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Original Article

A Comparison Between the Efficacy of Venlafaxine and Duloxetine in Improving Chemotherapy-Induced Chronic Neurotoxicity in Cancer Patients

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Abstract

Background: Chemotherapy-induced peripheral neuropathy is one of the most common side effects of chemotherapy. This study aimed to determine the effectiveness of venlafaxine and duloxetine in improving chronic neurotoxicity induced by chemotherapy in cancer patients.

Materials and Methods: The study was performed on cancer patients undergoing outpatient chemotherapy or hospitalization in Rasoul Akram hospital. The admitted patients were blindly divided into two groups. The first group was treated with venlafaxine, and the second group was treated with duloxetine. The treatment lasted up until the patients' full recovery up to 10 weeks. Different intensities of the patients' neuropathy were measured on all days of treatment based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 criteria. At the end of the treatment, the side effects of venlafaxine and duloxetine were identified.

Results: A total of 30 patients in two groups (n = 15 for each group) were treated with venlafaxine and duloxetine. There was no significant difference between the two groups in terms of age and gender. The severity of neuropathy was significantly reduced in the venlafaxine compared to the duloxetine group from 7 to 10 weeks. The results indicated that 75% and 85.7% fall asleep in the venlafaxine group and the duloxetine group, respectively. Further, there was no significant difference between the two groups in terms of drug side effects.

Conclusion: This study showed that venlafaxine is a suitable drug for the treatment of chronic neurotoxicity in patients with relatively fewer side effects compared to other used drugs. Although these results require further prospective studies due to the small sample size, future drug regimens may preferably contain venlafaxine.

Keywords: Chronic neurotoxicity, Venlafaxine, Duloxetine, Chemotherapy, Cancer

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Introduction

Chemotherapy-induced peripheral neuropathy is one of the most common side effects of chemotherapy that can cause many problems for patients (1,2). Moreover, similar to other side effects, its severity can reduce the treatment dose or even stop treatment. Furthermore, different prevalence (40-60 %) has been reported in different studies as it is influenced by different chemotherapy regimens, duration of treatment, and evaluation methods to evaluate the patient's neuropathy (2-4). The examination of drug combinations in chemotherapy showed that platinum, Vinca alkaloid, bortezomib, and taxanes can exhibit a higher prevalence of neuropathy (5,6).

Clinical manifestations are used to differentiate the type of neuropathy caused by different drugs. Most neuropathies caused by chemotherapy drugs are symmetrical, in the distal region, and along the limb, which is called "glove and sock" neuropathy. This type of neuropathy is often sensory, and the severity of the symptoms depends on the therapeutic dose. This means that if the cumulative dose of the drug is increased, the patient's symptoms will worsen. Nerve conduction examination shows evidence of damage to sensory axons due to the reduction in the amplitude of sensory nerve potential, while motor nerve function is maintained in most nontoxic drugs (4-7).

Some studies indicated that if treatment continues, the patient's symptoms will improve, but if treatment is stopped, partial recovery can be achieved in 80% of patients, and complete recovery can be achieved after 6-12 months in 40% of patients. Some chemotherapy drugs such as taxanes and oxaliplatin can cause acute neuropathy syndrome in addition to chemotherapy-induced neuropathy (8,9). Acute oxaliplatin-induced neurotoxicity has the same range of sensory and motor symptoms and occurs in the first hours and days after drug infusion. Some of these symptoms include sensitivity to the touch of cold objects, discomfort from drinking

cold liquids, discomfort in the throat, and muscle cramps. Patients with more severe neuropathy are at greater risk for chronic peripheral neuropathy (10-13).

Acute neuropathy caused by paclitaxel occurs as an acute pain syndrome. The pain is manifested as a combination of arthralgia and myalgia, which develops about 1-3 days after paclitaxel injection and usually resolves after a week. This syndrome occurs in most patients but is more severe in patients who have received higher doses of paclitaxel (14-16). Venlafaxine is an antidepressant drug that inhibits the reabsorption of serotonin and norepinephrine (17). The therapeutic effects of this drug in the treatment of chronic and neuropathic pain, especially in patients with diabetes mellitus have been found in various studies (18,19). Duloxetine is used to treat major depressive disorders as well as diabetic neuropathy. Recent studies have evaluated the efficacy of duloxetine in the treatment of chemotherapy-induced peripheral neurotoxicity (CIPN), which indicates a relative improvement in patients (20). The aim of this study was to determine the effectiveness of venlafaxine and duloxetine in improving chronic neurotoxicity induced by chemotherapy in cancer patients.

Materials and Methods

The study was conducted as a clinical trial. The inclusion criteria entailed the cancer patients aged 18-75 undergoing chemotherapy on an outpatient basis or hospitalization in Rasoul Akram hospital, Tehran. They were experiencing neuropathy after the start of chemotherapy with no underlying neuropathic diseases such as diabetes mellitus. In the cases of incomplete treatment as well as the intolerance of the patient due to drug side effects and death, the subjects were excluded from the study. Chemotherapy-induced neuropathy has been defined as the frequency of different neurotoxicity intensities throughout the treatment period, the severity of which was determined based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 criterion (18).

After the approval of the Iran University Ethics Committee, written consents were obtained from all patients expressing their approval to enter the project. The admitted patients were divided into two groups based on balancing randomization. The first group was treated with venlafaxine, and the second group was treated with duloxetine. The therapeutic dose of venlafaxine was initially recorded at 37.5 mg daily and was increased to 75 mg if the patient could tolerate it. The treatment continued until the patient fully recovered up until 10 weeks. In the case of duloxetine, the therapeutic dose was 30 mg daily for 10 days and then reached 60 mg until recovery, lasting up to maximum of 10 weeks (20,21). The different intensities of the patient's neuropathy were measured on all days of treatment, and the study was completed after 10 weeks. At the end of the treatment, the side effects of venlafaxine and duloxetine were identified and recorded separately.

After completing the checklists, the patients' information was entered into SPSS 21 software. In the descriptive analysis, central indices such as mean and dispersion indices such as standard deviation were used. Then, the independent *t* test or Man-Whitney test was used to compare quantitative variables, the chi-square or Fisher exact test was used to compare qualitative variables, and the correlation test was used to determine the relationship between quantitative data. Furthermore, a repeated measure test was employed to assess changes over time, and P values ≤ 0.05 was considered statistically significant.

Results

During the study period, 30 patients in two groups of 15 were treated with venlafaxine and duloxetine. Out of 30 patients, 15 (50%) were male, and 15 (50%) were female. The mean age of the patients was 52.07 years with a standard deviation of 10.116 years. The minimum and maximum age of patients was 36 years and 72 years, respectively. Moreover, the mean age of the patients in the venlafaxine group and duloxetine group was 49.87 and 54.27 years, respectively. There were no significant differences between the two groups in terms of age ($P=240.2$) and in terms of patients' gender ($P=0.715$). Furthermore, the severity of neuropathy significantly reduced from 7 to 10 weeks in the venlafaxine group compared to the duloxetine group (Table 1). In terms of drugs' side effects, 75% of subjects in the venlafaxine group and 85.7% in the duloxetine group fell asleep, as presented in Table 2. In addition, there was no significant difference between the two groups in terms of drug side effects ($P=0.4$), and the mean severity of neurotoxicity was significantly different between the two treatment groups, as shown in Figure 1.

Discussion

Venlafaxine is an antidepressant drug that inhibits the

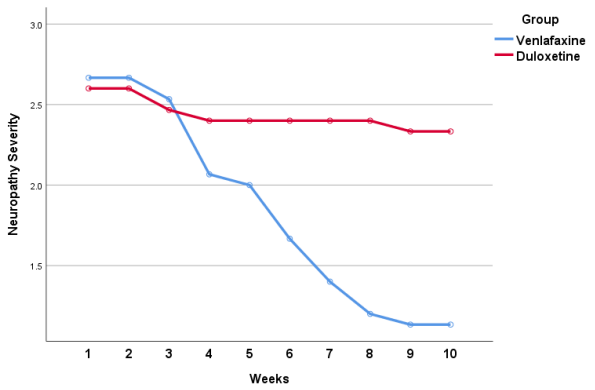

Figure 1. The Mean Severity of Chronic Neurotoxicity Due to Chemotherapy in Two Groups

Table 1. The Frequency Distribution of Neuropathy Severity in Patients according to the Prescribed Drug, Separated by Weeks of Follow-up

Weeks of Follow up	Prescribed Drugs										*P* value
	Duloxetine (n=15)					Venlafaxine (n=15)					
	G0	G1	G2	G3	G4	G0	G1	G2	G3	G4	
1st Week	0	0	7	7	1	0	0	6	8	1	0.931
2nd Week	0	0	7	7	1	0	0	6	8	1	0.931
3rd Week	0	0	9	5	1	0	1	6	7	1	0.586
4th Week	0	1	8	5	1	0	3	8	4	0	0.550
5th Week	0	1	8	5	1	0	4	7	4	0	0.395
6th Week	0	1	8	5	1	0	7	6	2	0	0.070
7th Week	0	1	8	5	1	0	11	2	2	0	0.003
8th Week	0	1	8	5	1	3	8	2	2	0	0.006
9th Week	0	2	7	5	1	4	7	2	2	0	0.019
10th Week	0	2	7	5	1	4	7	2	2	0	0.019

Table 2. The Frequency of Drug Side Effects in Study Patients

Drug Side Effects	Drug		Statistical Difference
	Venlafaxine (n=15)	Duloxetine (n=15)	
Nauseous	2 (25.0)	1 (7.1)	Chi-square test (*P*=0.4)
Lack of sleep	0 (0.0)	1 (7.1)	
Sleepless	6 (75.0)	12 (85.7)	

reabsorption of serotonin and norepinephrine (17) The therapeutic effects of this drug in the treatment of chronic and neuropathic pain, especially in patients with diabetes mellitus have been documented in various studies (18,19). In the present study, the efficacy of venlafaxine treatment in the last weeks of treatment was much better than that of the opposite group. Evidently, in the duloxetine group, a decrease in neurotoxicity was observed which was not considered significant. In a study by Durand et al (21), 48 patients with acute oxaliplatin-induced neuropathy were studied in two groups. The first group was treated with venlafaxine 50 mg once daily and then continued with 37.5 mg twice a day from day 2 to 11. The second group was treated with a placebo from day 1 to 11. The findings of the study suggested that 31.3% of the patients in the first group exhibited improvement in neuropathy, while this percentage was 5.3% in the second group. Moreover, 68.8% of the patients in the first group and 26.3% in the second group revealed therapeutic responses, which was consistent with the findings of the present study.

In another similar study by Piccolo and Kolesar, venlafaxine was evaluated for the prevention of neuropathy in a randomized, double-blind, and placebo-controlled Phase III trial of patients receiving an oxaliplatin-based regimen every two weeks, demonstrating significantly less acute neurotoxicity compared with the control group (22).

Furthermore, a cross-over study by Smith et al was conducted on patients with grade I or higher platinum-induced peripheral neuropathy or taxanes. To this end, 231 patients were enrolled in two groups: duloxetine-placebo (n=115) and placebo-duloxetine (n=116), and they received 60 mg of duloxetine daily (for 4 weeks). The findings revealed a pain reduction of 1.06 in the duloxetine group and 0.34 in the placebo group (23), which was consistent with the findings of the present study.

In the present study, we tracked the patients' symptoms until the 10th week (the time of full recovery of study patients). Although some similar studies such as Smith and have followed patients in even more limited time durations in comparison to our study, we do believe that a 10-week follow-up might be one of the limitations of the present study.

The dose of venlafaxine commonly used for neuropathy is 75 mg twice daily. Venlafaxine has a higher affinity for the 5-HT transporter than other serotonin and norepinephrine reuptake inhibitors but a lower affinity for norepinephrine transport. At lower doses, it seems to act as a selective serotonin reuptake inhibitor and may not have the same activity against painful neuropathy. At higher doses, venlafaxine toxicity (e.g., nausea and hypertension) is more pronounced and may cause side effects of chemotherapy during treatment (24). In the present study, the most common complication was drowsiness (6 out of 8 patients).

In another study, Chu et al investigated the evidence of the use of drugs affecting the central nervous system to alleviate CIPN in cancer patients using a systematic review. They found positive results for amitriptyline (topical), venlafaxine, and oxcarbazepine, but the results of the current study were not sufficient to conclude (25). Overall, insufficient randomized controlled trials exist to confirm the efficacy of central nervous system agents in reducing CIPN. Accordingly, more randomized controlled trials in this area are necessary to generate evidence on CIPN symptom management.

Conclusion

Finally, the findings of the study showed that venlafaxine

is a suitable drug in the treatment of chronic neurotoxicity in patients with relatively fewer side effects than other used drugs. Although these results require further prospective studies due to the small sample size, future drug regimens may contain venlafaxine.

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Conceptualization: Farshid Fardad, Nafiseh Ansarinejad.
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Supervision: Farshid Fardad.
Validation: Farshid Fardad.
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Writing – review & editing: Farshid Fardad, Nafiseh Ansarinejad.

Competing Interests
The authors declare no conflict of interests.

Ethical Approval
This study was approved by the Ethics Committee of Iran University of Medical Sciences (code of ethics: 1397.305) and registered in the Iranian Registry of Clinical Trials website (identifier: IRCT20230201057300N1). Written consent was obtained from all patients stating their consent to enter the project.

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