ORIGINAL RESEARCH

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Smoking increases chronic postsurgical pain in patients undergoing open abdominal hysterectomy

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Abstract

Objectives: Smoking cause severe postoperative complications. Cotinine is the end product of nicotine in the urine. Our primary hypothesis was that women with high preoperative urinary cotinine levels have more postsurgical chronic/acute pain is tested, and secondarily, that high cotinine levels are associated with more opioid consumption.

Method: 158 patients undergoing open abdominal hysterectomy were divided into three groups according to the cotinine level. 1) Low Cotinine group <10ng/dl (no exposure), 2) Intermediate Cotinine group =10-500ng/dl (exposure), 3) High Cotinine group >500ng/dl (smoker). In postoperative 3 months, postsurgical chronic pain, allodynia score, pain limiting daily activity, Brief Pain Inventory, SF 12 form, Douleur Neuropathique en 4 (DN4) questions test, and Sleep interference test were assessed. Visual Analogue Scale (VAS), morphine consumption, rescue analgesic consumption, and complications were recorded during postoperative 48 hours.

Results: The postsurgical chronic pain scores at the three months($p<0,007$), the postoperative pain scores and opioid consumption were significantly higher in the high cotinine group. High cotinine group had significantly worst HADS, SF 12 PCS, allodynia, and sleep interference test scores.

Conclusion: Smoking and tobacco smoke exposure are associated with high postsurgical chronic pain, and also postoperative acute pain with more opioid consumption.

Keywords: Cotinine, Pain, Smoke

INTRODUCTION

Approximately 20 of every 100 women in the world undergo hysterectomy operation at once in their lifetime (1). It is the second most common operation in women after caesarean section. Thus, accurate determination of the risk factors related to the female patient undergoing hysterectomy and effective management of the perioperative process will affect the lives of millions of women (2). After hysterectomy, acute and surgery-related chronic pain are the leading major problems. Although pain pathophysiology and treatment are well known today, 30-75% of the patients, who underwent hysterectomy, complain about severe pain in acute period and 20-50% about postsurgical chronic pain on the 3rd month (3, 4).

Chronic postsurgical pain is the pain that continues for three months after the surgery and not related to the out-of-surgery reasons. It has high incidence after some surgery types other than hysterectomy, such as 5-65% for thoracic surgery, 50-85% for mastectomy, 30-50%, for cardiac surgery, and 50-85% for amputation. The importance of this pain is that it seriously decreases the quality of life of the patient and causes socioeconomic problems (5).

It is known that approximately 15% of the female population in the world consumes cigarette and other 15% are exposed to tobacco smoke (6, 7). Such high smoking rates in women and the presence of intense pain after hysterectomy draw attention to the relationship between smoking and pain in the perioperative period. However, the relationship

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between pain and nicotine, which is the primary metabolite in cigarettes, is extremely complex. Despite there are studies claiming that nicotine has an antinociceptive effect that reduces acute and chronic pain in the postoperative period, there are some studies supporting the opposite (8-11). Studies that are conducted without measuring the level of cotinine, which is a biomarker of smoking in the body, have opposite results. Probably, the reasons are that the last nicotine exposure time of the patients before the surgery is not known, and the duration and amount of smoking are not equal (12).

Measurement of the amount of cotinine, which is a nicotine metabolite, in the body during the perioperative process is a more objective method than being informed with questionnaires. Today, it is known that nicotine primarily transforms into six separate metabolites in the body and is present in the urine as cotinine at a rate of 70-80% (13). Therefore, in the current study we tested the primary hypothesis that women with high preoperative urinary cotinine levels have more postsurgical chronic pain, and secondarily that high cotinine levels are associated with acute pain and more opioid consumption in the postoperative period.

METHOD

This prospective observational, double blinded study was conducted at the Hospital. The study approval was taken from the University Hospital Ethics Committee (number 181, 22/11/2017), and written consent was obtained from all the patients. The trial was registered with the Clinical Trials number NCT04274673.

We enrolled 158 American Society of Anesthesiologists Physical Status I-II women between 18 and 70 years old, who are scheduled for open abdominal hysterectomy under general anesthesia over the course of a year. The study was restricted to women undergoing open abdominal hysterectomies with a pfannenstiel approach (transverse incision through the external sheath of the recti muscles, about one inch above the pubes) who were able to operate a patient-controlled analgesia (PCA) device.

We excluded women with pre-existing chronic pain at any site requiring opioid analgesia; significant hepatic (ALT or AST >2 times normal) or renal (serum creatinine >2 mg/dl) impairment; allergy to study drugs; emergency or urgent procedures; who had a history of psychiatric diseases (major depressive disorder, bipolar disorder, schizophrenia, etc.)

Anesthesia Protocol

The patients participated in the study were premedicated with 0.15mg/kg intravenous (IV) midazolam. Routine monitoring (ECG, systolic, diastolic, mean noninvasive blood pressure, oxygen saturation) was performed after the patients were taken on the operating table. The first urine sample (10cc) was taken to evaluate the cotinine level of the patients to whom a foley catheter was attached. The cotinine level was measured via immunoassay by using the Immulite 2000 XPI Immun assay device (Siemens, US). According to these values, patients were divided into three groups, and the first group was evaluated as <10ng/dl (low cotinine), second as 10-500 ng/dl (intermediate cotinine), and third as >500ng/dl (high cotinine).

After 3 min 100% O2 administration with mask, anesthesia was induced with propofol (2mg/kg IV); intubation was facilitated by rocuronium (0.6 mg/kg IV); and anesthesia was maintained by sevoflurane in combination with nitrous oxide 50% in oxygen. Fentanyl 2µg/kg intravenously, was given 3-5 min before the surgical incision. After endotracheal intubation, lungs of the patients were mechanically ventilated to maintain end expiratory PCO2 between 34 and 36 mmHg. A Pfannenstiel technique was used in each operation, and the same surgeon conducted all the operations in the study. All patients received 0.03 mg/kg morphine IV 30 min before the skin closure. At the end of the surgery, IV 0.01 mg/kg atropine and 0.05 mg/kg neostigmine were administered to all the patients in order to remove the myorelaxant effect when respiration started.

After return of spontaneous ventilation and tracheal extubation, patients were transferred to the post anesthesia care unit (PACU). There, during postoperative 48 hours patients were connected to a patient-controlled analgesia (PCA) device programmed to provide 2 mg intravenous bolus injections of morphine at a lockout interval of 15 min with a maximum 4-hour limit of 24 mg. The PCA device was discontinued when women made no demands for morphine in the preceding 4-hour interval or at a maximum of 24 hours after surgery. 1 g acetaminophen IV was applied to the patients for 48 hours three times a day. When pain scores exceeded 5 cm on a 10-cm Visual Analog Scale, 75 mg diclofenac intramuscular IM was given as a rescue analgesic.

If the heart rate was <50 beats/minute, 0.5 mg atropine sulfate intravenous was given. When patients sustained nausea or vomiting lasting longer than 5 min, 4 mg ondansetron IV was given.

Measurements

All postoperative measurements were conducted by a researcher who was blinded to processes in the operation period. Heart rate (HR), systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation (SpO2), respiratory rate (RR), complications, antiemetic consumptions and sedation were assessed upon arrival on the PACU (0.h), 1, 4, 8, 12, 16, 20, 24, 32, 40, 48 hours thereafter. Sedation was

assessed using the Ramsey sedation scale and postoperative side effects (respiratory depression (RR<10min), headache, bradycardia (HR <50min), hypotension, and nausea-vomiting were recorded. First flatus, initial ambulation, and first oral intake of solid food were recorded.

Before operation all the patients were educated about how to decide VAS value on a 10 cm ruler: 0 cm was designated as no pain, and 10 cm as the worst imaginable pain. Postoperative pain was separately assessed with patients resting in bed and while sitting. Pain, opioid use in each measurement time, cumulative morphine consumption, PCA demand/supply, and rescue analgesic were recorded in the same measurement times specified above. At the end of the postoperative 48th hour, pain management was assessed as 1=unsatisfied, 2=slightly satisfied, 3=mostly satisfied, 4=completely satisfied. Furthermore, Hospital Anxiety and Depression Surveys were evaluated before discharge from the hospital. The Hospital Anxiety and Depression Scale (HADS) was constructed to allow a rapid and separate measure of depression and generalized anxiety in hospital. This scale has 14 questions, seven of them related to depression and the rest to anxiety. Six questions are coded from 0 to 3, and conversely eight questions are coded from 3 to 0.

An investigator blinded to group assignment evaluated all of the patients three months after the discharge day. Chronic postsurgical pain was evaluated as acute postoperative pain with VAS score at rest. Allodynia test was applied to all the patients and they were asked to provide the appropriate value in the form of VAS. In addition, the patients were asked to what extent their pain limits their daily activities according to VAS. Three months after discharge day, patients completed Douleur Neuropathique en 4 (DN4), Sleep Interference questionnaires, and SF-12 Health survey were assessed. SF-12 consists of two components (physical and mental) and assess the perceived health-related quality of life of the patient. Sleep Interference scores range from 0 (no interference) to 10 (complete interference). DN4 score ≥ 4 indicate that the pain is likely to be neuropathic in origin. Short brief pain inventory was assessed for the severity of the chronic pain and its impact on the functioning of the patient.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) Mac version 21 (SPSS Inc. Chicago, IL, USA) software program was used to assess the study data. Homogeneity of data was conducted according to the Levene's test and data were evaluated as homogeneous if p is >0.05. The Shapiro-Wilk normality test was used to evaluate whether the data comply with normality distribution. If p> 0.05, data complied with the normal distribution, and if p<0.05, data did not comply with normal distribution. The data conforming to normal distribution were compared with the One-Way ANOVA test and the results were given as mean ± SD. The Kruskal Wallis test was used to compare the data that did not conform to normal distribution, and the results were given as median±min-max (minimum-maximum). Nominal variables were examined by using the Chi-Square test of Pearson or Chi-Square test of Fisher. For all the tests, p value less than 0.05 at the confidence interval of 95% was considered as statistically significant.

RESULTS

In the study, 158 consenting patients, who fulfilled the entry criteria, were included. The patients were divided into three groups according to the level of urine cotinine taken after induction. Cotinine level of 96 patients was found as <10 ng/dl (Low Cotinine), of 38 patients as between 11 and 500 ng/dl (Intermediate Cotinine), and of 24 patients as >500 ng/dl (High Cotinine).

The three groups were comparable with respect to ASA physical status, age, body weight, and duration of surgery (Table 1).

Table 1. Demographics and baseline characteristics (n=158)

	Low Cotinine	Intermediate Cotinine	High Cotinine	p
	(n=96)	(n=38)	(n=24)	
ASA physical status I II	 29(30.2) 67(69.8)	 8(21.1) 30(78.9)	 5(20.8) 19(79.2)	>0.05
Age (year)	49.0(28-68)	47.5(37-72)	48.5(41-68)	>0.05
Weight (kg)	72.0(50-110)	71.0(52-105)	72.0(58-105)	>0.05
Duration of surgery	85.0(55-180)	85.0(50-140)	80.0(60-150)	>0.05

Kruskal Wallis Test was used and represented as percentage and median (min-max).

During the initial 48 hours after the surgery, systolic, diastolic, mean blood pressure, and Ramsey sedation scale values were found to be similar between three groups. During the same time period in all the measurement times, oxygen saturation values were higher in Low Cotinine and Intermediate Cotinine group than the High Cotinine group. Heart rate was found higher in the patients in High Cotinine group when compared to the patients in other groups.

At all the measurement times, oxygen saturations of the High Cotinine group were higher than the other groups. Moreover, except the measurement at the 8th hour, all the other oxygen saturation measurements in the postoperative 48th hour in Low Cotinine group were higher than

Intermediate Cotinine group. Except 32nd hour and 40th hour, respiratory rate values were higher in High Cotinine group in all the measurement times when compared with the Low Cotinine group and Intermediate Cotinine group.

Except the 1st hour, VAS scores while laying were higher in High Cotinine group than Low Cotinine group ($p<0.005$) in all the measurement times during postoperative 48 hours. Similar to these results, VAS scores on the 8th, 20th, 24th, 32nd, 40th, and 48th hours in High Cotinine group were higher than Intermediate Cotinine group (Figure 1).

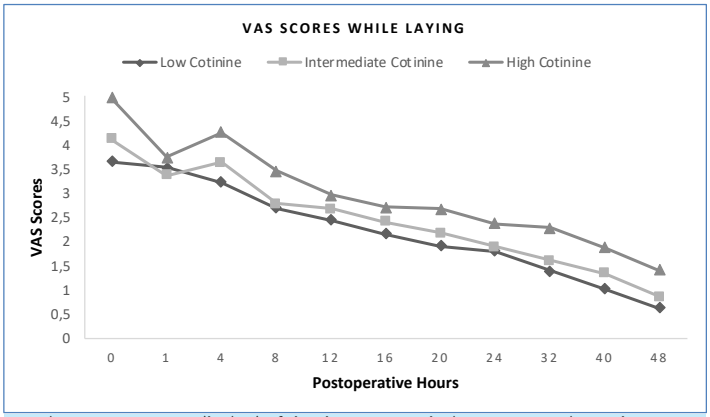

Figure 1. VAS scores (laying) of the three groups during postoperative 48 hours.

Except the 1st hour, VAS scores while sitting during postoperative 48 hours were higher in all the measurements in High Cotinine group than Low Cotinine group. Similarly, VAS scores while sitting at 8th, 32nd, and 40th hours were higher in High Cotinine group than Low Cotinine group. VAS scores while sitting at the 4th and 12th hours were higher in Intermediate Cotinine group than the Low Cotinine group (Figure 2).

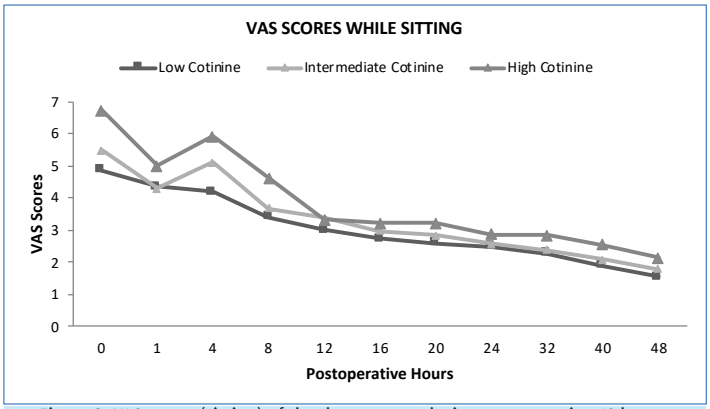

Figure 2. VAS scores (sitting) of the three groups during postoperative 48 hours.

PCA demand/delivery amounts of the patients in the High Cotinine group during postoperative 48 hours were higher than the patients in the Low Cotinine group and Intermediate Cotinine group in all the measurement times except the 0th hour.

Except for the first measurement time in the first 48 postoperative hours, the morphine consumption of the High Cotinine group was higher than the other groups. Only at the 4th hour measurement, the morphine consumption of the Intermediate Cotinine group was higher than the Low Cotinine group (Figure 3).

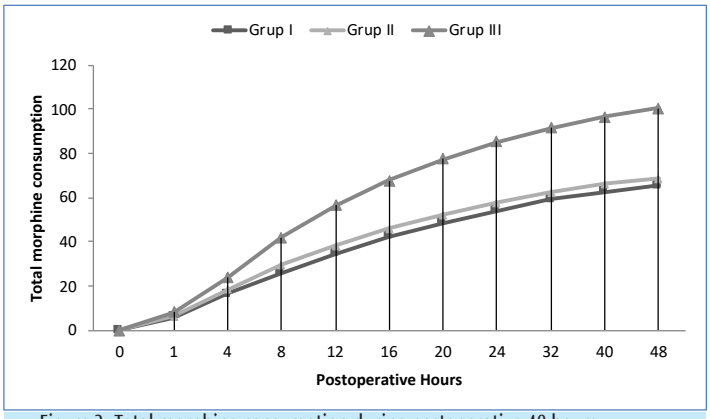

Figure 3. Total morphine consumption during postoperative 48 hours.

On the postoperative 0th, 4th, and 8th hours, additional analgesic consumption of High Cotinine was higher than other groups. In the same measurement times, additional analgesic consumption of the Intermediate Cotinine group was higher than Low Cotinine group.

During postoperative 48 hours, High Cotinine group PCA demand values were higher than other groups in all the measurements excluding the 0th hour. Intermediate Cotinine group PCA demand values were higher than the Low Cotinine group excluding the first two measurements. Similarly, PCA delivery values were similar excluding the last three measurement times.

The most common side effect during the postoperative period was postoperative nausea-vomiting. The rates decreased in time and were found as 61% on the 0th hour, 50% on the 1st hour, 32% on the 4th hour, 17% on the 8th hour, 6% on the 12th hour, 4% on the 16th hour, 1% on the 20th hour, and 0.6% on the 24th hour. In addition, bradycardia was observed for five times in three patients, and hypotension was observed in two different measurements in one patient.

The first flatus time of the patients in the High Cotinine group was longer than the patients in the other group. In addition, the first flatus time of the Intermediate Cotinine group was longer than the Low Cotinine group. First ambulation time were longest in the High Cotinine group. First oral intake time of all the three groups were similar.

Hospital anxiety and depression scores of the patients in the High Cotinine group and Intermediate Cotinine group were higher than the Low Cotinine group. The patients in the High Cotinine group and Intermediate Cotinine group had higher 3-month allodynia and VAS values that limit daily activity

when compared to the patients in the Low Cotinine group ($p<0.05$). SF-12 evaluation is divided into two as physical (SF12-PCS) and mental (SF12-MCS). Only SF12-PCS value of the High Cotinine group was lower than the other groups. However, there was no difference between the SF12-MCS values of all the three groups. Examination findings of 10% of the patients in the Low Cotinine group, 23% in the Intermediate Cotinine group, and 37% in the High Cotinine group were found to be positive in terms of allodynia. Allodynia VAS values of the High Cotinine group were higher than the Low Cotinine group. When the patients were evaluated in terms of pain that limit their daily activities, the rates were 10% in the Low Cotinine group, 23% in the Intermediate Cotinine group, and 33% in the High Cotinine group. VAS values limiting the daily activities of the High Cotinine group was higher than the Low Cotinine group (Table 2).

Table 2. Summary of the other parameters during hospital stay and at the third month.

Parameters				p		
	Low Cotinine	Intermediate Cotinine	High Cotinine	I-II	I-III	II-III
	(n=96)	(n=38)	(n=24)			
First flatus	21.0 (16-30)	23.0 (16-28)	25.5 (20-30)	0.009	<0.001	0.003
First Ambulation	7.0 (6-9)	7.0 (6-10)	7.5 (6-15)	0.075	<0.001	0.042
First oral intake	7.0 (6-17)	7.0 (6-9)	7.0 (6-8.5)	0.446	0.636	0.853
HADS (Anxiety)	4.0 (1-13)	6.0 (2-15)	8.0 (2-17)	<0.001	<0.001	0.065
HADS (Depression)	4.0 (1-14)	5.0 (1-18)	6.0 (2-12)	0.015	0.001	0.272
Allodynia (VAS)	0.0 (0-3)	0.0 (0-3)	0.0 (0-3)	0.037	0.001	0.253
Daily activity (VAS)	0.0 (0-4)	0.0 (0-4)	0.0 (0-4)	0.034	0.002	0.376
SF-12 PCS	60.16687 (22.86056-66.34308)	58.24415 (25.56015-64.63784)	48.56010 (22.25612-61.88461)	0.056	<0.001	0.009
SF-12 MCS	45.63875 (25.93175-54.96308)	45.71335 (35.37748-57.93845)	44.69428 (33.72698-50.88624)	0.735	0.223	0.133

Kruskal Wallis Test was used and represented as median (min-max)

Low Cotinine group was the completely satisfied patient group with pain management during the postoperative period (27%, 7%, 0%, respectively). None of the patients described this situation as unsatisfied (Table 3).

Table 3. Patient satisfaction with pain treatment

Patient satisfaction with pain treatment	Low Cotinine		Intermediate Cotinine		High Cotinine		p1	p2	p3
	%	(n)	%	(n)	%	(n)			
Slightly satisfied	3.1	(3)	13.2	(5)	50	(12)	p >0,05	0.001	0.001
Mostly satisfied	69.8	(67)	78.9	(30)	50	(12)	p >0,05		
Completely satisfied	27.1	(26)	7.9	(3)	0	(0,0)	0.001	0.001	p >0,05

Chi Square test was used and presented as percentage. p1: group I, II, p2: group I, III, p3: group II, III

In the sleep interference tests performed to understand the pain-induced sleep patterns of the patients, the highest values belonged to the High Cotinine group. There was no difference between the groups in terms of the DN4 test. No difference was found between the three groups to which brief pain inventory test was applied.

DISCUSSION

In the current study, there was a clear relevance between high urine cotinine level and postsurgical chronic pain in the patients undergoing open abdominal hysterectomy. Posturgical chronic pain scores were found to be higher on the third month in the patients with high cotinine levels due to smoking or tobacco smoke exposure than those with lower cotinine levels. In addition, situations related to life quality like pain-related sleep disturbances and limitation in the daily activities were more common in the patients with high cotinine levels. The results of the current study are broadly consistent with the previous studies in the literature (10, 14).

In a study evaluating the relation between smoking and postoperative third month pain, it was pointed out that the pain scores were higher in the active smokers than non-smokers and patients who quitted smoking. In the present study, sample size (n=239) was high, however, the included operation groups were different. It is well known that the incidence of postsurgical chronic pain is varied according to the type of surgery. Unlike this study, we included only the patients underwent open abdominal hysterectomy (10). In a multi-center study conducted on the patients who underwent operation, it was observed that non-smoking patients had less back and leg pain when they were evaluated one year later (11). Although direct cotinine levels were not determined in these studies, long-term results were generally consistent with the results of the present study. In case cotinine levels were determined in the patients, who were active smokers or exposed to tobacco smoke and included in these studies, it would naturally be high. A study with a large sample size (4429) was arranged in a cross-sectional design in which the participants, who did not have to undergo operation, were included. Patients with high plasma cotinine levels in the third month (cotinine level>10ng/ mg) had higher chronic pain levels when compared to the group with lower values (the unadjusted odds ratio 1.65 vs 1.04) (14).

The relationship between pain and smoking is quite complex. The first study evaluating the effect of nicotine on pain stated that nicotine reduces pain by releasing endogenous opioids. Also, it showed that smoking increased the β-endorphine level. In addition, nicotine activates the nicotinic acetylcholine receptors (nAChRs) that are present in the central nervous system, autonomic ganglions, neuromuscular junction and in various tissues. Especially, it antagonizes the α4β2 sub-type of these receptor groups and causes antinociceptive effect. Due to prolonged nicotine exposure, cholinergic and opioid systems are also affected. Continuous nicotine exposure is known to cause tolerance and reduce pain inhibition by causing changes in the endogenous opioid system (15).

Acute pain related to a previous surgery has great importantance in the development of chronic or persistent pain. It is known that the process of acute pain occurs at both molecular and cellular levels. Prolongation of neurogenic inflammation, peripheral and central sensitization affect the transmission and processing of pain. As a result, the sensitization process of pain changes. In case inflammation is not treated, inflammatory and algogenic mediators, which are persistent in the environment, cause permanent changes in the nociceptors by causing sensitization (16, 17). Due to all these reasons, effective management of acute postoperative pain is quite important in the development of chronic pain.

In a study related to the effects of smoking on postoperative analgesia and pain were investigated in 80 patients who underwent lower extremity surgery. The patients were divided into two groups as people smoking at least 20 cigarettes a day and people who never smoked. Postoperative 24-hour VAS scores and analgesic consumption were found to be higher in the smoking group. Although no difference was observed in the mean arterial pressure values in the group with high scores, peak heart rate values were found to be high, as in the present study (18). In the patients who underwent hepatectomy, in which both urine and plasma cotinine values were examined, analgesic consumption and pain scores were higher in the smoking patients (19). In the present study, high VAS scores and morphine PCA consumption were found in the patients with high urinary cotinine values in the acute postoperative period.

Anxiety and depression symptoms tend to be more common and severe in smokers (20). Similarly, anxiety and depression tendency of smokers is higher (21). Also, according to the fear avoidance model, fear and anxiety accompanying pain also facilitates the continuation and chronicity of pain (22). As expected, in the current study, anxiety and depression scale results were found to be higher in the patients with high cotinine levels.

The relationship between pain, smoking, and the quality of life was investigated in the patients with chronic pain complaints. The mood, enjoying work/life, and quality of sleep were lower in the smokers when compared to the non-smokers (23). Many studies supporting this situation also specify that smoking decreases the quality of sleep (24, 25). Several studies also state that smokers tend to delay falling asleep, prolonged sleep, daytime sleepiness, and depression when compared to the non-smokers (25). Similarly, in the

current study, patients with high cotinine levels had higher postsurgical chronic pain and lower quality of sleep. The results of the studies investigating the effects of smoking on the quality of life were similar to the results of the present study (26-29).

It was shown that smoking decreases the quality of life and as the number of smoking increases, this situation becomes more significant (26). In the present study, similar negative results in the patients with the increasing rate of urine cotinine were determined.

A methodological strength of the current study is measuring the level of urine cotinine of each patient. The reason is that cotinine, which is the main metabolite of nicotine, is a biomarker that clearly reveals smoking or tobacco smoke exposure. The determination of the amount of this in serum, urine, and saliva is a much more objective method than the questionnaires that are conducted by asking the patients and it saves us from the problems that may occur due to social desirability bias. Cotinine reacts with cytochrome p450 in the body and nicotine iminium ion is formed. It is converted into cotinine via aldehyde oxidase. Cotinine is partially secreted from the kidneys. There are various methods to determine the cotinine level (blood, urine, saliva etc.) (30, 31).

Cotinine is practically easily obtainable, rather than its pharmacokinetic properties recommended for the body fluid to be worked (32). In the present study, the amount of cotinine taken from the urine immediately after the first foley catheter inserted before surgery was studied. Also, the half life of cotinine is similar in different body fluids. Cotinin starts to decrease in the body on the fourth day and disappears at least on the seventh day (33).

Limitations of the study

The study has limitations. Only the female patients who underwent hysterectomy surgery were included in the current study. Women perceive pain more densely and thus, they tend to consume more analgesics (34). In case patients of both genders were included in the study, pain scores and associated opioid consumption of male patients would have been lower. Smoking is a type of addiction and smokers also tend to use opioids due to addiction, apart from pain (35). The same postoperative opioid consumption would have been less in a group of non-smoking patients or the patients exposed to tobacco smoke. Urine cut-off values of cotinine has distinctions in the literature (36). The general opinion is that patients having 500ng/dl cotinine values are regular smokers and having 10ng/dl are not exposed to tobacco smoke too much. In the study, the patients were categorized as <10ng/dl (non-smoking), 10-500 ng/dl (irregularly smoking or exposed to smoking), or <500ng/dl (continuously smoking). In the studies, differences in the cotinine levels depending on races are shown. In this regard, different results can be obtained when the study is conducted at different geographical regions and on different races (37, 38).

CONCLUSION

In the present study, it was found that tobacco smoke exposure increased pain and consequently, the analgesic consumption in acute and chronic periods, depending on the high cotinine level. In addition, it should not be neglected that the quality of life of the patients exposed to tobacco smoke in the chronic period is deteriorated due to pain.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Hatay Mustafa Kemal University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 22/11/2017 and number 181, and Helsinki Declaration rules were followed to conduct this study.

Thesis

This study was prepared by rearrangement of the specialty thesis by Sümeyra Gökdemir in 2019 entitled as “To investigate the effect of urinary cotinine level on postoperative acute and chronic pain in patients undergoing open abdominal hysterectomy”.

Authorship Contributions

Concept: OK, SG, ST, Design: OK, SG, SH, Supervising: OK, SG, SU, OÖ, SH, Financing and equipment: OK, SG, SH, ST, OÖ, Data collection and entry: OK, SG, SU, Analysis and interpretation: OK, SG, SU, Literature search: OK, SG, SU, ST Writing: OK, SG, SU, Critical review: OK, SG, SU, ST, SH, OÖ

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