Ventilator-associated pneumonia among ICU patients receiving mechanical ventilation and prophylaxis of gastrointestinal bleeding
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ABSTRACT

Background: Pneumonia in ventilated intensive care unit (ICU) patients is one of the most serious nosocomial infections with a frequently fatal outcome. Retrograde colonization of the oropharynx from the stomach by micro-aspiration of gastric fluid was shown to be associated with pneumonia. The purpose of the present study was to compare the frequency of ventilator-associated pneumonia (VAP) between two groups of ICU patients taking gastrointestinal bleeding prophylaxis including ranitidine or omeprazole.

Patients and methods: This double-blind randomized clinical trial was achieved on 129 subjects receiving at least 48 hours mechanical ventilation. They were assigned in 2 groups of ranitidine and omeprazole as the prophylactic regimen of stress-related gastrointestinal bleeding.

Results: In ranitidine group, 6 patients (9.7%) developed VAP compared to 8 subjects (13.1%) in the other group, however, chi square analysis failed to show a significant difference (P= 0.4).

Conclusion: The incidence of VAP in ICU patients receiving either ranitidine or omeprazole did not differ significantly, however, further studies with greater sample size are required to draw a firm decision.

Keywords: Ventilator-associated pneumonia, Prophylaxis, Omeprazole, Ranitidine.

INTRODUCTION

Pneumonia in ventilated ICU patients is one of the most serious nosocomial infections with a frequently fatal outcome (1). Retrograde colonization of the oropharynx from the stomach by micro-aspiration of gastric fluid is a recently recognized phenomenon associated with increased gastric pH that may result in pneumonia during mechanical ventilation (1). Recent studies have questioned the use of histamine (H2) receptor antagonists in stress ulcer prophylaxis because of an increased incidence of nosocomial pneumonia and subsequent death (2).

In a study conducted by Apte (3), it was found that pharmacologically increasing gastric pH increases the risk for developing pneumonia in intubated critically ill patients and also the pneumonia occurs earlier than in untreated control patients (3).

On the other hand, in a research by Bonten, it was indicated that intragastric acidity influenced gastric colonization but not colonization of the upper respiratory tract or the incidence of ventilator-associated pneumonia (VAP). Therefore,
it is unlikely that the gastropulmonary route is important for the development of VAP (4).

Thomason’s study showed no difference in the incidence of nosocomial pneumonia in mechanically ventilated trauma patients during the first 4 days of stress ulcer prophylaxis with sucralfate, antacid, or ranitidine. There was a trend toward decreased pneumonia in the sucralfate group after the fourth day of study. Even after controlling for injury severity, the mortality rate in the antacid group was significantly higher, the reasons for this issue are unknown (5).

The purpose of the present study was to compare the frequency of VAP between two groups of ICU patients taking gastrointestinal bleeding prophylaxis including intravenous ranitidine or enteral omeprazole.

**PATIENTS and METHODS**

This study was conducted as a double-blind randomized clinical trial from June 2001 to January 2002 at Imam Hossein hospital, Tehran, Iran.

Participants were 129 ICU patients under mechanical ventilation for more than 48 hours with gastrointestinal bleeding prophylaxis by intravenous ranitidine or enteral omeprazole suspension. During a 7-month period, patients were assigned in 2 groups according to the computer-generated random number table: group A (n=68) received 50 mg of ranitidine intravenously in 2 doses and group B (n=61) received omeprazole suspension 20 mg twice a day via the nasogastric tube that was flushed with 20 ml of sterile water. Enteral feeding was achieved via nasogastric (NG) tube in order to monitor any GI bleeding and also prescribe enteral omeprazole and placebo. Omeprazole suspension was prepared by adding omeprazole granules gathered from the original drug shape (capsules) and water to apple sauce prepared by chapped apple. This substance prevents degradation of omeprazole granules by optimizing gastric acidity.

We considered the following criteria to diagnose VAP: new infiltration in chest X ray along with two of the three following criteria: fever $\geq 38.3^\circ$C, leukocytosis $\geq 10000$, and pus in tracheal tube suction. Ultimate diagnosis was achieved by a positive culture of tracheal secretions. Existence of at least $10^5$ colonies of pathogenic microorganism was considered positive.

Cases with pneumonia, upper gastrointestinal bleeding and previous gastrectomy were excluded. Patients in group A were treated with 50 mg intravenous ranitidine plus nasogastric prescribed placebo twice a day. In group B, omeprazole suspension (20 mg) and intravenous placebo were prescribed twice a day. It was unavoidable to prepare omeprazole suspension a bit before use to prevent drug efficacy reduction and/or its color change. Dosages of drugs were adjusted based on renal and hepatic functions of the patients. Neither the physicians nor nurses knew the treatment regimens prescribed for the patients.

Vital signs including heart and respiratory rate, oral and auxiliary temperature as well as antibiotic order, history of major surgeries or dialysis, total parenteral nutrition, corticosteroid use, type of trauma, coagulation profile, sepsis profile and renal function were gathered. Although this study was planned based on Cook’s investigation in which APACHE scoring was not considered, we compare the major risk factors in ICU patients as mentioned. Internal and surgical cases were not separated since is not a major risk factor for gastrointestinal bleeding based on Cook’s study (6).

Data were analyzed by SPSS software (Version 13.0, SPSS Inc., USA) and chi square and independent t-test were used, when appropriate.

All participants’ family were requested to fill an informed consent.

**RESULTS**

The omeprazole group included 32 males and 29 females with the mean age of 52.4 years (a
range, 5-95 years) and the ranitidine group included 35 males and 33 females with the mean age of 49.2 years (a range, 5-85 years).

Most of the patients were admitted to ICU because of head trauma and cerebrovascular accidents (CVA) in ranitidine and omeprazole group, respectively. Causes of hospitalization are summarized in table 1.

Table 1. Causes of hospitalization in two study groups

<table>
<thead>
<tr>
<th>Cause of hospitalization</th>
<th>Ranitidine group</th>
<th>Omeprazole group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head trauma</td>
<td>22 (32.3)</td>
<td>12 (19.7)</td>
</tr>
<tr>
<td>CVA</td>
<td>20 (29.4)</td>
<td>22 (36.0)</td>
</tr>
<tr>
<td>ARF</td>
<td>3 (4.4)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>7 (10.3)</td>
<td>8 (13.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>0</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>DIC</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>DKA</td>
<td>1 (1.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Guillain Barre syndrome</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Hyperosmolar coma</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>1 (1.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Miassthenia</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>1 (1.5)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (1.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>3 (4.4)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3 (4.4)</td>
<td>5 (8.2)</td>
</tr>
<tr>
<td>Toxic megacolon</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

CVA: Cerebrovascular accidents, ARF: Acute renal failure, COPD: Chronic obstructive pulmonary disease, DKA: Diabetic ketoacidosis, MI: Myocardial infarction

Average duration of hospitalization in groups A and B was 6.16±8.04 days and 7.67±7.2 days, respectively, however, the difference did not reach a statistically significant level (NS).

Average duration of mechanical ventilation was 4.96±7.94 days and 6.54±6.94 days in ranitidine and omeprazole group, respectively (NS). Totally, 14 (20.6%) patients of ranitidine and 3 (4.9%) patients of omeprazole group were complicated by GI bleeding. The difference of GI bleeding frequency was statistically significant between the 2 groups (p<0.05).

In ranitidine group, 6 patients (9.7%) developed VAP, however, 8 (13.1%) patients of omeprazole-treated group developed VAP. The difference was not significant.

**DISCUSSION**

Pneumonia was indicated as the second common nosocomial infection in the U.S based on a study by Fagon (7), and had an important role in ICU mortality rate resulting in high burden of hospitalization and medical care.

Kappstein pointed out that micro-aspiration of gastric fluid colonized with great numbers of pathogens can lead to ventilator-associated pneumonia (8). Since the degree of microbial growth depends upon the pH of gastric fluid, pH values of gastric aspirated agents should not exceed 4 if stress ulcer prophylaxis is required.

In another study Tryba reviewed several published studies concerning the issue whether medicinal stress-bleeding prophylaxis increases gastric pH which favors the development of broncho-pulmonary infections (9). The author concluded that the risk of gastric bacterial colonization among ICU patients significantly increases due to the augmentation of gastric PH.

One of the beneficial effects of omeprazole as a prophylactic drug of choice for stress ulcer is low rate of ventilator-associated pneumonia (VAP) compared with other medicines such as ranitidine (10). This could be in part explained by the fact that keeping gastric pH at a level lower than 5.5 pursuant to omeprazole prescription can prevent bacterial growth in the stomach and consecutively reduce the risk of pharyngeal colonization of gram-negative bacilli which can cause VAP. The mentioned effect was observed in suspension-form more than others (10).

We have attempted to compare two prophylactic regimens in case of VAP rate without focusing on the reasons or mechanisms. This is why we did not care about gastric acidity. We also compared two forms of drugs available in ICU wards; IV ranitidine and enteral omeprazole. Thus,
this study does not have any idea about other drugs that could be helpful.

Our results did not show any difference between ranitidine and omeprazole when the occurrence of VAP among ICU patients was considered, however, we found a significant difference between the two groups for GI bleeding rate. This would be comparable with a study carried out by Yildizdas (11), in which, no difference was found between the incidence of VAP, macroscopic stress ulcer bleeding, and mortality in the mechanically ventilated PICU (pediatric ICU) patients treated with ranitidine, omeprazole, sucralfate, or untreated subjects.

Pickworth also concluded that there had been no statistically significant difference in pneumonia rate among mechanically ventilated trauma patients receiving stress ulcer prophylaxis with sucralfate vs. ranitidine (12).

Based on previous investigations detecting more GI protection by proton pomp inhibitors like omeprazole in comparison with H2 blockers, and with respect to our findings, we suggest enteral omeprazole instead of any H2 blocker as a GI prophylactic drug. Nevertheless, further large-scale studies are needed in order to draw a firm decision and confirm the probable beneficial effect of omeprazole to prevent stress-ulcer.

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REFERENCES


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