocaine. Katz et al (39) studied the efficacy of 5% lidocaine patch on patients with PHN and reported that the patients experienced less discomfort when treated with a 5% lidocaine patch. Smith et al (29) conducted a multicenter RCT on 231 cancer patients receiving chemotherapy and concluded that duloxetine improved overall QOL.

Limitations

A relatively small sample size so larger sample sizes are required to get more evidence about using lidocaine in TIPN. Limited references go with or against our results.

Conclusions

The finding of the current study concluded that lidocaine is as effective as duloxetine in reducing the incidence and the severity of NP induced by TT. Lidocaine infusion and oral duloxetine minimize taxane-induced axonal damage and demyelination of peripheral nerves; and therefore, the negative impact on QOL in patients with breast cancer. Both treatment modalities are safe in the prescribed dose.

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