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Influence of general anaesthesias on the changes of bacterial flora in bronchial tree

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The aim of the study was to assess the influence of general anesthesia on bacterial growth in bronchial tree, depending upon the applied method of anesthesia. The artificial airway is the additional gate for respiratory tract infections and mechanical ventilation which can have an influence on postoperative complications such as pneumonia and atelectasis. Patients undergoing 4h surgeries were sampled. Due to selection of anesthetics, volatile or intravenous, patients were divided into groups VGA (volatile general anesthesia) and TIVA (total intravenous anesthesia). Material collected with mini-bronchoalveolar lavage method directly after intubation and just before extubation. In 40% of all patients no bacteria growth was noted in both time points. In VGA group, from the bacteria cultured in 61.9% of patients in first sample, 62.5% of colonies diminished or eradicated, only 6.25% multiplied. In TIVA group 42.9% patients presented bacteria in first sample. All bacteria got reduced. Length of hospitalization preceding surgery (p=0.036) and number of smoked cigarettes (p=0.028) significantly correlated with colonization of bacteria. General anesthesia has no influence on the respiratory tract microorganism contamination and can even favour the eradication of the colonizing bacterial flora.

Key words: Respiratory tract, general anesthesia, contamination.

INTRODUCTION

Natural defensive mechanisms, such as mucociliary transport, lysozyme activity, lactoferrins, macrophages, natural killer (NK) cells, as well as, specific humoral and cell response play significant roles in prevention and control of respiratory system infections (Ficker, 2008). After general anaesthesia of long duration, due to incorrect ventilation and retention of secretion in bronchial tree, the risk of pulmonary infections and atelectasis increases (Sachdev and Napolitano, 2012). Endotracheal intubation can cause mucosal injury, loss of cilia and promotes metaplasia of respiratory epithelium. That artificial respiratory tract is an additional entry of infection. Bacteria reach the lower respiratory tract mainly via aspiration from the upper part of pharynx, as well as leakage of secretion containing bacteria around the sealing collar, which slows down the tracheal flow of mucus. Inhalation of colonized bacteria from oropharynx, sinus cavities, nares, dental plaque can be a reason of postoperative lungs infections (Brusselaers et al., 2013).

Mechanical ventilation disturbs the correct cough reflex, sneezing, and efficient mucociliary transport. The mucociliary clearance rate in bronchial tree is optimal in the temperature of 34 to 40°C. Greater sensitivity of lower respiratory tract to decreased temperature brings about the threat that substitutive ventilation with dry and cold gases may lead to impairment of ciliated epithelium functions. That may promote the development of microorganisms in respiratory tract environment. Anaesthetics, inhalants and intravenous drugs, also affect the movement and function of cilia. The mechanism of impaired cleaning

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of respiratory tract during anaesthesia has been suggested to exist, in the form of inhibition of Cl^- ions secretion and increased stickiness of mucus, caused by inhaled anaesthetics. Propofol, on the other hand, would enhance the activity of cilia by increasing the intracellular concentration of Ca^{2+} ions in cells of respiratory epithelium, stimulation of nitrogen oxide, and production of cGMP (Shirakami et al., 2000).

Some authors report inhibition of inflammatory reaction by anaesthetics being inhalants, or even their bactericidal properties noted in experiments *in vitro* (Molliex et al., 1998; Karabiyik et al., 2007). Among the risk factors for infections of lower respiratory tract in hospital conditions, apart from intubation, mechanical ventilation, surgery performed, one can also list prolonged hospitalization (Niedermann et al., 2005). Dependence has been proven to exist between the aetiology of hospital acquired pneumonia (HAP) and length of hospitalization. In early hospital infections, usually the dominating micro-organisms are those which are sensitive to antibiotics, in late ones the strains that dominate are resistant to treatment (Trouillet, 2012). The responsibility for infections of lower respiratory tract rests with pathogenic microorganisms, such as: Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, Moraxella catarrhalis, Pseudomonas aeruginosa, and in patients with hypoimmunity, also bacteria which colonize upper respiratory tract, such as: Streptococcus viridans, Neisseria species, Corynebacterium species (Ionas et al., 2002). The material for microbiological examinations concerning patients with suspected pulmonary pathology may be obtained by means of BAL (bronchoalveolar lavage) bronchoscopy or other, less invasive, techniques, such BPSB (blinded protected specimen brush) or mini-BAL (mini bronchoalveolar lavage).

The aim of the study was to assess the influence of mechanical ventilation used during general anaesthesia upon bacterial growth in bronchial tree, depending upon the applied method of anaesthesia: inhalation (VGA, volatile general anaesthesia), or purely intravenous administration (TIVA, total intravenous anaesthesia) and their influence on post-operative pneumonia development.

MATERIAL AND METHODS

Having obtained the consent of the Bioethics Committee of Medical University of Silesia in Katowice, Poland, the study comprised a group of 38 patients, operated in the Central University Hospital in Katowice, Poland, between May and November, 2011. Patients who have been qualified for the study met the physical status criteria for classes I and II according to ASA scale, also those patients had the predicted time of general anaesthesia exceeding four hours. Not included in the study have been those patients, whose general physical status was assessed according to ASA as ≥ class III, patients with history of chronic diseases of the respiratory system, namely asthma, COPD (Chronic Obstructive Pulmonary Disease), restrictive lesions, confirmed in spirometry, inflammatory and neoplastic tumours of the lungs. Patients who were currently treated with antibiotics as well as those who received recently antibiotic therapies have been excluded from the study. On the eve of the surgery, patients were consulted by an anaesthesiologist. Patients were informed about the study, potential threats, and gave informed consent for taking part in research study. Due to the selection of anaesthetics, patients have been divided into two groups.

Randomization was performed according to the number of patient's case history. In the VGA group, where patients were anaesthetized before the procedure by means of inhalants, 23 patients were studied, age range 41 to 78 years. In the TIVA group, 15 patients were studied, age range 29 to 66 years. Surgical procedures in that group were performed under general, total intravenous anaesthesia. All patients, 30 minutes before the scheduled procedure, were premedicated with midazolam in doses of 0.1 to 0.15 mg. kg^{-1} orally. After two-minute pre-oxygenation with 100% oxygen, anaesthesia was induced by means of two methods. In the VGA group, the following were used for inducing anaesthesia: midazolam in doses of 0.02 to 0 05 mg.kg^{-1} intravenously (i.v.), fentanyl 1 to 2 µg. kg^{-1} i.v., thiopental in doses of 4 to 5 mg. kg^{-1} i.v. rocuronium 0.8 mg. kg^{-1} i.v. Anaesthesia was sustained by a mixture of 50% oxygen with air and inhaled anaesthetic - sevoflurane (0.8 to 1.0 MAC), and repeated doses of fentanyl 0.1 to 0.2 mg i.v. and rocuronium 0.3 mg. kg^{-1} i.v. In the TIVA group anaesthesia was induced by propofol by means of infusion pump intravenous drop 1.5 to 2 mg. $kg^{-1}h^{-1}$, fentanyl in the dose of 0.1 mg i.v. After the cilial reflex subsided, rocuronium was administered in dose 0.8 mg. kg^{-1} i.v. After intubation anaesthesia was maintained by means of administration of propofol via pump in intravenous drop, at the rate of 6 mg. $kg^{-1}h^{-1}$, and of remifentanil at the rate of 0.05 to 0.25 µg. kg^{-1} $min.^{-1}$ the mixture of oxygen and air was used in proportion of 50/50%. Rocuronium was used for relaxation, in maintenance doses of 0.3 mg. kg^{-1} i.v.

Patients, in the supine position, after intubation were ventilated mechanically in the IPPV (intermittent positive pressure ventilation) mode, applying the volume of 8 ml kg^{-1} and frequency of 8-12 breaths per minute, depending upon end tidal CO_2, which was maintained at the range of 33-38 mmHg.

In order to provide qualitative and quantitative assessment of bacteria, the material from respiratory tracts has been collected twice: directly after induction of anaesthesia and again before the end of anaesthesia that is before extubation. All the procedures concerning tracheal intubation were performed by anaesthesiologist using surgical facemasks and sterile gloves after proper hands hygiene with sterile equipment (face mask, laryngoscope, single-use tracheal tube, single-use filter placed between the patient and the breathing circuit (a new filter for each patient) and standardised staff technique in order to minimise the contamination of tracheal tree. The mini-BAL technique has been used for collecting the material and was performed by the same single operator every time, carrying out a sterile procedure under full aseptic conditions.

The mini-BAL technique applied consisted of "blind" collection of washings from lower respiratory tract. After injecting, via endotracheal tube, of 20 ml of sterile solution of physiological saline, heated to body temperature, the patient was ventilated manually five times, by means of self-reinflating bag. After re-installation of the intrabronchial catheter, through endotracheal tube, the bronchoalveolar washings in the amount of 2 to 5 ml have been collected by means of aspirator directly to sterile test tubes. The material for the first test tube was obtained after intubation and stabilization of ventilation and circulation parameters, whereas the washings for the second test tube were collected after minimum four hours of anaesthesia, directly before extubation. Each test tube was immediately sent to microbiological laboratory for qualitative and quantitative assessment of bacterial flora. The time elapsing between collection of material and beginning of culture did not exceed 15 min. In laboratory of Central University Hospital, Katowice, Poland, the samples were processed in line with the generally accepted procedures mandatory in a microbiological laboratory. The material

Table 1. Data characterizing studied patients. Values are number (proportion) or mean (SD); n, number of patients.

Characteristic		Total number of patients	VGA group	TIVA group	p value
Patients		n=35	n=21	n=14	
Sex	Female	n=21 (60%)	n=12 (57.1%)	n=9 (64.3%)	
	Male	n=14 (40%)	n=9 (42.9%)	n=5 (35.7%)	
Average age		57.0 (11.31) (range 29-78)	59.81 (10.38) (range 41-78)	52.71 (11.67) (range 29-66)	p=0.21
Average BMI		24.99 (3.18)	24.83 (3.15)	25.22 (3.33)	
BMI 20-25		n=21	n=12	n=9	p=0.69
BMI 25-30		n=11	n=7	n=4	
BMI >30		n=3	n=2	n=1	
Smokers		n=12 (34.2%)	n=7 (33.3%)	n=5 (35.7%)	p=0.99
Number of smoked cigarettes		4.43 (7.25)	4.52 (7.40)	4.29 (7.30)	
Average number of days of hospitalization before the operation		9.31 (7.56) (range 1-32)	6.90 (6.46) (range 1-31)	12.93 (7.77) (range 2-32)	p=0.001
Type of operation					
Craniotomy		n=20	n=10	n=10	
Laparotomy		n=15	n=11	n=4	

obtained was cultured with use inoculating loop onto blood agar, chocolate agar, Chapman and MacConkey agar plates. Plates were incubated in the temperature of 35 to 37°C, in aerobic conditions. Then read after 48 h. Plates were visualized for growth by two different observers. CFU –colony forming unit was based on the laboratory formula: CFU= n × v where n stands for number of colony on space of plate, v means inverse of inoculating loop volume in 1 ml. Results more than 10^4 CFU implied infection of lower respiratory tract, results less than 10^4 CFU - bacterial colonization.

The statistical analysis has been prepared using the Statistica v8.0 package, by StatSoft. The graphic illustration of results has been prepared mainly by means of Statistica software, partly also by means of the graphics editor contained in the MS Office 2007 package. Verification of hypotheses concerning normal distribution of variables has been carried out using Kolmogorov-Smirnov test, and Shapiro-Wilk test. For variables having distribution consistent with normal distribution, the assessment of significance of differences between groups has been made by means of t-Student test. The use of that test required that the condition of variance homogeneity was met, which has been attained using Snedecor test. The significance of differences for variables, the distribution of which did not meet the condition of normality has been assessed by means of rank sum test by U Mann-Whitney. For analysis of significance of differences between groups resulting from division of the investigated sample, in accordance with a determined criterion for one variable in relation to another variable, the independence chi-squared test has been used. The condition required for the application of that test is that the number in each class established as a result of sample division must be greater than 8. For those subgroups, where the size of the group was smaller, the Yates's chi-squared independence test was used. In selected cases, for 2×2 tables, the Fisher's exact test has been used, while in case of tables of larger size that is, the test of highest likelihood. P value < 0.05 was considered statistically significant. Power analysis calculation was conduct using G Power software. The sample size calculation was based on a 95% confidence level with a power of 80%.

RESULTS

From the total of 38 patients, three patients have been excluded from the study. Two of them due to too short operation time, not exceeding two hours, one because of difficult intubation and early death caused by circulatory insufficiency, within 24 h after the procedure. 35 patients who have been subject to final analysis are characterized in Table 1.

Of the 35 patients studied, 14 (40%) no micro-organisms have been isolated in both points in time assumed for material collection. In the VGA group that amounted 38.1% of patients (n=8), in the TIVA group to 57.1% of cases (n=8).

In the VGA group, the average time of general anaesthesia amounted to 239.90 min. The most frequently isolated flora was alpha-hemolytic Streptococcus. The list of micro-organisms isolated in washings obtained is provided in Table 2.

In 13 patients (61.9%), on material collected before the operation micro-organisms have been cultured. The respiratory tracts of nine patients were colonized by one species of bacteria, in four patients by two or more species of micro-organisms. Of the bacteria cultured on preoperative material 62.5% of colonies diminished or

Table 2. Bacteria isolated from lower respiratory tract in the VGA group.

Case	Bacteria isolated	Number of colonies ml^{-1} in pre-surgery material, directly after intubation	Number of colonies ml^{-1} in post-surgery material directly before extubation
1.	*Streptococcus alpha-hemolytic*	10^4	10^4
2.	*Streptococcus alpha-hemolyti*	10^4	none
3.	*Streptococcus alpha-hemolytic*	10^3	10^3
4.	*Streptococcus alpha-hemolytic*	10^3	10^3
	Neisseria species	10^3	none
	Staphylococcus coagulase-negative	10^3	10^3
5.	*Streptococcus alpha-hemolytic*	10^3	none
	Moraxella species	10^3	none
6.	*Streptococcus alpha-hemolytic*	10^3	none
7.	*Streptococcus alpha-hemolytic*	10^3	none
8.	*Streptococcus alpha-hemolytic*	10^3	none
9.	*Streptococcus pneumonia*	10^3	10^6
	Klebsiella oxytoca	none	10^3
	Haemophilus influenzae	none	10^3
10.	*Streptococcus pneumoniae*	10^3	10^3
11.	*Streptococcus pneumoniae*	10^3	none
12.	*Staphylococcus epidermidis*	10^4	10^3
	Acinetobacter calcoaceticus baumani complex	none	10^3
13.	*Corynebacterium species*	10^3	none

Table 3. Bacteria isolated from lower respiratory tract in the TIVA group.

Case	Bacteria isolated	Number of colonies ml^{-1} in pre-surgery material, directly after intubation	Number of colonies ml^{-1} in post-surgery material, directly before extubation
1.	*Streptococcus pneumoniae*	10^6	10^3
	Acinetobacter calcoaceticus baumanii complex	none	10^4
2.	*Streptococcus pneumoniae*	10^5	10^3
3.	*Streptococcus alpha-hemolytic*	10^4	10^3
4.	*Streptococcus alpha-hemolytic*	10^4	none
	Moraxella species	10^3	none
5.	*Serratia marcescens*	10^4	none
6.	*Haemophilus influenzae*	10^3	none

eradicated, 31.25% of colonies remained unchanged, and 6.25% multiplied. In one patient bacteria culture increased to bacterial index level which may signify infection. In two patients, sample two revealed additional bacterial strains, which were not present in the first sample, having a bacterial index of 10^3 CFU.

In the TIVA group the average time of general anaesthesia amounted to 247.14 min. The bacteria most often isolated in the material analysed are presented in Table 3. In six cases (42.9%), bacteria were cultured from bronchoalveolar washings obtained just after intubation. In four patients the respiratory tracts were colonised by one species of bacteria, in two cases by two strains of bacteria. In two patients the titre of sample one indicated infection, however, bacterial colonies were reduced after the anaesthesia ended. The bacterial index of bacteria isolated in samples collected after intubation got reduced in all cases. 57.1% of bacterial colonies underwent total eradication. In one patient in sample two additional bacterial colonies were detected, in the amount of 10^4 CFU, which were not present in sample one.

In the analysis, to determine the predictors of bronchial bacterial colonization we have assessed variables: age, sex, BMI, smoking habits, hospitalization time preceding surgery. Three of these variables proved to be statistically significant in analysed VGA group: BMI (p=0,048)

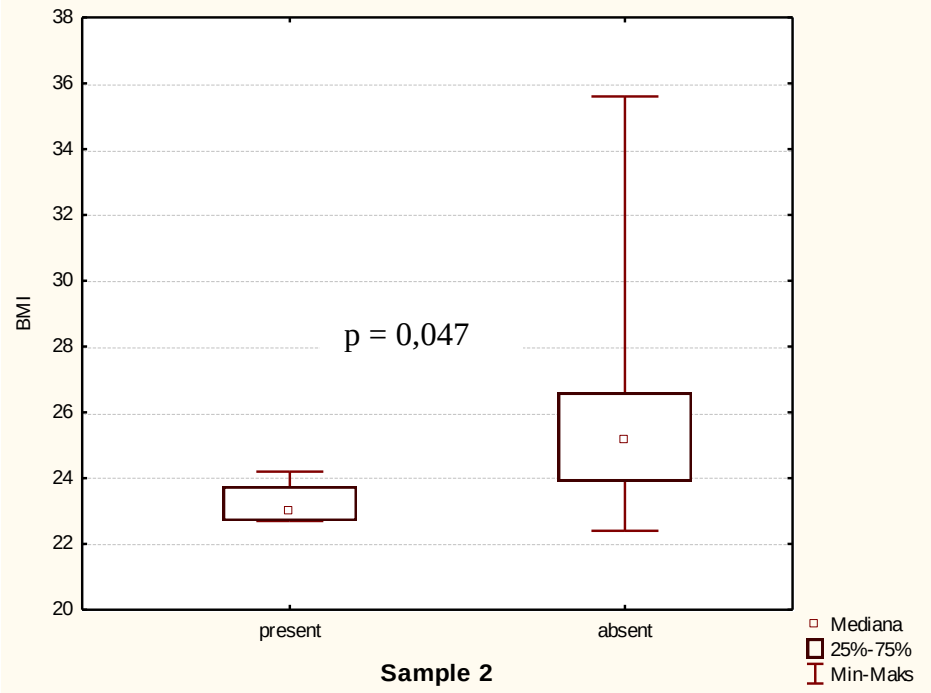

Figure 1. Comparison of bacteria presence in sample 2 according to BMI.

(Figure 1), hospitalization time preceding surgery (p = 0,036) and number of smoking cigarettes (p=0,028). Bacteria were cultured in smokers as well as non-smokers in both samples. Of the patients who had no bacteria cultured in samples more often were non-smoking patients (Figure 2 and 3). There was significant difference between patients smoking more cigarettes in comparison to patients smoking less in VGA group (Figure 4).

The complication in the form of bronchial spasm, which appeared immediately after administration of physiological saline and insertion of catheter to bronchial tree, occurred in nine patients (25.7%). Higher peak and plateau pressures were noted in respiratory tract, as well as changes on auscultation, in the form of wheezing, dry rales and absence of vesicular murmur. Bronchial spasm usually subsided after five to ten minutes after administration of 100 to 300 mg hydrocortison i.v. In two cases there was a significant drop of blood saturation to 84 and 90%, in case of ventilation with 100% oxygen. The patients required intravenous administration of aminophillin, repeated removal by sucking from intubation tube, and temporary change of ventilation mode to PCV (pressure controlled ventilation) mode.

DISCUSSION

Bacterial colonization of lower respiratory tract has been noted in 54.3% of patients in our study. Micro-organisms that have been most often isolated were Streptococcus alpha-hemolytic (37% of colonies cultured) and Streptococcus pneumoniae (18.5% of colonies cultured). As opposed to strains of bacteria, which dominate in VAP (ventilator associated-pneumonia) - the Gram negative bacteria, Gram positive bacteria dominated in our material. Probably time factor might play an important role there, especially the length of hospitalization preceding the operation. It is well known that prior hospitalization is a risk factor of bacterial colonization. Complications, in the form of post-operative pneumonia, depend also on the underlying disease and type of operation performed (Ficker, 2008). In our study, patients had the procedures of laparotomy and craniotomy. In such cases, suppression of the cough reflex, for example to prevent the increase of intracranial pressure or to restrain pain level might have promoted the retention of secretion in bronchial tree, and pulmonary infection. Decreased BMI<25 was also an independent risk factor for bronchial colonization. That conclusion differs from those noted in literature (Ionas et al., 2002). Despite the existing pneumonia risk factors in VGA and TIVA groups, no infections of lower respiratory tract have been recorded.

The amount of bacteria isolated in both groups, in the majority of cases decreased in relation to the initial bacteriological index. In literature the influence of inhalational anaesthetics: halothane, enflurane, isoflurane, as well as intravenous anesthetics upon the movement of cilia, and transport of mucus were presented. Inhalational anesthetics would inhibit ciliary movement and increase the volume of retained mucus. Propofol, due to the properties stimulating ciliary movement and influencing the mechanisms of secretion liquefaction would appear a safer drug in case of patients with history of pulmonary pathology

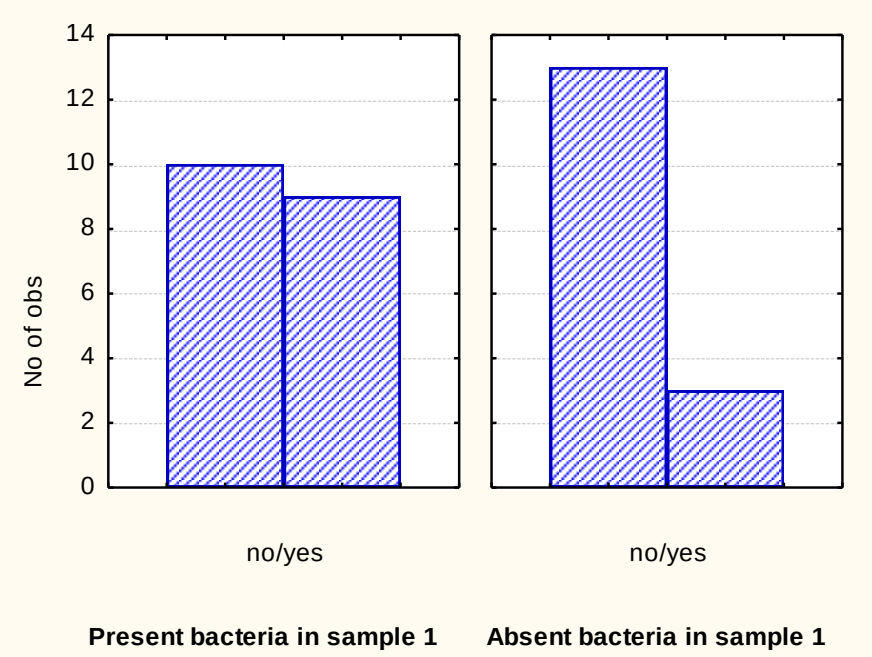

Figure 2. Comparison of bacteria presence in sample 1 according to smoking. No, non-smokers; Yes, smokers.

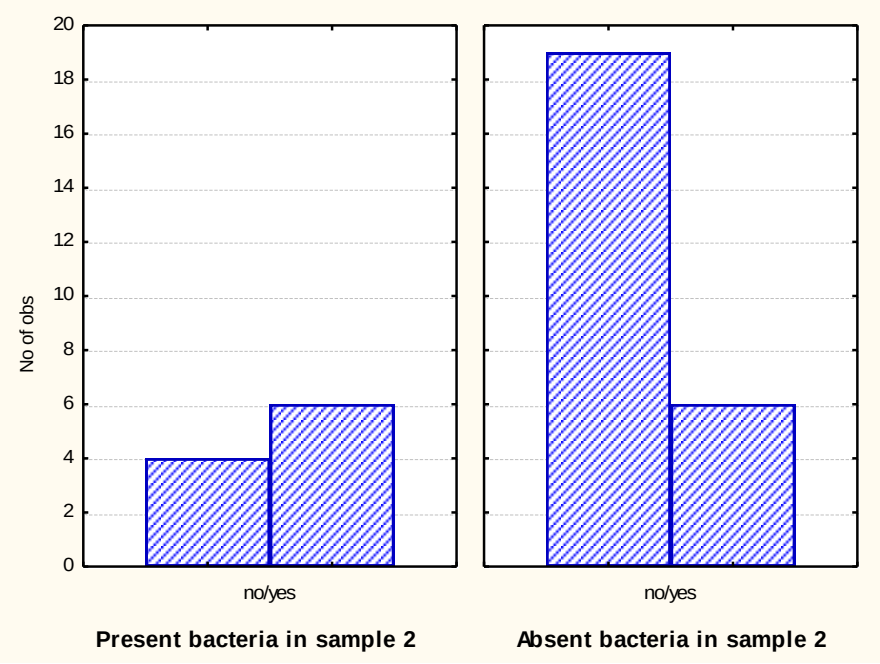

Figure 3. Comparison of bacteria presence in sample 2 according to smoking. No, non-smokers; Yes, smokers.

(Ledowski et al., 2006). In his study, Molliex in *in vitro* conditions demonstrated a direct influence of inhalational general anesthesia drugs upon bacterial cells of the Pseudomonas aeruginosa strain, a pathogen participating in hospital-acquired pneumonia. The author has proven a maximum inhibition of bacterial cultures after four hours of exposure to isoflurane, enflurane, halothane, greater in the concentration of anesthetic equal to

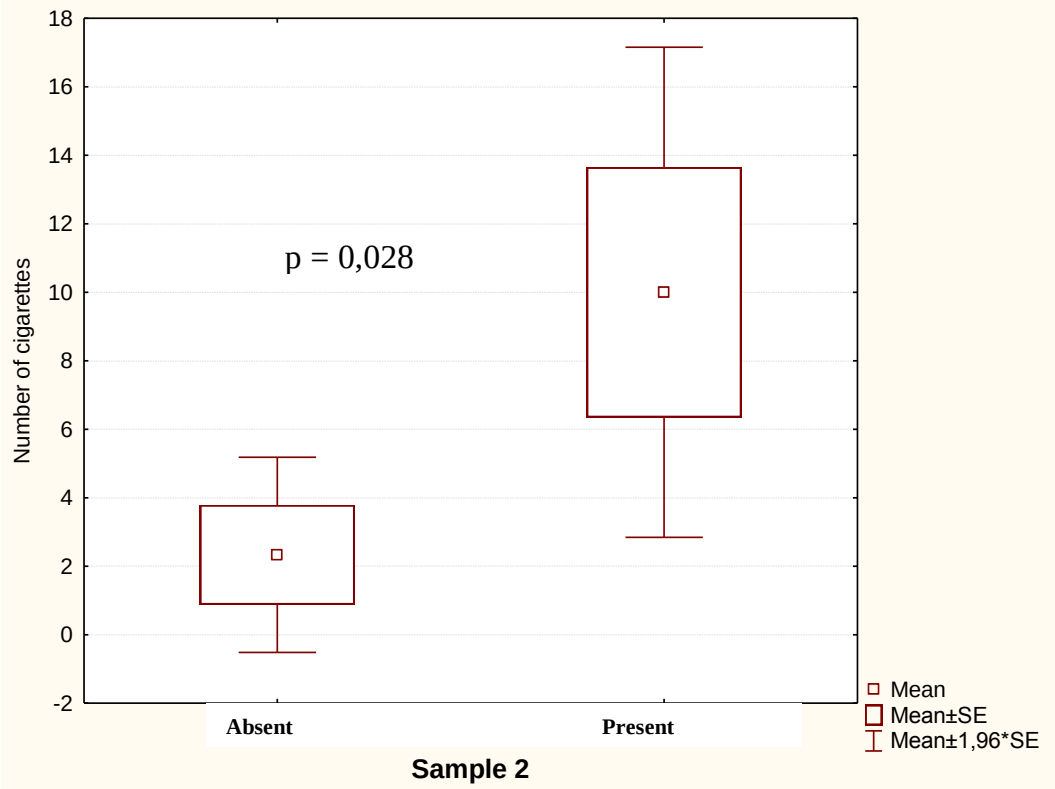

Figure 4. Comparison of bacteria presence in sample 2 according to number of cigarettes smoked per day.

2,0 MAC, in comparison with 1,0 MAC (Molliex et al., 1998).

Only in one patient, in the material examined was there an increase of bacteria to the value of 10^6 CFU and cultures of additional species from the family Klebsiella and Haemophilus influenzae. Suspicion of pneumonia, in accordance with the latest recommendations of American Thoracic Society, may be had on the basis of the following typical lesions detected in lung radiography, and minimum two of the following three criteria: body temperature, bronchial secretion, and leucocytosis. (American Thoracic Society, 2005). On the fifth day after operation, each patient participating in the project has been examined for parameters of inflammation - physical examination, leukocyte count, and taking body temperature. The woman patient whose bacteriological index could have indicated lung infection has been referred to her original ward and put under detailed observation. In the end, without signs of infection (no changes detected above lung fields on auscultation, leucocytosis, or elevated temperature). The woman has been discharged home.

Most studies concerning bacterial colonization of respiratory tract are devoted to patients with chronic obstructive pulmonary disease (COPD) (Domenech et al., 2012; King et al., 2013; Marin et al., 2012). A positive result of culture in one of our woman-patients, a compulsive smoker (20 cigarettes a day) may be considered colonization of respiratory tract.

In order to avoid the drawbacks of bronchoscopy, such as steep cost, side effects, experience required because of the performance technique, a cheaper and quicker mini-BAL method has been used. The method labelled as mini-BAL is an alternative for traditional bronchoscopy. Examination sensitivity is assessed at about 82% (63 to 100%), whereas the specificity compared with that of a bronchoscopy is assessed at 66 to 96% (Campbell, 2000).

Conclusion

To sum up, none of the patients participating in the study manifested marks of pneumonia in the postoperative period. It appears that general anesthesia does not have influence upon the increase of bacterial contamination of bronchial tree, and may even promote eradication of the colonizing bacterial flora. In the existing literature, there is no explicit standpoint concerning the influence of general anesthesia with the use of inhalants or intravenous anesthetics upon changes of bacterial flora in bronchial tree, especially in clinical aspect. However, it is too early to draw ultimate conclusions. The study reported here should be treated as preliminary communication.

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