Pharmaceutical Sciences, 2022, 28(4), 579-588
doi:10.34172/PS.2021.81
https://ps.tbzmed.ac.ir/

Research Article

Effect of Melatonin on Paclitaxel-Associated Acute and Chronic Pain: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Naeeme Talaee[1], Sholeh Ebrahimpour[2], Mohsen Sfandbod[3], Hossein Majedi[4], Aarefeh Jafarzadeh Kohneloo[5], Kheirollah Gholami[1], Zahra Jahangard-Rafsanjani[1,6,7*]

[1]*Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.*
[2]*Department of Clinical Pharmacy, School of Pharmacy, Alborz University of Medical Sciences, Alborz, Iran.*
[3]*Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran.*
[4]*Department of Anesthesiology, Critical Care and Pain Medicine, Tehran University of Medical Sciences, Tehran, Iran.*
[5]*Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.*
[6]*Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran.*
[7]*Breast Disease Research Center (BDRC), Tehran University of Medical Sciences, Tehran, Iran.*

Article Info

Article History:
Received: 17 October 2021
Accepted: 25 December 2021
ePublished: 30 December 2021

Keywords:
-Arthralgia-myalgia
-Melatonin
-Paclitaxel
-Peripheral neuropathy

Abstract

Background: Taxane-induced pain is a disabling condition. This trial was conducted to assess the effects of melatonin on preventing paclitaxel-associated acute and chronic pain or decreasing its severity in patients with breast cancer.

Methods: This randomized, double-blind, placebo-controlled clinical trial was conducted on breast cancer women who received weekly paclitaxel (80 mg/m^2) with or without trastuzumab after using doxorubicin + cyclophosphamide. The intervention group randomly received oral melatonin (10 mg/day) or placebo, which started from the first night of chemotherapy and continued through the planned 12 weeks of chemotherapy. The level of arthralgia-myalgia as acute pain was assessed every day in both groups using the Brief Pain Inventory (BPI). The Douleur Neuropathique 4 questionnaire (DN4) and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 were used to measure chemotherapy-induced peripheral neuropathy as chronic pain.

Results: Seventeen patients were enrolled in each group randomly. The incidence of neuropathy according to a DN4 score ≥ 4 was significantly lower in the melatonin group versus the placebo group at week 12 compared to baseline (5 vs 11, P-value= 0.039). In addition, the mean neuropathy severity was significantly lower in the melatonin group over time (β= -0.051, P-value= 0.01). However, there were no significant differences in the mean worst and least pain scores over the twelve cycles of treatment between arms (P-value= 0.633 and 0.34, respectively).

Conclusion: Co-administration of melatonin in women with breast cancer decreased the incidence of severe paclitaxel-associated neuropathy but melatonin was not effective against acute pain.

Introduction

Paclitaxel is an antineoplastic agent administered to treat various types of malignancies, such as breast, ovarian, and lung cancers.[1] Although taxanes are well-tolerated, pathological pain is an important therapeutic challenge because it can significantly affect the patients' quality of life and reduce the dose of chemotherapy or result in treatment discontinuation.[2,3]

Taxane-induced pain is divided into acute and chronic pain.[1] The clinical descriptions of these two kinds of pains vary according to the time of onset, symptoms, and location. Acute pain starts 1-3 days after paclitaxel administration, usually peaks on the fourth day, and then resolves within seven days. It is also known as paclitaxel-associated acute pain syndrome (P-APS). The most common P-APS symptoms include arthralgia and myalgia that may be diffuse or local.[4] The most common sites of pain are the back, pelvis, shoulders, thighs, and legs. Patients typically describe their pain as deep, radiating, shooting, stabbing, or pulsating pain.[5]

Chronic pain usually occurs within the first month of treatment and may persist for weeks to years after discontinuation of paclitaxel. It is also known as chemotherapy-induced peripheral neuropathy (CIPN).[1,6] Peripheral neuropathy usually presents with signs of numbness, tingling, burning, loss of proprioceptive sense,

*Corresponding Author: Zahra Jahangard-Rafsanjani, E-mail: zjahangard@sina.tums.ac.ir

and reduced reflexes in the hands and feet. According to several studies, numbness and tingling are more prominent than other symptoms.[4] Age, race (African-American), comorbid factors such as diabetes, and obesity may increase the risk of paclitaxel-induced neuropathy.[7]

The incidence of acute pain is reported to be up to 70%,[8,9] and is seen in breast cancer patients more than others.[10] Approximately 70% of these patients also show chronic peripheral neuropathy during treatment with taxanes.[11]

The exact pathophysiology of pain is unknown; however, several studies have shown that putative mechanisms are more common, including 1) activation of the toll-like receptor 4 (TLR4), 2) enormous activation of glutamate receptors,[1] 3) suppression of GABAergic synaptic activities,[12] 4) release of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α),[13] 5) reduction of C-fibre activity, 6) increased 8-isoprostane F2α levels,[14] and 7) impaired mitochondrial function.[15,16]

Many studies have attempted to evaluate the effects of various medications such as amifostine, gabapentin, pregabalin, glutathione, glutamine, prednisolone, melatonin, and the herbal composition Shakuyaku on both prevention and treatment of these pain conditions. However, there is not enough evidence to establish a standard practice and more studies are needed in this regard.[2,3]

Melatonin (N-acetyl-5-methoxytriptamine) is a hormone secreted from the pineal gland.[17] Apart from the effects of melatonin on the regulation of sleep disorders and antioxidant effects, melatonin and its analogs have a well-documented efficacy for treatment of various pain conditions such as fibromyalgia, inflammatory bowel syndrome, and migraine.[16,18-19] Different mechanisms have been suggested for pain control of melatonin, such as the inhibiting high-voltage calcium channels and reducing intracellular calcium concentrations in dorsal root ganglion (DRG) neurons,[20] strengthening the binding of gamma-aminobutyric acid (GABA) to central receptors in the brain,[21] and modulating the expression of N-methyl-D-aspartate (NMDA) receptors.[22] It also decreases paclitaxel-induced elevated levels of 8-isoprostane F2α and limits paclitaxel-induced reduction in C-fibre activity.[14] In vitro studies have also shown that melatonin in reducing the mitochondrial dysfunction is effective.[16] (Figure 1)

The above mechanisms led to the hypothesis that melatonin might be useful in the prevention or reduction of P-APS and CIPN.

The possible effect of melatonin on the underlying malignancy and chemotherapy regimen and its safety has been studied in many previous studies. According to these studies, melatonin not only has no adverse effects on the treatment of malignancy but also can exert antineoplastic effects through different mechanisms such as direct cytotoxic effects by inducing cell apoptosis, stimulation of anti-tumor immune responses, modulation of oncogene expression, disruption of EGF-receptor activation, and antioxidant effects against free radicals.[23,24]

Due to the analgesic mechanism of melatonin, its efficacy in the chemotherapy regimen, and its safety, this randomized, double-blind, placebo-controlled clinical trial was conducted to determine the effect of melatonin on preventing paclitaxel-associated acute and chronic pain or decreasing its severity for the first time.

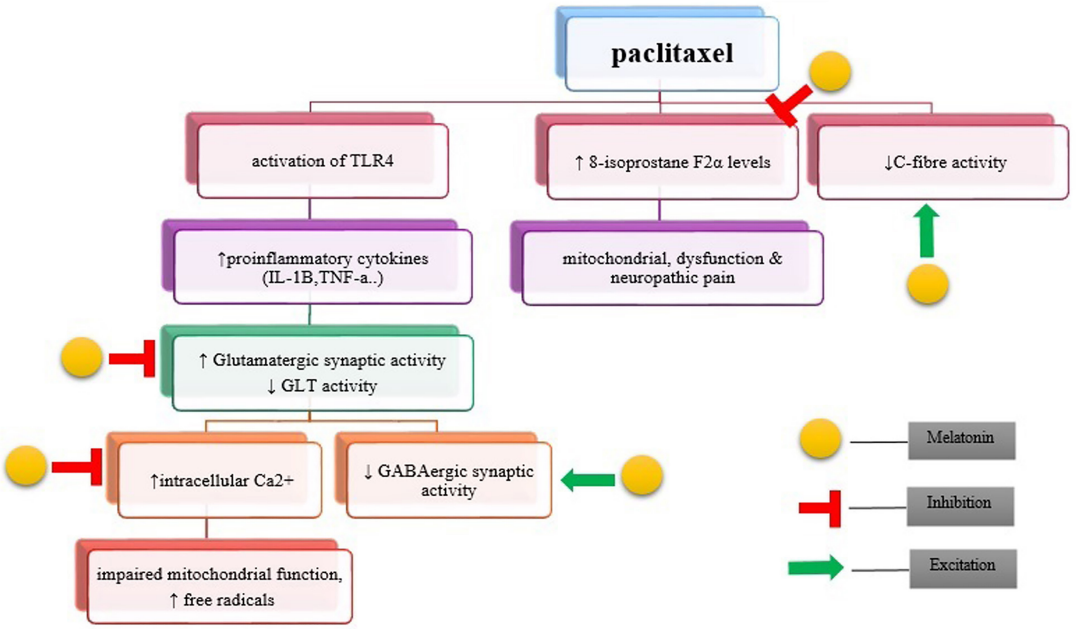

Figure 1. Mechanisms of the protective effects of melatonin on paclitaxel-induced pain
Abbreviations: ↑, Increase; ↓, Decrease; TLR4, toll-like receptor 4; IL-1β, Interleukin-1β; TNFα, Tumor necrosis factor-α; GLT, glial glutamate transporter; GABA, gamma-aminobutyric acid.

Methods

Study design

This randomized, double-blind, placebo-controlled clinical trial was conducted in Cancer Institute of Imam Khomeini Hospital complex affiliated with Tehran University of Medical Sciences between October 2019 and July 2020. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.TIPS.REC.1398.043) and registered at the Iranian Registry of Clinical Trial (IRCT20190630044057N1).

Eligibility characteristics

Adult women with breast cancer who received paclitaxel in a (neo) adjuvant setting at a dose of 80 mg/m^2 weekly after receiving doxorubicin + cyclophosphamide (AC) were included in the study. Other inclusion criteria were the ability to take oral medications and complete the study questionnaire and willingness to participate in the study.

In this study, patients with a history or current complaint of diseases that cause arthralgia-myalgia and neuropathy such as peripheral neuropathy, fibromyalgia, rheumatoid arthritis, osteoarthritis, hypothyroidism, diabetes, metastatic disease, were not included. In addition patients receiving medicines that cause neuropathy such as statins, colchicine, zidovudine, penicillamine, platinum derivatives (cisplatin, oxaliplatin), and vinca alkaloids were not included. Patients taking alcohol were not involved because of toxic neuropathies due to alcohol and patients taking granulocyte colony-stimulating factor (GCSF) were not enrolled due to filgrastim-induced bone pain. Moreover, patients who had experience of trauma, falling, or viral respiratory infections (influenza, covid 19) during study period were excluded from the trial due to myalgia associated with these conditions.

Randomization and blinding

After obtaining informed consent, the eligible patients were randomly divided into placebo (Osveh Pharmaceutical Company, Tehran, Iran) and treatment arms (melatonin 10 mg, Best Naturals, USA) using the block randomization method. Randomization was done using a computer-generated randomization schedule (a block size of 4) created by supervisor of the research. Boxes containing melatonin or placebo tablet with a similar appearance was numbered based on the randomization list and delivered to each participant based on its entry number. Patients and the investigator, who assessed the pain, were both blinded regarding to the study recruitment arms.

Protocol treatment

The participants received melatonin 10 mg or placebo daily, which started after the first dose of paclitaxel administration and continued through the planned 12 weeks of chemotherapy. To avoid daytime drowsiness, the patients were instructed to take the pill at bedtime. According to the Cancer Institute's Protocol, all patients received dexamethasone 20 mg IV, chlorpheniramine 10 mg IV, and cimetidine 200 mg IV before paclitaxel infusion to prevent an allergic reaction.

The patients' age, body surface area (BSA), chemotherapy regimen, paclitaxel dose, concomitant medications, previous disease history, and laboratory data were recorded on the first day of enrolment by the investigator. During the study, the type of the administered analgesics for example acetaminophen, Nonsteroidal Anti-inflammatory Drug (NSAIDs), cyclooxygenase 2 (COX-2) inhibitors, gabapentin, pregabalin, etc. as well as its dose and frequency of use were recorded by the researcher. The defined daily dose (DDD) scale was used to standardize the amount of analgesic consumption.[25]

Drugs were given to patients weekly to assess their acceptance of treatment. The participants were called two to three times a week to follow up for drug compliance, adverse reactions, and completing the questionnaires.

Outcome assessment

The main objective of the present study was to determine the effectiveness of melatonin in P-APS and CIPN. The Brief Pain Inventory (BPI) questionnaire was used to evaluate arthralgia-myalgia. The Douleur Neuropathique 4 (DN4) questionnaire and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale version 5.0 were applied to assess CIPN.

BPI questionnaire

The BPI consists of two sections. The first part evaluates pain intensity using eight questions to assess the worst, least and average pain score and the necessity for analgesics over the last 24 hr. The second part of the questionnaire assesses the degree to which pain interferes with seven daily activities including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. Each item is measured on a scale of 0 to 10. Majedi *et al.*[26] confirmed the validity and reliability of the BPI in Persian. The BPI was prepared as a weekly booklet. After each paclitaxel infusion, the patients were asked to complete it every day for seven days and return it to the researcher before receiving the next dose of chemotherapy.

DN4 questionnaire

The DN4 is a 10-item questionnaire that contains two scales. The first seven questions are related to neuropathic pain characteristics, including burning, painful cold, electric shock, tingling, pins and needles, numbness, and itching. Three other questions are related to symptoms of physical stimulation of the painful area (touch hypoesthesia, pricking hypoesthesia, and brushing). Each item is measured on a scale of 0 (asymptomatic) to 1 (neuropathic features). A total score of equal to or above four is considered neuropathic pain. Madani et al.[27] confirmed the validity and reliability of this questionnaire in Persian. The DN4 questionnaire was evaluated at baseline and then every week after each paclitaxel dose by an investigator.

NCI-CTCAE V.5.0 neuropathy scale

The NCI divides neuropathy into five grades from grade 1 (asymptomatic) to 5 (death) with unique clinical descriptions of severity for each adverse event based on its general guideline.[28] The NCI was applied at baseline and then every week after each paclitaxel dose by an investigator.

Sample size

As there was no prior randomized clinical trial on the protective effects of melatonin against P-APS or CIPN, by considering the incidence of acute pain is reported to be up to 70%,[8,9] and assuming a 35% decrease in the incidence rate of pain, α error of 5 % (α=0.05) and study power of 80 % (β=0.20), a sample size of 31 patients was calculated for each group.

Statistical methods

Data analysis was performed using SPSS 24. Independent-sample t-test and Mann-Whitney U test were used to compare quantitative data with a normal and non-normal distribution. The results are presented as number (percentage) for categorical variables and mean ± standard deviation (SD) for continuous variables. Chi-square or linear by linear test was used to compare categorical variables between the two groups. Spearman coefficient was applied to evaluate the correlation between variables. Since repeated data were obtained in 12 consecutive chemotherapy cycles, the Generalized Estimating Equation (GEE) was administered for data analysis. The level of significance was set at P= 0.05.

Results

Of 152 patients that received the AC regimen, 42 were enrolled according to the inclusion/exclusion criteria. Eight individuals were excluded during the study. Finally, 17 patients were evaluated in each group (Figure 2).

Table 1 illustrates the age, weight, cumulative dose of paclitaxel, baseline laboratory data, and chemotherapy regimens of the participants. There was no significant difference in the above variables between the two groups. Thirty-two out of 34 patients (94%) reported different degrees of acute pain. There was no significant difference in the mean worst and least pain scores over the twelve cycles of treatment between the two arms (P=0.633 and 0.341 respectively). The relevant data are detailed in Table 2 and Figure 3.

Regarding analgesic use, the mean (SD) DDD was 7.39 (8.90) and 10.65 (9.67) in the melatonin and placebo arms respectively, indicating no significant difference between the two groups (P=0.193). Information about type, dose, number of patients and DDD of analgesics between melatonin and placebo groups are shown in Table 3.

As for the seven daily activities (general activity, walking, work, mood, enjoyment of life, relations with others, and sleep), melatonin only had a positive effect on the sleep (P= 0.001) (Table 4).

According to the DN4 score, the incidence of neuropathy (DN4 score≥ 4) was significantly lower in the melatonin group at week 12 (5 patients vs 11 patients, P= 0.039) (Table 5).

In addition, all grades of neuropathy obtained from the NCI-CTCAE scale were compared between the two groups

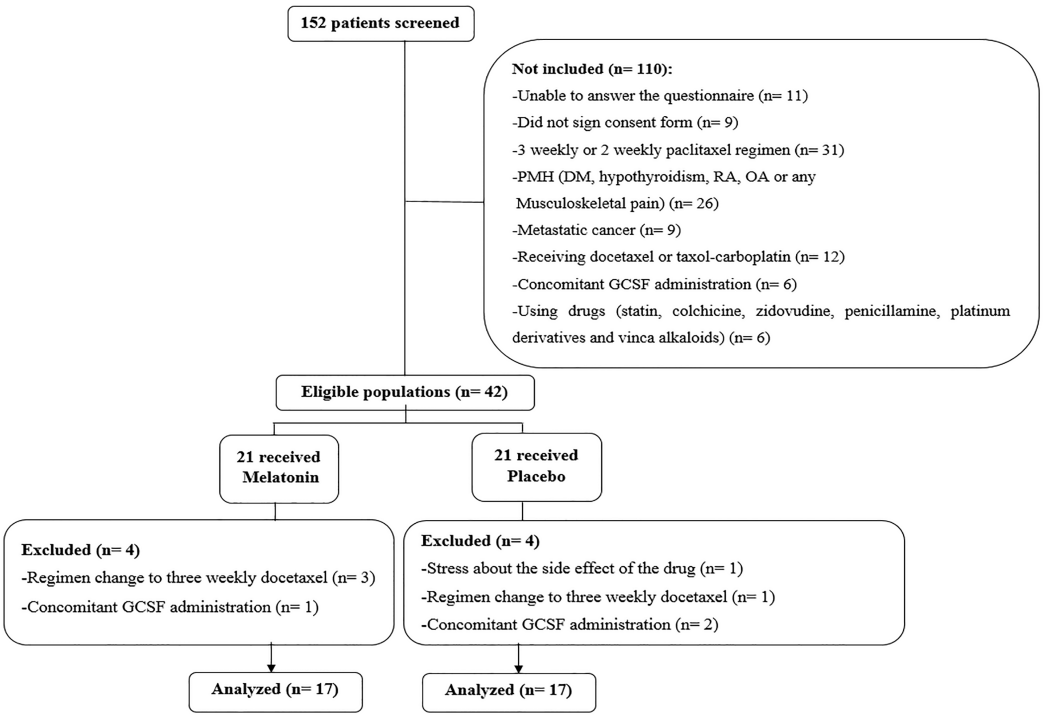

Figure 2. CONSORT flow diagram Abbreviations: PMH, past medical history; DM, diabetes mellitus; RA, rheumatoid arthritis; OA, osteo-arthritis; GCSF, granulocyte colony-stimulating factor.

Table 1. Demographic characteristics, lab data, and chemotherapy regimens in placebo and melatonin groups.

Parameters	Placebo group (n=17)	Melatonin group (n=17)	P-value*
Age (years) [mean± SD]	52.71 ± 8.80	51.24 ± 7.37	0.601[a]
Weight (Kg) [mean SD]	72.47 ± 8.559	72.53 ± 10.24	0.986[a]
Laboratory data [mean± SD]			
White cell count (×10³/mm³)	8.36 ± 6.70	8.61 ± 6.39	0.845[b]
Hemoglobin (g/dl)	11.11 ± 1.08	10.66 ± 2.13	0.873[b]
Platelet count (×10³/mm³)	291.50 ± 137.422	250.65 ± 110.51	0.444[b]
Chemotherapy regimens, n (%)			
T	11 (64.7%)	6 (35.3%)	0.086[c]
T+H	6 (35.3%)	11 (64.7%)	
Cumulative dose of paclitaxel (mg [mean± SD]	1662.35 ± 105.56	1676.47 ± 156.56	0.133[a]

Abbreviations- T: taxol® (paclitaxel); H: Herceptin® (trastuzumab); SD: standard deviation
*Statistical test- a: Independent sample t-test; b: Mann-Whitney U test; c: Chi-square test

Table 2. Comparison of pain severity measured by BPI between melatonin and placebo groups.

	Worst pain average		Least pain average	
	β (SE)	P-value*	β (SE)	P-value*
Melatonin	-0.156 (-0.036)	0.822	-0.415 (0.5527)	0.453
Time	0.143 (0.0487)	0.003	0.122 (0.0431)	0.005
Interaction between melatonin & time	-0.036 (0.0758)	0.633	-0.054 (0.0566)	0.341

Abbreviations- SE: standard error
*Statistical test: Generalized Estimating Equation (GEE)

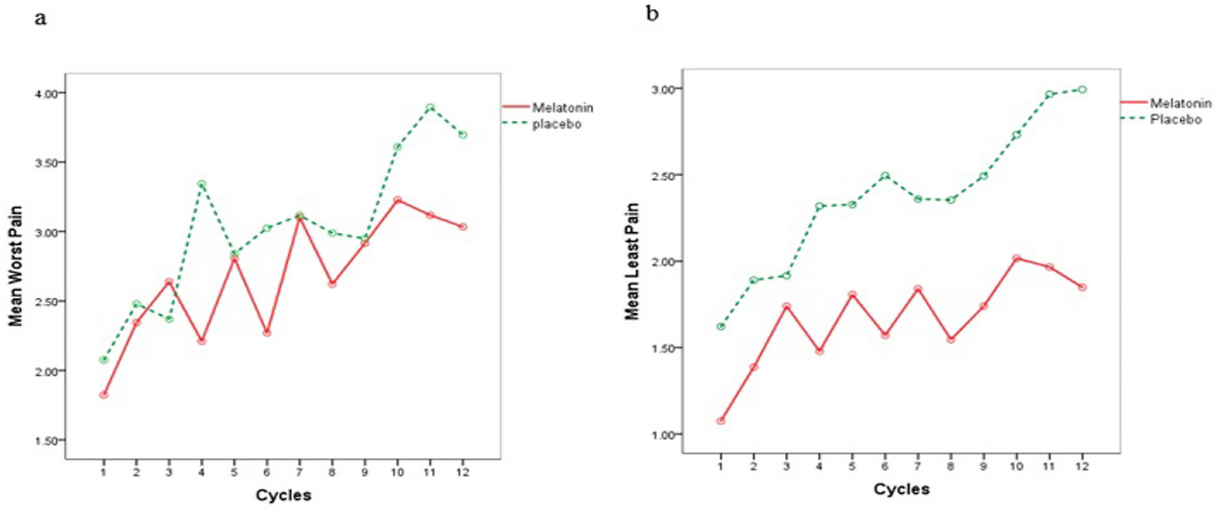

Figure 3. Comparison of average worst (a) and least pain (b) scores between melatonin and placebo groups in 12 cycles.

at week 12. According to Table 5, the incidence of grade 2 neuropathy was significantly lower in the melatonin group compared to the placebo group (P= 0.011).

The GEE analysis was applied to compare the average scores of the DN4 and NCI-CTCAE between the two groups over 12 weeks. The average score increased in both groups over time, but this increase was significantly less in the melatonin group compared to the placebo group (β= -0.114, P= 0.045 for DN4 and β= -0.051, P=0.010 for NCI). The results are presented in Table 6 and Figure 4. Compliance with melatonin (>80% of the doses) was seen in all the patients (100%).

Regarding adverse effects, melatonin and placebo tablets were well tolerated by patients, and there were no significant differences in adverse events (daytime drowsiness, dizziness, headache, and nightmare) between the two groups. There was only one case of the nightmare in the placebo group and one case of daytime drowsiness in the melatonin group.

Discussion

Taxane-induced pain is still an important and challenging adverse event affecting the treatment regimen or quality of life of the patients. To the best of our knowledge, it is the

Table 3. Comparison of type, dose, number and DDD of analgesics between melatonin and placebo groups.

	DDD					
	Melatonin (n= 17)	**Placebo (n= 17)**	**P-value***	**Melatonin (n= 17)**	**Placebo (n= 17)**	**P-value****
Acetaminophen 500 mg						
Number of patients (%)	15 (87.23)	15 (87.23)	1.00	82. 5	113.66	-
Mean of usage (SD)	29.12 (31.64)	40.12 (35.67)	0.433			
Ibuprofen 400 mg						
Number of patients (%)	1 (5.88)	0.94 (2.74)	0.54	1.25	2	-
Mean of usage (SD)	.59 (2.42)	2(11.76)	0.786			
Naproxen 500mg						
Number of patients (%)	5 (29.41)	6 (35.29)	0.71	31.6	27.6	-
Mean of usage (SD)	4.65 (9.55)	4.06 (7.70)	0.892			
Celecoxib 100 mg						
Number of patients (%)	1 (5.88)	0 (0)	0.31	1	0	-
Mean of usage (SD)	.24 (.97)	0 (0)	0.786			
Diclofenac 100 mg						
Number of patients (%)	3 (17.64)	4 (23.52)	0.67	7	29	-
Mean of usage (SD)	.41 (1.06)	1.71 (.00)	0.658			
Pregabalin 75 mg						
Number of patients (%)	0 (0)	1 (5.88)	0.31	0	1.75	-
Mean of usage (SD)	0 (0)	0.82 (3.39)	0.786			
Gabapentin 100 mg						
Number of patients (%)	2 (11.76)	4 (23.52)	0.36	2.36	6.58	-
Mean of usage (SD)	5.00 (14.16)	13.94 (34.98)	0.586			
Ketorolac amp 30 mg						
Number of patients (%)	0 (0)	1 (5.88)	0.31	0	0.5	-
Mean of usage (SD)	0 (0)	0.12 (.48)	0.786			
Mean of DDD (SD)	-	-	-	7.39 (8.90)	10.64 (9.67)	**0.193**

Abbreviations: DDD: defined daily dose; SD: standard deviation; *Statistical test: chi-square test; **Statistical test: Mann-Whitney U test

Table 4. Effect of melatonin on pain interference with seven daily activities.

Variables	**Melatonin (mean ±SD)**	**Placebo (mean ±SD)**	**P-value***
General activity	2.25±1.89	2.78±2.38	0.812
Mood	0.73±1.24	1.21±1.31	0.357
Walking ability	2.11±1.90	2.55±2.17	0.586
Work	2.25±1.89	2.78±2.38	0.812
Relations with others	0.33±.92	0.77±1.01	0.218
Sleep	0.20±.65	1.40±1.15	**0.001**
Enjoyment of life	0.55±.97	1.11± 1.06	0.106

Abbreviations: SD: standard deviation; *Statistical test: Mann-Whitney U test

Table 5. Evaluation of CIPN measured by DN4 and NCI-CTCAE version 5.0 between melatonin and placebo groups in week 12.

	Melatonin (n=17)	**Placebo(n=17)**	**P-value ***
DN4 Score, n(%)			
CIPN (>4)	5 (29.4%)	11 (64.7%)	**0.039**
Non-CIPN (<4)	12 (70.6%)	6 (35.3%)	
Grade of NCI-CTCAE V.5			
Grade 0	1 (5.9%)	0 (0.0%)	
Grade 1	13 (76.5%)	7 (41.2%)	
Grade 2	3 (17.6)	9 (52.9%)	**0.011**
Grade 3	0 (0.0%)	1 (5.9%)	
Grade 4	0 (0.0%)	0 (0.0%)	

Abbreviations: CIPN: chemotherapy-induced peripheral neuropathy;*Statistical test: Chi-square test

Table 6. Evaluation of CIPN measured by DN4 and NCI-CTCAE V.5.0 between melatonin and placebo groups during 12 weeks.

Variable	DN4		NCI-CTCAE V.5	
	β (SE)	P-value *	β (SE)	P-value *
Melatonin	0.380 (.2161)	0.079	0.030 (.1191)	0.799
Time	0.328 (.0447)	0.000	0.140 (.0156)	0.000
Interaction between melatonin & time	-0.114 (.0569)	**0.045**	-0.051 (.0200)	**0.010**

Abbreviations: SE: standard error

* Statistical test: Generalized Estimating Equation (GEE)

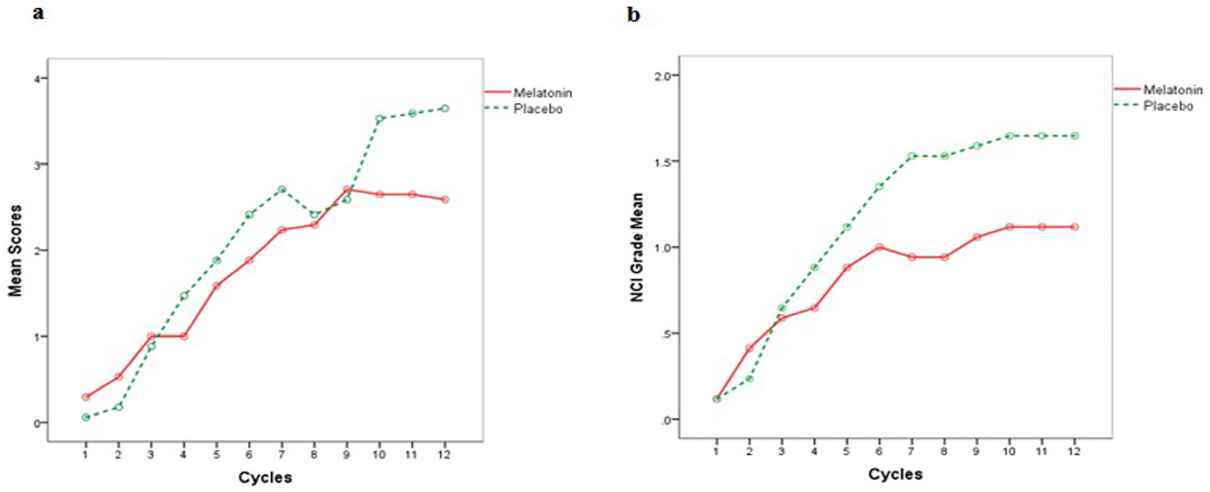

Figure 4. CIPN scores of DN4 (a) and NCI-CTCAE version 5.0 (b) during 12 weeks.

first randomized, double-blind, placebo-controlled clinical trial of the effectiveness of melatonin in the prevention of paclitaxel-associated acute and chronic pain.

The results showed that melatonin was effective in improving chronic pain caused by paclitaxel. Based on the DN4 questionnaire and the NCI scale, melatonin significantly reduced the incidence and severity of peripheral neuropathy. This finding agrees with a study by Nahle *et al.*[29] that showed a lower incidence of neuropathy in patients receiving melatonin. This was an open-labeled, phase II pilot study in breast cancer patients that received taxanes (paclitaxel, docetaxel and nab-paclitaxel). Melatonin (21 mg) was given daily for the duration of taxane chemotherapy and continue for 28 days after discontinuation of taxane. NCI-CTC 3.0 scale and FACT-Taxane quality of life questionnaire were used for assessment of neuropathy.

In a pilot study by Lissoni *et al.*[30] 80 patients with a variety of metastatic solid tumors (lung cancer: 35; breast cancer: 31; gastrointestinal tract tumors: 14) were randomly assigned to receive chemotherapy alone or chemotherapy with melatonin 20 mg daily for all cycles of chemotherapy.[30] The clinical response and side effect were evaluated according to WHO criteria. The results of study showed that melatonin may prevent chemotherapy induced neuropathy.

In another study by Lissoni *et al.*[31] examined 70 patients with advanced non-small cell lung cancer. Patients received chemotherapy with or without melatonin 20 mg/day for every day. The WHO criteria were used to assess clinical response and toxicity. Findings showed melatonin was effective in reducing the severity of platinum-induced neuropathy. Therefore, it seems that melatonin, as a supplement drug, may have a special place in reducing CIPN according to the results of the present study and prior studies. Regarding paclitaxel-associated acute pain, although the trend was increasing in both groups, it was higher in the placebo group. However, no significant difference was observed in the mean worst and least pain score between melatonin and placebo groups.

Several studies have shown that melatonin (3-6 mg) may be effective in reducing chronic pain such as fibromyalgia, inflammatory bowel syndrome, and migraine. However, the effect of melatonin on acute pain control such as perioperative pain is controversial and dose-dependent.[19] Considering the complication of daytime drowsiness and consumption of melatonin for a long time (twelve weeks) in this study, a 10 mg daily dose was selected in the present study. Other studies administered higher doses of melatonin (up to 50 mg) to reduce the side effects of chemotherapy.[24] Therefore, higher doses of melatonin might be effective in decreasing acute pain and could be tried in future studies.

On the other hand, there were no restrictions on analgesic use in the present study and the patients could take OTC analgesics or those prescribed by their physicians for acute

pain. Since no significant difference was observed in the mean analgesic use between the two groups, melatonin may not be more effective for acute pain control.

Sleep disorders are one of the most common and annoying problems in breast cancer patients with a prevalence of 50-65% in different studies. Sleep disorders are reported to be more severe in the elderly.[32-34] The findings of the present study showed a significant improvement in sleep quality in the melatonin group. Consistent with the results of the present study, Innominato *et al.*[35] and Palmer *et al.*[36] found that melatonin could improve sleep and quality of life in breast cancer patients as secondary outcomes. Because chronic pain syndrome causes disturbances in the sleep-wake cycle,[19] and it is well-documented that pain and anxiety interact and exacerbate each other,[37] melatonin administration may help relieve chronic pain and improve sleep.

Limitations

One of the limitations of the present study was its small sample size. Due to the Covid-19 pandemic conditions and the change of the weekly chemotherapy regimen to three weeks, so we could not complete the study with the calculated sample size. Larger studies investigating different doses of melatonin may be needed to confirm the effectiveness of this drug in controlling paclitaxel-induced acute and chronic pain.

Conclusion

The results of this randomized double-blind, placebo-controlled study support the value of melatonin as an effective option in reducing the incidence and severity of peripheral neuropathy associated with the use of paclitaxel in patients undergoing weekly chemotherapy, but melatonin was not effective against acute pain.

Ethical Issues

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.TIPS.REC.1398.043) and registered at the Iranian Registry of Clinical Trial (IRCT20190630044057N1). All methods in this study were performed in accordance with the relevant guidelines and regulations including the declaration of Helsinki. Participants signed an informed consent form before recruitment.

Data Sharing

All data has been included in the manuscript. Patients' data would be available by sending request to corresponding author.

Author Contributions

NT: Literature search, selection of patients, clinically assessment the patients, acquisition of data, statistical analysis, and writing the original and revised manuscript. ZJ-R: Conceptualizing and designing the study, supervising the research process, interpreting the data, drafting and finalizing the manuscript. SE and KG: Supervising of methods regulation and writing of the manuscript. MS: Designing the study, assisting in the patient's recruitment process, and revision the manuscript. HM: Designing questionnaires, assisting in the evaluation of pain in patients, and revision the manuscript. AJK: data analyzing and interpretation. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to express deep and sincere gratitude to the Research Center for Rational Use of Drugs, affiliated with Tehran University of Medical Sciences for providing invaluable guidance throughout this research.

Conflict of Interest

The authors report no conflicts of interest.

References

1. Yan X, Maixner DW, Yadav R, Gao M, Li P, Bartlett MG, et al. Paclitaxel induces acute pain via directly activating toll like receptor 4. Mol Pain. 2015;11:10. doi:10.1186/s12990-015-0005-6
2. Chiu N, Chiu L, Chow R, Lam H, Verma S, Pasetka M, et al. Taxane-induced arthralgia and myalgia: A literature review. J Oncol Pharm Pract. 2017;23(1):56-67. doi:10.1177/1078155215627502
3. Imai A, Matsunami K, Takagi H, Ichigo S. Proposed medications for taxane-induced myalgia and arthralgia. Oncol Lett. 2012;3(6):1181-5. doi:10.3892/ol.2012.651
4. Loprinzi CL, Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, et al. Natural history of paclitaxel-associated acute pain syndrome: Prospective cohort study ncctg n08c1. J Clin Oncol. 2011;29(11):1472. doi:10.1200/JCO.2010.33.0308
5. Loprinzi CL, Maddocks-Christianson K, Wolf SL, Rao RD, Dyck PJB, Mantyh P, et al. The paclitaxel acute pain syndrome: Sensitization of nociceptors as the putative mechanism. The Cancer Journal. 2007;13(6):399-403. doi:10.1097/PPO.0b013e31815a999b
6. Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy. Front Mol Neurosci. 2017;10:174. doi:10.3389/fnmol.2017.00174
7. Rivera E, Cianfrocca M. Overview of neuropathy associated with taxanes for the treatment of metastatic breast cancer. Cancer Chemother Pharmacol. 2015;75(4):659-70. doi:10.1007/s00280-014-2607-5
8. Eckhoff L, Nielsen M, Moeller S, Knoop A. Taxtox–a retrospective study regarding the side effects of docetaxel given as part of the adjuvant treatment to patients with primary breast cancer in denmark from 2007 to 2009. Acta Oncol. 2011;50(7):1075-82. doi:10.3109/0284186X.2011.602111
9. Saibil S, Fitzgerald B, Freedman O, Amir E, Napolskikh J, Salvo N, et al. Incidence of taxane-induced pain and distress in patients receiving chemotherapy for early-stage breast cancer: A retrospective, outcomes-

based survey. Curr Oncol. 2010;17(4):42. doi:10.3747/co.v17i4.562
10. Fernandes R, Mazzarello S, Joy A, Pond G, Hilton J, Ibrahim M, et al. Taxane acute pain syndrome (TAPS) in patients receiving chemotherapy for breast or prostate cancer: A prospective multi-center study. Support Care Cancer. 2018;26(9):3073-81. doi:10.1007/s00520-018-4161-x
11. Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, Kamal A, et al. Further data supporting that paclitaxel-associated acute pain syndrome is associated with development of peripheral neuropathy: North central cancer treatment group trial n08c1. Cancer. 2012;118(20):5171-8. doi:10.1002/cncr.27489
12. Yan X, Jiang E, Weng H-R. Activation of toll like receptor 4 attenuates gaba synthesis and postsynaptic gaba receptor activities in the spinal dorsal horn via releasing interleukin-1 beta. J Neuroinflammation. 2015;12(1):222. doi:10.1186/s12974-014-0222-3
13. Su M, Ran Y, He Z, Zhang M, Hu G, Tang W, et al. Inhibition of toll-like receptor 4 alleviates hyperalgesia induced by acute dural inflammation in experimental migraine. Mol Pain. 2018;14:1744806918754612. doi:10.1177/1744806918754612
14. Galley HF, McCormick B, Wilson KL, Lowes DA, Colvin L, Torsney C. Melatonin limits paclitaxel-induced mitochondrial dysfunction in vitro and protects against paclitaxel-induced neuropathic pain in the rat. J Pineal Res. 2017;63(4):e12444. doi:10.1111/jpi.12444
15. Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. Nature Reviews Neurology. 2010;6(12):657-66. doi:10.1038/nrneurol.2010.160
16. Kuthati Y, Lin S-H, Chen J, Wong C-S. Melatonin and their analogs as a potential use in the management of neuropathic pain. J Formos Med Assoc. 2019;118(8):1177-86. doi:10.1016/j.jfma.2018.09.017
17. Kilic U, Kilic E, Tuzcu Z, Tuzcu M, Ozercan IH, Yilmaz O, et al. Melatonin suppresses cisplatin-induced nephrotoxicity via activation of nrf-2/ho-1 pathway. Nutr Metab (Lond). 2013;10(1):7. doi:10.1186/1743-7075-10-7
18. Zahn PK, Lansmann T, Berger E, Speckmann EJ, Musshoff U. Gene expression and functional characterization of melatonin receptors in the spinal cord of the rat: Implications for pain modulation. J Pineal Res. 2003;35(1):24-31. doi:10.1034/j.1600-079X.2003.00047.x
19. Chen WW, Zhang X, Huang WJ. Pain control by melatonin: Physiological and pharmacological effects. Exp Ther Med. 2016;12(4):1963-8. doi:10.3892/etm.2016.3565
20. Lin J-J, Lin Y, Zhao T-Z, Zhang C-K, Zhang T, Chen X-L, et al. Melatonin suppresses neuropathic pain via mt2-dependent and-independent pathways in dorsal root ganglia neurons of mice. Theranostics. 2017;7(7):2015. doi:10.7150/thno.19500
21. Coloma FM, Niles LP. Melatonin enhancement of [3h]-γ-aminobutyric acid and [3h] muscimol binding in rat brain. Biochem Pharmacol. 1988;37(7):1271-4. doi:10.1016/0006-2952(88)90781-2
22. Bavithra S, Priya ES, Selvakumar K, Krishnamoorthy G, Arunakaran J. Effect of melatonin on glutamate: Bdnf signaling in the cerebral cortex of polychlorinated biphenyls (PCBs)—exposed adult male rats. Neurochem Res. 2015;40(9):1858-69. doi:10.1007/s11064-015-1677-z
23. Cerea G, Vaghi M, Ardizzoia A, Villa S, Bucovec R, Mengo S, et al. Biomodulation of cancer chemotherapy for metastatic colorectal cancer: A randomized study of weekly low-dose irinotecan alone versus irinotecan plus the oncostatic pineal hormone melatonin in metastatic colorectal cancer patients progressing on 5-fluorouracil-containing combinations. Anticancer Res. 2003;23(2C):1951-4.
24. Seely D, Wu P, Fritz H, Kennedy DA, Tsui T, Seely AJ, et al. Melatonin as adjuvant cancer care with and without chemotherapy: A systematic review and meta-analysis of randomized trials. Integr Cancer Ther. 2012;11(4):293-303. doi:10.1177/1534735411425484
25. Who collaborating centre for drug statistics methodology. Whocc—atc/ddd index. Available online: Https://www.Whocc.No/atc_ddd_index/ (Accessed on 18 December 2019).
26. Majedi H, Dehghani SS, Soleyman-Jahi S, Emami Meibodi SA, Mireskandari SM, Hajiaghababaei M, et al. Validation of the persian version of the brief pain inventory (bpi-p) in chronic pain patients. J Pain Symptom Manage. 2017;54(1):132-8. doi:10.1016/j.jpainsymman.2017.02.017
27. Madani SP, Fateh HR, Forogh B, Fereshtehnejad SM, Ahadi T, Ghaboussi P, et al. Validity and reliability of the persian (farsi) version of the dn 4 (douleur neuropathique 4 questions) questionnaire for differential diagnosis of neuropathic from non-neuropathic pains. Pain Practice. 2014;14(5):427-36. doi:10.1111/papr.12088
28. Common Terminology Criteria for Adverse Events (CTCAE) v5. 0, (2017) https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc
29. Nahleh Z, Pruemer J, Lafollette J, Sweany S. Melatonin, a promising role in taxane-related neuropathy. Clin Med Insights Oncol. 2010;4:35-41. doi:10.4137/cmo.s4132
30. Lissoni P, Tancini G, Barni S, Paolorossi F, Ardizzoia A, Conti A, et al. Treatment of cancer chemotherapy-induced toxicity with the pineal hormone melatonin. Support Care Cancer. 1997;5(2):126-9. doi:10.1007/BF01262569
31. Lissoni P, Paolorossi F, Ardizzoia A, Barni S, Chilelli M, Mancuso M, et al. A randomized study of chemotherapy with cisplatin plus etoposide versus chemoendocrine therapy with cisplatin, etoposide and the pineal hormone melatonin as a first-line treatment

of advanced non-small cell lung cancer patients in a poor clinical state. J Pineal Res. 1997;23(1):15-9. doi:10.1111/j.1600-079X.1997.tb00329.x
32. Otte JL, Carpenter JS, Russell KM, Bigatti S, Champion VL. Prevalence, severity, and correlates of sleep-wake disturbances in long-term breast cancer survivors. J Pain Symptom Manage. 2010;39(3):535-47. doi:10.1016/j.jpainsymman.2009.07.004
33. Colagiuri B, Christensen S, Jensen AB, Price MA, Butow PN, Zachariae R. Prevalence and predictors of sleep difficulty in a national cohort of women with primary breast cancer three to four months postsurgery. J Pain Symptom Manage. 2011;42(5):710-20. doi:10.1016/j.jpainsymman.2011.02.012
34. Costantini C, Ale-Ali A, Helsten T. Sleep aid prescribing practices during neoadjuvant or adjuvant chemotherapy for breast cancer. J Palliat Med. 2011;14(5):563-6. doi:10.1089/jpm.2010.0465
35. Innominato PF, Lim AS, Palesh O, Clemons M, Trudeau M, Eisen A, et al. The effect of melatonin on sleep and quality of life in patients with advanced breast cancer. Support Care Cancer. 2016;24(3):1097-105. doi:10.1007/s00520-015-2883-6
36. Palmer ACS, Zortea M, Souza A, Santos V, Biazús JV, Torres IL, et al. Clinical impact of melatonin on breast cancer patients undergoing chemotherapy; effects on cognition, sleep and depressive symptoms: A randomized, double-blind, placebo-controlled trial. PLoS One. 2020;15(4):e0231379. doi:10.1371/journal.pone.0231379
37. Wiech K, Tracey I. The influence of negative emotions on pain: Behavioral effects and neural mechanisms. Neuroimage. 2009;47(3):987-94. doi:10.1016/j.neuroimage.2009.05.059