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Effect of Melatonin on Oxaliplatin Induced Neuropathy in Patients Receiving Folfox Chemotherapy Regimens for Stage II–IV Colorectal Cancer: A Randomized, Placebo Controlled, Double Blind Trial

Raziyeh Kheshti[1] | Mehdi Dehghani[2] | Soha Namazi[3,4] | Dena Firouzabadi[1,5] | Laleh Mahmoudi[1] | Elham Haem[6]

[1]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran | [2]Hematology Research Center, Department of Hematology and Medical Oncology, Shiraz University of Medical Sciences, Shiraz, Iran | [3]Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran | [4]Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran | [5]Shahid Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran | [6]Department of Biostatistics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence: Laleh Mahmoudi (mahmoudi_l@sums.ac.ir)

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ABSTRACT

Background and Aims: Peripheral neuropathy is a major side effect of oxaliplatin-based chemotherapy. The aim of this placebo-controlled double-blind randomized study was to evaluate the effect of melatonin on prevention of oxaliplatin induced peripheral neuropathy (OXIPN) in patients receiving oxaliplatin for colorectal cancer.

Methods: Patients with stage II–IV colorectal cancer, who were to receive oxaliplatin-based chemotherapy, were enrolled according to the inclusion criteria and randomly assigned to take either melatonin (20 mg/day) or placebo, during chemotherapy and 1 month after. Neuropathy was assessed by several patient- and physician-based reports, including the National Cancer Institute Common Terminology Criteria for Adverse Events scale (NCI-CTCAE), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20) scale, and oxaliplatin specific scale (OSS).

Results: From a total of 80 selected patients, 54 completed the study and were evaluated for the final analysis. Grade 3 neuropathy measured by NCI-CTCAE and OSS in the melatonin arm was significantly lower than the placebo group. But according to EORTC QLQ-CIPN20 scale, no statistically significant difference was observed between the groups. In addition, melatonin use did not improve patients' quality of life compared with placebo.

Conclusion: Reduction in grade 3 neuropathy based on NCI-CTCAE and OSS can be of great importance, as it is the higher-grade neuropathy that may lead to functional impairment. Given that to date no medication has been approved for prevention of OXIPN and considering the limited number of patients in the present study, conducting a larger clinical trial on the effect of melatonin may lead to beneficial results in this group of patients.

Trial Registration: Study registered (Date: 23 July, 2018) in the Iranian Registry of Clinical Trials (IRCT); IRCT20170326033139N1 (https://www.irct.ir/search/result?query=IRCT20170326033139N1)

Summary

What is the current knowledge?

- Melatonin has shown analgesic, anti-inflammatory, antioxidant, and antitumor effects.
- Use of melatonin in chronic pain, non-oxaliplatin-based chemotherapy-induced peripheral neuropathy (CIPN), and platinum-based neuropathy in vitro or in animal models has shown acceptable results.

What is new here?

- It is the first trial to study Melatonin use in preventing OXIPN in CRC patients while receiving chemotherapy.
- Melatonin could decrease Oxaliplatin Induced Neuropathy of grade 3.

1 | Introduction

Neuropathy is a major dose-limiting side effect of Oxaliplatin, a platinum derivative frequently used as a part of the chemotherapy regimen of choice in colorectal cancer (CRC) [1]. Oxaliplatin-induced peripheral neuropathy (OXIPN) can present as tingling, numbness, or burning sensation in the toes and fingers, and can rarely cause motor dysfunction. This complication may occur acutely after a single dose of drug infusion presenting with paresthesia and dysesthesia [2]. Acute neuropathies during chemotherapy courses are mostly reversible and rarely lead to cessation of treatment [3, 4]. However, chronic neuropathy may develop following oxaliplatin accumulation in dorsal root ganglia (DRG) of neurons, which may persist for months or years after cessation of treatment, with cumulative doses of oxaliplatin. Oxidative stress, neuro inflammation, and mitochondrial damage have all been identified as mechanisms involved in chronic OXIPN [5, 6]. Chronic neuropathy can cause major functional neurologic disturbances during or after treatment that may resolve with prolonging infusion time, reducing dose, delaying, or even discontinuing treatment [7, 8]. In addition to the mentioned interventions, various approaches have been proposed to prevent or reduce peripheral neuropathy. Various supplements such as vitamin E, oral glutamine, natural products such as AC591, calcium and magnesium infusions, amifostine, mood stabilizers such as venlafaxine and antiepileptic agents have long been studied to prevent and alleviate OXIPN [9, 10]. To date, however, modification of dose and chemotherapy regimens have been the most effective approach to OXIPN management [11].

Melatonin is a natural hormone that is mainly secreted by the pineal gland and is responsible for the sleep–wake cycles in the human species. Previous studies have shown that melatonin, as an antioxidant and anti-inflammatory agent, has promising neuroprotective properties by preventing mitochondrial damage [12, 13]. It's neurologic and pain relief properties have been attributed to various receptors such as dopamine, opioid, GABA, and MT2 receptors [13]. It is hypothesized that sleep deprivation may lead to a decrease in pain tolerance threshold and if the effect of melatonin on circadian rhythm regulation is evident, it may also increase pain threshold and thus be effective in modulating neuropathic pain [13]. Platinum agents can induce mitochondrial and also nuclear DNA damage thereby disrupting electron transfer and causing oxidative stress (OS) [14]. The effectiveness of melatonin in reducing mitochondrial OS has been demonstrated by reducing its oxygen demand as well as reducing the production of superoxide anion and hydrogen peroxide [15]. Given the significant analgesic, anti-inflammatory, antioxidant, and antitumor effects alongside the few side effects reported in previous studies of melatonin [13], this agent may be suggested as a potential treatment in the management of OXIPN [16, 17]. Although the use of melatonin in chronic pain [18], non-oxaliplatin-based chemotherapy-induced peripheral neuropathy (CIPN) [19, 20] and platinum-based neuropathy in vitro or in animal models [21, 22], has shown acceptable results, its use in preventing OXIPN in CRC patients while receiving chemotherapy has not yet been studied. Therefore, in this randomized controlled trial (RCT), the authors decided to evaluate the potential protective effects of melatonin on OXIPN in CRC patients receiving conventional oxaliplatin-containing chemotherapy regimens (FOLFOX and XELOX regimens).

2 | Patients and Methods

This study was designed as a parallel RCT to evaluate the effect of melatonin versus placebo for the prevention of OXIPN in CRC patients treated with FOLFOX or XELOX regimens.

2.1 | Patient Selection

All CRC patients with a confirmed pathologic diagnosis of stage II–IV malignancy were eligible for inclusion in the study only if they met the following inclusion and exclusion criteria [23].

2.1.1 | Inclusion Criteria

Age 18 years and older, Eastern Cooperative Oncology Group (ECOG) Performance Status Score 0–2 [24], normal values of laboratory data up to 30 days before the start of chemotherapy, including normal cell blood count (CBC) (WBC $\geq 3\times10^9$/L; platelets $\geq 100\times10^9$/L; hemoglobin ≥ 10 g/dL), liver function tests (LFT) (total serum bilirubin ≤ 1.5 upper limit of normal (ULN); serum transaminase ≤ 2.5 ULN) and renal function (Serum creatinine ≤ 1.5 ULN).

2.1.2 | Exclusion Criteria

Pregnancy, lactation, female patients of reproductive age unwilling to use contraceptives during chemotherapy, previous medical history of peripheral neuropathy (sensory or motor) to any extent, family history of neuropathy, use of medications with known efficacy in reducing or preventing neuropathic pain [23], known medical history of diabetes mellitus, hypersensitivity to any component of the chemotherapy regimen or melatonin, and inability of the patient to swallow capsules.

2.2 | Study Design

This study was designed as a double-blind clinical trial. Patients, the clinical oncologist who administered and evaluated the treatment and the clinical pharmacist who collected the data were blinded to the grouping of patients. Permuted block randomization method was used to assign patients to each group.

Since no other studies have previously been performed on the effect of melatonin on prevention of OXIPN, a similar study on venlafaxine used for the same purpose [25], was used to calculate the number of patients required to perform this study. Considering $\alpha = 0.05$ and $\beta = 0.2$, and based on the mentioned study [25] in which the percentage of neuropathy in the case and control groups was 5.6% and 38.5%, the estimated sample size of 22 patients in each group was calculated. To increase the accuracy of the study and since in some studies estimating the sample size based on the above-mentioned difference, the resulting sample size was not sufficient to detect the difference between the two groups [26], and considering an estimated 20% loss in patient population in each group for follow up during the study, the final total number of 80 patients, 40 in each arm, was confirmed as the study population.

Ethics approval for this study was obtained from ethics committee of the Shiraz University of Medical Sciences (approval number: IR.SUMS. REC.1397.275). Thereafter the study was registered in the Iranian Registry of Clinical Trials (IRCT) and was allocated a unique code (IRCT20170326033139N1). Written informed consent was obtained from all patients taking part in this study and patients were all made aware that they could leave the study process at any time if desired.

2.3 | Study Procedure

Soft gelatin capsules consisting of 5 mg of melatonin were provided from Zahravi pharmaceutical company, Tabriz, Iran. Capsules with a completely similar appearance filled with inactive substance were provided as placebo by the same company for the control group. Depending on the intervention or control group, each patient received a 30-day pack of melatonin or placebo capsules on the first day of chemotherapy. Patients were to take the capsules (4 capsules at nighttime) during the course of chemotherapy and 1 month after the last dose of oxaliplatin. Patient's compliance with the study protocol was assessed by counting the remaining capsules in the returned bottle. If the patient had consumed $\geq 80\%$ of the capsules, patient's compliance was considered sufficient [27]. Demographic, clinical, pathological and laboratory data of patients along with adverse events (AE) encountered during chemotherapy courses were recorded.

Before starting chemotherapy, all patients underwent a complete neurologic examination and were given a score of 1–5 based on NCI-CTCAE [28]. Neuropathy was re-evaluated before each course of chemotherapy. Evaluation of neuropathy continued for 1 month after the last cycle of chemotherapy or 6 months after start of melatonin or placebo in patients receiving chemotherapy for more than 6 months.

Baseline and serial laboratory data were collected for each patient during the study process, and probable AEs were recorded at time intervals of every 4 cycles of chemotherapy (baseline, before cycle 4, 8, and 12) according to the "Common Terminology Criteria for Adverse Events" (CTCAE v4.03) [28]. Anemia, thrombocytopenia, leukopenia, hepatotoxicity in terms of LFT change, rise in serum creatinine, gastrointestinal complications including diarrhea, constipation and vomiting, electrolyte abnormalities including hypercalcemia, hyponatremia, and hypokalemia were evaluated and compared in both groups.

2.4 | Neuropathy Evaluation

Evaluation of the final outcome, prevention of neuropathy, was performed based on two different reports; physician-based and patient-based.

2.4.1 | Physician Reports

1. The NCI-CTCAE v.4.03 was used to assess cumulative OXIPN along with a number of clarifying questions that were asked from the patient each time the CTCAE scale was used to assess neuropathy. As in the Loprinzi trial [23], clarifying questions were prepared and patient-reported symptoms were classified as grade 1, 2, 3, or 4 based on the NCI-CTCAE.
2. Oxaliplatin-Specific Scale (OSS): OSS was used as a complementary asset to the NCI-CTCAE scale to evaluate OXIPN.

2.4.2 | Patient Reports

1. Side effect questionnaire [23]: Acute and reversible neurotoxicity were recorded using a questionnaire that was completed by the patient exactly after each chemotherapy and five consecutive days after chemotherapy. Symptoms including sensitivity touching cold items, discomfort in swallowing cold liquids, discomfort in the throat, muscle cramps, and difficulty in buttoning a shirt or tying shoelaces were rated from 0 to 10 based on their severity.
2. EORTC QLQ CIPN20 neuropathy [29]: A 20-item questionnaire for Chemotherapy Induced Peripheral Neuropathy was used. This includes three subscales of sensory (9 items), motor (8 items), and autonomic (3 items) neuropathy. Since the Persian translation of CIPN-20 was not available, translation and pilot testing of this questionnaire was done according to the instructions and under the supervision of EORTC institute and the required permission was given by the institute to use the translated questionnaire in this study.
3. Quality of life questionnaire (EORTC-QLQ-C30) [30]: In addition to neuropathy assessment, patients' general health and wellbeing was assessed using this questionnaire, which was collected exactly parallel with AE questionnaire.

2.5 | Statistical Analysis

SPSS software version 25 was used for data analysis. Quantitative variables with normal and non-normal distribution were compared between the groups by using the independent Sample *t*-test and Mann–Whitney, respectively. Kolmogorov–Smirnov test was used to determine normal distribution of the data.

Moreover, qualitative variables were compared between the two groups by using χ^2 test. We applied Fisher Exact test when data sparsity was observed.

Comparison of time to onset of grade ≥ 1 and grade ≥ 2 chronic cumulative neurotoxicity was done by using Kaplan–Meier survival curves and log-rank test.

The CIPN sensory, motor, and autonomic subscales were calculated separately by a standard scoring algorithm [31]. Repeated measure ANOVA was used to compare the three CIPN subscales between the two study arms. Due to the high rate of data loss during cycles 9–12, repeated measure ANOVA was done for cycles 1–8.

Patients' quality of life was calculated based on the EORTC-QLQ-C30 using a standard scoring manual [32] and a summary score [33] that was calculated for each chemotherapy cycle for the two study groups. Summary scores were compared between the two groups. Independent samples *t*-test was used to compare quantitative variables with normal distribution between groups. If the data distribution was normal, the summary score was reported as mean ± SD. If the data distribution was not normal, the summary score was reported as a range (maximum−minimum) and Mann–Whitney test was used to obtain the *p*-value. p-value < 0.05 was considered significant.

Flow diagram of the RCT process is demonstrated in Figure 1.

3 | Results

Out of 118 participants who were screened for eligibility from November 2018 to June 2020, 80 patients were selected to participate in the study. However, due to patient loss to follow-up (32.5%), 29 patients in the melatonin group and 25 patients in the placebo group eventually completed the study (Figure 1). As demonstrated, only 8 patients received XELOX regimen and none of them completed the minimum 8 required cycles of chemotherapy and therefore were excluded from further analysis.

Baseline characteristics of the 54 final patients who completed the study are listed in Table 1. As shown, no significant difference (p value > 0.05) was observed between the two groups regarding their baseline characteristics.

3.1 | Clinician-Assessed Neuropathy

Neuropathy was evaluated in each chemotherapy cycle based on NCI-CTCAE and OSS. There was no significant difference between the two groups in terms of the number of patients who experienced different grades of neuropathy at the different courses of chemotherapy (all p-values were > 0.05). However, as shown in Table 2, grade 3 neuropathy, which was assessed based on both NCI-CTCAE and OSS, was significantly lower in the melatonin arm throughout the study period. In total, 3 of the 29 patients in the melatonin arm as well as 2 out of 25 patients in the placebo arm did not experience any neuropathy based on the NCI-CTCAE score. This means that 89.7% of the patients in the melatonin arm and 92.0% of the patients in the placebo arm suffered from grade ≥ 1 of neuropathy during the study. The percentage of patients who experienced NCI-CTCAE grade ≥ 2 of neuropathy was 31.0% and 36.0% in the melatonin and placebo groups, respectively. Subgroup analysis of the melatonin group showed that highest NCI-CTCAE neuropathy scores had no significant relationship with tumor stage (p-value > 0.99), tumor location (p-value $= 0.07$), ECOG performance status (p-value $= 0.82$), and gender (p-value $= 0.84$). Similarly, patients' NCI-CTCAE neuropathy scores in the melatonin arm were not related to age (p-value $= 0.66$) and weight (p-value $= 0.87$).

Time to onset of neuropathy considered as survival time assessed based on Kaplan–Meier survival curves did not also differ between the two groups based on both scales (NCI-CTCAE and OSS). p-values were extracted from log rank test and there was no significant difference between melatonin and placebo groups (Figure 2).

3.2 | Patient-Assessed Neuropathy

The five main symptoms of acute neurotoxicity were assessed based on self-completion of a prepared questionnaire on six consecutive days after each chemotherapy cycle. The mean scores of patients' daily answers to each question for all 12 cycles of chemotherapy were calculated and compared between groups. All five p-values attributed to each symptom of acute neuropathy were greater than 0.05 (Figure 3).

There were no statistically significant differences in CIPN-20 scores of sensory ($p = 0.80$), motor ($p = 0.62$), and autonomic ($p = 0.24$) neuropathy between the two groups.

EORTC QLQ C-30 summary score was calculated for each chemotherapy cycle and compared between the two groups. Table 3 shows the summary scores and p-values for this comparison.

As p values in the Table 3 show, summary scores of QOL were not statistically different between the melatonin and the placebo groups in the 12 chemotherapy cycles.

3.3 | Chemotherapy Induced Adverse Events

Chemotherapy induced AEs were evaluated in both groups at 4 time points based on NCI-CTCAE v 4.03. No difference was observed in the melatonin group compared to the placebo group showing minimum toxicity of melatonin in such patients.

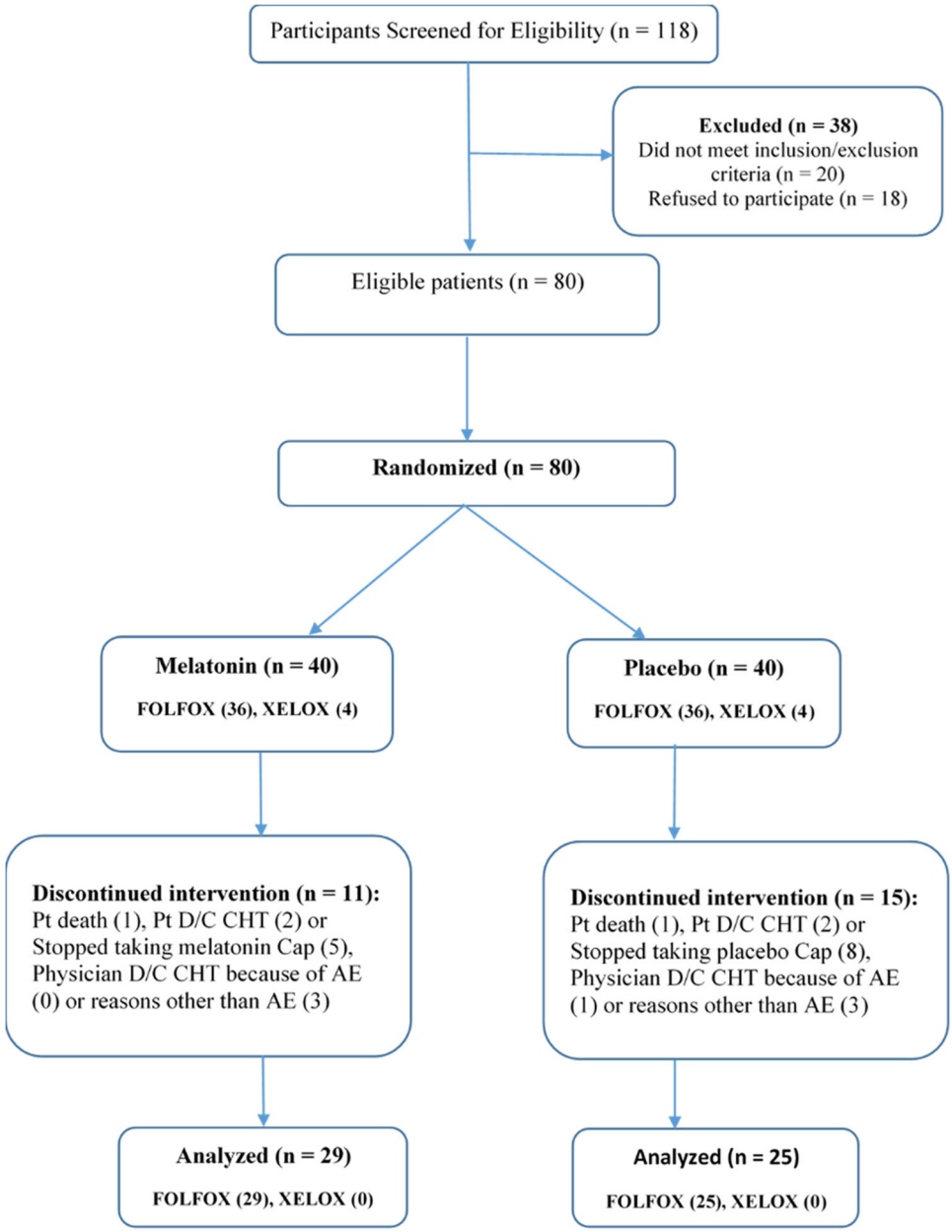

FIGURE 1 | CONSORT flow diagram of the randomized controlled trial (RCT). AE, adverse event; Cap, capsule; CHT, chemotherapy; D/C, discontinued; Pt, patient.

Also, the results of the AE self-completed questionnaire showed that no significant difference was evident between the two groups regarding occurrence of the following AEs: diarrhea (p-value = 0.45), constipation (p-value = 0.43), abdominal cramps (p-value = 0.46), bowel problems in general (p-value = 0.43), swallowing problems (p-value > 0.99), numbness in fingers and toes (p-value = 0.42), and tingling in fingers and toes (p-value = 0.79).

4 | Discussion

OXIPN can be a bothersome side effect of oxaliplatin-containing chemotherapy regimens. There have been many studies and trials that have evaluated the effectiveness of various agents on reducing oxaliplatin neuropathy, mostly being non-conclusive. In this study, clinician assessed neuropathy using NCI-CTCAE and OSS grading showed no difference in patients receiving melatonin in 12 chemotherapy cycles compared with placebo. This result may be attributed to the small study population in both groups and the subjective nature of reporting neuropathic symptoms, which may be misreported under the influence of personal judgment. Previous studies supporting the neuro-protective properties of melatonin by reducing pro-inflammatory cytokines and its anti-nociceptive quality, were based on molecular research in animal models and in-vitro studies [21, 34, 35], and no studies have examined these effects in patients undergoing chemotherapy. Another factor affecting this study's results may be route of administration. Systemic injection of melatonin has been supported to be effective in preventing peripheral nerve and DRG damage [14, 21] along with other studies confirming the low bioavailability of the

TABLE 1 | Baseline characteristics of patients in the melatonin group versus the placebo group.

Characteristics	Melatonin ($n = 29$)		Placebo ($n = 25$)		p value
	No. (%)	Mean ± SD	No. (%)	Mean ± SD	
Age, years		56.21 ± 12.25		57.92 ± 11.26	0.59[a]
Weight, kg		68.89 ± 13.35		71.92 ± 15.40	0.44[a]
Sex					0.85[b]
Male	19 (65.5%)		17 (68.0%)		
Female	10 (34.5%)		8 (32.0%)		
Tumor location					0.51[b]
Colon	21 (72.4%)		16 (64.0%)		
Rectum	8 (27.6%)		9 (36.0%)		
Stage					0.70[c]
II	2 (6.9%)		3 (12.0%)		
III	18 (62.1%)		16 (64.0%)		
IV	9 (31.0%)		6 (24.0%)		
Prior surgery for cancer					0.21[b]
Yes	23 (79.3%)		16 (64.0%)		
No	6 (20.7%)		9 (36.0%)		
Prior radiotherapy					0.72[c]
Yes	1 (3.4%)		1 (4.0%)		
No	28 (96.6%)		24 (96.0%)		
ECOG-PS					0.48[c]
0	23 (79.3%)		22 (88.0%)		
1	6 (20.7%)		3 (12.0%)		

Abbreviation: ECOG-PS, eastern cooperative oncology group performance status.
[a] t-test.
[b] Pearson χ^2.
[c] Fisher's exact test. p-value < 0.05 was considered as significant.

TABLE 2 | Comparison of patients' highest neuropathy score according to NCI-CTCAE and oxaliplatin specific scale in the melatonin ($n = 29$) and placebo ($n = 25$) arms during the whole study period (first cycle of chemotherapy till the last cycle each patient received).

Factor	Group	Neuropathy score			
		No neuropathy	1	2	3
NCI-CTCAE scale	M	3 (10.3%)[a]	17 (58.6%)	9 (31.0%)	0
	P	2 (8.0%)	14 (56.0%)	5 (20.0%)	4 (16.0%)
p value		0.76	0.84	0.35	0.02*
Oxaliplatin specific scale	M	3 (10.3%)	19 (65.5%)	7 (24.1%)	0
	P	2 (8.0%)	9 (36.0%)	9 (36.0%)	5 (20.0%)
p value		0.99[b]	0.03	0.34	0.02[b]

Note: M, melatonin group; P, placebo group.
[a] Number of patients experienced neuropathy are shown and the percent are written in parentheses.
[b] p values were derived from χ^2 or fisher exact test.
*$p < 0.05$.

product due to high first pass effect when taken orally [36, 37]. However due to unavailability of the melatonin injection form, oral capsules were selected for this study. According to the precise pharmacokinetic (PK) properties of melatonin discussed in a recent review article, different formulations of exogenous melatonin may show different clinical efficacy although the presented data has not been conclusive in introducing the best and most effective dosage form [37]. This difference in efficacy presented may be a justification for the difference in treatment response to melatonin in animal and human models. And therefore, the results of the present study have indicated the need for a concise PK study of melatonin in human models. On the other hand, all previous clinical studies reported have been performed on healthy volunteers with different study designs

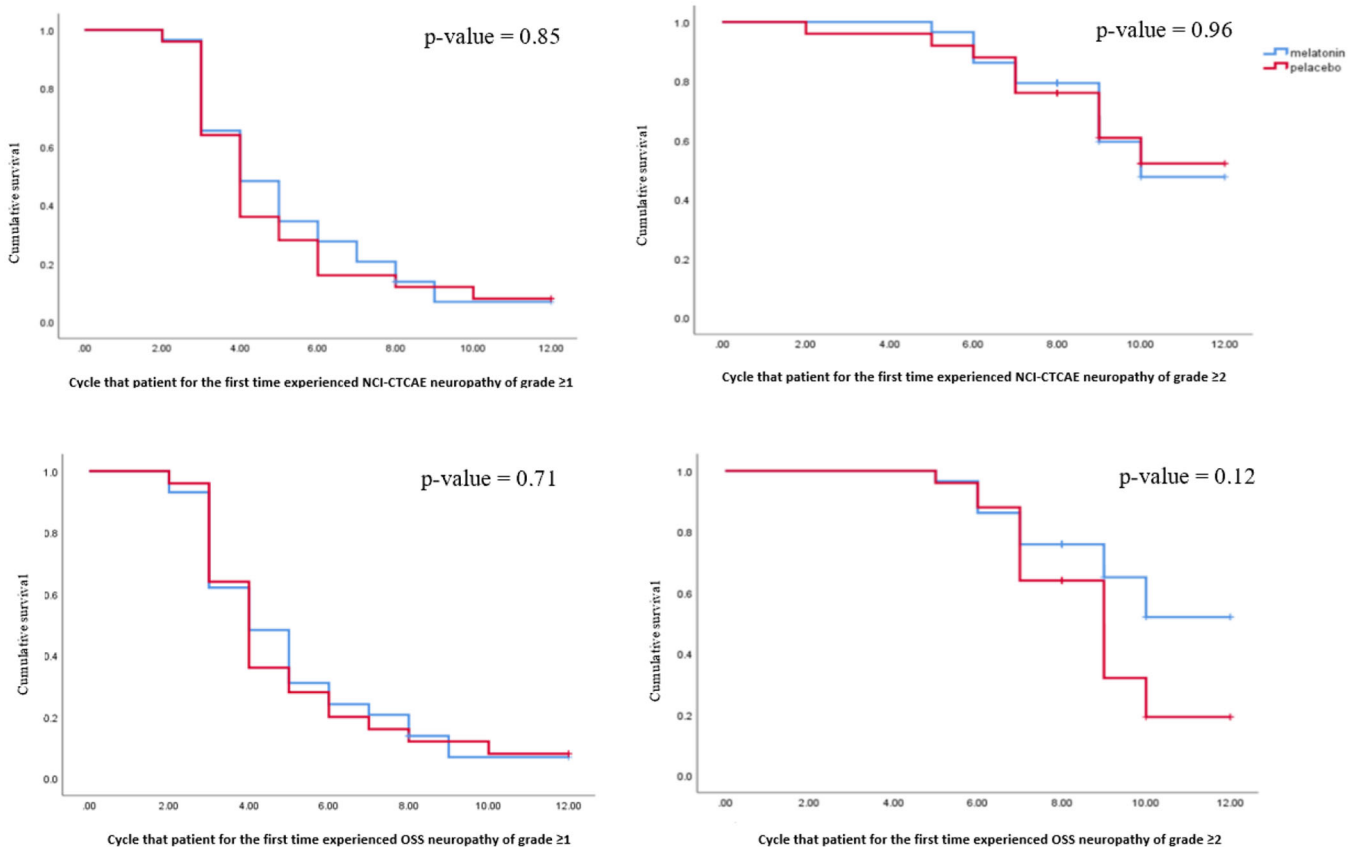

FIGURE 2 | Kaplan–Meier survival curves of time until grade ≥ 1, and grade ≥ 2 Oxaliplatin-induced peripheral neuropathy according to NCI-CTCAE and Oxaliplatin Specific Scale (OSS) scoring systems. *p* values were derived from Log Rank test.

but all with small study populations and therefore no definite data has been extracted yet [37]. Dose-dependent efficacy has been reported for the neuroprotective effects of melatonin [38] suggesting that increasing the dose may also induce a better clinical effect.

Also, due to the fact that rectum has been identified as one of the main sites for melatonin absorption [39], removal of parts of the rectum in patients with rectal cancer may interfere with melatonin absorption. According to the results of our study, the reduction of grade 3 neuropathy in melatonin users based on both NCI-CTCAE and OSS assessments can be of great value because CIPN is more disabling at higher grades.

In this study, grade 3 neuropathy based on both NCI-CTCAE (p-value = 0.02) and OSS (p-value = 0.02) was significantly lower in the melatonin arm (Table 2). Furthermore, time to onset of grade ≥ 2 neuropathy according to NCI-CTCAE v.4 Scale (p-value = 0.96) and OSS (p-value = 0.12) were not statistically different in the two study arms (Figure 2). Loprinzi et al. [23], studied effect of calcium/magnesium on OXIPN, also couldn't find any significant differences regarding time to onset of grade ≥ 2 neuropathy according to NCI-CTCAE v.4 Scale (p-value = 0.34) and OSS (p-value = 0.97) between their three study groups (CaMg/CaMg, CaMg/placebo, and placebo/placebo). However, in their study the incidence rates of CTCAE grade ≥ 2 neurotoxicity were 43%, 46%, and 45% for CaMg/CaMg, CaMg/placebo, and placebo/placebo arms, respectively, which is higher than ours (melatonin = 31% vs. placebo = 36%).

Another pilot RCT on the prevention of OXIPN also confirmed that time to onset of grade ≥ 2 neuropathy according to NCI-CTCAE Scale (p-value = 0.35) and OSS (p-value = 0.35) were not different between their two study arms (venlafaxine and placebo). In that study, 50% of the patients in the venlafaxine arm and 38% of the patients in the placebo arm experienced grade ≥ 2 neuropathy according to NCI-CTCAE [26].

On the other hand, some studies which used NCI-CTCAE Scale as an assessment tool for the evaluation of OXIPN detected decrease in neuropathy score among their studied groups. For example, a RCT which evaluated the preventive effect of amifostine on OXIPN in patients with CRC and gastric cancer, reported decrease in grade 1–4 neurotoxicity (assessed by NCI-CTCAE) in the amifostine arm comparing to the placebo arm [40]. Also, a study on the effect of glutamine versus placebo on the prevention of OXIPN could find a decrease in the incidence of grade 1–4 neuropathy in glutamine arm, assessed by NCI-CTCAE scale [4].

Patients who experience more acute neuropathy are more likely to experience chronic neuropathy, which is a serious adverse effect that impairs QOL [11, 41]. Also, cancer patients receiving chemotherapy may be involved with various AEs related to their course of treatment, and as a result their quality of life may be affected. Previous studies have shown melatonin to have a positive effect on improving sleep and QOL in patients with breast cancer, while also minimizing toxicity in short-term treatment [42, 43]. Its use in metastatic cancer of geriatric

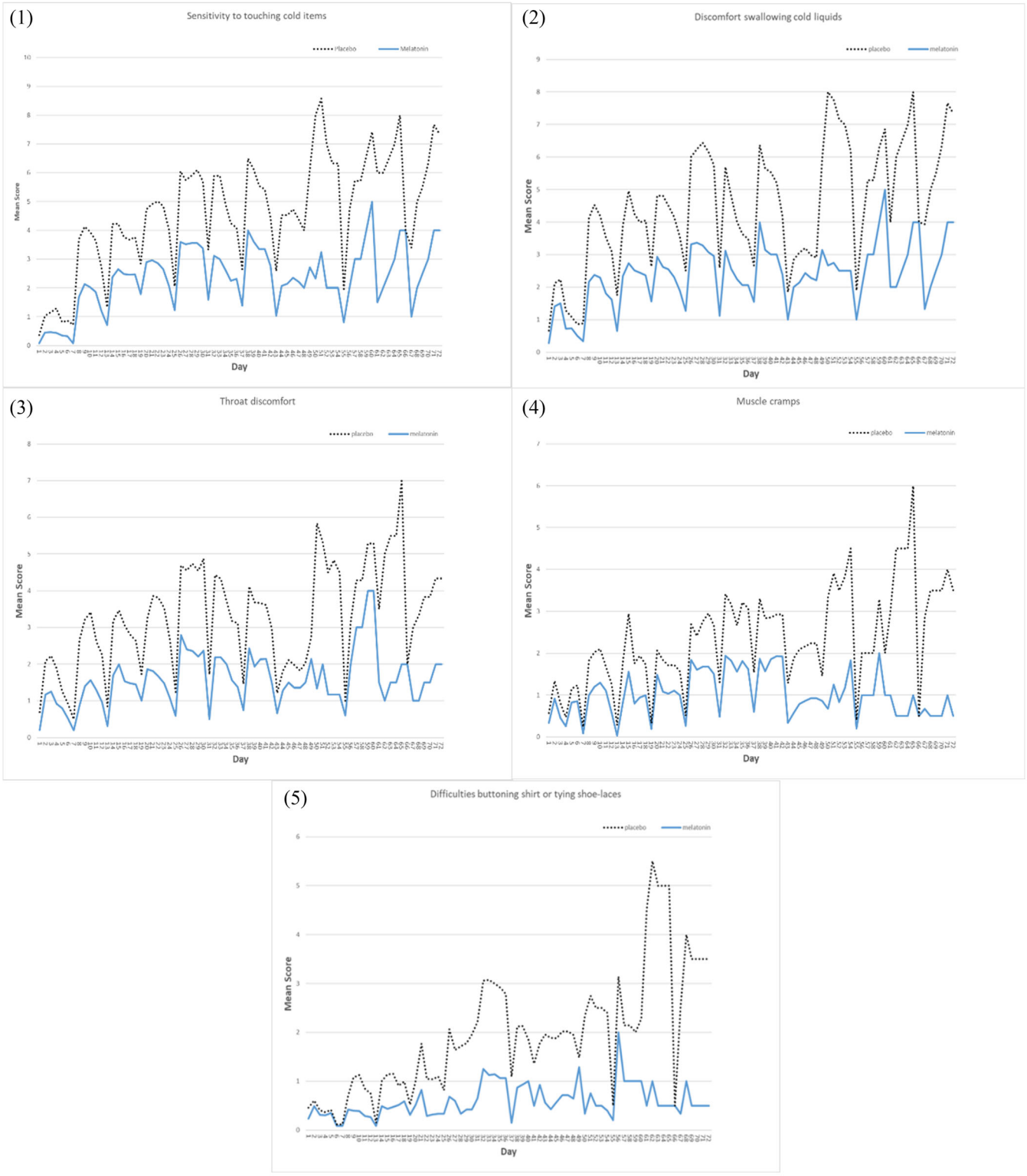

FIGURE 3 | Acute symptoms regarding (1) sensitivities to touching cold items, (2) discomfort in swallowing cold liquids, (3) throat discomfort, (4) muscle cramps, and (5) difficulties buttoning a shirt or tying shoe laces between melatonin and placebo groups evaluated for 6 days after each cycle of chemotherapy ($6 \times 12 = 72$ days).

patients has been supported by improving sleep habits and survival as well as reducing side effects of chemotherapy and cancer [44]. However, in the present study, no effect was found on improving QOL. Although patients' general health and wellbeing was assessed using a questionnaire, QOL affected by neuropathic AEs was assessed using the EORTC QLQ CIPN20 questionnaire. Despite evaluating all patients' functions, including physical, emotional, and cognitive aspects, no differences were observed between patients taking melatonin and those receiving placebo. The promising effects of melatonin in breast cancer patients may be attributed to the difference in the nature of the malignancy and the different

TABLE 3 | Comparison of quality of life of patients in the melatonin and placebo groups in 12 chemotherapy cycles, using the summary scores of the EORTC QLQ-C30 questionnaire.

Cycle	Summary Score[a]		*p* value[b]
	Melatonin	Placebo	
1	89.49 ± 1.62	90.08 ± 1.37	0.78
2	91.92 ± 1.76	90.08 ± 1.54	0.43
3	87.55 ± 2.11	84.85 ± 2.38	0.40
4	85.51 ± 2.15	84.10 ± 2.51	0.67
5	86.10 ± 2.41	83.84 ± 2.60	0.52
6	84.55 ± 3.19	81.53 ± 4.25	0.57
7	87.90 ± 3.42	84.42 ± 4.22	0.52
8	85.71 ± 2.82	82.85 ± 3.88	0.54
9	88.55 ± 2.72	90.06 ± 3.80	0.75
10	(92.40–95.10)	(80.64–96.31)	0.49
11	(92.95–92.95)	(88.08–98.72)	0.67
12	(91.67–96.15)	(82.03–96.15)	0.76

[a]Summary score was shown as mean ± SD or range.
[b]*p* values were derived from independent samples *t*-test for cycle 1–9, and Mann-Whitney test for cycle 10–12. *p* value < 0.05 was considered as significant.

complications that CRC patients may experience compared to those with breast cancer. Also, differences in chemotherapy regimens and assessment methods may have contributed to differences in outcomes. The use of different cognitive tests as well as depression assessment tests was observed in previous studies, although the same dose and comparable study populations were used [43]. Unfortunately, the subjective nature of questionnaire-based assessments interferes with concise and reliable results, especially in communities with less general knowledge of such studies. The lack of a gold standard assessment tool for the evaluation of OXIPN can be introduced as another limiting factor in the evaluation of this type of neuropathy. Although the reliability of different assessment tools has been tested in different settings, there are many differences between patient perception and objective tools, especially in intermediate grades, which increase the need for more effective and standardized assessment tools [45]. Although all patients admitted to a thorough compliance with the trial routines and proper administration of the medication, the conflicting results may also be a result of noncompliance.

Although study population was calculated based on similar conclusive studies, the number of patients studied may be a limiting factor in achieving outstanding results. In addition, the unknown PK of melatonin in the human body may have attributed to conflicting results.

5 | Conclusion

Despite strong evidence for the efficacy of melatonin in vitro and in vivo (mostly animal studies) in preventing and reducing neuropathic pain, this RCT could not confirm the superiority of melatonin over placebo in the prevention of OXIPN in CRC patients based on most endpoints. Also, contrary to our initial theory, melatonin was not effective in increasing QOL of CRC patients receiving oxaliplatin-based chemotherapy. However, reduction of grade 3 neuropathy in both NCI-CTCAE and OSS can be clinically significant. Due to financial constraints and poor patient collaboration, we were unable to conduct a larger sample trial. It may be possible to demonstrate the effectiveness of melatonin on all grades of OXIPN, as well as on QOL, in a trial with a larger sample size.

Author Contributions

Laleh Mahmoudi: design of methodology, oversight and leadership responsibility for the research activity planning and execution, acquisition of financial support for the research activity planning, and execution and revising the article draft. **Raziyeh Kheshti:** conceptualization, design of methodology, conducting the research and investigation process, acquisition of data, and drafting the article. **Soha Namazi:** design of methodology and revising the article draft. **Mehdi Dehghani:** provision of the study materials and patients and revising the article draft. **Dena Firouzabadi:** data curation, and drafting the article. **Elham Haem:** data analysis, interpretation, and revising the article draft. All authors have read and approved the final version of the manuscript. Laleh Mahmoudi had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethics Statement

Ethics approval for this study was obtained from ethics committee of the Shiraz University of Medical Sciences (approval number: IR.SUMS. REC.1397.275). Thereafter the study was registered on July 23, 2018, in the Iranian Registry of Clinical Trials (IRCT). Trial Registration: IRCT20170326033139N1 (https://www.irct.ir/search/result?query=IRCT20170326033139N1).

Consent

Written informed consent was obtained from all patients taking part in this study and patients were all made aware that they could leave the study process at any time if desired. All methods were performed in accordance with the relevant guidelines and regulations.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Transparency Statement

The lead author Laleh Mahmoudi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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