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Proton pump inhibitor vs histamine 2 receptor antagonists for prophylaxis of stress ulcer in critically ill patients

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Abstract---Introduction: stress ulcer is one of the serious complications in critically ill patients admitted to intensive care unit and associated with increase in mortality rate among them, proton pump inhibitor and histamine 2 receptor antagonist have been widely used as stress ulcer prophylaxis (SUP) in critically ill patients, however its efficacy and safety remain unclear. This study aimed to assess the efficacy of SUP on clinical outcomes in critically ill patients. Aim of study: To compare between proton pump inhibitors and histamine 2 receptor antagonists in prevention of stress ulcer. Material and method: We do a single, blind, randomized trial on two hundred critically ill patients admitted to intensive care unit divided into two groups, group A took famotidine 40mg single daily enterally and group B took omeprazole 40mg single daily intravenously. Results: Statistically there is no difference in incidence of stress ulcer among the two group of patients with P value of 0.25. Conclusion: The use of histamine 2 receptor antagonist is equal to proton pump inhibitor in prevention of stress ulcer and associated with less side effect than proton pump inhibitor

Keywords---stress ulcer, famotidine, omeprazole.

Introduction

Stress ulcers: are multiple, superficial erosions or deeper to the submucosa, which occur mainly in the fundus and body of the stomach. They develop after shock, sepsis, and trauma and other chronic medical illness ⁽¹⁾. Stress ulcers, as defined by overt bleeding and hemodynamic instability, decreased hemoglobin, and/or need for transfusion ⁽²⁾. People with stress ulcers have a longer ICU length of stay (up to 8 days) and a higher mortality (up to 4-fold) than patients who do not have stress ulceration and bleeding ⁽³⁾. The ulcerations may be superficial and confined to the mucosa, in which case they are more appropriately called erosions, or they may penetrate deeper into the submucosa. The former may cause diffuse mucosal oozing of blood, whereas the latter may erode into a submucosal vessel and produce frank hemorrhage ⁽¹⁾. The characteristic lesions may be multiple, superficial mucosal erosions similar to erosive gastroduodenitis. Occasionally, there may be a large acute ulcer in the duodenum (Curling's ulcer) ⁽⁴⁾. It is unclear which agent is best or if prevention is needed at all ^(5,6). Possible agents include antacids, H₂-receptor blockers, sucralfate, and proton pump inhibitors (PPIs). Tentative evidence supports that PPIs may be better than H₂ blockers ⁽⁷⁾. The principles of management are the same as for the chronic ulcer. The steps of management are similar as in erosive gastritis ⁽⁴⁾. Endoscopic means of treating stress ulceration may be ineffective and operation required ⁽⁸⁾. It is believed that shunting of blood away from the mucosa makes the mucous membrane ischemic and more susceptible to injury ⁽⁴⁾. Omeprazole, is a medication used in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger–Ellison syndrome, it is also used to prevent upper gastrointestinal bleeding in people who are at high risk ⁽⁹⁾. Is a histamine H₂ receptor antagonist medication that decreases stomach acid production. It is used to treat peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome. It is taken by mouth or by injection into a vein. It begins working within an hour ⁽¹⁰⁾. Treatment of stress ulceration usually begins with prevention. Careful attention to respiratory status, acid-base balance, and treatment of other illnesses helps prevent the conditions under which stress ulcers occur. Patients who develop stress ulcers typically do not secrete large quantities of gastric acid; however, acid does appear to be involved in the pathogenesis of the lesions. Thus, it is reasonable either to neutralize acid or to inhibit its secretion in patients at high risk ⁽¹¹⁾. In case of severe hemorrhagic or erosive gastritis and stress ulcers, a combination of antacids and H₂-blockers may stop active bleeding and prevent re bleeding. In selected patients, either endoscopic therapy or selective infusion of vasopressin into the left gastric artery may help control the hemorrhage ^(9,12). The aim of study is to compare between proton pump inhibitors and histamine 2 receptor antagonists in prevention of stress ulcer.

Method

A prospective, single blind trial was conducted at Al-Kadhimiya teaching hospital, Baghdad, Iraq, which started at 1st of October 2020 to 25th of September 2021. After approval of ethical committee of the Arab board of medical specializations, and written informed consent was obtained from the patients relative before including them in the study, a detailed history was taken from their relatives,

clinical examination was performed. A total of 200 patients who were admitted to intensive care unit and intubated were divided into two groups: Group A was one hundred patients took famotidine tab 40mg single daily entirely. Group B also were one hundred who took omeprazole 40mg single daily intravenously. They kept under supervision and monitored daily to see if any side effect appears on them and to assess our research if any sign of stress ulcer appears on them, they kept on omeprazole and famotidine as long as they stayed in ICU and they were shifted to omeprazole 80mg bolus and then 200mg infusion for 24hr when there was a sign of stress ulcer. It was considered that hematemesis and melena are sign of upper GI bleeding and stress ulcer

The inclusion criteria were

Critically ill patient, Age above 18 years' old

Exclusion criteria

1. Patients with history of peptic ulcer
2. Patients with history of chronic use of antacid
3. Patients with history of laparotomy involving stomach recently
4. Had coagulation disorder
5. History of aspirin, and warfarin ingestion
6. Allergic to famotidine or omeprazole
7. There is contraindication to any of the drugs
8. Patients with renal or liver failure

Statistical analysis done by SPSS 22, frequency and percentage used for categorical data, mean, median and SD for continuous data. Chi-square used for assessed association between variables. P-value less or equal to 0.05 is consider significant.

Results

Table 3-1. Subjects' sociodemographic characteristics (N = 200)

Variable	Frequency	Percent
Age (Years): Mean (SD): 46.58 ±		
15-61	37	18.5
19-29	23	11.5
30-39	51	25.5
40-49	43	21.5
50-59	33	16.5
60-69	13	6.5
70-80		
Gender		
Male	158	79.0
Female	42	21.0
$\chi^2 = 0.537, df = 1, p\text{-value} = 0.464$		

SD = Standard deviation, p-value = Level of significance, χ^2 = Chi- square

The age mean is 46.58 ± 15.61 ; around a quarter age 40-49-years ($n = 51$; 25.5%), followed by those who age 50-59-years ($n = 43$; 21.5%), those who age 19-29-years ($n = 37$; 18.5%), those who age 60-69-years ($n = 33$; 16.5%), those who age 30-39-years ($n = 23$; 11.5%), and those who age 70-80-years ($n = 13$; 6.5%). Concerning gender, most are males ($n = 158$; 79.0%) compared to females ($n = 42$; 21.0%) and there is no statistically significant association between gender and developing peptic ulcer.

Table 3-2. Subjects' medical profile (N = 200)

Variable	Frequency	Percent
Hospitalization Duration (Days): Mean (SD): 12.63 ± 8.64		
Reason of hospitalization Disturb level of consciousness	173	86.5
Respiratory failure	15	7.5
Vitally unstable	10	5
Status epilepticus	2	1

SD = Standard deviation

The hospitalization duration mean is 10.2 ± 8.6 days.

Concerning the reason of hospitalization, the majority are due to disturb level of consciousness ($n=173$; 86.5%), respiratory failure ($n=15$: 7.5%), vitally unstable ($n=10$: 5.0%), status epilepticus ($n=2$; 1.0%) for each of them.

Table 3-3. Subjects' developing of peptic ulcer (N = 200)

Variable	Frequency	Percent
Developing peptic ulcer		
Yes	2	1.0
No	198	99.0

The clear majority did not develop peptic ulcer ($n = 198$; 99.0%) compared to those who developed it ($n = 2$; 1.0%).

Table 3-4 average duration of drug administration

drug	famotidine	omeprazole
Average duration of administration	9.3	10.9

There is a mild increase in the average duration of use of omeprazole 10.9 day to the use of famotidine 9.3 day due to various cause of admission and different duration of stay between the patients.

Table 3-5. Cross-tabulation between medication received and developing peptic ulcer

			Outcome		Total
			Yes	No	
Medication	Omeprazole	Count	2	98	100
		% within Medication	2.0%	98.0%	100.0%
		% of Total	1.0%	49.0%	50.0%
	Famotidine	Count	0	100	100
		% within Medication	0.0%	100.0%	100.0%
		% of Total	0.0%	50.0%	50.0%
Total		Count	2	198	200
		% of Total	1.0%	99.0%	100.0%

Fisher's Exact Test = .2.020; df = 1; p-value = 0.249

df = Degree of freedom; p-value = Level of significance

Of two hundred patients were involved in our study only two of them develop stress ulcer and they both were taken omeprazole and none of them develop stress ulcer who were on famotidine with incidence of 1% and 0% respectively. There is no statistically significant association between type of medication received and developing peptic ulcer.

Discussion

Stress ulcer is one of the serious complications in ICU and there are a lot of medication to prevent it. In our study we use Omeprazole and Famotidine and try to compare between them. In group A, we gave them Famotidine 40mg single dose daily entirely and no one of them showed sign of stress ulcer. In group B, we gave them omeprazole 40mg single dose daily intravenously and only two of them develop stress ulcer by appearance of coffee-ground discharge from the nasogastric tube. Although two patients in group B develop stress ulcer and no one in group A develop that but statistically shows no significantly association between type of medication received and developing peptic ulcer with P value = 0.249. In a study done by Kantorova I et al, in 2004 goes against our result with Famotidine which shows incidence 3% of stress ulcer in their study which is against our result ⁽¹³⁾. Other trial done by M.J. Song et al in 2021, used omeprazole vs histamine 2 receptor antagonists on 1870 patients in ICU shows incidence of stress ulcer by 1.6% and 1.7% respectively which shows no significant difference between both drugs ⁽¹⁴⁾. In our study we did not take in our consideration the mortality or pneumonia between each group, but several studies showed that there is increase in mortality or incidence of pneumonia in patients on omeprazole compared to those on histamine 2 receptor antagonists ⁽¹⁵⁾. This study had several limitations, first the number of patients is low. Second, we depend on malena and hematemesis so other simple erosion didn't be noticed ^(13,15).

Conclusion

Statistically there is no difference between the use of proton pump inhibitors or histamine 2 receptor antagonists in prevention of stress ulcer in critically ill patients in intensive care unit but associated with less drug interaction and less side effect for famotidine compared to omeprazole.

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