SPECTRUM OF CULTURE POSITIVE HOSPITAL ACQUIRED PNEUMONIA IN PATIENTS RECEIVING PROTON PUMP INHIBITORS

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ABSTRACT

Objective: To identify the spectrum of organisms in intensive care unit (ICU) in patients who were receiving proton pump inhibitors for stress ulcer prophylaxis and diagnosed as having hospital-acquired pneumonia (HAP).

Study Design: Cross sectional study.

Place and Duration of Study: Shifa International Hospital Islamabad, from Apr 2016 to Aug 2016.

Material and Methods: One hundred and forty eight patients (134 receiving PPI's and 14 not receiving) in MICU of Shifa International Hospital were included in this study. Hospital acquired pneumonia was defined as New chest infiltrates developing within 48 hours of admission, Fever of greater than 38 degrees Celsius and total leucocyte count of more than 11000 or less than 3500. In all patients tracheal cultures were followed at 24 and 48 hours and microbiologic spectrum was defined.

Results: Out of 148 patients admitted to ICU during the study period, 45 patients (33.6 percent) developed HAP in PPI group compared to 1 in non PPI group. The initial tracheal cultures at admission were negative. Out of the 45 patients who fulfilled criteria for HAP 40 patients (89%) had positive tracheal cultures for gram negative bacteria which included Acinetobacter, Klebsiella and Escheria species. The cultures remained negative for 5 patients (11%) with HAP. The 89 patients who didn't fulfill the criteria for HAP, 25 patients still had positive tracheal cultures but more than fifty percent of the cultures yielded Candida Albicans. In the non PPI group only 1 patient developed HAP. HAP incidence was PPI group (p 0.042).

Conclusion: Gram negative bacteria was prevailed as the causative organism in patients who developed hospital acquired pneumonia (89 percent) and receiving proton pump inhibitors in medical intensive care unit with greater number incidence of HAP in PPI group.

Keywords: Hospital acquired pneumonia, Proton pump inhibitors, Stress ulcer prophylaxis.

INTRODUCTION

Stress ulceration is a commonly encountered problem in critically ill patients. Major risk factors for stress ulcers in such patients are coagulopathy and mechanical ventilation for a duration of more than 48 hours[1]. Stress ulcer prophylaxis therapy is associated with adverse effects. One of them is the association of stress ulcer prophylaxis is higher incidence of hospital acquired pneumonia. Various studies have been carried out to analyze this association. Two meta-analyses done by Alhazzani *et al* and Barkun *et al* failed to show any effect on the rate of nosocomial and/or ventilator associated pneumonia[2,3]. In contrary, however, a small (n=137) but prospective and randomized trial showed a strong increase in ventilator associated pneumonia within the PPI group compared to placebo (36.4% vs 14.1%, p=0.001)[4].

A retrospective study was conducted by Beaulieu[5] to explore the relation between proton pump inhibitors and hospital acquired pneumonia at MICU of the L' hospital du Sacre-Coeur de Montreal between March 14, 2002 and May 31, 2004. Nosocomial pneumonia was defined as a pneumonia diagnosis made after the first 48 h of their ICU admission. This study failed to show a clear relationship between the above two entities. However, this study did sowed a statistical significance in patients in

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Received: 07 Jun 2017; revised received: 07 Jul 2017; accepted: 25 Jul 2017

whom there was administration of sedatives or neuromuscular antagonists for two or more days, an APACHE II score greater than 15 and the presence of a central venous catheter.

The mechanism of HAP in patients receiving PPI's can be divided into aspiration and non-aspiration. Study by Herzig and collegues[6] which included 63,878 admissions to a large, urban, academic medical center in Boston, it was shown that HAP is associated with aspiration pneumonia (1.4, 95% CI: 1.1-1.8) than non-aspiration pneumonia (1.2, 95% CI: 1.1-1.4) .

Another mechanism is loss of protective gastric acidic pH which is targeted both by PPI's and H2RA's. Suppression of this acidic pH leads to alkaline pH, which causes twofold effects. First it causes retrograde colonization of the aero digestive tract and secondly the micro-aspiration of gastric fluid into the upper respiratory tract and lung have been shown to facilitate the occurrence of pneumonia[7,8]. Alternative to PPI's Sucralfate is widely a cytoprotective agent and has been listed as an acceptable prophylaxis for stress ulcer by practice guidelines with the caveat of slightly higher rate of clinically significant gastric bleeding compared with H2 antagonists[9,10]. Among the pathogens that were identified causing HAP in patients taking PPI's, gram negative bacteria outnumbered all pathogens[11].

The purpose of our study was to find the association of HAP with stress ulcer prophylaxis and spectrum of organisms causing hospital acquired pneumonia in MICU patients at Shifa International Hospital.

MATERIAL AND METHODS

This cross sectional study was conducted for a period of 4 month, from April 10, 2016 till August 2016 with non-probability convenient sampling technique after approval from IRB and ethics committee Shifa International Hospital. In all patients in the study admitted in MICU at Shifa International Hospital who were receiving or otherwise proton pump inhibitors as stress ulcer prophylaxis, tracheal cultures were followed on day 1 and day 2 and the spectrum of hospital acquired pneumonia (HAP) was defined. Hospital acquired pneumonia (HAP) was defined based upon the following criteria[9]:

- New chest infiltrates developing within 48 hours of admission.
- Fever of greater than 38 degrees Celsius.
- Total leucocyte count of more than 11000 or less than 3500/mcL.

There were two end points of this study. Firstly, it was established the selected patients who fulfilled the criteria for HAP and therefore were labelled as HAP. Secondly, in all patients who fulfilled the criteria for HAP tracheal cultures were followed to elucidate the spectrum of organisms causing HAP in PPI and non PPI group. All patients admitted in MICU during the above mentioned period were included in the study. Pediatric age group patients who were mainly an overflow from PICU having age of age <12 y were excluded from the study. Similarly patients having any contraindications to stress ulcer prophylaxis like having severe thrombo-cytopenia were excluded from the study.

Data was collected on prescribed performa. Results were analyzed using statistical package for the social sciences (SPSS) version 21. Qualitative data has been analyzed as frequency and percentages and quantitative variables as mean ± standard deviation. Chi-square test was performed to determine the association of HAP between patient receiving proton pump inhibitors verses non proton pump inhibitors.

RESULTS

One hundred and thirty-four patients (n=148) with mean age of 49 ± SD 4.81 years fulfilled the inclusion criteria. Eighty three patients (62.8%) of the included patients were males and 51 (37.2%) were females majority of patients were having medical problems with bulk of patients from neurology (table-I).

Forty five patients (33.6 %) out of a total of 134 patients developed HAP in the PPI group while 1 patient out of 14 patients (7.1%) develo-

ped HAP in non-PPI group and included in the study. All the initial tracheal cultures at admission were negative. Out of the 45 (33.6%) patients in the PPI group who fulfilled criteria for HAP 40 (88.6%) patients had positive tracheal cultures while in non PPI group 2 (14%) patients had positive cultures. The 89 (66%) patients who didn't fall into the criteria for HAP in the PPI group, 25 (28%) patients still had positive tracheal cultures but more than fifty percent of the cultures yielded Candida Albicans. Cultures after 48 hours patients fulfilling HAP criteria (table-II).

Table-I: Distribution of patients admitted to ICU, according to the source of referral.

	Frequency	Percentage (%)
Cardiology	12	8.1
Sepsis and septic shock	14	9.5
Gastroenterology	16	10.8
Nephrology	10	6.8
Pulmonology	19	12.8
Neurology	39	26.4
Drug overdose	4	2.7
Oncology	9	6.1
Endocrinology	4	2.7
Surgical	10	6.8
Others	2	1.4
Infectious disease	3	2.0
Rheumatology	3	2.0
HIV	2	1.4
Haematology	1	0.7
Total	148	100.0

Compared to non PPI group patients in PPI group developed HAP more frequently. Most of the HAP patients in PPI group, cultures yielded gram negative bacteria with majority being Acinetobacter baumannii MDR, *E coli* ESBL, *E. coli* MDR, Klebsiella pneumoniae ESBL and Klebsiella pneumoniae MDR major organisms while the 2 cultures positive in non PPI group were Acinetobacter baumannii MDR and Candida albicans.

DISCUSSION

Acid suppression therapy is a key part of ICU bundle in patients receiving mechanical ventilation for greater than 48 hours and patients having any bleeding tendency such as coagulopathy or thrombocytopenia[1]. However initiating stress ulcer prophylaxis is not free of risk. One of the common adverse effects for stress ulcer prophylaxis (SUP) is the association of this therapy with the development of hospital acquired pneumonia (HAP) especially ventilator associated pneumonia (VAP).

Most common agents used for SUP are either proton pump inhibitors (PPI's) or histamine 2 receptor blockers (H2RA's). Although other antacids like sucralfate can be used for SUP, their administration requires frequent dosing and can affect bioavailability of various dugs used in critical care areas. There have been various head to head trials comparing PPI's vs H2RA's in causing HAP. One such study was conduction by Miano which included 834 cardiothoracic surgery who received stress ulcer prophylaxis with either pantoprazole or ranitidine. Inclusion criteria included patients aged 18 years or more in Forest University Baptist Medical Center cardiothoracic surgery service between Jan 2004 and Mar 2007. Patients were randomized to either receive PPI's or H2RA's for SUP. This study concluded that

nosocomial pneumonia occurred in 35/377 (9.3%) of patients with pantoprazole compared to just 7/457 (1.5%) in the ranitidine treated population (OR = 6.6, 95% CI: 2.9-14.9). Pantoprazole group had high incidence of ventilator-associated pneumonia 31 of the 35 (88.5%). After propensity was adjusted, multivariable logistic regression, pantoprazole was found to be an independent risk factor for nosocomial pneumonia (OR = 2.7, 95% CI: 1.1 to 6.7, *p*=0.034).

Diagnosis of ventilator associated pneumonia can be established by various modalities. They included invasive bronchoscopic (BAL) vs noninvasive techniques like nonbronchoscopic BAL including the mini-BAL, blinded protected specimen brushing PSB, and blinded bronchial sampling (BBS). Nowadays trend is more towards noninvasive techniques because of their quick reproducibility and earlier initiation of empiric therapy[12]. In our study, we used tracheal cultures as a criterion for diagnosis of hospital acquired pneumonia.

The association between the usefulness of gram staining on tracheal aspirates showed that Negative predictive value of Gram stain for a VAP prevalence of 20%-30% was 91%, suggesting that VAP is unlikely with a negative Gram stain but the positive predictive value of Gram stain was only 40%. So, a negative Gram stain doesn't warrant discontinuation of empiric antibiotic therapy[13].

Our study demonstrated two end points in consideration of SUP and HAP. Firstly, 45 out of total 134 (n=134) patients suffered from HAP in the PPI group compared to 1 in non PPI group. The culture positivity of these patients was very good with tracheal aspirates yielding 40 patients demonstrating positive cultures in the PPI group. Most of the tracheal aspirates yielded gram negative organisms with Acinetobacter baumannii MDR, *E coli* ESBL, *E coli* MDR, Klebsiella pneumoniae ESBL and Klebsiella pneumoniae MDR major organisms. This prevalence of gram negative organisms very well explains one of the proposed mechanisms of actions of HAP in patients receiving PPI's i.e. microaspiration of gut contents[7,8]. Compared to our study, a study done in Canadian which

Table-II: Patients fulfilling hospital-acquired pneumonia criteria (PPI and non PPI group).

	Patients Fulfilling HAP Criteria		
	Yes	**No**	**Total**
Klebsiella pneumoniae ESBL	4	0	4
Klebsiella pneumoniae MDR	5	0	5
E. coli ESBL	2	0	2
E. coli MDR	4	0	4
MSSA	1	1	2
MRSA	1	0	1
Stenotrphomonas maltophilia	1	2	3
Moraxella SPP	1	0	1
Streptococcus pneumoniae	1	0	1
Pseudomonas aeruginosa	3	0	3
Polymicrobial	7	1	8
Candida albicans	1	16	17
Candida tropicalis	0	1	1
Mucor SPP	0	1	1
Aspergillus flavus	1	2	3
Acinetobacter baumannii MDR	9	1	10
Negative	5	76	81
Total	46	102	148

patients in general ICU group revealed that 35% to 80% of individuals were infected with Gram-negative bacilli, 9% to 46% with Gram-positive cocci and 0% to 54% with anaerobes[14].

Our study also revealed that 25 patients in the PPI group and 1 in non PPI group who didn't fulfill the criteria for HAP had positive tracheal cultures where Candida tropicalis was isolated from around 60 percent of the specimen. Treating decision in such patients should take into account other characteristics like immune competence, age and other baseline ICU severity risk scores. The true incidence of candida pneumonia is such patients is only 8 percent and candida pneumonia is a rare entity in ICU patients[15,16].

CONCLUSION

Gram negative bacteria was prevailed as the causative organism in patients who developed hospital acquired pneumonia (89 percent) and receiving proton pump inhibitors in medical intensive care unit with greater number incidence of HAP in PPI group.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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