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Submission date: 18-Jul-2020 07:42PM (UTC+0700)
Submission ID: 1358991267
File name: Artikel.pdf (130.14K)
Word count: 5218
Character count: 29069

Journal of Pharmacy and Pharmacology 8 (2020) 44-52
doi: 10.17265/2328-2150/2020.02.002

Nasal Irrigation Effects towards Nasal Mucociliary Transport Time in Active Smokers

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Abstract: Nasal irrigation is often recommended as an adjuctive therapy for treating many sinonasal conditions. It provides mechanical cleansing of mucus, crust, cell debris and various air contaminants. The study was done to analyze the effect of nasal irrigation on change of nasal mucociliary transport time, in active smokers. This study was experimental using pre and post test controlled group design. Samples were divided into two groups; treatment and control group. The mucociliary transport time were tested with saccharin method for two times; before and fourteen days after treatment. On the day fourteen after nasal irrigation there was a significant decreased of the mucociliary transport time than before (p = 0,000). In the control group on second measurement was significantly longer compared to the first measurement (p = 0,003). In the comparison of mucociliary transport time change between treatment group and control group was found significant differences (p = 0,000).

Key words: Nasal irrigation, nasal mucociliary clearance, active smoker.

1. Introduction

Currently, there are about six million people died each year from smoking all over the world. The prevalence of smokers in the world aged 15 years and above was 21% in 2013 [1]. The increased prevalence of smokers in Indonesia occurred in 2013 from 34.2% to 36.3%; 64.9% for men and 2.1 % for women with the average number of cigarettes per day are 12.3 cigarettes [2]. Cigarette smoke contains 5,000 kinds of toxins which consist of gases component and particles that can cause a chronic irritation and affect the defense mechanisms of local humoral and cell-mediated immunity in the respiratory system. Therefore, smoking is often related with health problems in the respiratory system [3].

Cigarette smoke contains acrolein which is irritants to the respiratory system. It induces proinflammatory responses in epithelial cells of respiratory tract [4, 5]. A study proves that smoking leads to an inflammatory with the discovery of lymphocytes CD8 T and eosinophils in the nasal mucosa of smokers [6]. Formaldehyde, acrolein, ammonia, and phenols in cigarette smoke are proven to damage cilia and to delay mucociliary clearance [7]. Mucociliary transport time that extends leads to stagnation of mucus and drainage mucus disorders, so it becomes the factors of predispose to infection, the changes in complement levels, lysozyme, and immunoglobulin which resulted in the decreasing of immunological protection [8]. Smoking is a risk factor for chronic rhinosinusitis. A research shows that smokers have a risk factor of chronic rhinosinusitis by 14% [9].

Nasal irrigation is used as an additional therapy to treat various complaints of sinonasal because this therapy is inexpensive, simple, and effective. Nasal irrigation may improve nasal mucociliary function through a mechanism of nasal mucosa clearance from inflammatory mediators along with inhalant which is trapped in the nasal mucosa [10, 11]. The solution that can be used for nasal irrigation is the solution isotonic, hypertonic, buffered and unbuffered. Isotonic saline

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solution contains 0.9% sodium chloride with sodium composition 154mEq / L and chloride 154mEq / L, with a total of 308 mOsm / L. Hypertonic saline solution contains 2-3a% NaCl with sodium composition 513mEq / L and chloride 513mEq / L, with a total of 1026 mOsm / L [3-5].

Nasal irrigation does not improve mucosal immunity and the functions of cilia directly. Hypertonic saline only act as a provocation to the respiratory tract. On mucus hypersecretion conditions, such as chronic rhinosinusitis, nasal irrigation is used to improve the rheology of mucus while the elimination of inflammation, thus improving the mucociliary funtion [12]. Nasal irrigation through the mechanism of clearance of mucus, debris and various air contaminants (pathogens, allergens, airborne particles, etc), increases mucociliary transport time, reduces the contact time between mucus and air elements, reduces the concentration of proinflammatory mediators local and moisturize the nasal mucosa [13].

The study shows that patients with chronic sinusitis symptoms who use saline irrigation 2% every day other than regular treatment have experienced improvement in their symptoms by 64% [11]. Hypertonic saline irrigation can accelerate mucociliary transport time of patients with chronic rhinosinusitis by 85%, while nasal irrigation by using isotonic saline increases mucociliary transport time by 31.19% [14].

Based on the background above and the lack of studies on this, the researchers were interested in conducting a study on the effects of nasal irrigation towards nasal mucociliary transport time in active smokers.

2. Materials and Methods

Ethical clearance were obtained from Health Research Ethics Committee Faculty of Medicine, Diponegoro University / Dr. Kariadi Semarang Hospital 180/EC/FK-RSDK/2016. The study was conducted at Diponegoro National Hospital from March to May 2016. This study was an experimental study with pre and posttest controlled group design made. The inclusion criteria of this study were active smokers at least a year with their age 18 to 45 years old, male, and willing to be the subject of this study. The exclusion criteria of this study were active smokers with BMI > 29, having rhinosinusitis disease, nasal polyps, consuming aspirin, antihistamines, β blockers, decongestants, mucolytics, bronchodilators, and corticosteroids.

The samples were taken by consecutive sampling and divided into two groups; the group that receive nasal irrigation treatment once a day for two weeks and the group that did not receive nasal irrigation treatment for two weeks. The mucociliary transport time were tested with saccharin method for two times; before treatment and fourteen days after treatment. The independent variable of this study was nasal irrigation. The dependent variable was nasal mucociliary transport time. The confounding variables were smoking duration, the degree of smoking, septum deviation, and allergic rhinitis.

Materials and instruments for data collection in this study were saccharine tablet, NaCl 0.9% saline solution, alcohol 70%, nose speculum, tongue depressor, head lamp, bayonet tweezers, spuit 10 cc, stopwatch, rhinitis allergy questionnaire, informed consent form, basic data of samples.

For data collection techniques, the collected data was primary obtained from anamnesis, physical examination, and measurement of mucociliary transport time. Anamnesis and physical examination were done to determine whether the samples have an exclusion criterion, confounding variables. Saccharine test was done with these following steps: a) sample were asked to gargle with water, b) sample took a rest in the examination room for 15 minutes, c) sample was positioned to sit in a chair with back straight, d) examine the sample's nose with anterior rhinoscopy, e) cleaned the nasal secretion, f) put the speculum on one

of the nasal cavity, g) put a saccharin particle size of 2 mm at the front end of the inferior turbinate / 1 cm posterior from the anterior border of the inferior turbinate using tweezers bayonet, h) sample was asked to breathe through the nose with the mouth closed and swallowed every single minute, i) calculated the length of time when saccharin is placed until the sample feels the sensation of sweet with a stopwatch, j) the test was stopped if more than 60 minutes the sample did not feel the sweet sensation, then saccharin placed on sample's tongue to rule out the possibility of interference tasting [15]. The treatment group was given treatment for nasal irrigation once a day for two weeks in one place with the assistance of researchers, nasal irrigation was done with these following steps: a) setting up a 10 cc syringe containing 0.9% saline solution, b) the sample's head is positioned slightly tilted with turned towards the nose to be sprayed, mouth slightly opened, c) slowly insert the tip of the syringe into the nostrils and face the nasal septum, d) press the tip of the syringe for 3 seconds, e) let the solution brings out the mucus from the nose, f) repeat for the other nostril, g) after use, wash the tip of the syringe with 70% alcohol or soapy water, rinse and dry [13].

Prior to the data analysis, completeness and correctness of the data were checked. Data were coded, tabulated, and entered into a computer. The data was processed by a computer program Statistical Product Services Solution (SPSS 23) and presented in narrative form and tables. Data analysis included descriptive statistical analysis of the age variable and Brinkman index. Static analysis of variable frequency for longer smoking, BMI category, septum deviation and allergic rhinitis. The test of hypothesis was conducted through normality test data with the Shapiro-Wilk test. Hypothesis test for nasal mucociliary transport time differences between the study groups conducted by the unpaired t test if distribution of data was normal, or Mann-Whitney test when the distribution was not normal. Mucociliary transport time difference before and after administration of nasal irrigation in each group will be tested by paired t test when the normal distribution or the Wilcoxon test when the distribution was not normal. Analysis of confounding variables using Pearson Chi-square test, the variables with $p < 0.25$ continued multivariate analysis using logistic regression. The statistical test for nasal mucociliary transport time difference between the study groups were done by Mann-Whitney test. Mucociliary transport time difference before and after giving nasal irrigation to each group was tested by paired t test. The summary of research activities was stated in the Consolidated Report of Trial presented in Fig 1.

3. Results and Discussion

The study was conducted in a population of active smokers at the University of Diponegoro during March to May 2016. Prior to the study, conducted the recording of basic data sample based on inclusion and exclusion criteria used primary data, thus obtained 68 samples of the study. Each sample then conducted a physical examination of the nose and saccharin test. During the study, there were two samples that dropped out because samples could not be contacted by a researcher (loss of follow-up), so the number of samples analyzed were as many as 66 people.

The study sample consisted of two groups. The treatment group (33 people) get the treatment of nasal irrigation once a day for two weeks under the supervision of researchers and the control group (33 people) were not given the treatment for two weeks. Mucociliary transport time checks using saccharin test was done twice, before treatment and after treatment.

The characteristics of study sample are presented in table 1.

Distribution mean age in both groups were homogeneous ($p = 0.824$). BMI of samples, the lowest at 16.4 and the highest at 29.8 with a mean BMI of 22.5 ± 3.23. Distribution group homogeneous BMI in both groups ($p = 0.369$).

Table 1 Characteristics of study sample.

Variables	Groups		*p*
	Treatment (n=33)	Control (n=33)	
Age	21,00 (20-25)	21,00 (18-30)	0,824(1)
BMI categories			
Underweight	4 (12.1%)	2 (6.1%)	0,369(2)
Normal	15 (45.5%)	19 (57.6%)	
Overweight at risk	5 (15.2%)	6 (18.2%)	
Obese I	9 (27.3%)	6 (18.2%)	
Smoking duration			
< 5 years	15 (45.5%)	16 (48.5%)	0,805(3)
> 5 years	18 (54.5%)	17 (51.5%)	
Brinkman Index	48,00 (4-144)	30,00 (2-168)	0,152(1)
Allergic Rhinitis			
Yes	23 (69.7%)	24 (72.7%)	0,786(3)
No	10 (30.3%)	9 (27.3%)	
Septum deviation			
`Yes	20 (60.6%)	8 (24.2%)	0,001(3)
No	13 (39.4%)	25 (75.8%)	

Source: primary data

(1) Mann-Whitney, (2)Kolmogorov Smirnov, (3)Pearson Chi Square

Smoking duration is divided into two, less than 5 years and more than 5 years. The group with the most samples is > 5 years as many as 35 people (53%). Distribution of smoking duration between control and treatment groups were homogeneous (p = 0.805). The entire sample was categorized as light smokers based on Brinkman index. Average Brinkman index in both groups was 41 (2-168) with the highest rates found in the treatment group. Brinkman index distribution in both groups were homogeneous (p = 0.152).

Allergic rhinitis was diagnosed by a questionnaire that has been filled by the sample. The number of samples with allergic rhinitis as many as 47 people (71.2%) with a proportion of 51% of controls and 49% of the treatment group. Distribution of allergic rhinits in both groups were homogeneous (p = 0.786). Septum deviation was divided into two, which had septum deviation and no septum deviation was determined based on a physical examination. A total of 28 samples (42.4%) had septal deviation with the highest proportion found in the treatment group, while 38 samples (57.6%) without septum deviation with the highest proportion found in the control group. Distribution septum deviation in both groups were not homogeneous (p = 0.001).

Intervention analysis was conducted to test the nasal mucociliary transport time difference before and after nasal irrigation. Distributed data of mucociliary transport time in the treatment group was normal, so analysis of mucociliary transport time was done using paired t test. Distribution of data in the control group was not normal, so the data was transformed. Normality test results show that transformed data were normally distributed, then the analysis was done using paired t test.

In the treatment group, there was an abridgment of the average mucociliary transport time after nasal irrigation treatment for two weeks. The analysis shows the value of p = 0.000 (p <0.05), implies that there was a significant abrigment of mucociliary transport time between before and after nasal irrigation for two weeks. In the control group, there was a lengthening of the average mucociliary transport time after two weeks. The analysis showing

the value of p = 0.003 (p < 0.05) implies that there was a significant elongation of mucociliary transport time after two weeks without treatment (Table 2).

The delta of mucociliary transport time represents the difference between mucociliary transport time after treatment and before treatment. The analysis reveals the difference delta of average mucociliary transport time between groups was significant (p = 0.000).

The factors that considered as a confounding variable in this study was the duration of smoking, septum deviation, and allergic rhinitis. The result of the bivariate analysis shows the value of p < 0.05, which indicates that the duration of smoking, septum deviation, and allergic rhinitis have no effect on the reduction of mucociliary transport time (Table 3).

Mucociliary transport system is an active defense system of the nasal cavity against microorganisms (bacteria, viruses, fungi) or other inhaled dangerous substances. The functions of mucociliary transport system is influenced by the quality of the cilia and mucus produced by goblet cells in the epithelium and glands submucosa [8, 16].

Mucociliary transport time is affected by internal and external factors. Age, temperature, physical condition, environment, coexisting diseases, and drugs affect the duration of mucociliary transport time [8, 15]. Elongation of mucociliary transport time found in patients with septal deviation, upper respiratory tract infections, rhinosinusitis, cystic fibrosis, and congenital defects or disruption in the function of cilia [17]. In this study, the factors that may affect the timing of transport mucociliary was minimized by way of equalizing the age, gender, smoking duration in each group, as well as exclude smokers with chronic rhinosinusitis, acute rhinosinusitis, nasal polyps, obesity BMI > 29, and smokers taking medication that could affect mucociliary transport time.

Age affects mucociliary transport time. Age causes changes in the anatomy and physiology of the nasal

Table 2 Mucociliary transport time in the treatment and control group.

Time Mucociliary Transport	n	Max (second)	Min (second)	Average±SD (second)	*p*
Treatment group					
Before Treatment	33	2479	441	1380,64±501,99	0,000(1)
After Treatment Control group	33	2940	241	1111,42±557,06	
Before Treatment	33	2900	629	1330,91±631,6	0,003(1)
After Treatment	33	3479	554	1573,243±704,8	

Source: primary data
(1)Paired T-test

Table 3 The bivariate test results of confounding variables toward the changes of mucociliary transport time.

Variables	The delta of mucociliary transport time		*p*	RR	95% CI	
	Decrease	Not decrease			Down	Up
Smoking duration						
<5 years	16	15	0,805(1)	1,063	0,429	2,971
>5 years	17	18				
Septum deviation						
Yes	18	11	0,083(1)	1,531	0,945	2,482
No	15	22				
Allergic Rhinitis						
Yes	23	24	0,786(1)	0,930	0,554	1,559
No	10	9				

Source: primary data
(1)Pearson Chi Square

mucociliary system. Anatomical changes that occur with ageing include nasal mucosal damage which has accumulated from infections over the years dan ciliary ultrastructural defects. Physiological alterations that could impair mucociliary clearance include abnormally slow or uncoordinated ciliary beatingwhere neighbouring cilia do not beat in a coordinated fashion and in the same direction [18]. Temperature <10 ^{o}C and >45 ^{o}C slow mucociliary transport time [15]. BMI determines a person's health by affecting a variety of physiological parameters. In Tamilselvan study found that the mucociliary transport time prolonged in subjects with BMI > 29 kg/m^2 due to an interruption in the mechanism of mucociliary escalators that predispose to the disease state [19].

Nasal septal deviation may either cause osteomeatal obstruction or may interfere with proper airflow that cause airflow exceeds the capacity of the air moisturizing mucosa function. This process causes an increase in viscosity of the mucus lining nasal, resulting in inefficient performence of cilia [20]. One of the nasal polyp symptoms is increased mucous secretion that can impair mucociliary function. Increased mucous secretion in the nasal polyps are caused by an infection that can sometimes be a complication of nasal polyps, increased mucus area for the formation of polyps, increase in the number of goblet cells / submucosal glands that serve to mucus secretion and release of inflammatory mediators [21].

Patients with chronic rhinosinusitis experienced a cycle of infection and inflammation that constantly cause the loss of cilia and mucus hypervicocity resulting mucociliary [22]. Antigen binds to IgE on mast cells, causing release of mediators such as histamine which is responsible for the production of excessive secretions. Production of excessive secretions causes a slowing of mucociliary transport [23].

We used the saccharine clearance test that has been considered the most accurate technique for obtaining mucociliary clearance time in our study. Mucociliary transport time measurement using saccharin test is one of the measurements to determine the function of mucociliary transport [8, 15]. Elongation time mucociliary transport can occur in smokers through an inflammatory process that can be prevented by administration of nasal irrigation.

Multivariate analysis was conducted by using logistic regression. The variable that was analyzed was the variable with the value of $p < 0.25$ in bivariate test, which was septum deviation. Septum deviation variable has the value of $p = 0.443$ ($p > 0.05$), which means septum deviation as confounding variable does not affect the abridgment mucociliary transport time.

Based on the results of this study, the average mucociliary transport time of smokers was 1355.77 ± 566.67 seconds. These results are corresponding to the study by Baby Court which shows that among smokers occur the elongation of mucociliary transport time (481.2 ± 29.83 seconds) compared to non-smokers (300.32 ± 17.42 seconds) ($p < 0.01$) [8].

The elongation of mucociliary transport time of the smokers is in accordance with Tamashiro's opinion that cigarette smoke contains 5000 chemical substances which are toxic to the respiratory epithelium. Cigarette smoke affects the physiological and structural aspects of nasal. The changes that occurred due to cigarette smoke exposure are ciliary rate decreases, Cl ion transport is delayed, mucus secretion increases, the changes in respiratory epithelial cell morphology, cell viability decreases, and apoptosis of ciliary cells, which lead to deceleration of nasal mucociliary transport time. Cigarette smoke impairs the physiological aspects of nasal, it causes cilia pulse is reduced, the transport of chloride ions is inhibited, change in the mechanism of mucus production. Kotinin as a metabolite of nicotine inhibits epithelial cell cilia beat in vitro. Chronic exposure to cigarette smoke causes respiratory mucous metaplasia, increasing the number and size of goblet cells, so that mucus secretion increases. Cigarette smoke impairs the structural aspects of nasal,

it changes the morphology of epithelium respiratory system, reduces cell viability and apoptosis in respiratory ciliary cells. Exposure to cigarette smoke at low concentrations causes epithelial hyperplasia and a loss of all cilia, whereas high concentrations can cause metaplasia with keratinization epithelium, submucosal thickening, inflammation with neutrophils and mononuclear cell infiltrates [9, 6].

The control group has the elongation of mucociliary transport time by 242.33 ± 403.19 seconds (18.2%) after two weeks without treatment ($p = 0.003$). The elongation of mucociliary transport time that occurs in the control group was caused by chronic cigarette smoke exposure without any precautions in inflammatory process. Inflammatory process of nasal caused by ROS compounds in cigarettes leads to the activation of inflammatory cells such as neutrophils, macrophages, eosinophils infiltration, CD8 T lymphocytes, squamous cell metaplasia [4, 5, 24].

Exposure to cigarette smoke affects the respiratory immune system. ROS contained in the gas components of cigarette smoke induces lipid peroxidation and DNA damage, activating a cascade of intracellular signals epithelial cells leading to activation of proinflammatory cytokines. The secretion of proinflammatory cytokines causes inflammation [25]. Inflammatory cells, such as neutrophils and macrophages are activated to produce proinflammatory cytokines (IL-8, TNF-α, MCP-1, and others). Macrophages were exposed to secondhand smoke lowers the clearance of bacteria through the mechanism of the loss of receptors TLR2 and MARCO. TLR2 is a receptor that serves to recognize and respond to Gram-positive bacteria, while MARCO receptors play a role in the binding of Gram positive and Gram negative. Exposure to tobacco smoke in PMN increases the production of superoxide radicals [4].

In this study, nasal irrigation was done using isotonic saline for 14 days. There is no limit how long a given nasal irrigation. Administration of nasal irrigation for 10 days in patients with acute rhinosinusitis, chronic rhinosinusitis and allergic rhinitis shown to improve mucociliary transport system. Isotonic saline proved to have been widely used for many years and is the cheapest treatment. There are no reports of side effects from use of isotonic saline nasal irrigation. Disadvantages of nasal irrigation with hypertonic saline is hypertonic saline has been reported to cause the release of histamine and increased permeability of tight junctions, which can cause hyperactivity and hypersecretion of the nose [26, 27].

In the treatment group, the average mucociliary transport time before treatment was 1380.64 ± 501.99 seconds which experiences a significant abridgment by 269.21 ± 276.54 seconds (19.5%) after giving nasal irrigation by using isotonic saline for two weeks ($p = 0.000$). Prolonged mucociliary transport time in the treatment group caused by nasal irrigation act as prevention of nasal inflammatory process. These results are corresponding to previous studies that show that nasal irrigation is proven effective to accelerate mucociliary transport time in patients with chronic rhinosinusitis, allergic rhinitis, and irritant rhinitis [14]. There have been no studies on the effectiveness of nasal irrigation in the population of active smokers.

The study by Talbot shows that isotonic saline for nasal irrigation accelerates mucociliary transport time by 2% in a population of healthy adults [28]. Hermelingmeier in his study reports that giving isotonic saline for nasal irrigation for 7 weeks can accelerate mucociliary transport time up to 31% in patients with allergic rhinitis ($p < 0.001$) [10]. Another study by Chodankar proves that nasal irrigation with saline hypertonic for 10 days is confirmed to show an improvement in mucociliary transport time in various pathological conditions of nasal, such as allergic rhinitis ($p = 0.001$), acute rhinosinusitis ($p = 0.000$), while in chronic rhinosinusitis, giving hypertonic or isotonic saline for nasal irrigation shows an improvement of mucociliary transport time up to 85% ($p = 0.000$) [14].

Sodium ions can inhibit the movement of calcium ions on ciliary cells, thus reducing the pulse frequency silia [13]. Calcium plays a role in the regulation of ciliary beat frequency due to the calcium receptor on the cell surface of cilia, the increase of calcium intake will activate acetylcholine and serotonin [29]. Magnesium ions reduce local inflammation by inhibiting the secretion of mediators and degranulation of cells involved in inflammation. At the time of the inflammatory process, zinc and magnesium play a role in reducing respiratory mucosal cells apoptosis [13]. Potassium stimulates the respiratory epithelium improvement through the EGF / EGFR [30]. Bicarbonate ions, acts as a buffer, reducing the viscosity of mucus, thus simplifying the movement of the cilia. Also affect the air flow rate through mechanotransduction cilia which induces a shift in pressure [29]. The effectiveness of nasal irrigation in improving the function of mucociliary in smokers is supported by Bastier's study, who reports that nasal irrigation cleans up mucus, debris, and various airborne contaminants (pathogens, allergens, airborne particles, etc.), reducing the mediator of local proinflammatory, and moisturize the nasal mucosa [13].

The limitations of this study were no adjustment frequency of smoking in the sample before the treatment and on the treatment time, which can affect the measurement of nasal mucociliary transport time before and after treatment. Mucociliary transport time measurement using saccharine test is a subjective examination because the test is affected by samples' testing threshold.

4. Conclusions

On the day fourteen after nasal irrigation there was a significant decreased of the mucociliary transport time than before. There was a significant elongation of mucociliary transport time after two weeks without nasal irrigation. There were significant differences between the time difference nasal mucociliary transport time before and after nasal irrigation in active smokers who use nasal irrigation and active smokers without nasal irrigation.

For further studies on the effects on the nasal irrigation nasal mucociliary transport time have to do with the number of more samples and timing of nasal irrigation is longer. Examination of the nasal mucociliary transport time can be done by using more objective examination, ie rhinoscintigraphy.

Acknowledgments

My biggest gratitude is addressed to Medical Faculty, Diponegoro University and Diponegoro National Hospital that has supported this research, as well as to all those who have participated in the completion of this study.

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