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Research Article

Effect of Lidocaine Transdermal Patch as Add-On Therapy in Treatment of Oxaliplatin Induced Peripheral Neuropathy in Colorectal Cancer Patients: A Randomized Double-Blind Placebo-Controlled Trial

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Abstract

Objective: Oxaliplatin-induced peripheral neuropathy (OIPN) is one of the most frequent dose-limiting side effects that impair optimal treatment regimens. Thus, OIPN is impacting not only on quality of life but also on patient's survival. OIPN is a clinical challenge and health care professionals are facing this challenge with a limited selection of analgesics and nonpharmacological therapies.

Methods: Participants were randomly assigned into two intervention groups. Group A (45) received a lidocaine transdermal patch (1 patch/day for 12 hours) along with standard treatment for 6 weeks and group B (45) received a placebo patch (1patch/day for 12 hours) along with standard treatment for 6 weeks. Peripheral neuropathy was measured by FACT/GOG-NTX (S/C) and quality of life was measured by EORTC QLQ C-30 questionnaire.

Results: After 6 weeks of treatment, the FACT/GOG-NTX (S/C) score in OIPN in colorectal cancer patients improved neuropathy significantly ($p<0.05$). After 6 weeks The EORTC QLQ C-30 scores also reduces significantly in the intervention arm compared to the placebo arm. VAS score was improved significantly from baseline to 6 weeks in the intervention arm compared to the placebo arm.

Conclusions: Therefore, the findings of this study reveal that the superiority of L5%P is clearly a matter of thinking where similar drugs are not effective, or any special circumstances arise or the demand of the situations.

Brief Abstract

This study is found out role of L5%P in the improvement of OIPN in cancer patients. Each patient was assessed by FACT/GOG-NTX (S/C) L5%P might be a potential alternative in OIPN.

Abbreviations: CIPN: Chemo-induced peripheral neuropathy; OX: Oxaliplatin; 5% LP: 5% Lidocaine Patch; ECOG: Eastern Cooperative Oncology Group; EORTC : European Organization for Research and Treatment; OIPN: Oxaliplatin-induced peripheral neuropathy; BSMMU: Bangabandhu Sheikh Mujib Medical University

Introduction

Colorectal Cancer (CRC) is one of the most rapidly emerging illnesses worldwide and is a dangerous epithelial carcinoma with metastatic profile, associated with significant morbidity and mortality. In 2020, estimated number of new cases are19.3 million, the Crude Death Rate (CDR) is 24.8 and the Age-Standardized Rate (ASR) is 19.5 per 100000 population. In Bangladesh, CRC death reached 63% of total deaths.CDR is 23.4 and ASR is 18.4 per 100000 of the population, ranking Bangladesh 172 in the world [1]. Despite being an efficacious drug and allowing 80% 6-year survival rates in patients with stageII and stageIII CRC [2]. OXA causes distal symmetric peripheral neuropathy (PN) in about 72% of patients [3]. This neuropathy is typically painful and is with characteristics of negative neurological and positive neurological sign. The mechanisms of OIPN are not fully understood. Oxidative stress to axonal mitochondria has been suggested as a possible mechanism [4]. The most important mechanism involved in acute OIPN was that oxalate metabolite can alter the functional properties of voltage-gated sodium channels resulting in a prolonged open state of the channels and hyper-excitability of Dorsal Root Ganglion (DRG) sensory neurons [5]. Another topical pain-relieving treatment is 5% lidocaine patch. The lidocaine component reduces the excitability of C and A delta fibers of peripheral nerves and thus provides local pain relief through localized analgesia without inducing anesthesia or numbness. In addition, it builds a barrier protecting the skin from mechanical stimuli which can trigger pain sensation [6]. Lidocaine can suppress the expression of EGFR by up-regulating miR-520a-3p, and it could induce apoptosis and inhibit proliferation in CRC cells. In patients experiencing inadequate response to oral therapy (pregabalin and duloxetine) or at risk of adverse effects, topical analgesics are more appropriate as these allow only a small amount of medication to enter the systemic circulation [7]. Topical application has a lower risk of drug-drug interactions, lower systemic levels of medication, and fewer side effects and overdose, when compared to systemic administration of treatment. At the site of local application, lidocaine acts by nonselective blockade of the Na+ channels. Penetration into the intact skin after transdermal diffusion does not produce a complete sensory block of Na+ channels on large myelinated Aβ sensory fibers, so, improvement in pain reduction [8]. Results of the studies support and add to the previously reported efficacy of the combination of the L5% P with an existing partially effective systemic agent [9]. The aim of this study is to evaluate the effect of a lidocaine transdermal patch along with pregabalin in the treatment of OIPN in colorectal carcinoma patients as currently no standard medication is proven to be effective alone.

Methods

Study design and participants

This research was a randomized, double-blind, multicenter trial. The study was conducted on outdoor colorectal cancer patients receiving oxaliplatin-based chemotherapy regimens who have developed oxaliplatin-induced peripheral neuropathy (OIPN) from the Department of Clinical Oncology of one hospital from January 2022 to September 2023. In this study, a total of 90 patients participated with 45 patients in each group, A and B. Eligible patients were Adults with stage II, III and IV colorectal cancers, scheduled to receive an oxaliplatin-based chemotherapy regimen.; and patient ECOG performance status 0-3. Eligible patients could begin a new line of chemotherapy within 14 days of randomization be receiving maintenance chemotherapy or have completed chemotherapy more than 14 days before randomisation with no plan to initiate additional treatment during the study period. Pre-existing symmetric peripheral painful neuropathy due to diabetes mellitus or other causes were not eligible for study participation. Patients with presence of brain metastases and liver, renal insufficiency ere also excluded. All patients provided written informed consent. The protocol was reviewed and the institutional review board (IRB) of BSMMU issued a clearance Letter Memo No. BSMMU/2023/265 and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, and the Declaration of Helsinki.

Sample Size

$$n = \frac{P_1(100 - P_1) + P_2(100 - P_2)}{(P_1 - P_2)^2} \times (Z_\alpha + Z_\beta)^2$$

n = Sample size in each group

Zα = Z value at a definite level of significance 1.96 at 5% level of significance

Zβ = Z value at a definite power 0.842 at 80% power

P1 = Treatment group response 63%

P2 = Control group response 33.5%

$$n = \frac{63(100 - 63) + 35.5(100 - 35.5)}{(63 - 35.5)^2} \times (1.96 + 0.842)^2$$

=41

In this study, a total of 90 patients participated with 45 patients in each group, A and B. The dropout rate was 10%, which brought down the actual same sample size for each participating group to 41 patients.

Group A-A total of 45 Patients before dropout

Group B-A total of 45 Patients before dropout

Outcomes

The primary outcome was a change in changes from FACT-GOG-NTX (S/C) assessment score. The secondary outcomes were changes in VAS pain score, changes in quality of life in the EORTC QLQ-C30 score and incidence of treatment-related adverse events.

Patient Assessment Tools

Functional Assessment Cancer Treatment/Gynecologic Oncology Group Neurotoxicity (FACT-GOG-NTX) questionnaire (Bengali v 4) to assess peripheral neuropathy Visual Analogue Scale (VAS) Bangla version 11.0 to assess neuropathic pain European Organization for Research and Treatment of Cancer (EORTC) -

questionnaire to assess the quality-of-life Eastern Cooperative Oncology Group (ECOG) performance status scale to assess performance status.

Study Procedure

According to the principle of Consolidated Standards of Reporting Trials (CONSORT), recruitment and enrollment of patients were done. It should be mentioned that medicines were purchased from the manufacturer at the original market price so that there was no conflict of interest. Lidocaine 5% Patch was purchased from United States, and placebo patch was purchased from Incepta Pharmaceuticals Limited are leading pharmaceutical company in Bangladesh. After determining the sample size, patients were randomly allocated into two arms. Randomization was done by online graph pad software using the computer. The software automatically generated two distinct sets of random numbers after giving the necessary inputs (sample size, sets of numbers). Here every patient had an equal chance to be assigned to any one of the groups (Group A and Group B). Immediately after randomization, random numbers of the two sets were assigned as patient code numbers. One set was designated for Group A, and the other set was for Group B. Then the set of code numbers that belongs to group A was written as patient ID numbers on the packages containing the Lidocaine 5% Patch. On the other hand, the set belonging to group B was designated as patient ID numbers on the packages containing placebo patch. This total procedure was conducted by persons unrelated to this research. Thus, the participants and the investigator who require being blind for such a study were effectively blinded from the knowledge about intervention allocation.

Intervention and Assessments

A total of 90 patients were enrolled after returning informed written consent. Then demographic information, address, mobile number, and other information were recorded in a preformed data sheet. Ten (10) patients were dropped from the research due to discontinued intervention (9) and death (1). The dropout cases were from per-protocol analysis. A total of 80 patients were available to complete the study making the per-protocol treatment number 80. The study consisted of three visits, a baseline visit, a follow-up visit at 21 ± 4 days, and another follow-up visit at the end of 42 ± 4 days of administration of5% Lidocaine Patch and placebo patch. At the baseline, the patients were assessed by the translated and validated Bengali version VAS and FACT-GOG-NTX (S/C). Then patients had given 5% Lidocaine Patch and placebo patches. Regular intake of medicine was confirmed by talking to the patients through the telephone and from the compliance sheet of the patients. Patients were asked to report any unwanted effects of the medication given during the study period.

Statistical Analysis

Statistical analysis was done by Microsoft Office Excel 2013. A significant p-value is <0.05.

Results

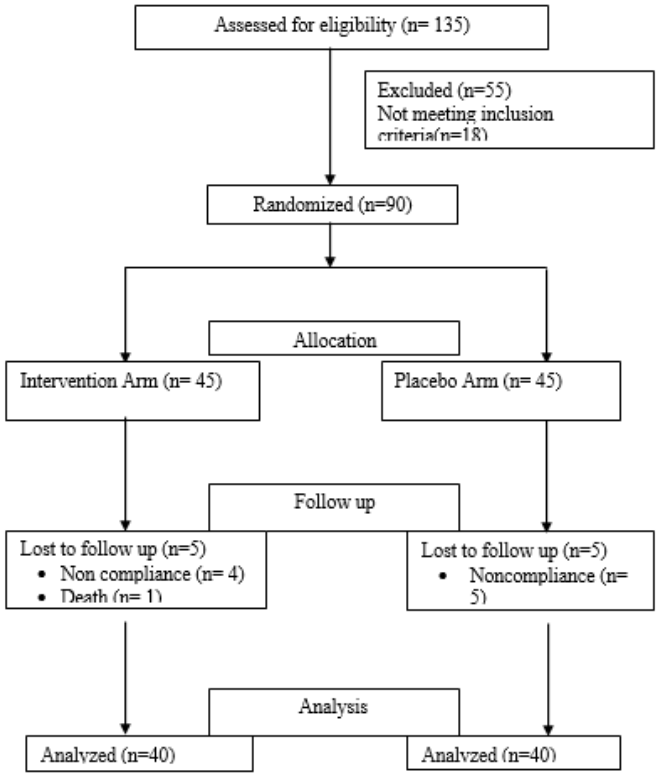

Figure 1:

Figure 1 shows total of ninety (90) patients were enrolled based on study's the eligibility criteria. Of which, after decoding, forty-five (45) patients were found to receive 5%LP which was the intervention arm, and forty-five (45) patients received a placebo patch whichwas the control arm. Ten (10) patients dropped out during the study due to discontinued intervention (n=9) and death (n=1). The dropout cases were excluded from per-protocol analysis. At the end of the study, a total of total of eighty (80) patients were assessed and evaluated.

Baseline Characteristics of Patients at the Time of Enrollment

Table-I shows, there is a female predominance in both groups. In the intervention arm, 53.33% of patients were female, which was 55.55% in the placeboarm. Whereas,46.66% of patients were male in the intervention arm, which was 46.76.% in the placebo arm. Comparison of FACT/GOG-NTX (S/C) Score of Patients Between The Intervention Arm and Placeo Arm Table-II shows, after 6 weeks of treatment, peripheral neuropathy scores increased both in the intervention and placebo arm in comparison to baseline. In the case of the placebo arm the score was not statistically significant (21.38 ± 4.88) and in the intervention arm peripheral neuropathy scores increased significantly (23.02 ± 5.15). Comparison of VAS Score of Patients Between The Intervention Arm and Placeo Arm. Table-III shows, after 3 weeks of treatment, VAS scores were significantly lower both in the intervention arm (5.64 ± 1.11) and placebo arm (6.20 ± 1.27) in comparison to score at the end of 3 Weeks. But at the end of 3 weeks difference between scores of the intervention and placebo arm was statistically significant (p=0.01).

Table I: Baseline Characteristics of Patients at the Time of Enrollment.

Variables	L5% P N = 45 Mean ± SD	Placebo Patch N = 45 Mean ± SD	
Age (years)		47.49 ± 12.77	50.80 ± 12.22
Gender	Male	21	20
	Female	24	25
Site	Rectum	26	22
	Colon	19	23
Stage	Stage III	10	12
	Stage III	12	13
	Stage IV	23	20
ECOG		1.88 ± 0.61	1.91 ± 0.63

Table I I: Comparison of FACT/GOG-NTX (S/C) Score of Patients Between the Intervention Arm and Placeo Arm.

	L5% P N = 40 Mean ± SD	Placebo Patch N = 40 Mean ± SD	p value
At baseline	20.71 ± 2.91	19.78 ± 2.82	0.08
Range, 95% CI	23.62 – 17.80	22.60 – 16.96	
After 6 weeks	23.02 ± 5.15	21.38 ± 4.88	0.03
Range, 95% CI	28.17 – 17.87	26.27 – 16.49	

Table III: Comparison of VAS Score of Patients Between The Intervention Arm and Placeo Arm.

	L5% P N = 40 Mean ± SD	PlaceboPatch N = 40 Mean ± SD	P value[x]
At baseline	20.71 ± 2.91	19.78 ± 2.82	0.08
Range, 95% CI	23.62 – 17.80	22.60 – 16.96	
After 6 weeks	23.02 ± 5.15	21.38 ± 4.88	0.03
Range, 95% CI	28.17 – 17.87	26.27 – 16.49	

After 6 weeks of treatment, VAS scores were significantly lowerboth in theintervention arm (4.76 ± 1.84) andplacebo arm (5.71±1.47) in comparison to score at the end of 6 Weeks. But at the end of 6 weeks difference between scores of the intervention and placeboarm was statistically significant (p=0.00).

Comparison of Quality of Life of Cancer Patients Between The Intervention Arm and Placeo Arm by EORTC QLQ-C30. Table-IV shows, Symptom Assessment scores decreased significantly in the intervention arm but not in placebo arm in comparison to baseline. In case of the intervention arm the score was 30.78 ± 10.69 and in the placebo arm scores was 38.04 ± 11.07. The difference between scores of the Intervention and Placebo arm was statistically significant (p=0.00). Functional Assessmentscores increased non-significantly both in the intervention and placebo arm in comparison to baseline. In case of the intervention arm the score was 53.44 ± 11.48 and in the placebo arm score was 56.71 ± 9.21. The difference between scores of the intervention and placebo arm was not statistically significant (p=0.13). Global Assessment scores increased significantly in the intervention but in the placebo arm score was not significant in comparison to baseline. In case of the intervention arm the score was 52.22 ± 16.14and in the placebo arm score was 50.36 ± 14.32. The difference between scores of the intervention and placebo arm was statistically significant (p=0.04).Adverse Events During Treatment. Table V shows the adverse events in the intervention arm and placebo arm that occurred during the treatment period. There was no significant difference found between adverse events of the interventionand placebo arm after 6 weeks of treatment (p=0.52). Adverse events of the intervention arm were Burning sensation (3), Pruritus (1), and Rash (1) whereas, adverse events ofthe placebo armwere Skin discoloration(5), Rash (2). All the events were mild in form and did not require discontinuation of treatment.

Table IV: Comparison of Quality of Life of Cancer Patients between the intervention Arm and Placebo Arm by EORTC QLQ-C30.

EORTC QLQ-C30		L5% P n=40 Mean ± SD	Placebo Arm n= 40 Mean ± SD	p value
Symptom Assessment	At baseline	43.98 **± 8.32**	41.72 **±** 7.99	0.10
	Range, 95% Cl	52.30 – 35.66	49.71 – 33.73	
	After 6 weeks	30.78 **±** 10.69	38.04 **±** 11.07	0.00
	Range, 95% Cl	41.47 – 20.09	41.11 – 18.97	
Functional Assessment	At baseline	49.56 ± 9.32	46.82 ± 8.56	0.09
	Range, 95% Cl	58.88 – 40.24	95.38 – 78.26	
	After 6 weeks	53.44 ± 11.48	56.71 ± 9.21	0.13
	Range, 95% Cl	64.92 – 41.96	65.92 – 47.50	
Global Assessment	At baseline	43.89 **±** 12.11	45.74 **±** 14.06	0.53
	Range, 95% Cl	56.00 **±** 31.78	59.76 **±** 31.72	
	After 6 weeks	52.22 **±** 16.14	50.36 **±** 14.32	0.04
	Range, 95% Cl	68.36 **±** 36.08	64.68 **±** 36,04	

Table V: Adverse Events reported by patients in the Intervention Arm and Placebo Arm.

Adverse events	L5% P n=40	placebo arm n=40	p value
Yes	5(13.51%)	7(18.52%)	0.52
No	32(86.49%)	30(81.48%)	

Discussion

There was no significant difference in age, gender, site of cancer, and stage of cancer at baseline between the intervention arm and placebo arm. In this study, administration of a lidocaine 5% patch daily at night in addition to standard treatment produces significant improvement of neuropathy in colorectal cancer patients after 6 weeks of treatment ($p<0.05$). Significant ($p<0.05$) improvement in neuropathy after 6 weeks of treatment with L5% P is observed with respect to placebo patch, assessed by FACT-GOG/NTX (S/C) scoring system. In the case of the administration of lidocaine 5% patch improvement of peripheral neuropathy in OIPN patients, similar findings are also observed by other researchers [10, 11]. oxaliplatin's direct toxicity to neuronal voltage-gated Na+ channels (Navs) [12, 13]. Oxaliplatin affects the activation and inactivation of voltage-gated Na+ channels but not K+ channels because oxaliplatin considerably lengthens sodium currents and increases refractory time without being impacted by extracellular calcium concentrations, it is most likely that it works directly on certain Nav isoforms such as Nav1.6, Nav1.7, or Nav 1.9. It is known that L5%P decreases the pain intensity of diabetic neuropathy patients, which is also observed in this research ($p<0.05$). In this regard, the improvement of pain in colorectal cancer patients is observed from the baseline of the treatment with lidocaine patch 5%; which is not observed in placebo patches. The efficacy of L5%P is also observed by [14], 5% lidocaine medicated plaster has been shown to have reduced pain intensity where day 7 pain levels were lower than day 0 pain levels. Additionally, they were lower than at baseline on day 14 and during the final evaluation. The first week of treatment showed the most notable decreases in these parameters [15]. At the final evaluation, over 60% of patients said that they had experienced moderate to total pain alleviation [16]. More importantly, like this study, other Studies also demonstrated that pain reduction related to the lidocaine patch 5% was associated with improvements in pain interference with quality of life. Pregabalin has been shown to be effective in the treatment of PHN and DPN in clinical trials but is commonly associated with systemic side effects, including central nervous system (CNS) effects, such as dizziness, somnolence, and gait disturbance. The excellent safety profile of the 5% lidocaine medicated plaster is supported by data from trials of up to 2 years duration which showed that the 5% lidocaine medicated plaster is effective and well tolerated for long-term use in patients with Post herpetic neuralgia [6]. The present study demonstrated administration of a lidocaine 5% patch was statistically significant in the assessment of the symptom scales (fatigue, insomnia, nausea, and vomiting) improvement assessed by the EORTC QLQ-C30 v 3.0 questionnaire ($p<0.05$) in comparison to placebo patch. The finding is consistent with the previous study [17] in which a similar reduction was observed in symptom improvement. Open literature indicates that lidocaine can improve the QoL: pain intensity, food intake, mood, and patient well-being [18, 19]. However, the current study clearly demonstrates that lidocaine 5% patch promotes symptom-specific aspects of QoL in OIPN patients with pain ($p<0.05$), as measured by the same instrument, compared with the placebo patch.

The results indicate that both arms are individually not significant ($p>0.05$) in improving functional assessment (physical, emotional, and social) scores. These findings are consistent with other researchers too [20]. The current study observed that the lidocaine 5% patch significantly improves ($p<0.05$) global health status/ QoL, as measured by the EORTC QLQ-C30 questionnaire but placebo patch cannot show such type of response in global health status/ QoL ($p>0.05$). Similar results are also found by the EORTC QLQ-C30 instrument, with the use of lidocaine 5% patch as compared with a placebo patch alone. Multiple placebo-controlled trials have demonstrated that lidocaine 5% patch improves overall QoL in OIPN patients with pain.

As it is mentioned that L%P promotes global health status/ QoL in OIPN patients with pain ($p<0.05$), compared with placebo patch. The present study demonstrates that L5%P has the potential ability to be an effective drug for OIPN and QoL. Moreover, it is also a safe drug for the treatment of OIPN. The result of the current study will help OIPN, also can help to manage side effects and improve QoL during standard chemotherapy treatment. Therefore, the findings indicate that the lidocaine 5% patch was similarly beneficial in long-standing OIPN, it appears prudent to begin therapy as early as feasible in the course of OIPN.

Conclusion

To sum up, in a randomized, double-blind trial L5%Psignificantly improved neuropathy and QoL in patients with OIPN in CRC patients. To control OIPN in CRC patients, L5%P has shown efficacy and the patients will have more treatment options to manage side effects, improve QoL. Therefore, throughout this research, the superiority of L5%P is clearly a matter of thinking where similar drugs are not effective, or any special circumstances arise or the demand of the situations.

Limitations

First, Nerve conduction test is not estimated in this study.

Second, Changes of immune cells and cytokines in blood could be conducted to diagnose neuroinflammation accurately.

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Author contributions

SS: Conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources and software, validation, writing original draft, editing, and review. SR: Conceptualization, funding acquisition, methodology, supervision, validation, writing original draft, editing, and review. IC: Conceptualization, methodology, supervision, writing original draft, editing, and review. YF: Conceptualization, methodology, supervision, writing original draft, editing, and review. FM: Conceptualization, methodology, supervision, writing original draft, editing, and review. SA: Conceptualization, methodology, supervision, writing original draft, editing, and review.

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