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Effects of Smoking Cessation on Peak Nasal Inspiratory Flow and Nasal Mucociliary Clearance

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ABSTRACT

Introduction: In this study, the aim was to investigate smoking cessation on peak nasal inspiratory flow (PNIF) and nasal mucociliary clearance (MCC).

Methods: Sixty-two (32 male and 30 female) smokers were included in this prospective study. Varenicline (Champix®, R-Pharm, Germany) was prescribed to all subjects who want to quit smoking as supportive therapy. Three-month treatment is planned. Day 0 (baseline), 3rd month (after smoking cessation), and 6 h (3 months after smoking cessation) PNIF values with decongestant (PNIFwD) and without decongestant (PNIFsD) and nasal mucociliary clearance time (MCT) with the saccharine test were determined. The acquired data were evaluated statistically.

Results: The mean age of the subjects was 36.77±9.63 (minimum: 18, maximum: 60) years. Significant differences were found between the PNIF and MCT values during different study periods ($p<0.05$). The medians of nasal MCT values for the 3rd and 6th months were significantly lower than the median of baseline values ($p<0.05$). Additionally, the median of nasal MCT values for the 6th month was significantly lower than the median of nasal MCT values for the 3rd month ($p=0.0003$, $p<0.05$). The medians of PNIFsD values for the 3rd and 6th months were significantly higher than the median of baseline values ($p<0.05$). Additionally, the median of the 6th-month values was significantly higher than the median of the 3rd-month values ($p=0.023$, $p<0.05$). There was no significant difference in terms of PNIFwD evaluations ($p=0.06$, $p>0.05$).

Conclusion: The results of this study showed that smoking cessation improves nasal MCC and airflow.

Keywords: Smoking, mucociliary clearance, nasal obstruction/diagnosis, nose/physiology, saccharin/pharmacokinetics

Introduction

Tobacco use is one of the major public health problem, killing more than 8 million people worldwide each year (1). The most commonly used tobacco product in the world is cigarettes (2). Smoking is a chronic disease and since the 20th century, this epidemic has been the most common reason for preventable deaths (2,3). More than 80% of all smokers worldwide live in low- and middle-income countries (3). Although smoking is one of the most common causes of mortality and morbidity in these countries, it has devastating effects on the economies of these countries (3). Turkey is a country with the most frequent smoking in the world, with 14.8 million smokers (4). Because of its effects on health and the economy, removing smoking is one of the most important common goals of the world. To achieve this goal, countries have their projects besides international projects. The World Health Organization Framework Convention on Tobacco Control, which has been accepted by 182 countries where more than 90% of the world's population lives, is one of these projects (2).

Smoking, which shortens the lifetime, is involved in the etiology of malignant neoplasms of many organs, especially the lung, and chronic diseases of many systems, especially the cardiovascular and respiratory systems (5). One of these organs is the nose, which is the entrance to the respiratory tract (6-10). Two of the main nasal functions are respiration and mucociliary clearance (MCC). The insufficiency of nasal respiration function is clinically manifested by nasal congestion characterized by raised nasal resistance and decreased airflow (11). MCC, which is the initial and key defense mechanism of the airways, can be described as the retention and removal of detrimental foreign particles in the inspired air by the mucosa (12). The impairment of this function of the nose may present with many chronic diseases, especially infectious diseases, in the clinic (12).

To give up smoking, which has all these harmful effects, both the addiction of the person should be treated and the behavior and habits of the person should be changed (3). Smoking cessation needs psychological and pharmacological supports. In smoking cessation, the main psychological support is behavioral counseling and the main pharmacological

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treatments are nicotine replacement therapy, bupropion, varenicline, and cytisine (5). Varenicline is a selective partial agonist for one of the nicotine receptors, α4β2 nicotinic acetylcholine receptor (5). It alleviates withdrawal symptoms via this receptor (agonist activity), while reducing rewards by preventing nicotine binding (antagonist activity) (5,13). There are many studies showing the effectiveness of the use of varenicline, which helps quit smoking by preventing withdrawal symptoms, alone or along with other treatment methods (14).

Nasal damage can be alleviated or completely healed by smoking cessation like many damages caused by smoking (5,15). In this study, we purposed to examine the effect of smoking cessation in nasal respiratory and nasal MCC functions.

Methods

This prospective study was performed at Cerrahpaşa School of Medicine and Eyüpsultan State Hospital between April 2021 and January 2022 with the confirmation of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: E-83045809-604.01.02.74209, date: 14.04.2021).

Participants, Inclusion, and Exclusion Criteria

All subjects of the study consulted the Smoking Cessation Clinic of Eyüpsultan State Hospital. A detailed anamnesis was obtained from every subject and a full otorhinolaryngological examination was done. All participants signed an informed consent form. Subjects who had been smoking for at least one year were included in the study. A smoker was defined as a person who currently smokes daily and has smoked at least one-hundred cigarettes in her/his lifetime (16).

The subjects under 18 and over 60 years of age, with an abnormality (ontological or respiratory) in full-endoscopic examination, with anamnesis of cranial trauma, with a neurological disease and/or a chronic disease such as obstructive pulmonary disease, with anamnesis of airway infection in the last three months, with anamnesis of otologic or airway procedure, with anamnesis of regular drug use in the last six months, with an anamnesis of taste and/or odor disturbance were excluded from this study.

Subject Size

The minimal subject size was determined based on the article of Develioglu et al. (17). The minimal subject number with a 95% reliance gap and 5% bearable mistake assumptions was 62.

Data Collection

Study Design

Day 0 (baseline): Detailed medical histories of the subjects were recorded. Varenicline (Champix®, R-Pharm, Germany) was prescribed to all subjects as supportive therapy for smoking cessation. Three-month treatment is planned. The drug dose was planned to be 1x0.5 mg for the first 3 days, 2x0.5 mg between the 4th and 7th days, and 2x1 mg between the 8th and 90th days (5). The subjects were then referred to the otorhinolaryngology clinic. A complete endoscopic otorhinolaryngological examination was performed. Nasal MCT was determined by the saccharine test method, and Peak Nasal Inspiratory Flow (PNIF) was examined with a PNIFmeter.

Day 90 (3rd month): After the treatment, all subjects gave up smoking, and the tests were repeated.

Day 180 (6th month): At the end of the study, the measurements were repeated 3 months after smoking cessation.

All measurements of the patients were performed after a 30-minute relaxation at the same place at a temperature of 20-25 °C and 50-70% humidity. Evaluation of all subjects was done by the same internal medicine and the same otorhinolaryngology specialists. For success in varenicline therapy, smokers should stop smoking 1 to 2 weeks after starting treatment (5). All subjects stopped smoking on the 10th day of treatment.

Methods

Endoscopic Examination

The nose was first examined with a Hartmann nasal speculum (Karl Storz, Germany). Then, the nasal cavity, pharynx, and oral cavity were examined with a 3.5 mm flexible fiberscope (Karl Storz, Germany).

Saccharine Test Method

The smoker was positioned in a chair. The subjects were instructed to not move, to not sniff, not sneeze, to open her/his mouth, and to perform nasal and oral breathing. For the nasal MCC test, 5 mg saccharin (Sakarin-oro, Oro İlaç, Turkey) was placed on the medial surface 0.5 centimeters behind the anterior of the inferior turbinate with alligator forceps (Karl Storz, Germany). The subjects swallowed every 30 seconds. When the subject notices that she/he has tasted saccharin was determined as mucociliary clearance time (MCT; second, sec.) (17). The nasal MCT alters approximately 720-900 seconds in healthy people (17).

PNIFmeter

Twenty minutes later the saccharine test, PNIF values were calculated using a PNIFmeter (Clement Clarke International Limited, England). The smokers were placed in a chair and the PNIFmeter mask was positioned to cover the mount and nose, deep and rapid inspiration was performed then forced expiration with the mouth closed. The evaluation was repeated 10 min after nasal decongestant, with one puff to each nasal cavity, xylometazoline (Otrivine®, GlaxoSmithKline, UK) administration. To provide subject compliance, the measurement was repeated 3 times and the highest value of the PNIF with decongestant (PNIFwD) and the PNIF without decongestant (PNIFsD) were saved as liters/minute (L/min). The PNIF value of a healthy person is 138.4 L/min (18).

Statistical Analysis

The minimal subject number was estimated using the G*Power software 3.1 (19). Statistical analyses were performed with the SPSS 21 (SPSS Inc., USA) program. Normal distribution and homogeneity of data were analyzed with the Kolmogorov-Smirnov test and Levene's tests, respectively. Wilcoxon signed ranks test and Friedman test were used for analysis. The significance level was defined as $p<0.05$.

Results

A total of 62, 32 male and 30 female, smokers were included in this study. All subjects gave up smoking and completed the study. The mean

age of the individuals was 36.77±9.63 (minimum: 18, maximum: 60) years. No serious drug-related side effects were observed.

There was a significant difference according to the nasal mucociliary clearance time values of the smokers at different periods (p=0.00001, p<0.05). In the evaluation of nasal mucociliary clearance time, the median of the 6th-month values was significantly lower than the medians of baseline and the 3rd-month values (p=0.000001; p=0.000001, respectively, p<0.05). Additionally, the median of the 3rd-month values was significantly lower than the median of initial values (p=0.0003, p<0.05) (Table 1, 2) (Figure 1).

There was a significant difference according to the PNIFsD values of the smokers in different study periods (p=0.00001, p<0.05). In the evaluation of PNIFsD values, the median of the 6th-month values was significantly higher than the medians of baseline and the 3rd-month values (p=0.000001; p=0.000001, respectively, p<0.05). Additionally, the median of the 3rd-month values was significantly higher than the median of initial values (p=0.023, p<0.05) There was no significant difference in terms of PNIFwD evaluations (p=0.06, p>0.05) (Table 1, 2) (Figure 2).

Discussion

Smoking is involved in the pathophysiology of chronic diseases and malignancies of many organs, and systems, particularly the lung and the respiratory system (1-5). Because of these chronic diseases, smoking shortens the average life expectancy by 10 years (20). Many strategies are being implemented at the national and international levels against smoking, which is the most common cause of preventable deaths. Depending on these strategies, the number of people who quit smoking increases day by day. In parallel, many studies have been conducted examining the effects of smoking cessation (8,15,21). In this study, we investigated the effect of smoking cessation on nasal MCC and nasal respiratory functions. In this study, mucociliary clearance time values at the end of the smoking cessation period (3rd month) and 3 months after smoking cessation (6th month) were significantly lower than the initial values (p<0.05). Besides, the 3rd-month MCT values were significantly lower than the baseline values (p=0.0003). Additionally, 3rd-month and 6th-month PNIFsD values were significantly higher than the initial values (p<0.05), and the 3rd-month PNIFsD values were significantly lower than the initial values (p=0.023).

Respiration, airway defense, and olfaction are the basic physiological functions of the nose (11). Optimal nasal respiration is essential for the other basic functions (11,12). Nasal obstruction, which is the most common rhinological problem, leads to decreased nasal airflow and insufficiency in nasal respiratory function (11,12). Nasal endoscopy, computed tomography scan, and anterior active rhinomanometry (AARM) are some methods used in the diagnosis of nasal obstruction and evaluation of nasal respiration function (22,23). AARM is the most commonly used and most accurate method to determine nasal airflow and resistance (18,24). Measurement of PNIF with a PNIFmeter is an objective and cheap method, that is faster and easier to apply compared to AARM, to examine nasal airflow and indirectly nasal resistance with a high correlation with rhinomanometry in normal and pathological noses (18,24). A high PNIF value is compatible with low nasal resistance (24).

Nasal MCC is one of the major nasal functions and is described as the removal of pathogenic particles from the inspired air by the mucosa and their transport from anterior to posterior by epithelial ciliary movements (12). It is the first and basic defense mechanism of the upper airways (12). MCC can be studied *in vivo* tests using different materials such as dyes, radiopaque materials, and saccharin (12,17). The saccharine test is an inexpensive, safe, and easily applicable test that measures MCT, which is an indicator of MCC (12,17,25). With these features, it is the most commonly used MCC evaluation method in clinical studies (12,17,25).

The normal MCC depends on the volume and composition of airway surface liquid (mucus and underlying periciliary layer), the healthy ciliary epithelium and structure, appropriate beating frequency, and airway surface liquid-cilia interaction (10-12,25). The disturbances in the MCC mechanism can lead to obstructions in the respiratory tract, airway infections, structural changes in the respiratory tract, and damage to the respiratory organs (8,12). The MCC can be affected by various factors such as environmental heat, drugs, toxins, pH, fasting, chronic diseases, and rhinological surgeries (8,11,12,25). One of these factors is active or passive smoking (8,26).

Various studies have reported the damage caused by smoking on different tissue and organ functions (8,26). One of these organs is the nose. There are various studies examining the effects of smoking on different nasal functions (6,8,15,26). However, the number of studies on the reversibility of the damage caused by smoking on nasal functions is limited (8,15). We planned this study to examine the effects of smoking cessation on nasal defense (MCC) and respiratory functions. In this study, the factors affect MCC negatively, such as being over 60 years old, and having a history of nasal pathology or surgery were accepted as

Table 1. Evaluation of peak nasal inspiratory flow and nasal mucociliary clearance time measurements

Parameter	Baseline	3rd month	6th month	p*
	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
MCT	809.68±196.9 (840)	711.45±205.51 (727.5)	694.03±196.18 (720)	**0.00001***
PNIF without decongestant	119.06±19.21 (120)	120.02±20.17 (125)	125.5±19.8 (130)	**0.00001***
PNIF with decongestant	135.64±20.95 (140)	136.16±22.53 (140)	136.97±21.85 (140)	0.06

*Friedman test, p<0.05. PNIF: Peak nasal inspiratory flow, MCT: Mucociliary clearance time, SD: Standard deviation

Table 2. Pairwise comparison of data according to study periods

	Compared values	MCT[a]	PNIFsD[b]
p	Baseline-3rd month	0.0003*	0.023*
	3rd-6th month	0.000001*	0.000001*
	Baseline-6th month	0.000001*	0.000001*

[a]Nasal mucociliary clearance time, [b]Peak nasal inspiratory flow without decongestant, *Wilcoxon signed ranks test, p<0.05, MCT: Mucociliary clearance time, PNIFsD: Peak nasal inspiratory flow without decongestant

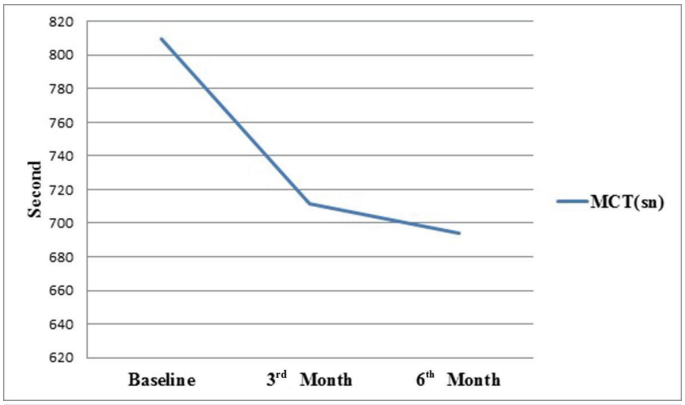

Figure 1. Nasal mucociliary clearance time values at baseline, 3rd month and 6th month
MCT: Mucociliary clearance time

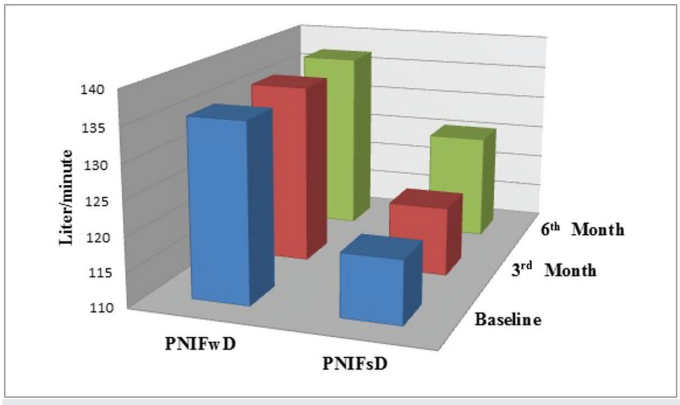

Figure 2. Peak nasal inspiratory flow with decongestant and peak nasal inspiratory flow without decongestant values at baseline, 3rd month, and 6th month
PNIFwD: Peak nasal inspiratory flow with decongestant, PNIFsD: Peak nasal inspiratory flow without decongestant

exclusion criteria from the study (25). All measurements were performed by the same person for standardization.

Various previous studies have examined the relationship between smoking and nasal MCC (7,8,10,26). Active or passive smoking increases inflammation and oxidative stress in the mucosa and induces changes in the epithelial structure and functions (8). Smoking causes produce high viscosity mucus by goblet cell hyperplasia and causes spread of an epithelium without ciliary functions in the airways by squamous metaplasia (8,27,28). Cigarette smoke impairs cilia structure and cilia regeneration (8,27,28). Additionally, cotinine, a metabolite of nicotine in cigarettes, decreases ciliary beat frequency (29). With all these effects, smoking, which impairs epithelial ciliary functions, leads to MCC deterioration and MCT elongation. This effect of smoking gradually returns with smoking cessation (8,28). Epithelial and ciliary regeneration increases after smoking cessation (8,28). Nasal MCC improve 1 month after smoking cessation, while nasal mucus properties return to normal 12 months after smoking cessation (8). In our study, the gradually decreasing MCT values in the first and 6th months in people who quit smoking support the existing information in the literature.

There are a limited number of studies in the English literature that objectively examine the effect of smoking on nasal respiratory functions (7-9,30). In these studies, increased nasal resistance and decreased airflow levels were found in smokers compared with normal individuals (7-9,30). The reasons for the deterioration in nasal respiratory function include increased nasal mucosal inflammation, increased mucosal edema, increased nasal mucosal congestion and decreased nasal decongestion capacity (7-9). In this study, we found a progressive increase in PNIFsD values after smoking cessation ($p<0.05$). Although the increase detected in the measurements made after the decongestion application (PNIFwD) was close to a significant level, it was not statistically significant ($p=0.06$). While there is a significant difference between PNIFsD values, the absence of a significant difference between PNIFwD values can be explained by the fact that smoking reduces the nasal decongestion capacity. Since the measurement value of the decongestion capacity is lost with the use of decongestion, the increase we obtained may not have been at a significant level.

Study Limitations

This study has several limitations. One of these limitations is the use of a PNIFmeter for nasal respiratory function. Although PNIFmeter show a high correlation with AARM in the evaluation of nasal respiratory function, they are not as valuable as AARM in clinical practice. Additionally, patient-related problems may occur during the PNIFmeter application. To limit the effect of this limitation on this study, we iterated the PNIFmeter tests 3 times and recorded the highest value we detected. Another limitation is the absence of a control group. In our opinion, there was no need for a control group because the effects of smoking on nasal functions are well known and our study aimed to investigate the effect of smoking cessation on nasal functions. Another parameter limiting the value of this study is that we did not determine the duration of smoking of the smokers included in this study. The pathologies related to smoking increase with the duration and amount of smoking (28).

Conclusion

In this study, we found that smoking cessation increases nasal MCC and airflow. This effect can be explained by the reversible nature of the changes caused by smoking in the nasal mucosa. More comprehensive studies, including biochemical, immunological, and histopathological examinations, are needed to reveal these effects more clearly.

Ethics Committee Approval: This prospective study was performed between April 2021 and January 2022 with the confirmation of İstanbul

University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: E-83045809-604.01.02.74209, date: 14.04.2021).

Informed Consent: All participants signed an informed consent form.

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Authorship Contributions: Surgical and Medical Practices - D.Ç.; Concept - D.Ç.; Design - D.Ç.; Data Collection or Processing - D.Ç.; Analysis or Interpretation - S.U.; Literature Search - S.U.; Writing - D.Ç., S.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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