Original Article

Comparing the Ventilator-associated Pneumonia Incidence when Pantoprazole or Ranitidine is used for Stress Ulcer Prophylaxis in Critically Ill Adult Patients

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Abstract

Aim: Prophylaxis against stress ulcer in mechanically ventilated patients is one of the causes for ventilator-associated pneumonia (VAP). Our aim was evaluating the effect of intravenous pantoprazole and ranitidine in the incidence of VAP in critically ill patients. **Materials and Methods:** Patients with at least 48 h of expected mechanical ventilation were allocated randomly to receive either 50 mg ranitidine (R) every 8 h or 40 mg pantoprazole (P) every 12 h intravenously from admission. VAP diagnosis was according to the Clinical Pneumonia Infection Score and positive culture. **Results:** Eighty-six patients during a 15-month period were analyzed; the study showed a low difference between VAP incidence in the ranitidine and pantoprazole groups. No significant difference was observed in terms of gastrointestinal bleeding, intensive care unit, hospital length of stay, and mortality between the groups. **Conclusion:** VAP incidence is hardly related to the type of stress ulcer prophylaxis agent with a high rate of VAP and low utilization of VAP prophylaxis bundle.

Keywords: Anti-ulcer agents, intensive care units, pneumonia

Introduction

Nowadays, hospital-acquired infections are the most widespread phenomena among the critically ill patients.[1,2] Comparing to the patients who are not admitted to the intensive care unit (ICU), pneumonia is one of the most lethal hospital-acquired infections which is 5–10 times higher among the ICU patients and twenty times higher among those under mechanical ventilation.[1] Based on morbidity and the consequences cost rise due to hospital-acquired pneumonia, the recommended clinical guidelines have been established to avoid the related risk factors.[3-5]

Ventilator-associated pneumonia (VAP) is a pneumonia which develops under mechanical ventilation condition for longer than 48 h with no clinical evidence of presence or possibility of pneumonia since the early intubation.[6,7] The mortality rates of VAP were evaluated about 20%–75%[8] which is mainly due to the multidrug-resistance bacteria.[9-11]

VAP is spread by microorganisms entering the sterilized lower respiratory system through oral-aspiratory secretions, including endemic or external bacteria of the digestive system produced by the contamination of health-care instruments or personnel.[12,13] Prophylaxis of gastric stress ulcer with acid-suppressive therapy increases the risk of VAP in critically ill patients. Gastrointestinal PH rise could lead to overgrowth

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of gastric bacteria and consequently the aspiration of gastric contents into the trachea may cause respiratory infection development.[7,12,14]

The preventive strategies include reduction of bacterial colonization in the mouth and throat, reduction of aspiration frequencies, preservation of immunity system, and hooking off the patient from the ventilator.[7] Intervention strategies to reduce the patient-related risk factors have focused on intubation, duration of mechanical ventilation, aspiration and nutrition, and nutrition and modulation of colonization.[15]

Prophylaxis of gastric stress ulcers by H2RA in patients under mechanical ventilation, in comparison with those receiving no medication, has led to less stomach hemorrhage but still more VAP.[16] On the other hand, the findings suggested that the outbreak of VAP in the patients of intravenous pantoprazole was three times higher than the patients of intravenous ranitidine.[17] While two meta-analyses comparing proton-pump inhibitor (PPI) and H2RA in terms of prophylactic effectiveness for gastric stress ulcer in critical patients have showed no apparent differences in both the groups with regard to upper gastric ulcer prophylaxis, pneumonia, and mortality in patients admitted to ICU.[18,19]

Our aim in this study was to compare the outbreak of VAP in the two groups of patients receiving either intravenous ranitidine or intravenous pantoprazole in prophylaxis of gastric stress ulcers.

Materials and Methods

This double-blind pilot study (IRCT2013072014079N1) was conducted on the admitted patients in the ICU wards of Nemazee Hospital affiliated to Shiraz University of Medical Sciences, Shiraz, Iran, from June 2013 to September 2014. Ethical approval was received from the Ethics Committee of Shiraz University of Medical Sciences, and the written consent was obtained from the legal guardian of patients >18 years old who met the inclusion criterion. The patients were allocated into two groups based on the generated random numbers from http://www.randomizer.org/. In this study, main investigator and patients are blind.

Inclusion criteria covered all the medical and surgical patients admitted to the ICU and were >18 years old and needed intubation for more than 48 h. Patients with diagnosed pneumonia within the past 3 months and on admission, significant dysphagia clinical symptoms, definite aspiration during hospitalization, case history of receiving immunosuppressant, gastrointestinal hemorrhage, previous gastrectomy, erosive gastritis, gastroesophageal reflux, history of lung cancer and transferring of patient from other ICUs, drug interference, drug side effects, and kidney failure were excluded from the study.

Following admission to the ICU, Group P received 40 mg intravenous pantoprazole every 12 h and Group R received 50 mg intravenous ranitidine every 8 h. For all the patients, either nasogastric or orogastric tube was inserted. In these patients the aspirated contents of nasogastric or orogastric tubes were monitored and in case there were symptoms of gastric hemorrhage, the patient was excluded from the study.

Gastrointestinal bleeding was characterized as evident hemorrhage complicated by one of the following factors within 24 h: sudden decrease of more than 20 mm Hg of systolic blood pressure, increase in heart rate more than 20 beats/min, and reduction of hemoglobin more than 2 g/dl.[3,20,21]

Tracheostomy and reintubation time were also recorded. Patients' feeding was done according to intensivist diagnosis and based on their condition through nasogastric or orogastric tube. Gastric ulcer prophylaxis was continued during the patient stay in ICU. Intravenous forms of medications were persisted until the patient caught VAP or 48 h after extubation or hooking off from the mechanical ventilator and then were turned into nutritional forms.

Patient's profile, record of underline disease, addiction to smoke or narcotics, the cause of admission to ICU, APACHE IV score, and vital signs were checked, and routine laboratory examinations (e.g., complete blood count, blood urea nitrogen, creatinine, electrolyte, and arterial blood gas) conducted until the required time and the scores were documented in information gathering forms.

Forty-eight hours after the mechanical ventilation, Clinical Pneumonia Infection Score (CPIS) which included five parts was checked. The score was calculated as follows: fever: 0 (36.5°C–38.4°C), 1 (38.5–39), and 2 (<36.0 or >39.0); leukocytosis: 0 (4000–11,000 white blood cells/mm^3 of blood), 1 (11,000–17,000), and 2 (>17,000); new infiltrate: 0 (none), 1 (patchy), and 2 (localized); secretions: 0 (none to minimal), 1 (moderate), 2 (large); and PaO_2/FiO_2: 0 (more than 240 and acute respiratory distress syndrome [ARDS]) and 2 (<240 and no ARDS).[22]

If CPIS was more than 6 or the patient was clinically suspicion to infection, the sputum sample taken by the mini-bronchoalveolar lavage technique was sent to the laboratory. The results of cultivation were semiquantitatively reported. In case it was moderate or severe, the patient was diagnosed with VAP and examined for other consequences (such as being hooked off from mechanical ventilation, discharged from ICU, transferred to the ward, and listed as mortality). If the result of the cultivation was reported negative, the patient was monitored 48 h after extubation or off-hook from the mechanical ventilation, and the intravenous medication was turned into enteral medication.

In this study, the primary outcome is the incidence of VAP and the secondary outcome, including ICU and hospital mortality and length of stay, ventilator free days, and mechanical ventilation days in two groups of patients receiving either intravenous ranitidine or intravenous pantoprazole.

The data were analyzed using the SPSS version 19 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov, Chi-square, Student *t*-test, and Mann–Whitney U-tests were utilized to examine the normality and to compare the variables between the two groups.

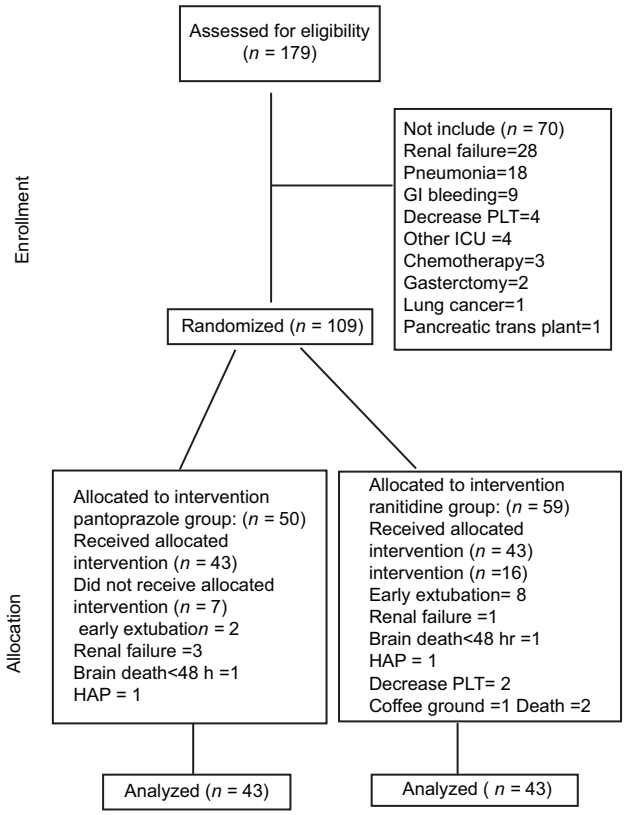

Figure 1: Consort flow diagram

Results

Of 179 patients who were screened for enrollment, 70 patients were excluded from the trial. Beyond 109 qualified patients, 86 were brought to the statistical analysis [Figure 1].

Outbreak of VAP in both groups of intravenous pantoprazole and intravenous ranitidine were 27.9 and 32.6%, respectively (odds ratio: 0.496–3.137, $P = 0.63$). The mean and standard deviation for number of age and APACHE IV in the pantoprazole group and ranitidine group are 51 ± 19 and 51.5 ± 17.2 and 72.8 ± 19.7 and 71 ± 21.3, respectively. No significant differences were detected regarding demographic data of patients, including sex, underlying disease, smoking, pervious use of antibiotic, tracheostomy, and reintubation ($P > 0.05$) [Table 1].

There were no statistically detectable differences in the important outcomes of both groups of pantoprazole and ranitidine, including ICU and hospital mortality or length of stay, ventilator-free days, and mechanical ventilation days ($P > 0.05$) [Table 2].

A large number of patients had no underline disease, but in the population of patients with such illnesses, the majority was belonged to hypertension and hypertension/diabetic mellitus. Furthermore, intracranial hemorrhage, cerebrovascular attack, and traumatic patients were the major causes of admission to ICU, affecting 28%, 24.4%, and 10% of patients,

Table 1: Patients' demographic information in both groups of pantoprazole and ranitidine and data are presented as patients' numbers (percentage)

Variable	Pantoprazole	Ranitidine	*P*
Sex (male)	25 (58.1)	24 (55.8)	0.8
Underline disease	28 (40.9)	24 (47.6)	0.37
Smoking	6 (14)	11 (25.6)	0.17
Pervious use of antibiotics	24 (55.8)	24 (55.8)	0.38
Tracheostomy	14 (32.6)	13 (30.2)	0.81
Reintubation	0	2 (4.7)	0.15

Table 2: Consequences comparison in both groups of pantoprazole and ranitidine and data are presented as mean±standard deviation or patients' numbers (percentage)

Variable	Pantoprazole	Ranitidine	*P*
Hospital stay length (day)	21.7±13.5	25.8±15.33	0.2
ICU stay length (day)	18.2±12.7	20.4±14.3	0.38
Mechanical ventilation length (day)	12.39±13.4	10.9±10.22	0.77
Ventilator-free (day)	7.48±7.83	9.48±10.6	0.51
Mechanical ventilation irrespective of ICU death (day)	10.7±8.4	9.26±5.53	0.85
ICU mortality	8 (18.6)	5 (11.6)	0.36
Hospital mortality	9 (20.9)	6 (14)	0.39

ICU: Intensive care unit

respectively. Overall, neurologic causes constituted the majority of ICU hospitalization cases with 59% incidence. A fairly large amount of 30.2% in outbreak of VAP in the study set for the patients were enrolled in this study.

Discussion

The present study aimed to compare the effects of intravenous pantoprazole (as a PPI) and intravenous ranitidine (as a H_2 blockers [H2RA]) on VAP incidence in critically ill patients. The findings of our study demonstrated no significant difference in terms of increase in outbreak of VAP between the two groups of patients receiving intravenous pantoprazole and intravenous ranitidine as a gastric stress ulcers prophylactic medication.

Our data are in consistence with the study of Beaulieu *et al*. showed no significant correlation between prior use of proton-pump inhibitor and developing risk of nosocomial pneumonia.[23] Although it is shown that in critically ill patients, PPI seem to be more effective than H2RA preventing gastrointestinal bleeding,[19] the results of Miano *et al*. represented that PPI could increase the chance of nosocomial infection comparing to H2RA.[12] In another study, intravenous omeprazole and ranitidine were compared, and the outcomes showed ICU patients using PPI have a three-fold increase risk of developing VAP comparing to H2RA receivers.[17]

In our study, no significant difference was observed in both medication groups regarding the factors affecting VAP. One of the reasons could be the low number of samples, despite

being identical in terms of other factors affecting VAP. Another reason may be the lack of enough time to choose the high-risk patients. Moreover, a number of factors, chiefly the intubation and mechanical ventilation, are more effective in the development of VAP than the drug of choice for the prevention of stress ulcers and gastrointestinal bleeding.[23] On the other hand, PH elevation of the stomach, growth of bacteria, aspiration of the oropharynx contents into the upper respiratory tract, and lower esophageal sphincter relaxation could contribute to increased incidence of pneumonia.

Our results showed that the pervious use of antibiotic, tracheostomy, and reintubation incidence is higher in the patients with VAP which are in consistent with other studies showing antibiotic usage can increase the incidence of pneumonia and infections resistant to antibiotics.[24] Furthermore, the length of ICU and hospital stay and mechanical ventilation were higher in the group with VAP which could be predictable according to the previous studies.[25]

Limitations

In addition to time constraints, lack of similar protocol performance and acceptance of different kinds of patients in the ICU caused only three ICUs eligible for the pilot project, which, in turn, slowed the study. On the other hand, the lack of postICU for patients who required only mechanical ventilation but not further diagnostic evaluation and specific medical support led to longer hospitalization in ICU. This also prevents the entry of eligible patients to the ICU and sending them to the wards. The high prevalence of renal failure in patients admitted to ICU and their need for drug dose adjustment was the other restriction in patients' recruitment of this study.

Conclusion

In the present study, we have shown that intravenous pantoprazole and ranitidine as a stress ulcer prophylactic agent could not increase the outbreak of VAP in critically ill patients. In addition, length of ICU and hospital stay and mechanical ventilation would increase in patients with VAP which also related to the previous antibiotic use, tracheostomy, and reintubation in these patients. It is recommended that other factors be taken into consideration such as the severity of illness, medicine price, drug interferences, drug side-effects, and factors causing gastric hemorrhage in critical patients. More studies are warranted to find the safety of these prophylactic medications in ICU patients.

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Conflicts of interest

There are no conflicts of interest.

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