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STRESS ULCER PROPHYLAXIS IN ICU PATIENTS

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ABSTRACT

Proton Pump Inhibitors (PPIs) are class of medications that work on the cell that line the stomach, reducing the production of acid. Histamine-2 receptor antagonists are having similar effects as that of PPIs but different mode of action. H2-receptor blockers (H2RBs) are class of medication that block the action of histamine at the histamine H2 receptor of the parietal cells in the stomach and decreases acid secretion. The use of PPIs and H2-Receptor Blockers for the prevention of stress ulcer has been well defined in ICU patients. To compare the effect of both these drugs on hospital mortality, several crossover randomization studies was conducted. Patients receiving invasive mechanical ventilation within 24 hours of index hospitalisation were followed up for 90 days with 6 months preferential use of PPIs vs. H2- RBs, followed by 6 month alternative therapy. Studies suggest that the primary outcome was mortality within 90 days & secondary outcome was the rates of patients with Upper Gastrointestinal Bleeding (UGIB) and Clostridioides difficile infection. As per the data, the mortality rates were high among patients receiving PPIs than H2-RBs and the absolute risk difference was about 0.93%. UGIB occurred more in PPIs group while comparing to H2-RBs group. Rates of Clostridioides difficile and ICU length of stay were not different by treatment group. Post hoc analysis revealed that patient at higher risk strata had greater mortality after assignment to PPIs compared to H-2RBs. The PPIs vs. H-2RBs for stress ulcer prophylaxis had higher 90 day mortality that did not reach significant threshold.

KEYWORDS: Proton Pump Inhibitors, Histamine-2 receptor blocker, ICU patients, Stress ulcer prophylaxis.

INTRODUCTION

Stress ulcer is a single or multiple mucosal defect. Stress ulcer prophylaxis is commonly administered to critically ill patients for the prevention of clinically important stress-related mucosal bleeding from the upper gastrointestinal tract. Both stress ulcers and gastric ulcers cause sores in the lining of the stomach and intestine leading to GI bleeding, but stomach ulcer usually tends to emerge gradually as drugs or infections weaken the gastrointestinal lining while stress ulcers are come on suddenly, usually as a result of physiological stress.

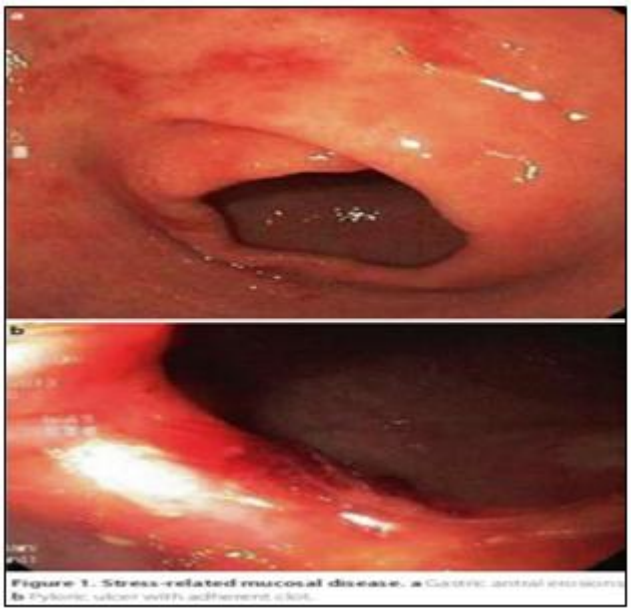

Figure 1: Stress-related mucosal disease.

Stress ulcerations are common in intensive care unit (ICU) patients, some of which can cause haemorrhage. Clinically important gastrointestinal bleeding can cause haemorrhagic instability and the increase the need for RBC transfusions.[1] As a consequence; many critically ill patients require prophylaxis for primary prevention of bleeding from stress ulceration or treatment for stress-ulcer-related bleeding.

Epidemiology of Stress Ulcer

Data from latest studies suggested that overt gastrointestinal bleeding occurred frequently and in case of some studies up to 25% of critically ill patient's development overt GI bleeding.[2] Stress ulceration was first described in 1969. As per the endoscopic studies, 74-100% of critically ill patients have stress-related mucosal erosions and sub epithelial haemorrhage within 24 hours of admission.[2,3]

Table 1: Demographic data of children with & without Stress-induced GI bleeding.

Characteristics	Bleeding (n=74)	No Bleeding (n= 96)	P
Age (yr.)	3.82	3.84	0.977
Sex, male	41	48	0.484
Duration of admission	8.23	6.41	0.062
Underlying diseases(Respiratory, Cardiovascular, GI system & others)	8 9 19 11 14 5 8	15 18 12 11 9 6 12	0.445

According to the demographic data in table 1 52.4% of males with an average age of 3.8 years were found to be haemorrhagic.[4]

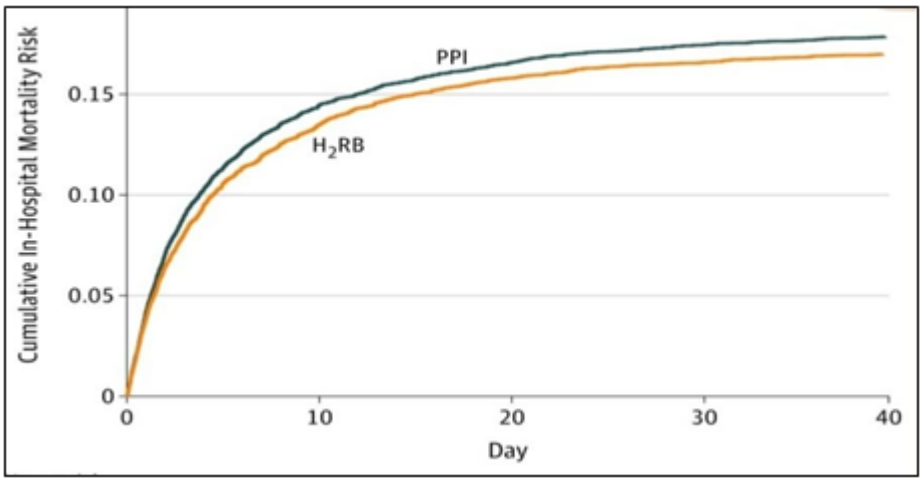

Figure 2: Cumulative Incidence In-hospital mortality.

The fig.2 explains the cumulative incidence of hospital mortality among critically ill patients admitted in ICU.[5] While comparing the effect of both class of drug PPIs and H2RBs, there is only a slight variation in the mortality rates. 18.3% of patients in PPIs died while 17.5% of patient in H2RBs at the hospital by day 90. So, that the absolute risk difference is 0.93%. The curve truncated at 40 days beyond which less than 10% of the population remained at risk as in fig.2.

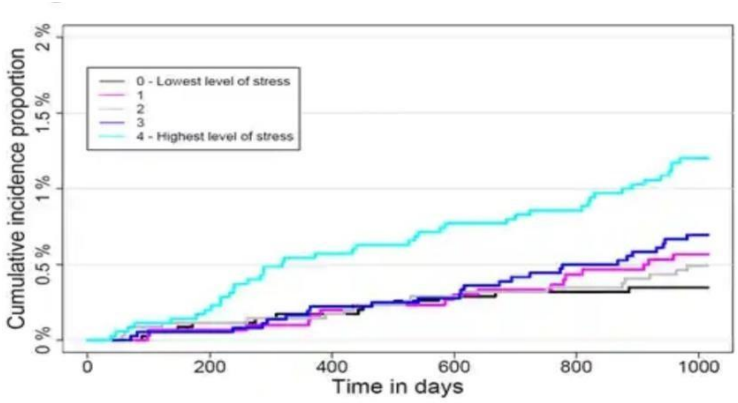

Figure 3: Cumulative incidence of peptic ulcer due to stress.

The incidence of defined peptic ulcers is more than 1% in patients with highly increasing level of stress.[6] Although occult bleeding, as defined by guaiac stool positivity in samples from nasogastric tube or emesis, has been proposed as a working definition of stress-ulcer bleeding, the more relevant clinical presentation is that overt bleeding manifesting as haemostasis, coffee ground emesis, melena or bloody nasogastric aspirate.[7] The important clinical risks related primarily to the patients underlying illness are SRMD (Stress Related Mucosal Disease) and clinically significant bleeding. The recent reports suggest that the incidence of SRDM- associated clinically significant bleeding or stress ulcer bleeding has markedly decreased in the past 10 years.

Pathogenesis of Stress Ulcer

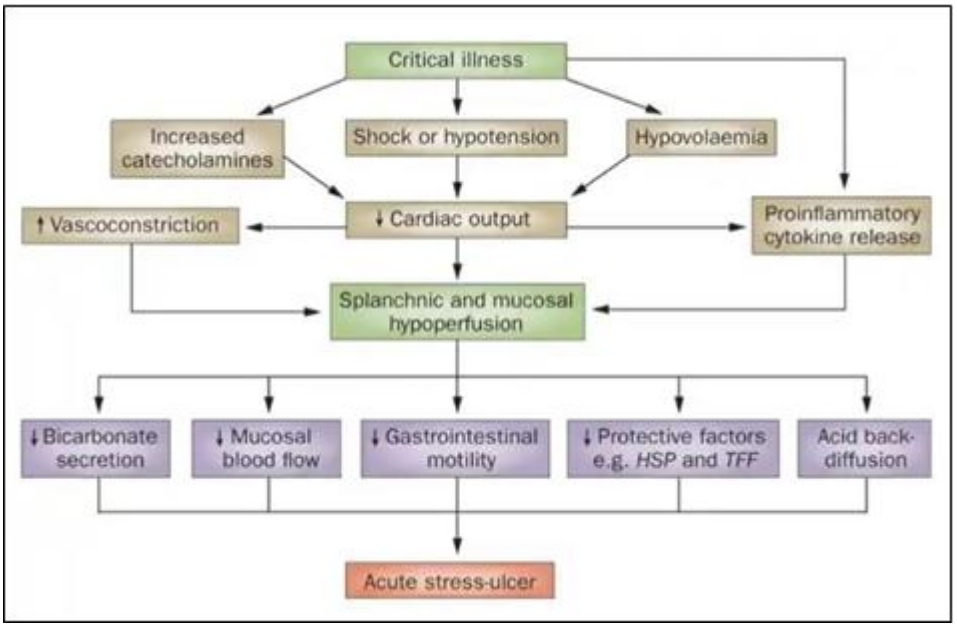

Figure 4: Pathophysiology of Stress-ulcer.

Fig 4 represents the pathogenesis of stress ulcer.[7] The critical illness can lead to three major conditions of shock/hypertension, hypovolemia and also causes increased release of catecholamine. All these conditions together can cause decrease in the cardiac output. The increased vasoconstriction and also the release of pro-inflammatory cytokine release can occur as a result of decreased cardiac output. This will contribute to the splanchnic & mucosal hypo perfusion, which causes five different manifestations including decreased bicarbonate secretion, mucosal blood flow, gastrointestinal motility, protective factors (eg: HSP & TFF) and also acid back diffusion, whole of these conditions finally leads to acute stress ulcer. Putative mechanisms underlying SRDM include reduced gastric blood flow, mucosal ischemia & reperfusion injury, all of which occur frequently in the critically ill.[3] Mucosal ischemia is the major inclining event in the pathogenesis of acute stress ulceration of the stomach and that the presence of luminal acid and pepsin are required for overt ulceration to develop. The severe acidosis and base deficit together with depression of acid secretion and consequent lowering of alkaline tide are important contributing factors. Back diffusion of acid occurs in the absence of overt disruption of the gastric mucosal barrier, is closely related to the formation of ulcers, and may be enhanced by reflux of duodenal content into the stomach by diffusion of blood urea into the stomach.[8] Commonly stress-related response are seen in patients with respiratory failure requiring mechanical ventilation, coagulopathy, acute renal insufficiency, acute hepatic failure, sepsis, hypotension and severe head or spinal cord injury. There is an association of between severe physiologic stress and GI ulceration, which form stress ulcer but still the mechanism behind the stress-ulcers are incompletely understood. Although, recent publications address the overuse of stress ulcer prophylaxis both inside and outside of ICU is also critical in pathology of stress ulcers.

Indications & Complications of Stress-ulcer bleeding

The major medications for stress ulcer prophylaxis include past history of gastric ulcer or GI bleeding in past 12 months, Trauma: TBI, spinal cord injury or due to burns, 2 or more of: > 1 week in ICU, occult GI bleeding, steroids (>250 mg hydrocortisone per week). SRMD represents a continuum from asymptomatic superficial lesions found incidentally during endoscopy, occult GI bleeding causing anaemia overt GI bleeding and clinically significant GI bleeding. The very high risk factors for stress ulcer prophylaxis include mechanical ventilation for more than 48 hours & also coagulopathy – defined as INR over 1.5, platelets <50 or a partial thromboplastin time (PPT)> 2 times the control value. Enteral nutrition is a protective measure against stress ulcer but it is uncertain of with withholding stress ulcer

prophylaxis from patients who are at high risk of GI bleeding.

Table 2: Risk factors of SRMD.

Type	Risk Factor
Independent	1. Coagulopathy: Platelet count < 50,000mm^3 2. Respiratory failure: mechanical ventilation >48 hours
Other	1. Spinal cord injuries 2. multiple trauma 3. Hepatic failure (total bilirubin level > 5mg/dl 4.Thermal injuries 5. Partial hepatectomy 6. Head injury with Glasgow coma score of <10. 7. Hepatic or renal transplantation 8. History of gastric ulceration or bleeding 9. Sepsis/septic shock 10. Intensive care unit stay >1week 11. Occult or overt bleeding >6 days 12. Corticosteroid therapy

The table 2 provides the risk factors as provided by ASHP and a literature review noting a landmark trial by Cook et.al.[1,9] There is controversy surrounding the relationship between the use of stress ulcer prophylaxis and the development of infectious complications, particularly infection related ventilator associated complications (IVAI) and Clostridium difficle infection. There are some general complications for stress ulcer prophylaxis which include drug allergy, drug side-effects and drug interactions (especially cimetidine), pneumonia (HAP & IAA). There can be some drugs including PPIs and H2RBs causing complications. PPIs rarely causes interstitial nephritis, clostridium difficile. endocarditis is another condition in which PPIs are having dose- dependent relationship, GI upset & headache, long term use of PPIs associated with fracture, hypomagnesaemia, hypocalcaemia etc. H2 blockers causes CNS side effects like slurred speech, poor concentration, confusion, light-headedness, dizziness, problem with movement and memory etc. & also develop tolerance after 72 hour.

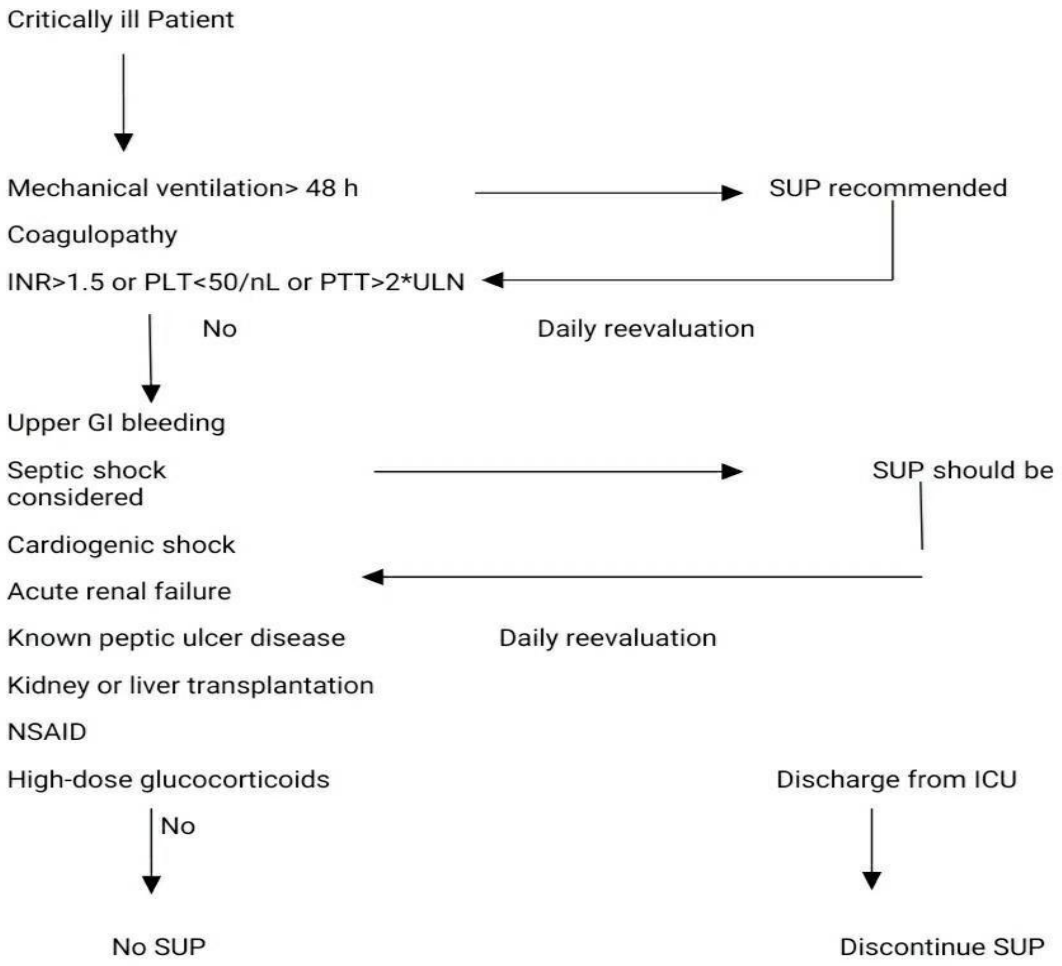

Figure 5: Algorithm for Stress-ulcer prophylaxis Fig 5 represents the proposed Algorithm for Stress-ulcer prophylaxis. [10] Mortality Risk of Stress-ulcer related Bleeding

In ICU patients risk of death increasing due to stress ulcer with an acute bleeding episode. In a large prospective trial by Cook et al. the mortality of patients with stress ulcer bleeding was 49% compared to 9% in those without an episode of GI bleeding. Both ASHP (American Society of Health system Pharmacists) & the Surviving Sepsis Campaign guidelines recommend Stress Ulcer Prophylaxis (SUP) with either Histamine-2 receptor antagonists (H-2RAs) or Proton Pump Inhibitors (PPIs) as standard in patients with a high risk of stress related GI bleeding.[12,13] The recent meta-analysis showed that PPIs were more effective than H-2RAs in preventing UGI bleeding in critically ill patients. Neurological injury, combined with severe physiological stress and critical illness has been shown to increase the morbidity and mortality associated with stress-related UGI bleeding in the setting of acute neurological diseases including traumatic brain injury, spontaneous intracerebral haemorrhage, ischemic

stroke, spinal cord injury, central nervous system infections etc.[11] The hospital mortality rate trended higher with a strategy giving preference to proton pump inhibitors at 18.3% versus 17.5% with H-2RB- recurrent prophylaxis, whereas clinically important upper GI bleeding was less common with the PPI strategy (1.3% vs. 1.8%).[14] A study presented at the Critical Care Reviews Meeting 2020 in Belfast, Northern Ireland and simultaneously published online in JAMA states that "Although the trial was powered for a difference of 2.4% in 90-day mortality the smaller difference of 0.89% would be meaningful, if real, given that hundreds of thousands of patients are at risk annually",[14] The post hoc analysis also suggested the similar findings. Other studies estimated 2.6% of adults acutely admitted to the intensive care unit developed. Clinically significant upper GI bleeding and 70% were prescribed stress ulcer prophylaxis to proffer this.

Pharmacological Prophylaxis

Table 3: Drugs used for stress ulcer prophylaxis.

SI no	Drug class	Frequency of use	%
1	Proton Pump Inhibitor	76	92.7%
2	Histamine-2 Receptor Antagonist	6	7.3%

Table 3 represents the prophylactic drugs used for stress ulcer.[15] PPIs was the most commonly used drug class in the prevention of stress ulcer. The critically ill patients with moderate to severe physiologically stressful event are at high risk of developing stress ulcers. The incidence of stress ulcer in high risk patients seems to be reduced with the use of pharmacological prophylaxis. Proton pump inhibitors and Histamine-2 receptor blockers are used to prevent the acid injury and stress ulcer or to decrease the acid secretions / to enhance protective mechanisms. However, antacids and sucralfate are rarely used, the PPIs and H2RAs tend to be better tolerated and are easily administered while comparing to antacids and sucralfate. According to the study conducted by Boressa Adugna et al.[15] in United States, reported the use of SUP in 90% of ICU patients. This may be due to the increased risk for stress ulcer developing among patients admitted in ICU having risk factors for stress ulcer like mechanical ventilation, enteral feeding, hypo perfusion etc.

Adverse Events of SUP Therapy

Many investigations found increased rate of infectious complications in critically ill patients receiving stress ulcer prophylaxis, primarily Clostridium difficile associated colitis and nosocomial pneumonia.[16] The use of PPI might be associated with adverse cardiovascular events, independently of clopidogrel use[17], as well as with osteoporosis.[18] There can be incidence of PPI toxicity in the liver and bone marrow as well as drug-drug interactions among ICU patients. The PPI favour the intestinal colonization with multi-drug resistant bacteria such as vancomycin resistant Klebsiella pneumonia. The C.difficile produces toxins which are the major cause of diarrhoea and colitis in hospitalized patients taking SUP, with an increase in incidence, severity and mortality in recent years. Several studies have found an association between the use of ASDs and an increased risk of respiratory tract infections. Along with enteric infections, ASDs are thought to increase the risk of pneumonia by inhibiting the acid secretion thus allowing the bacterial overgrowth of colonization.[19] The ASDs may also impair the function of neutrophils and the activity of natural killer cells. Medications with P^H dependent absorption i.e., digoxin, nifedipine, indinavir, midazolam, didanosine, alendronate, methadone, aspirin may be affected by both PPIs and H2RAs resulting on increased rate of absorption whereas drugs like ketoconazole, cefpodoxime, dipyridamole, atazonavir, itraconazole etc. are having decreased rate of absorption.[19] Hypomagnesaemia and subsequent hypokalemia & hypocalcaemia occur in several cases of critically ill patients, the use of PPIs for 12 months or longer can lead to Vitamin B_{12} deficiency and also increased incidence of fractures due to decreased calcium absorption. Other adverse effects include nausea, diarrhoea, abdominal pain, fatigue and dizziness. Rashes, itch, flatulence, constipation, anxiety, myopathy are infrequent. Rare but serious reaction rhabdomyolysis is associated with the use of PPIs.

Preventive Measures

The stress ulcer prophylaxis (SUP) is recommended in high risk patients, especially those mechanically ventilated > 48 hours and those with a manifest coagulopathy. PPIs as less effectively, H-2RAs prevent GI bleeding in critically ill patients in ICU. Alternative strategies like enteral feeding or restricting SUP can be employed to the early phase of ICU treatment or to patients with an exceptional high risk profile. Enteral feeding is an alternative which improves splanchnic blood flow, macroscopic ulceration, stimulates GALT, decreased GI bleeding etc. Choice of prophylaxis include H2 blockers (tolerable after 72 hours), PPIs, they are potent and long acting but maximal effect can take up to 2days, Sucralfate & Antacids

(they are not a viable option as labor-intensive dosing regimen and side effects). AST is often used to prevent rebleeding caused by SRMD because acid impairs clot stability. Among H2RAs, Cimetidine is the least potent, Ranitidine is the middle potent & Famotidine is the most potent and it can be administered either orally or intravenously.[1] Esomeprazole, Omeprazole, Lansoprazole, Rabeprazole, and Pantoprazole are the available PPIs used for SUP therapy.[1]

CONCLUSION

Stress ulcer prophylaxis is generally given for critically ill patients in ICU with an acute bleeding episode. Histamine-2 receptor blockers and Proton pump blockers are the class of drugs administered for reducing events of death. Most of the reviews state that Histamine-2 receptor blockers are more effective than Proton pump blockers due its less adverse effects. Significantly fewer upper GI bleeding events occurred among those assigned to Proton pump inhibitors compared to Histamine-2 receptor blockers. Antacids and sucralfate are also effective drugs for the prevention of stress bleeding that minimizes the risk of nosocomial pneumonia in long-term ventilated ICU patients.

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