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A comparison of the side effects of morphine between the smoking and non-smoking patients

Abstract

Background and aim: Opioids have various side-effects that are known to compromise patient satisfaction. Side-effects of opioids were not evaluated extensively between smokers and non-smokers before. We aimed to investigate whether side-effects of morphine, a pure agonist used in preanesthetic medication, differ between smokers and non-smokers.

Materials and methods: This clinical study performed between January and September in 2014. Patients >16 years, with American Society of Anesthesiology physical status (ASA) I or II, with no analgesic and sedative drugs use within the previous 24hours, with administered intramuscularly morphine (10mg) before surgery were conducted in this study. Patients were scheduled for elective operations divided into two groups as smokers (n=26) and non-smokers (n=25). Pre- and post-treatment vitals and side effects of the patients were recorded.

Results: Overall side effects of non-smokers were statistically higher than smokers (42.3% vs. 16.0%, ***p*=0.039**). Specifically, non-smokers felt higher nausea than smokers (26.9% vs. 4.0%, ***p*=0.024**). Although pruritus, fatigue and sweating were higher in non-smokers compared to smokers, they did not reach to statistical significance.

Conclusion: We showed that smokers tolerate morphine pretreatment better than non-smokers. We suggest that when using morphine pretreatment, an additional pretreatment therapy may be necessary to reduce the side-effects for non-smokers, or another pretreatment option may be selected for non-smokers.

Keywords: smokers, non-smokers, morphine, side effects

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Introduction

Opioids, which have been used for thousands of years for pain relief and pleasure, are today highly important and essential for anesthetic procedures. Although opioids are frequently used in the perioperative period due to their anxiolytic, sedative and powerful analgesic effects,[1,2] they can also cause adverse effects, such as constipation, nausea, somnolence, urinary retention, respiratory depression, itching, sweating, mental confusion, physical dependence and misuse.[3,4] Opioids are known to compromise patient satisfaction because of these side-effects. The complex relationship between nicotine and opioids frequently used in society and pain is a controversial one and is not fully understood. Several studies have reported that smokers have a greater opioid requirement for pain control in the perioperative period.[5–8] While nicotine has analgesic properties it is also a risk factor for chronic pain.[9] One study investigating the effects of nicotine on the sexes showed that it increases the pain threshold and pain tolerance in males but has no effect on females' pain perception.[8] The purpose of this study was to investigate whether the sedation induced by and side-effects of morphine, a pure agonist used in preanesthetic medication, differ between smokers and non-smokers.

Materials and methods

Study sample

After the approval of ethical committee by our hospital (decision number: 2014/12) for the following study, the files of 75 patients who were used morphine for premedication and had elective surgery and taken informed consent forms in the General Surgery Clinic between January and September 2014 have been examined retrospectively. Patients aged over 16, with American Society of Anesthesiology (ASA) physical status I or II, who did not take any additional analgesic, sedative or anxiolytic medicine within the previous 24hours, had morphine at 10mg/mL intramuscularly approximately two hours before surgery (10mg/mL flask, morphine HCL, Galen, Turkey) and underwent surgery under general anesthesia electively (thyroidectomy, cholecystectomy and mastectomy) were included to the study. Patients with a history of sedative, analgesic or anxiolytic usage in the previous 24 hours before the operation (n=7), with the risk of ASA III or above (n=9) and hypertension (n=8) were excluded from the study. Finally fifty-one patients who were suitable for the study protocol were evaluated. These patients were divided into two groups as smokers (n=26) and non-smokers (n=25).

Collection of data and definitions

Patients' demographic variables such as age, weight, height, sex, and ASA status, and also type of surgery were recorded. Hemodynamics of the patients such as mean arterial pressure and heart rate were also recorded. Mean blood pressure (MBP1) and heart rate (HR1) before given morphine, and mean blood pressure (MBP2) and heart rates (HR2) after given morphine, and mean blood pressure (MBP3) and heart rates (HR3) in the operating room were measured and recorded. MBP of 70mmHg or less was regarded as hypotension and a heart rate of 120/min or more was regarded as tachycardia. Acute side-effects in the time between administration of morphine and the operating table (itching, perspiration, nausea-vomiting, palpitations, hypotension, dizziness, somnolence and facial numbness) were recorded. The state of sedation of patients was assessed in operations room using Ramsey Sedation Scale (RSS).[10]

Statistics

Continuous and categorical variables were given with mean ± SD and percentages or number, respectively. Fischer's exact test

and Mann Whitney U test were used for continuous and categorical variables, respectively. Statistical analyses were done using SPSS v 20.0 (IBM, Chicago, USA). A P value <0.05 was accepted as statistically significant.

Results

The baseline characteristics and vital signs of patients in both non-smokers and smokers groups were shown in Table 1. Morphine did not change the vital signs between two groups significantly except the preoperative mean heart rate which was higher in smokers group than those of non-smokers. There was no difference between the groups according to the performed surgery (Table 2). Overall side effects of non-smokers were statistically higher than smokers (42.3% vs. 16.0%, P=0.039). Specifically, non-smokers felt higher nausea than smokers (26.9% vs. 4.0%, P=0.024). Although pruritus, fatigue and sweating were higher in non-smokers compared to smokers, they did not reach to statistical significance (Table 3).

Table 1 Baseline characteristics of patients in both groups

Characteristics	Non-smokers	Smokers	P
Age (years)	39.8±17	42±14.6	0.54
Male % (n)	61.5% (16)	72% (18)	0.555
Weight (kg)	72±10	75.5±12	0.462
Height (centimeter)	166±6.6	166.2±8.6	0.911
BMI (kg/m2)	26.4±3.3	27.1±2.7	0.349
ASA I % (n)	69.2% (18)	76% (19)	0.755
RSS	2.3±0.5	2.2±0.4	0.22
MBP1 (mmHg)	96±13	97±16	0.85
HR1 (minute)	75±7.1	82±8.4	<0.0001
MBP2 (mmHg)	88±15	87.5±14	0.94
HR2 (minute)	83±12.5	81±11	0.692
MBP3 (mmHg)	96±13	97±12	0.947
HR3 (minute)	89±17	88±15	0.932

ASA, american society of anesthesiologists; MBP, mean arterial pressure; MBP1, before given morphine mean blood pressure; HR1, before given morphine heart rate; MBP2, after given morphine mean blood pressure; HR2, after given morphine heart rate; MBP3, preoperative mean blood pressure; HR3, preoperative heart rate; RSS, ramsey sedation scale

Table 2 The distribution of operations performed in both groups

Operations	Non-smokers	Smokers	P
Thyroidectomy; % (n)	23.1% (6)	32.0% (8)	0.541
Cholecystectomy; % (n)	53.8% (14)	44.0% (11)	0.579
Mastectomy; % (n)	23.1% (6)	24.0% (6)	1

Table 3 Side effects of morphine in both groups

Side effects	Non-smokers	Smokers	P
Total % (n)	42.3% (11)	16.0% (4)	0.039
Pruritus % (n)	15.4% (4)	0.0% (0)	0.11
Nausea % (n)	26.9% (7)	4.0% (1)	0.024
Fatique % (n)	19.2% (5)	4.0% (1)	0.191
Palpitation % (n)	7.7% (2)	4.0% (1)	1
Sweating % (n)	11.5% (3)	0.0% (0)	0.235
Numbness% (n)	3.8% (1)	4.0% (1)	1
Dizziness % (n)	3.8% (1)	4.0% (1)	1
Sleeping % (n)	7.7% (2)	0.0% (0)	0.49
Hypotension % (n)	3.8% (1)	0.0% (0)	1

Discussion

This study showed that smokers tolerate morphine pretreatment better than non-smokers. Our findings therefore suggest that when using morphine pretreatment, an additional pretreatment therapy may be necessary to reduce the side-effects for non-smokers, or another pretreatment option may be selected for non-smokers. Morphine is a pure agonist of phenanthrene, an opium alkaloid, and exhibits its effects on the central nervous system through mu (analgesia, euphoria), kappa (κ) (respiratory depression, sedation, analgesia, miosis), delta (Δ) (analgesia, excitement, euphoria), epsilon (ε) and sigma (δ) receptors. A sedated state, lack of interest in surroundings, slowed movements and mental confusion may develop in individuals taking morphine, and it can lead to euphoria by reducing anxiety and psychological tension. In addition, since its analgesic effect lasts 4-6h, it is an opioid that can be used for balanced anesthesia and preanesthetic medication.

Opioids are becoming increasingly used in the preoperative term in case of acute, chronic and various types of pain.[3] They are indispensible to anesthetists because of their sedative, anxiolytic and powerful analgesic effects, particularly in the preoperative period.[2] However, with the exception of chronic cancer pain, their use is controversial for reasons such as psychological dependence, recreational and improper use, complications and side-effects. Patient satisfaction is reduced by the most common side-effects, including nausea, constipation, sleeplessness, vomiting and sweating, and this can lead to refusal of treatment. Deaths due to misuse of opioids are another important problem.[2–11]

There are several studies concerning the still not fully understood relationship between nicotine, pain and opioids.[9] Studies have reported greater opioid consumption in the postoperative period in smokers than in non-smokers.[5–7] Creekmore et al.[6] showed that smokers deprived of nicotine had a greater opioid requirement than non-smokers in the first 48h after coronary artery bypass graft surgery. In a clinical study, Aydogan et al.[5] reported greater postoperative opioid (fentanyl) consumption among both active and passive smokers compared to non-smokers. Another gender-based study reported a greater opioid requirement for postoperative pain control in female smokers, and that the same result has been seen in non-smokers in recent years.[7] ByJamner et al.[7] investigated whether the hypoalgesic effect of nicotine varies between the sexes (30 male patients and 44 female). They reported that nicotine raised the pain threshold in males and increased pain tolerance, while it had no effect on female patients' pain levels, and suggested that this difference in pain perception reflected a direct pain-reducing effect of nicotine. At the same time, many animal and human studies have shown that nicotine possesses analgesic properties. The analgesic effect of nicotine probably derives from its effect on central and peripheral nicotine acetylcholine receptors (nAChRs), since AChR ligands have potent analgesic effects.[9,12,13]

It is not completely clear why although nicotine has analgesic properties, patients deprived of nicotine have greater opioid requirements for pain control. This can probably be explained in one of two ways; first, this effect may be due to a pharmacokinetic interaction between cigarettes and opioids or to cigarettes altering the pharmacokinetic characteristics of opioids.[9] Alternatively, cigarettes induce the isoenzyme CYP1A2 and therefore, as a result of their ability to increase the metabolism of certain drugs, patients may have a greater drug requirement for pain control.[14] *In vitro* studies of nerve physiology have shown that nicotine can stimulate firing of the sensory nerves and that nicotine can increase the perception of pain by increasing the firing rate of these nerves.[15] Cross-tolerance is known to develop between exogenous and endogenous (b-endorphins) in animals. Deprivation in laboratory animals exposed to nicotine enhances nociceptive transmission, because both

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(opioids and nicotine) exhibit their effects by binding to the same opioid receptors.[16,17] On the other hand, Schein et al.[14] showed that nicotine deprivation symptoms in animal scan be ameliorated with the administration of the opioid fentanyl.

Another study also reported less postoperative nausea and vomiting in smokers (6%) compared to non-smokers (15%) and hypothesized that this might be due to enzyme induction.[18] Therefore, tolerance to opioids means greater opioid administration for pain control.[17] Parallel to the above studies, development of tolerance to opioids strengthens the idea that tolerance may also develop to adverse side-effects. Our study findings also support this idea. We observed fewer side-effects of morphine in smokers compared to non-smokers. We attribute the higher heart rates in smokers before administration of morphine in this study to cigarettes' capacity to cause sympathetic activity and tachycardia.[19] Hypotension developed in one non-smoking patient, although this was not statistically significant. This is also associated with morphine being able to cause histamine release-related vasodilatation, and therefore hypotension.[20] Although not statistically significant, the anticholinergic effect of morphine[2] caused tiredness-fatigue in 5 non-smoking patients and somnolence in two, while tiredness-fatigue was observed in only one patient in the smoking group, and no somnolence was observed in any patient in that group. Another parameter we compared in this study of the effects of morphine on smoking and non-smoking patients was RSS, although no statistically significant difference was determined. This study did not investigate opioid-induced side-effects between the sexes since our female patient numbers were not sufficient. Main limitation of our study is that we did not evaluate the difference of consumption of the anesthetic agents used in two groups. We also did not check out the analgesic effect of morphine. Our results include one center data conducted in relatively low number of patients.

Conclusion

There is a significant difference in terms of side effects between smoking and non-smoking patients. Higher levels of opioid induced adverse effects are observed in non-smokers. Further studies with more participants are now needed to clarify these adverse effects, especially between the sexes.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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