Use of Azelastine and Sodium Chloride Spray for Prevention of Sinusitis in ICU Admitted Patients: A Randomized Clinical Trial

Abstract

Background: Nosocomial sinusitis is a common and less attended complication in patients admitted to intensive care units (ICU). It can cause several problems, such as prolongation of hospitalization, comorbidity, and mortality in patients. The present study aimed to evaluate the effect of azelastine (second-generation antihistamine) and sodium chloride spray on sinusitis prevention in ICU admitted patients. Methods: In this randomized, open-label, and parallel clinical trial a total of 126 patients were enrolled (63 patients per arm). Finally, 121 patients (61 patients in the control group and 60 patients in the treatment group) completed the study, and 120 patients entered the final analysis. In the treatment group, during 24 h after the insertion of nasogastric tube azelastine and sodium chloride sprays were administered (one puff from each spray every 12 h) while no intervention was conducted in the control group. Primary and secondary end-points were evaluated within 10 days of the study period. Results: The incidence of sinusitis and pneumonia (18.3% and 16.6% in the control group compared to 8.3% and 3.3% in the treatment group, respectively) in the treatment group showed a decreasing trend; however, only the difference of pneumonia was statistically significant between groups (P = 0.03). In addition to the clinical pulmonary infection score, nasal and tracheal secretions were significantly improved in the treatment group (P = 0.03, P < 0.001, and P = 0.01, respectively). Conclusions: The findings of the present study offer an inexpensive, low-risk, and efficacious intervention for the prevention of upper respiratory tract infections in ICU patients.

Keywords: Intensive care unit, histamine H1 antagonists, sinusitis, sodium chloride

Introduction

Hospital-acquired sinusitis is one of the common and less be presented causes of fever in intensive care unit (ICU) patients. According to the literature, the incidence of this problem has been reported between 1 and 53 percent based on different clinical diagnostic criteria and conditions. The presence of a nasogastric tube (NG tube) as well as mechanical ventilation are two main risk factors for nosocomial sinusitis in patients. These factors are influential in the occurrence of sinusitis regardless of usage time. Several studies have shown that the treatment of sinusitis in patients can improve symptoms, including fever of unknown origin, within 24 to 48 h. However, limited studies have been conducted on the prevention of sinusitis. Using decongestants (such as xylometazoline) in combination with nasal corticosteroid (budesonide) have been effective in the prevention of nosocomial sinusitis but had little impact on secondary infections. Use of topical antibiotics along with chlorhexidine mouthwash and body wash reduces the risk of sinusitis and subsequently pneumonia. Nevertheless, due to the risk of microbial resistance, this procedure is not highly recommended.

In recent years, there are some theories, which express a relationship between allergic sinusitis and acute or chronic bacterial sinusitis. In some clinical trials, the inflammatory mechanisms involved in the development of acute bacterial sinusitis and its progression have been studied. In nasal lavage examination of acute bacterial rhinosinusitis (ARS)’s patients, increased in different inflammatory markers such as interleukin-1, interleukin-6, interleukin-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) has been observed in comparison with the control group. Regarding the mechanisms proposed in this field, it

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seems that the use of compounds with preventive effect on initiation or progression of inflammatory processes can be considered in the prevention of sinusitis. Azelastine is a second-generation antihistamine that is used topically for the treatment of allergic rhinitis. Compared to systemic antihistamines because of local effects with low systemic bioavailability, azelastine causes fewer anticholinergic complications such as constipation and dry mouth for patients. In a previous study, azelastine spray has shown the efficacy for the reduction of inflammatory cytokines. Recent studies have shown that combination therapy with sodium chloride increases the efficacy of other sinusitis treatment. However, the use of sodium chloride alone did not affect the clearance of mucosal secretions. Considering the faster onset of action of azelastine compared to corticosteroids, and its higher efficacy than mometasone, in addition to its effect on proinflammatory cytokines, azelastine application in combination to sodium chloride spray seems to be a good option for preventing sinusitis in hospitalized patients.

Due to the similarity of infectious microorganisms in hospitalized sinusitis and pneumonia and the determined mechanisms of sinusitis, the present study aimed to evaluate the effect of azelastine and sodium chloride spray on the incidence of sinusitis, pneumonia, and other indicators of respiratory tract infection.

Methods

Study design and participants

The present randomized, parallel, and open-label trial was conducted in patients admitted to ICU at Imam Reza Hospital between September 2017 to September 2018. Patients aged more than 18 years old admitted to the medical intensive care unit, during the first 24 h after NG tube insertion were randomized into either the treatment or control group. Patients with the following criteria were excluded from the study: trauma to the head and face or anatomical abnormalities preventing NG tube placement; the history of sinusitis in the last three months; leukopenia (WBC <3500/mL); coagulation disorders (PLT <100000/mL, INR >1.5 or PTT more than two times higher than normal); the presence of a tumor in the patient’s head and neck.

The present study was approved by the ethics committee of Aja University of Medical Sciences with IR.AJAUMS.REC.1396.72 identifier, and it was conducted in accordance with the Helsinki Declaration principles. The informed consent was obtained from the patient or his/her legal guardian before initiating any study-related procedures. This study was registered with (IRCT. ir) Iranian Registry of Clinical Trials, trial number IRCT20190312043037N1.

Sample size and randomization

The sample size of this study was calculated based on the incidence of the disease and previous studies. By considering sinusitis incidence equal to 38%, treatment difference of 20%, and α = 0.05, the sample size was calculated 60 patients in each group to achieve 80% power. The test statistic used is the one-sided Z test with un-pooled variance. Assuming a 5% drop-out rate, results in 126 patient’s requirement for enrollment. Complete randomization was performed using the simple randomization method, bypass software version 11. Patients assigned to the treatment or control group with a 1:1 allocation ratio.

Intervention

Eligible adult patients admitted to ICU within 24 h of NG tube insertion were randomized into treatment or control group. Patients were evaluated by the physician for the symptoms of sinusitis including throat secretions, nasal discharge, painful and swollen sinuses (if possible), fever, and leukocytosis. Patients’ background information including age, sex, underlying illnesses, concomitant medications, liver and kidney function, CBC, temperature, vital signs, and living conditions were registered. In the treatment group, one puff of 0.15% azelastine spray and 0.65% sodium chloride spray was administered every 12 h per nostril while patients in the control group received routine care. Patients in both groups were followed up for 10 days. If the patient was discharged before 10 days or if the NG tube had to be removed, a secondary check was done earlier than 10 days while the patient should remain in the study at least for 7 days. In the case of patient exclusion before the 7th day of the study, patient data were not included in the final analysis. During the study and at its end (day 10), postnasal drip, nasal discharge, fever, and leukocytosis were monitored and recorded daily. In case there was a high clinical suspicion of sinusitis in patients; defined as fever of unknown origin, purulent discharge at the back of the throat, or exacerbation of fever while the patient is on antibiotic treatment and there is no other reason for the fever, CT scan of paranasal sinuses was performed for the confirmation of sinusitis diagnosis. In case of high fever (above 38.3°C), the culture of blood, urine, and tracheal secretions were performed, and if an infection was detected, appropriate antibiotics were prescribed for the patient.

The primary end-point of this study was to investigate the incidence of sinusitis confirmed by imaging between the two treatment groups. The secondary end-points were to compare the incidence of pneumonia, changes in clinical pulmonary infection score (CPIS) score, WBC, temperature, tracheal and nasal secretions, and finally, the isolated organisms from the patients’ tracheal secretions. In order to facilitate the evaluation of patients’ tracheal and nasal secretions, purulent secretions were scored from 0 to
Statistical analyses
The normality of data was checked and confirmed using the Kolmogorov–Smirnov test. Analysis of continuous variables with normal distribution was performed with independent sample t-test for between groups assessment and paired t-test for within-group evaluation. Categorical variables between the two groups were compared by the Chi-square test. Besides, the longitudinal data were analyzed using a generalized estimating equation (GEE) model in the effectiveness analysis set. The significance level was considered as P value less than 0.05. All analysis was done using Statistical Package for Social Sciences (version 18.0; SPSS Inc., Chicago, IL, USA).

Results
A total of 126 patients were enrolled in this study. Of these, three patients in the treatment group and two patients in the control group left the study before the seventh day. In the final analysis, 75 men and 45 women were examined. One patient was discarded from the final analysis due to missing data. The consort diagram of the study is shown in Figure 1.

As is summarized in Table 1, there was no statistically significant difference between groups regarding the baseline information of patients including age, gender, and CPIS score.

The primary end-point of this study that was to investigate the incidence of sinusitis in both groups indicates the effectiveness of the treatment regimen in the studied patients. The percentage of patients that after evaluation of clinical symptoms and imaging had sinusitis was 8.3% and 18.3% in the treatment and control group. Although the difference was not statistically significant (P = 0.11), a lower incidence rate was noted in the treatment arm.

The incidence of pneumonia on the 10th day of study based on the CPIS index was lower in the treatment group compared to the control group (3.3% vs. 16.6%, P = 0.03). Besides, the decreasing trend of this score on day 10 compared to the first day of the study, was significantly (P = 0.03) more in the treatment group compared to the control group. In the treatment group mean CPIS score decreased from 3.68 ± 2.81 to 3.02 ± 2.23 during the study (P = 0.15) while in the control group changes were less apparent from 3.68 ± 2.33 to 3.62 ± 2.48 (P = 0.88). Changes in nasal purulent secretions and tracheal secretions in the treatment group were significantly better than the control
group ($P < 0.001$, and $P = 0.01$; respectively). In the evaluation of both nasal and tracheal secretions score, the rate of discharge in the treatment group had a decreasing trend ($P = 0.22$) and ($P = 0.32$), respectively. While in the control group, the rate of discharge increased moderately. In control group nasal secretion score increased ($P = 0.045$) and also tracheal secretion score showed increasing trend ($P = 0.4$). All data has been shown as mean ± SD. Results of within and between groups data have been shown in Tables 2 and 3, respectively.

The trend of WBC change and temperature is shown in Figure 2. The changes in these indices did not differ significantly between the two groups. The longitudinal analysis of these indices by the GEE method indicates their stability in both groups during the study ($P = 0.39$ and $P = 0.97$, respectively).

The microorganisms found after the culture of tracheal secretions are listed in Table 4. The positive culture was lower in the treatment group (57%) compared to the control group (70%) with no significant statistical difference ($P = 0.13$). In addition, gram-negative microorganisms were less common in the microbial culture of the treatment group compared to the control group (40% vs. 52%); however, the difference was not statistically significant ($P = 0.19$).

### Table 1: Baseline demographic and variables data

| Variable                  | Treatment Group $n=60$ | Control Group $n=60$ | $P$   |
|---------------------------|------------------------|----------------------|-------|
| Sex N (%)                 |                         |                      |       |
| Male                      | 41 (68.33%)            | 34 (56.67%)          | 0.19**|
| Female                    | 19 (31.67%)            | 26 (43.33%)          |       |
| Age (year)                | 72.33±13.36            | 74.30±10.75          | 0.38* |
| Weight (kilogram)         | 71±18.51               | 72.67±10             | 0.83* |
| Temperature (°C)          | 37.31±0.48             | 37.38±0.46           | 0.42* |
| WBC (count/ml) × 1000     | 9.68±5.26              | 10.68±5.66           | 0.32* |
| Mean arterial pressure (MAP) (mmHg) | 97.63±16.60            | 101.63±14.16         | 0.16* |
| Nasal secretion score     | 2.23±1.41              | 2.07±1.27            | 0.50* |
| Tracheal secretion score  | 2.25±1.39              | 2.25±1.39            | 0.99* |
| CPIS score                | 3.68±2.81              | 3.68±2.33            | 0.99* |

*Data are shown as Mean±SD and analyzed by independent $t$-test. **Data are shown as number (percentage) and analyzed by Chi square test

### Table 2: Within group comparison of CPIS score, nasal and tracheal secretion between last day and baseline

| Variable                  | Treatment group $n=60$ | Control group $n=60$ | $P$   |
|---------------------------|------------------------|----------------------|-------|
| CPIS score (baseline)     | 3.68±2.81              | 3.68±2.33            | 0.88  |
| CPIS score (last day)     | 3.02±2.23              | 3.62±2.48            |       |
| Nasal secretion score (baseline) | 2.23±1.41              | 2.07±1.27            | 0.045 |
| Nasal secretion score (last day) | 1.93±1.26              | 2.52±1.16            |       |
| Tracheal secretion score (baseline) | 2.25±1.39              | 2.25±1.39            | 0.4   |
| Tracheal secretion score (last day) | 2.00±1.37              | 2.47±1.40            |       |

*Data are shown as Mean±SD and analyzed by paired $t$-test

### Table 3: Between groups comparison of change in CPIS score, nasal and tracheal secretion from baseline to last day

| Variable                  | Treatment group $n=60$ | Control group $n=60$ | $P$   |
|---------------------------|------------------------|----------------------|-------|
| Change in CPIS score      | -0.67±1.55             | -0.07±1.41           | 0.03* |
| Change in nasal secretion | -0.30±0.93             | 0.45±1.02            | <0.001*|
| Change in tracheal secretion | -0.25±1.00             | 0.22±0.96            | 0.01* |

*Data are shown as Mean±SD and analyzed by independent $t$-test

### Table 4: Tracheal secretion culture result during study

| Culture                   | Treatment group $n=60$ | Control group $n=60$ | $P$   |
|---------------------------|------------------------|----------------------|-------|
| Methicillin-resistant     | 7 (11.67%)             | 4 (6.67%)            | 0.47* |
| Staphylococcus aureus     | 8 (13.33%)             | 13 (21.67%)          |       |
| Pseudomonas aeruginosa    | 8 (13.33%)             | 13 (21.67%)          |       |
| Escherichia. coli         | 4 (6.67%)              | 5 (8.33%)            |       |
| Enterococcus              | 3 (5.00%)              | 5 (8.33%)            |       |
| Klebsiella pneumoniae     | 8 (13.33%)             | 8 (13.33%)           |       |
| Acinetobacter baumannii   | 1 (1.67%)              | 0 (0.00%)            |       |
| Streptococcus hemolytic   | 3 (5.00%)              | 7 (11.67%)           |       |

*Data are shown as number (percentage) and analyzed by Chi square test
Discussion

In this randomized, parallel, and open-label study in patients who were admitted to ICU and had NG tube, the effect of azelastine and sodium chloride sprays on the prevention of sinusitis was investigated. The primary end-point of this study was to investigate the effect of the mentioned regimen on reducing the incidence of sinusitis in high-risk patients. Other outcomes that have been studied in this study included a reduction in the incidence of pneumonia and the symptoms of sinusitis and respiratory tract infections, as discussed below.

The results of the study showed that the incidence of sinusitis confirmed with imaging was lower in patients in the treatment group rather than the control group while in the control group it was similar to previous studies without prevention. The decrease in the incidence of sinusitis was associated with a decrease in the incidence of pneumonia in the treatment group. In addition, the treatment regimen reduced the positive culture of tracheal discharges as well as the positive culture of gram-negative microorganisms, which is one of the medical challenges in hospitalized patients.

Several studies have investigated the incidence of sinusitis in hospitalized patients. Van Zanten et al. studying the incidence of sinusitis as a cause of fever in patients undergoing mechanical ventilation in ICU, showed that the incidence of fever caused by sinusitis as the main and secondary causes was 16% and 13%, respectively.

In a meta-analysis by Agrafiotis et al. that evaluated the incidence of sinusitis in patients undergoing mechanical ventilation in various studies, sinusitis was reported in 27% of patients and was the cause of 25% of fevers of unknown origin. Based on different clinical diagnostic criteria, the risk of sinusitis in patients admitted to ICU was reported between 1 and 53 percent in this study. Therefore, it can be argued that sinusitis is one of the lesser studied and common infections in ICU. Measures to prevent sinusitis can have a significant impact on ICU patients. In the present study, the incidence of sinusitis in the control group was about 18%, which is largely similar to previous studies. While in the treatment group, a decrease in the incidence of sinusitis was observed, and it seems that the regimen used may reduce the incidence of sinusitis in the studied patients.

Limited strategies for prevention of sinusitis have been evaluated in previous studies, which has been accompanied by practical restrictions. Camus et al. investigated the use of different regimens in the prevention of respiratory infections in patients with mechanical ventilation. These regimens included topical polymyxin/tobramycin (or placebo) and intranasal mupirocin plus chlorhexidine body wash, and using a topical placebo and body wash soap. The combined regimen was the only effective regimen in reducing the risk of infections, including sinusitis. It is noteworthy that using antibiotic decontamination regimens is associated with an increased risk of microbial resistance and other infections other than pneumonia.

In another study, Pneumatikos et al. suggested that using xylocaine and budesonide reduces the risk of sinusitis in patients admitted to ICU. However, it should be considered that using inhaled corticosteroid was remarked as a risk factor for respiratory fungal infections and this type of infection is common in patients with sinusitis.

Previous studies have shown that inflammatory reactions occur in the development of acute and chronic microbial sinusitis. Controlling and reducing inflammatory factors can, therefore, improve sinusoidal emptying and reduce the risk of sinusitis. On the other hand, in the case of sinusitis, it helps to drain the sinuses more easily and helps to control the infection. In one study evaluation of azelastine spray, fluticasone nasal spray, and their combination effects on inflammatory markers have shown the efficacy of both drugs on the reduction of inflammatory indices such as interleukin-6, interleukin-8, GM-CSF, and eosinophil survival time while the combination regime had the most effect. According to the results of this study, azelastine not only works on histamine receptor but also can control and reduce other inflammatory mediators. In other studies that evaluated the effect of different local compounds on the treatment of acute bacterial sinusitis, the administration of isotonic sodium chloride monotherapy did no affect on mucociliary clearance. However, the addition of isotonic saline along with nasal corticosteroids or routine care had an increased effect on the improvement of patient symptoms. As mentioned above Azelastine can effectively decrease inflammatory factors such as interleukins and sodium chloride irrigation also has an additive effect in the treatment of sinusitis.

Considering the inflammatory mechanisms involved in sinusitis and the effects of the mentioned drugs, the combination regimen has been used. In the present study, using intranasal sodium chloride spray and topical antihistamines in the treatment group lowered the incidence of sinusitis by less than half compared to the control group. Our intervention had a positive impact on the prevention of sinusitis within 10 days of admission to ICU; however, the difference between groups was not statistically significant. In contrary to the previous studies, the treatment regimen in this study did not increase the risk of infection and microbial resistance.

One of the important effects of sinusitis prevention is the risk reduction of other respiratory infections, such as pneumonia. In Camus and Pneumatikos studies, the incidence of pneumonia has been investigated as a secondary end-point. In both studies, reduction of sinusitis was associated with a reduction in the risk of pneumonia.

In the present study, the incidence of pneumonia was lower in the treatment group compared with the control group. This can be attributed to the reduced colonization of microorganisms in the respiratory tract and easier discharge.
of sinuses in the patients. Due to the high mortality rate of pneumonia in ICU admitted patients, which reported 15% to 50%, reducing the incidence of sinusitis and therefore reducing the incidence of pneumonia can indirectly decrease the mortality rate. The extent of this decline in mortality requires long-term investigation.[29]

Microbial evaluation in preventive regimens has great importance because the prophylaxis regimen should not increase microbial resistance or increase colonization with resistant microorganisms. Van Zanten et al. evaluated the microorganisms in sinus and tracheal discharges in patients admitted to ICU. They found a similarity between microorganisms isolated from both secretions in patients. In this study, the most isolated organisms were gram-negative bacteria. Among them, *Pseudomonas aeruginosa* was the most common bacteria.[21] In Pneumatikos et al. study, the most commonly observed organism was gram-negative bacteria and in particular *Acinetobacter*. They found a reduction in the positive culture of gram-negative microorganisms in the treatment group compared to the control group.[8] Finally, in the study by Camus et al., the most frequent organisms were gram-negative bacteria. A significant reduction in the number of these organisms was observed in the combination therapy group compared to the control group.[7] In our study, therapeutic regimens did not have much impact on gram-positive bacteria, such as *Staphylococcus aureus*. The treatment regimen reduced the number of gram-negative organisms. The positive culture of methicillin-resistant *Staphylococcus aureus* (MRSA) did not differ significantly between groups. Based on our study and previous findings, it seems that preventive regimens used to prevent sinusitis reduce the risk of infection with gram-negative organisms and have little effect on gram-positive bacteria, such as MRSA.

The cost of treatment with these medications for 10 days is equal to 300,000 Iranian Rial (IRR) while the only one additional day of hospitalization due to respiratory infections in the intensive care unit inside the studied hospital, imposes a cost of 6,000,000 IRR on the health care system. In regard to this simple cost evaluation, it seems that the treatment would be cost-effective, while the cost-effectiveness should be closely examined in other studies.

Limitations of this study included the duration of evaluation, lack of long-term efficacy assessment, evaluation of each drug effect as monotherapy and open-label design that the last one could have some impacts on physician assessment. However, due to the lack of patient influence in the evaluations, there was little interference in this regard. By considering the positive effect of preventive protocol, further study with a longer duration by considering the mortality rate and groups containing any of the treatments used alone are recommended. Also, cost-effectiveness evaluation can be more accurately assessed.

**Conclusions**

Based on our findings on the preventive regimen for sinusitis and pneumonia, it seems that the combination of sodium chloride and azelastine sprays can effectively reduce the risk of infections in ICU patients that have NG tube and are mechanically ventilated. In addition, this prophylactic regimen reduces the positive culture of Gram-negative microorganisms. In addition to low cost and limited side effects, this therapeutic regimen is an effective option in ICU patients.

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**Conflicts of interest**

There are no conflicts of interest.

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**References**

1. Agrafiotis M, Vardakas KZ, Gkegkes ID, Kapaskelis A, Falagas ME. Ventilator-associated sinusitis in adults: Systematic review and meta-analysis. Respir Med 2012;106:1082-95.
2. George DL, Falk PS, Umberto Meduri G, Leeper KV Jr., Wunderink RG, Steere EL, et al. Nosocomial sinusitis in patients in the medical intensive care unit: A prospective epidemiological study. Clin Infect Dis 1998;27:463-70.
3. Stein M, Caplan ES. Nosocomial sinusitis: A unique subset of sinusitis. Curr Opin Infect Dis 2005;18:147-50.
4. Adeyemo AA, Fasunla AJ, Adeosun AA, Abdullahi H. Rhinosinusitis: A potential hazard of nasogastric tube insertion. Ann Ib Postgrad Med 2007;5:44-5.
5. McCormick J, O’Mara M, Wakefield W, Goldfarb I, Slater H, Causahaj P. Effect of diagnosis and treatment of sinusitis in critically ill burn victims. Burns 2003;29:79-81.
6. Aggarwal S, Azim A, Baronia A, Kumar R. Evaluation and management of nosocomial sinusitis in intensive care unit patients for pyrexia of unknown origin: Case report and review of literature. Int J Med Biomed Res 2012;1:161-6.
7. Camus C, Bellissant E, Sebille V, Perrotin D, Baro G, Legras A, et al. Prevention of acquired infections in intubated patients with the combination of two decontamination regimens. Crit Care Med 2005;33:307-14.
8. Pneumatikos I, Konstantonis D, Tsigaridis I, Theodorou V, Vrettakos G, Danilides V, et al. Prevention of nosocomial maxillary sinusitis in the ICU: The effects of topicaly applied alpha-adrenergic agonists and corticosteroids. Intensive Care Med 2006;32:532-7.
9. Schweickert WD, Gehlbach BK, Pohlman AS, Hall JB, Kress JP.
Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. Crit Care Med 2004;32:1272-6.

10. Aebert H, Hunefeld G, Regel G. Paranasal sinusitis and sepsis in ICU patients with nasotracheal intubation. Intensive Care Med 1988;15:27-30.

11. Hoffmans R, Wagemakers A, van Drunen C, Hellings P, Fokkens W. Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment. PLoS One 2018;13:e0192330.

12. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otolarhinoaryngologists. Rhinology. 2012;50:1-12.

13. Repka-Ramirez S, Naranch K, Park YJ, Clauw D, Baraniuk JN. Cytokines in nasal lavage fluids from acute sinusitis, allergic rhinitis, and chronic fatigue syndrome subjects. Allergy Asthma Proc 2002;23:185-90.

14. Rudack C, Hauser U, Wagenmann M, Bachert C, Ganzer U. Cytokine pattern in various forms of sinusitis. Laryngorhinootologie 1998;77:34-7.

15. Jiao J, Zhang L. Influence of intranasal drugs on human nasal mucociliary clearance and ciliary beat frequency. Allergy Asthma Immunol Res 2019;11:306-19.

16. Roca-Ferrer J, Pujols L, Perez-Gonzalez M, Alobid I, Callejas B, Vicens-Artes S, et al. Superior effect of MP-AzeFlu than azelastine or fluticasone propionate alone on reducing inflammatory markers. Allergy Asthma Clin Immunol 2018;14:86.

17. Inanli S, Ozturk O, Korkmaz M, Tutkun A, Batman C. The effects of topical agents of fluticasone propionate, oxymetazoline, and 3% and 0.9% sodium chloride solutions on mucociliary clearance in the therapy of acute bacterial rhinosinusitis in vivo. Laryngoscope 2002;112:320-5.

18. Jurkiewicz D, Rapiejko P. Use of isotonic NaCl solution in patients with acute rhinosinusitis. Otolaryngol Pol 2011;65:47-53.

19. King D, Mitchell B, Williams CP, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. Cochrane Database Syst Rev 2015:CD006821.

20. Horak F. Effectiveness of twice daily azelastine nasal spray in patients with seasonal allergic rhinitis. Ther Clin Risk Manag 2008;4:1009-22.

21. van Zanten AR, Dixon JM, Nipshagen MD, de Bree R, Gürbes AR, Polderman KH. Hospital-acquired sinusitis is a common cause of fever of unknown origin in orotracheally intubated critically ill patients. Crit Care 2005;9:R583-90.

22. Abad CL, Pulia MS, Safdar N. Does the nose know? An update on MRSA decolonization strategies. Curr Infect Dis Rep 2013;15:455-64.

23. Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: Diagnosis and treatment. J Crit Care 2008;23:138-47.

24. Aun MV, Ribeiro MR, Costa Garcia CL, Alobid I, Paone L, Giavina-Bianchi P. Esophageal candidiasis: An adverse effect of inhaled corticosteroids therapy. J Asthma 2009;46:399-401.

25. Babu S, Samuel P. The effect of inhaled steroids on the upper respiratory tract. J Laryngol Otol 1988;102:592-4.

26. John P, Jayasree V. Oropharyngeal candidiasis associated with use of steroid inhaler in a chronic asthmatic patient: Case report. Int J Oral Maxillofac Pathol 2013;4:40-3.

27. Peter E, Bakri F, Ball DM, Cheney RT, Segal BH. Invasive pulmonary filamentous fungal infection in a patient receiving inhaled corticosteroid therapy. Clin Infect Dis 2002;35:e54-6.

28. Mohammad M, Hashemi SM, Abtahi SH, Lajevardi SM, Kianpour S, Mohammadi R. An investigation on non-invasive fungal sinusitis; Molecular identification of etiologic agents. J Res Med Sci 2017;22:67.

29. Li G, Cook DJ, Thabane L, Friedrich JQ, Crozier TM, Muscedere J, et al. Risk factors for mortality in patients admitted to intensive care units with pneumonia. Respir Res 2016;17:80.

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