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Original Article

Nosocomial Infection in Critically Ill Patient Receiving Stress Ulcer Prophylactic Drugs

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Abstract

Acidic pH of stomach, which is a normal physiological barrier against bacterial overgrowth, would increase by stress ulcer prophylaxis initiation and may lead to bacterial colonization and play as a source for infection transmission to the respiratory system which results in ventilator related pneumonia in patients admitted to the Intensive Care Units (ICUs). Therefore, finding methods to decrease the prevalence of aspiration pneumonia is an old debate. The current survey has been performed to evaluate the effect of ranitidine and sucralfate on bacterial colonization and development of aspiration pneumonia. This is a randomized clinical trial in two groups of fifteen critically ill patients older than 20 years of age admitted to the ICU of Sina Hospital, Tehran, Iran. All patients were under mechanical ventilation. One group had a regimen of 1 g sucralfate every 6 h by gavage and the other had 50 mg of intravenous ranitidine every 8 h with a loading dose of 100 mg. Gastric juice was sampled every 24 h for determining the pH and pathogen type. The gastric pH of ranitidine group was higher than of sucralfate group. Common microorganisms colonized in the gastric juice of patients were *Pseudomonas, Staphylococcus aureus, Klebsiella,* and *Candida albicans*. Aspiration pneumonia occurred in 4 patients in the ranitidine group and 2 patients in the sucralfate group. Similar frequency of colonized microorganisms in the two groups suggests that the effect of pH on bacterial colonization is negligible. Therefore, concurrent consumption of ranitidine and other acid lowering medications may lower the risk of aspiration pneumonia and stress ulcer in patients taking ranitidine. If it is the case, administration of ranitidine would be preferred to sucralfate.

Keywords: Aspiration pneumonia; Microbial colonization; Ranitidine; Sucralfate.
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1. Introduction

Acute ulcers caused by stress or gastric and duodenal erosions following hospitalization in Intensive Care Units (ICU), leading to severe bleeding, was first described in traumatic Couching patients, known as Cushing's ulcer [1, 2]. The incidence of stress ulcer in patients hospitalized in the ICU is 75-80% and in about half of these patients, some evidence of bleeding is observed. About 20% of them develop apparent hemorrhage and in case of surgery to control bleeding, mortality rate is about 70% [3, 4]. Therefore, prevention of stress ulcer is mandatory.

To prevent bleeding in stress ulcer, gastric acidity should be controlled so that the gastric and intramucosal pH stay above 4 and 3.5, respectively [3]. Gastric pH functions as a natural physiological barrier against bacterial growth in stomach. By commencing prophylactic therapy in stress ulcer, gastric pH is elevated leading to bacterial colonization. It also creates a source for infection transmission to the respiratory system and causes aspiration pneumonia in ICU patients. In fact, aspiration pneumonia is considered as a common problem in ICU patients with a prevalence rate of about 17-22% [5, 6].

Recent studies suggest that H_2 blockers may increase load of gram negative bacteria in stomach through increasing gastric pH which can lead to pulmonary infection, if aspiration of gastric contents occurs. Certain mucosal lining compounds such as sucralfate, an octasulfate sucrose plus aluminum hydroxide, show an effect equivalent to H_2 blockers, if administered 1-2 g four times daily [1]. Sucralfate, as a stimulatory mediator for prostaglandins, can increase gastric mucosal secretions and produce a mucosal resistance against gastric acid irritation. Because sucralfate does not change gastric pH, compared to H_2 blockers, it reduces colonization of intragastric bacteria and consequently aspiration pneumonia [7-9].

While ranitidine is shown to be more effective than sucralfate in preventing stress ulcer bleeding prophylaxis, some studies found no significant difference between ranitidine and sucralfate regimens in developing aspiration pneumonia [4, 6]. Maier *et al*. reported a prevalence of 27.5% for pneumonia in ranitidine group and about 20.8% in sucralfate group [9]. In other studies, however, sucralfate is suggested as the regimen of choice due to its better prophylactic action in gastric ulcer and lower prevalence of aspiration pneumonia [8]. Some studies have recommended a combination of sucralfate and oral antibiotics for aspiration pneumonia prophylaxis [10-12].

Despite the great number of studies on stress ulcer and aspiration pneumonia, variations in the study conditions, place of conducting the study, as well as native and individualized characteristics of different populations renders an accurate conclusion difficult. Therefore, this research has been conducted to compare the effects of sucralfate and ranitidine on gastric juice bacterial colonization and development of associated aspiration pneumonia in critically ill patients under mechanical ventilation in Sina Hospital, Tehran, Iran.

Table 1. Base line information of patients receiving ranitidine *vs* sucralfate.

Variable	Ranitidine	Sucralfate	*p*-Value
No. of patients	15	15	-
Male/female ratio	8:7	15:0	0.001
Age	63.67±14.8	63.6±6.04	0.987
Glasgow Coma Scale	7±3.07	6.93±1.03	0.937
Admission duration	16.67±15.67	25.93±15.5	0.116
APACHE score	19.33±6.81	19.27±4.2	0.974

Data presented as mean ± standard deviation.

2. Material and methods

2.1. Patients and settings

This research was a randomized clinical trial on 30 critically ill patients under mechanical ventilation which were hospitalized after a traumatic accident in the general ICU of Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran, from October 2005 to March, 2005.

Patients entered the study if they were over 20 years of age, were under mechanical ventilation in ICU and had a nasogastric (NG) tube. Patients who were likely to be extubated or their NG tube was likely to be removed within 24 h were excluded [13, 14]. After preliminary therapeutic measures, eligible patients were randomly assigned to two prophylactic regimen groups and were intubated. After nasogastric tube was inserted, the first sample of gastric juice was taken. Then in one group, patients received a primary loading dose of ranitidine (100 mg, IV), followed by 50 mg, IV, TDS. Patients in the other group received one g of sucralfate by gavage every 6 h.

2.2. Data collection

For all patients, demographic characteristics were recorded. Glasgow Coma Scale (GCS) was calculated at the time of admission and on the third day. Acute Physiologic and Chronic Health Evaluation (APACHE II) scores were calculated and recorded in a daily fashion.

Aspiration pneumonia, was diagnosed according to physicians' opinions. This diagnosis was often made based on chest X-ray (diffused or localized infiltration particularly in the right lung), positive result of blood culture, infectious secretions in endotracheal tube, and its compatibility with blood culture and fever. Due to our limitations in performing endoscopy in stress ulcer patients, stress ulcer was diagnosed based on the presence of blood in the NG tube (in sucralfate group) and pH under 4 (in ranitidine group) [6]. Gastric juice (93-4 ml) was obtained every 6 h. It was then evaluated for pH and cultured for pathogens.

2.3. Pathogen identification

Gastric juice specimens were cultured on blood agar media in the form of 4 zones. The culture media was incubated for 24 h before pathogen(s) were identified. In this research, isolation of microorganisms was performed according to standard microbiological, biochemical and mycological methods in accordance with National Committee on Clinical Laboratory Standards (NCCLS) [15, 16].

2.4. Statistical analysis

Data was presented as frequency (percentage) and mean±SD for qualitative and quantitative variables using Chi-Square and t-test, respectively via SPSS 13. A *p*-value less than 0.05 was considered statistically significant.

Table 2. pH and APACHE Score of patients receiving ranitidine *vs* sucralfate.

		At admission time	During day 1	During day 2	During day 3
pH	Ranitidine	5.1±1.7	5.0±1.7	5.3±1.6	5.8±1.0
	Sucralfate	3.3±1.8	2.8±1.4	3.4±0.5	3.5±0.5
	p-value	0.014	<0.001	<0.001	<0.001
Difference of pH	Ranitidine	-	-0.07±1.25	0.18±1.24	0.50±0.90
	Sucralfate	-	-0.62±1.40	0.01±1.53	0.10±2.30
	p-value	-	0.270	0.745	0.564
APACHE Score	Ranitidine	19.33±6.81	20.21±7.59	18.47±8.54	19.62±10.39
	Sucralfate	19.27±4.20	18.26±4.44	20.67±5.22	20.07±2.24
	p-value	0.974	0.386	0.402	0.890

Data presented as mean ± standard deviation.

3. Results

This study was performed on 30 individuals. Patients were divided into two groups; sucralfate group and ranitidine group. Each group consisted of 15 patients. Table one delineates baseline specifications of the two study groups, separately. Measurements were done at the beginning of the study prior to drug administration. Comparison of the two groups showed that except for gender and pH other specifications were matched in both groups.

The mean baseline pH, mean pH on day one, day two and day three are presented in Table 2 for ranitidine and sucralfate groups. The results demonstrate that the mean gastric pH in ranitidine group is significantly higher than in sucralfate group at the baseline (p=0.014) and on day one through three (p<0.001 for each day). Because the mean baseline pH difference was significant, comparison between prophylaxis regimens inside each group was made via subtracting pH of days one to three from baseline pH. Table 2 shows pH changes on day one to three relative to the baseline. There was no significant difference in pH changes relative to the baseline on days one, two and three, between the two groups, p=0.270, 0.745 and 0.564, respectively.

APACHE II score did not show a significant difference between the two groups at the baseline (p=0.974) day one (p=0.386), two (p=0.402) and three (p=0.890).

Mean GCS value at the beginning of the study (before drug administration) was 7.00±3.07 in the ranitidine group, and 6.93±1.03 in the sucralfate group with no significant difference (p=0.937). At the end of study (after 72 h), it reached 7.33±3.98 in the ranitidine group and 6.48±2.59 in the sucralfate group, again with no significant difference (p=0.485).

None of the patients in the sucralfate group had blood in their NG tubes. However, in the ranitidine group, 4 patients at the baseline and during the first day and 3 individuals during day 2 had pH less than 4. But during day 3, pH of all patients in this group was above 4. As a result, at the end of the study, no patients were suspected of stress ulcer in the ranitidine or sucralfate groups.

Aspiration pneumonia occurred in 2 individuals (13.3%) in the sucralfate group and in 4 patients (26.7%) in the ranitidine group. The difference was not significant (p=0.361).

Comparison of microorganisms colonization showed that the result of culturing from 22, 23, 20, and 25 individuals out of 30 patients were negative at the baseline, on the first day, second day and third day after ICU admission, respectively. Also, *Pseudomonas, Staphylococcus aureus, Klebsiella, Candida albicans* were identified as the most common microorganisms in culture positive gastric juice samples. The prevalence of these microorganisms is delineated in Table 3, for

Table 3. Gastric juice colonization in patient receiving ranitidine *vs* sucralfate.

Culture results	At admission time		During day 1		During day 2		During day 3	
	R*	S	R	S	R	S	R	S
Negative	10 (66.7%)	12 (80.0%)	9 (60.0%)	14 (93.3%)	9 (60.0%)	11 (73.3%)	11 (73.3%)	14 (93.3%)
Pseudomonas	0 (0.0%)	3 (20.0%)	1 (6.7%)	1 (6.7%)	2 (13.3%)	1 (6.7%)	1 (6.7%)	0 (0.0%)
Candida Albicans	0 (0.0%)	0 (0.0%)	2 (13.0%)	0 (0.0%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	0 (0.0%)
S. aureus	2 (13.3%)	0 (0.0%)	2 (13.0%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	2 (13.3%)	1 (6.7%)
Klebsiella	3 (20.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.7%)	0 (0.0%)

* S= Sucralfate, R= Ranitidine; data presented as the number and % of patients.

both ranitidine and sucralfate groups.

Of 28 individuals who passed away during this research, 13 individuals were from the ranitidine group (46.4%), and 15 individuals from the sucralfate group (53.6%), showing no significant difference (p=0.143). None of these death cases were due to aspiration pneumonia or stress ulcer bleeding. Patients in the ranitidine and sucralfate groups stayed in ICU for 16.67±15.67 and 25.93±15.5 days, respectively. Length of stay was not significantly different in the two groups (p=0.116).

4. Discussion

This study was conducted with the purpose of making comparisons between the frequency of microorganism colonization, and aspiration pneumonia in mechanically ventilated ICU patients who receive sucralfate or ranitidine prophylaxis.

According to the results, stress ulcer risk factors were observed only in the group receiving ranitidine which indicates the optimal efficacy of sucralfate as prophylaxis for this condition. But, it must be noted that the above-mentioned individuals in the ranitidine group were suspicious of having stress ulcer at baseline because they had a pH of less than 4. This problem was resolved in 72 h. This increase in pH as a result of ranitidine administration was found to be compatible with the results of two separate studies conducted by Cook and colleagues [6, 17].

A significant difference was observed in the pH mean values over 72 h of follow-up between ranitidine and sucralfate groups. In general, mean pH value was higher (more alkaline) in the ranitidine group than that seen in sucralfate group (more acidic). A similar finding was observed in a study by Kappstein *et al*. [18], but Oritz *et al*. did not find the same phenomenon in their research [19].

Incidence of aspiration pneumonia was higher in the ranitidine group compared to the sucralfate group (4 versus 2 individuals) but this difference was not significant. In studies by Cook *et al*. [4], Apte *et al*. [5], and Torres *et al*. [20], incidence of aspiration pneumonia among patients taking these drugs did not show any significant difference either.

One reason for the higher incidence of aspiration pneumonia in those who received ranitidine, was higher gastric pH during the study. With increase in the gastric juice pH, bacterial colonization in GI system increases which may elevate the risk of aspiration pneumonia. In the ranitidine receiving group, mean pH was higher for all samples throughout the study in comparison with the sucralfate group and as a result, more cases of pneumonia occurred, although this difference was not significant. This difference was found to be more prominent and significant in studies by Simms *et al*. [21] and Bonton *et al*. [22], but it is in line with Peura *et al*. [23], and Torres *et al*. [20].

No significant difference was found in general condition of patients in the two groups, but APACHE score changes from the first day to the 4th day was indicative of better conditions in the ranitidine group. This is because from the 2nd day (after 34 h), APACHE score declined in ranitidine group but elevated in sucralfate group and the general condition of sucralfate group patients aggravated during the 3rd and 4th days. Mortality rate did not show a significant difference between the two groups.

Four microorganisms were found more commonly in the gastric juice of patients: *Klebsiella, Pseudomonas, Staphylococcus aureus,* and *Candida albicans*. These microorganisms were observed in a study by Garrouste-orgeas and colleagues [22] while *Staphylococcus aureus* and *Klebsiella* were the most common pathogens in the ranitidine receiving group and *Pseudomonas* and *Candida albicans* were found more in the sucralfate receiving group in a study by

Kappstein *et al*. [18]. Within 24 h after beginning of the treatment, about 23.3% of patients developed bacterial colonization. This weak correlation was also observed in a study by Oritz *et al*. [19].

As mentioned earlier, the majority of the specifications of both groups had no significant difference. But the gender and gastric juice pH in both groups differed significantly prior to commencing prophylaxis. Half of the patients from the ranitidine group were women while there was no female in the sucralfate group. Due to the low number of patients who required monitoring in ICU and had the inclusion criteria, it was not possible to perform multistage randomization in this project and for the same reason, some non-homogenous demographical specifications are observed in these two groups. Also, it was not possible to perform endoscopy or other invasive diagnostics due to limitations in critically ill patients. These facts along with the low number of patients who fulfilled the inclusion criteria could have caused a bias in our study findings.

Lack of significant difference between the two groups in terms of rate and type of colonized microorganisms indicates that increase in pH does not affect bacterial colonization and despite creating an acidic environment with sucralfate, bacterial colonization is still observed. Furthermore, presence of these microorganisms even before drug therapy suggests the necessity for GI system decontamination for patients at high risk of developing stress ulcer.

Lack of significant difference in frequency of microorganism colonization in the two groups suggests that the effect of pH on bacterial colonization is negligible and, therefore, consumption of ranitidine and other acid lowering medications like proton pump inhibitors (PPIs) or antacids which increase intragastric pH to over 4, does not increase risk of developing aspiration pneumonia. Of course, such an exact implication requires further investigation.

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