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SUCRALFATE VERSUS ANTACIDS OR HISTAMINE$_2$ (H_2) RECEPTOR ANTAGONISTS FOR STRESS ULCER BLEEDING PROPHYLAXIS

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Abstract:

BACKGROUND: *Histamine$_2$ (H_2)-receptor antagonists and antacids have been the mainstay pharmacologic agents for the prevention of stress ulcers and incumbent ulcer bleeding in hospital in-patients during the past decade. Recently, drugs without major influence on gastric pH have been investigated in stress bleeding prophylaxis, with one being sucralfate.*

OBJECTIVE: *To study the efficacy of sucralfate in the prevention of macroscopically visible stress bleeding, in comparison to Histamine$_2$ (H_2)-receptor antagonists and antacids.*

METHODOLOGY*: This prospective cohort was conducted upon a sample of 400 patients (aged 18 and above) admitted to the Dept. of Medicine & Allied at Abbasi Shaheed Hospital, Karachi from January 2018 to December 2018. No gender bias was observed and all patients were chosen via multistage sampling (with enrollment carried out on the basis of non-probability consecutive sampling and pharmacologic agent allotment done on the basis of simple random sampling. Data was recorded onto a structured questionnaire containing inquiries about the study variables, inferences obtained from clinical examination notes and details of all morbidity and mortality during hospitalization. The data obtained was analyzed using SPSS v.21 & Microsoft Excel 2016.*

RESULTS: *We observed that there is a trend toward decreased overt bleeding when either of the pharmacologic agents are compared with no therapy. Histamine$_2$ receptor antagonists and antacids are associated with a trend toward lower clinically important bleeding rates than sucralfate. However, sucralfate does outperform the other two pharmacologic agents in terms of limiting undesirable outcomes.*

CONCLUSION: *After careful consideration, it can be concluded that histamine$_2$ receptor antagonists and antacids have a higher efficacy in preventing stress ulcer bleeding than sucralfate. However, given the added benefits of sucralfate and its cumulative effect on reducing eventual arte of mortality among inpatients, it's use should be considered in conjunction with either histamine$_2$ receptor antagonists and antacids, with the use of histamine$_2$ receptor antagonists recommended owing to the fact that it is most efficacious and prophylaxis with this pharmacologic agent decreases the incidence of overt gastrointestinal bleeding and clinically important bleeding, more than any other tested drug.*

KEYWORDS: *Histamine$_2$ Receptor Antagonist, Antacid, Sucralfate, Stress Ulcer Prophylaxis and Bleeding.*

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INTRODUCTION:

Stress ulcers or stress-related mucosal disease (SRMD) is defined as "acute superficial inflammatory lesions of the gastric mucosa induced when an individual is subjected to abnormally high physiologic demands." Multiple lesions are typically associated with stress ulcers and are usually located in the acid and pepsin secreting mucosa. [1] Studies have reported evidence of mucosal damage within 24 hours of admission in 75–100% of intensive care unit (ICU) patients, and slightly less (54-63%) in regular medical in-patients. [2, 3]

However, these lesions generally heal as the patients' clinical status improves. Risk of bleeding from stress ulcers appears to be on the decline, from 20–30% in the 1970s to 1.5–14% in the 1990s. This is largely thought to be due to improvements in the treatment of underlying conditions and the appropriate use of stress ulcer prophylaxis. [4] Even with this decline in the risk of bleeding, however, mortality from stress-related bleeding in critically ill patients approaches 50%. [5]

The use of proton pump inhibitors (PPIs) and histamine H2-receptor antagonists for the prevention of stress ulcers has been well-defined. In 1999, the American Society of Health-System Pharmacists (ASHP) published guidelines on the use of stress ulcer prophylaxis in medical, surgical, respiratory, and pediatric ICU patients. [6] In recent years, this practice has become increasingly more common in general medicine patients, with little to no evidence to support it, and often yielding adverse events. Recently, drugs without major influence on gastric pH have been investigated in stress bleeding prophylaxis, with one being sucralfate. [7]

Sucralfate, a complex of aluminum hydroxide and sulfated sucrose, is a cytoprotective agent that provides a physical barrier over the surface of a gastric ulcer and enhances the gastric mucosal protective system. After oral administration the drug disperses in the stomach and, in the presence of acid, forms a viscous suspension that binds with high affinity at the ulcer site. The negatively charged sucrose sulfate is thought to bind to the positively charged proteins of the ulcer. A physical cytoprotective barrier is produced that covers the ulcer and protects it from further attack by damaging agents such as acid, pepsin, and bile salts. [8]

Although sucralfate possesses no meaningful antacid properties and a precise mechanism of action is unclear, a key element in the acute gastroprotective actions of sucralfate is its ability to maintain mucosal vascular integrity and blood flow. It enhances bicarbonate and mucus secretion, increases mucosal hydrophobicity, and induces an increase in mucosal concentration of prostaglandin—all factors considered important in tissue healing. [9]

Positive randomized trials in stress ulcer prophylaxis have led to recommendations that prophylaxis be administered to a large proportion of critically ill patients. However, no individual study has definitively established whether these agents decrease either clinically important gastrointestinal bleeding or mortality, nor has any study elucidated the relative merits or risks of different prophylactic regimens. [10] Several systematic reviews too have evaluated stress ulcer prophylaxis, however, the results of these overviews are plagued with some inconsistencies. [11, 12] This study was thus needed to provide a fresher, more valid perspective regarding the matter and offer deeper insight using a direct comparison of all major pharmacologic agents.

METHODOLOGY:

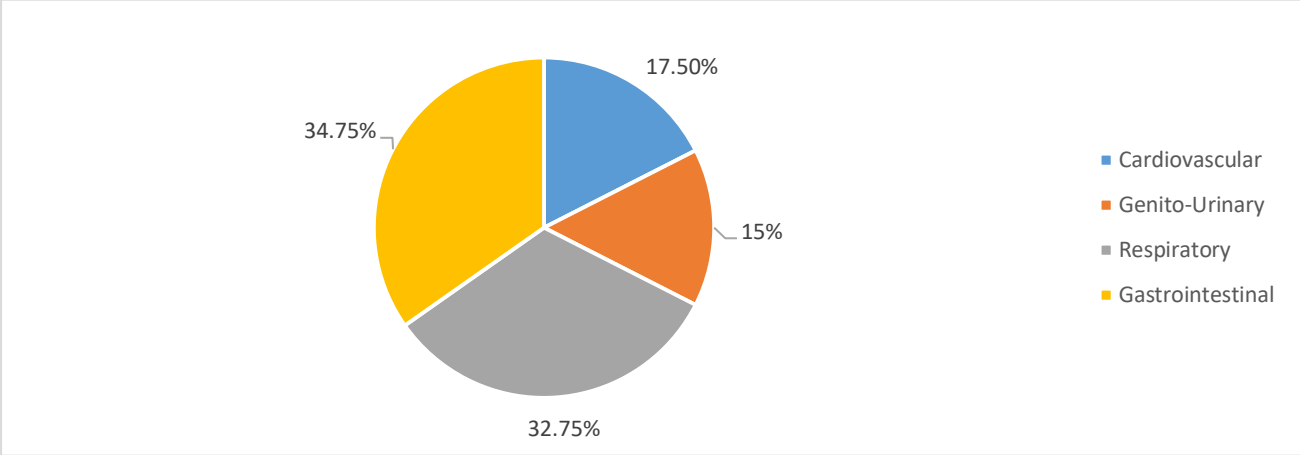
This prospective cohort was conducted upon a sample of 400 patients (aged 18 and above) admitted to the Dept. of Medicine & Allied at Abbasi Shaheed Hospital, Karachi from January 2018 to December 2018. No gender bias was observed and all patients were chosen via multistage sampling (with enrollment carried out on the basis of non-probability consecutive sampling and pharmacologic agent allotment done on the basis of simple random sampling. Data was recorded onto a structured questionnaire containing inquiries about the study variables, inferences obtained from clinical examination notes and details of all morbidity and mortality during hospitalization. The data obtained was analyzed using SPSS v.21 & Microsoft Excel 2016.

RESULTS:

Among the 400 patients studied, 291 were males while the remaining 109 were females. The mean age of the sample stood at 34 (SD ±13). A majority (62.25%) of the patients hailed from an urban background while just 37.75% belonged to a rural setting.

Age	Males	Females
Up to 30 years	*83*	*34*
31 to 40 years	*167*	*44*
41 to 50 years	*37*	*22*
51 years and above	*04*	*09*

The reasons for admission included gastrointestinal (34.75%), respiratory (32.75%), cardiovascular (17.5%) and genito-urinary (15%)



A total of 100 patients each were administered either of the three pharmacologic agents and the remaining 100 were kept as control. We observed that there is a trend toward decreased overt bleeding when either of the pharmacologic agents are compared with no therapy. Histamine$_2$ receptor antagonists and antacids are associated with a trend toward lower clinically important bleeding rates than sucralfate. However, sucralfate does outperform the other two pharmacologic agents in terms of limiting undesirable outcomes.

Prophylactic Agent	Bleeding Present	Bleeding Absent
Administered	19.67%	80.33%
Not Administered	39%	61%

Prophylactic Agent	Bleeding Present	Bleeding Absent
H_2 Receptor Antagonist	11%	89%
Antacid	26%	74%
Sucralfate	31%	69%

DISCUSSION:

Only three studies to date have looked at the benefit of stress ulcer prophylaxis in general medicine patients. Estruch et al. [13] conducted a randomized, placebo-controlled, eight-month trial to evaluate the efficacy of antacid in the prevention of acute GI bleeding in seriously ill patients admitted to general medicine wards at a large teaching hospital in Spain. Patients with a diagnosis of respiratory failure (excluding mechanical ventilation or intubation); heart failure (requiring inotropic agents); sepsis; thrombotic or hemorrhagic stroke; liver failure; renal insufficiency (serum creatinine of >4 mg/dL); or treatment with corticosteroids (>250 mg/day of prednisone), heparin, or warfarin were included in the study.

Patients were excluded if they demonstrated prior evidence of upper-GI bleeding or had cardiac, gastric, or esophageal surgery or GI symptoms such as regurgitation, heartburn, dysphagia, and epigastric pain. Patients were randomized to placebo or magaldrate 800 mg p.o. given five times daily. Evidence of upper-GI-tract bleeding occurred in 12 patients, 1 of 52 in the antacid group and 11 of 48 in the placebo group ($p < 0.01$). None of the antacid patients and 3 of the placebo patients had at least a 10% decrease in hematocrit and required transfusions for these bleeding episodes.

Grau et al. [14] performed a randomized controlled trial comparing the efficacy of cimetidine and sucralfate in the prevention of GI-tract bleeding in general medicine patients admitted to the same teaching hospital as described above over a period of eight months. Using the same criteria as described for the preceding trial, 74 patients were randomized to cimetidine 800 mg p.o. at bedtime and 70 patients were randomized to receive sucralfate solution 1 g p.o. every six hours.

Bleeding was noted in 2 patients (2.7%) in the cimetidine group and 2 patients (2.8%) in the sucralfate group, although bleeding was noted to be more severe in the sucralfate group, necessitating 3 units of packed red blood cells in both sucralfate patients.

Both of these trials had limitations that make extrapolation of the results difficult. Many patients had multiple risk factors for bleeding, such as sepsis,

respiratory failure, cardiac failure, high-dose corticosteroids, and stroke. Second, all bleeding that caused declines in hematocrit were included in the analysis, and serious bleeding that required transfusions were not analyzed separately from minor bleeding that quickly resolved. In the study performed by Estruch et al., [13] only three patients in the placebo-controlled group had serious bleeding.

Recently, a retrospective, case–control study was published by Qadeer et al. [15] This trial was designed to identify risk factors that would predict hospital-acquired GI bleeding and to assess whether prophylaxis with acid suppressants was associated with less bleeding. Cases were defined as patients on a general internal medicine ward who either were admitted for a non-GI illness and developed bleeding 24 hours or longer after admission or were admitted with GI bleeding and had been hospitalized within the preceding four weeks for a non-GI illness. The major risk factor identified in the study for hospitalacquired GI bleeding was treatment with any anticoagulant (warfarin, clopidogrel, full-dose unfractionated heparin, or full-dose low-molecularweight heparin) with a combined odds ratio (OR) of 5.4.

After adjustment for full-dose anticoagulants, PPI use before hospitalization was also associated with GI bleeding (OR, 2.7; 95% CI, 1.1–7.0). Although the sample size of cases was small, no association between the use of acid suppression and GI bleeding was found (OR, 1.0; 95% CI, 0.4–2.4). In this study, hospital-acquired bleeding in the general medicine population was very infrequent and the routine use of acid suppression was not beneficial. This study, although retrospective in nature, reinforces the conclusion of the ASHP treatment guidelines to not routinely recommend stress ulcer prophylaxis to general medicine patients

CONCLUSION:

After careful consideration, it can be concluded that histamine$_2$ receptor antagonists and antacids have a higher efficacy in preventing stress ulcer bleeding than sucralfate. However, given the added benefits of sucralfate and its cumulative effect on reducing eventual arte of mortality amog inpatients, it's use should be considered in conjunction with either histamine$_2$ receptor antagonists and antacids, with the use of histamine$_2$ receptor antagonists recommended owing to the fact that it is most efficacious and prophylaxis with this pharmacologic agent decreases the incidence of overt gastrointestinal bleeding (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.42 to 0.79) and clinically important bleeding (OR, 0.44; 95% CI, 0.22 to 0.88), more than any other tested drug.

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