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Evaluation of Stress Ulcer Prophylaxis Benefits and Outcomes: A Simple Literature Review

Alghamdi, Mohammed Yaan Allah M [1], Abdulelah Hassan Alluhaybi [2], Abdullah Abdulaziz Alzahid [3], Murad Abdullah Akkur [4], Mohammed Abdulaziz A Alshenaiber [5], Riyadh Othman Abdullah Shati [6], Wed Ziyad Alnajjar [6], Sanaa Mahmoud Anbarserri [7], Reem Awad Alqahtani [8], Lamees Hassan Alzahrani [9]

1- Al-Baha University, 2- Umm Al-Qura University, 3- Imam Abdulrahman Bin Faisal University, 4- Jazan University, 5- Misr University for Science and Technology, 6- King Abdulaziz University, 7- Taibah University, 8- King Khalid University, 9- Ibn Sina National College

ABSTRACT

Background: One of the commonest complications in critically ill patients is stress related mucosal disease (SRMD). It can be associated with increase in the risk of development of overt gastrointestinal bleeding. As a result, a lot of literatures have been done to evaluate the pathogenesis that stands behind it's development, and assessment of the measures that can be used to lower the risk of it's 'occurrence.

Aim of the Work: In this review we aimed at discussing the pathogenesis that stands behind stress ulcer development, Also, discussing the role of anta- acid as a prophylaxis against harms and benefits. In addition to providing an intensive study that analyzed the recent literatures considered this field of study.

Methodology: A comprehensive search was done using biomedical databases; Medline, and Pubmed, for studies concerned with assessment of stress ulcer prophylaxis. Keywords used in our search through the databases were as; "stress ulcer", "stress ulcer prophylaxis", "stress ulcer in ICU patients".

Conclusion: Stress related mucosal disease is associated with increase in the risk of clinically overt gastrointestinal bleeding. As a result, patients who require mechanically ventilation for more than 48 h and those with a manifest of coagulopathy are highly recommended for having stress ulcer prophylaxis (SUP). Anta- acid such as Proton Pump Inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA) help in prevention of gastrointestinal bleeding, but did not have any effect on mortality risk reduction. Still further prospective randomizes trials needs to be done to evaluate our scientific research survey to guide the physicians in making a decision about the use of SUP in ICU patients.

Keywords: Stress, Ulcer, Prophylaxis.

INTRODUCTION

Stress-related mucosal damage (SRMD) is a term used to describe an acute, erosive, inflammatory insult to the upper gastrointestinal tract associated with critical illness[(1)]. SRMD can present as an asymptomatic superficial lesions found incidentally during endoscopy, occult gastrointestinal bleeding causing anemia, overt gastrointestinal bleeding and clinically significant gastrointestinal bleeding. Stress ulcer described for the first time in 1969 when small focal lesions were found in mucosa of gastric fundus during post-mortem examinations in 7 (out of 150) critically ill patients[2]. Since that time, and as a result of the increase use of diagnostic endoscopy in the medical field, health care providers found that between 74–100 % of critically ill patients have stress-related mucosal erosions and subepithelial hemorrhage within 24 hours of admission. In most of time the lesions are superficial and asymptomatic, but can extend into the submucosa and muscularis propria and erode significant vessels which will cause a clinically overt and significant bleeding (figure 1). The prevalence of overt bleeding depends on depends on this condition is defined. According to **Cook *et al.*[(3)]** overt gastrointestinal bleeding is defined as the presence of hematemesis, bloody gastrointestinal aspirate or melena, while clinically significant bleeding is the association of overt gastrointestinal bleeding and either hemodynamic compromise, or the requirement for blood transfusion, or surgery [(3)] . According to the data from earlier studies the prevalence of overt gastrointestinal bleeding is about 25 % of critically ill patients[(4)]. Nowadays the condition is far more infrequent with the prevalence reported as between 0.6 and 4 % of patients [(3, 4)]. The reduction in the incidence in more recent epidemiological studies probably reflects an improvement in the overall management of the critically ill patient, including a focus on early aggressive resuscitation, attenuating mucosal hypoperfusion, and an awareness of the importance of early enteral nutrition[(5)].

METHODOLOGY

Sample: We performed comprehensive search using biomedical databases; Medline, and Pubmed, for the studies concerned with the assessment of stress ulcer prophylaxis published in

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English language between 2013 and 2018. Keywords used in our search through the databases were as; "stress ulcer", "stress ulcer prophylaxis", "stress ulcer in ICU patients". More relevant articles were recruited from references lists scanning of each included study.

Analysis: No software was used, the data were extracted based on specific form that contain (Title of the study, name of the author, Objective, Summary, Results, and Outcomes). Double revision of each member's outcomes was applied to ensure the validity and minimize the errors.

DISCUSSION

Stress ulcer is a term used to describe an acute, erosive, inflammatory insult to the upper gastrointestinal tract associated with critical illness [(1)] Stress ulcer can present as an asymptomatic superficial lesions found incidentally during endoscopy, occult gastrointestinal bleeding causing anemia, overt gastrointestinal bleeding and clinically significant gastrointestinal bleeding. A clinical overt gastrointestinal bleeding is significantly important, because according to the recent studies up to half of all patients with clinically significant upper gastrointestinal bleeding die in the intensive care unit (ICU) and, in survivors, the length of ICU stay increases by approximately 8 days[(6)]. It is, therefore, prevention of clinically significant gastrointestinal bleeding will lead to better outcomes for the patients. In this review, we aimed to: 1- Assess the various measures of stress ulcer prophylaxis. 2) Evaluate the benefits and the harms of stress ulcer prophylaxis in adult hospitalised acutely ill. 3) Provide updated important knowledge on use of stress ulcer prophylaxis.

Pathophysiology:

SRMD occur mostly in critical ill patients as a result of impaired gastric mucosal blood flow. This impairment in blood flow occurs as a result of systemic hypodynamic changes (hypotension and/or vasopressor therapy) and/or local alterations, e.g., reduced splanchnic blood flow because of positive end-expiratory pressure in mechanically ventilated patients. As a result of blood flow reduction, tissue damage occurs due to ischemia. Also, mucosal hypoperfusion leads to reduction in the production of various protective substances such as mucus, phospholipid, and bicarbonate that help in the protection of gastric mucosa (figure1)[(7)]. In an experimental rat model exposed to ischemic injury, there was a reduction in the prostaglandin production, bicarbonate levels, and decrease in the gastric mucosal defense mechanism as a result of both cyclooxygenase and lipoxygenase pathways. Also, there was a reduction in the nitric oxide levels which act as a vasodilator, with increase in the levels of endothelin-1, which acts as a strong vasoconstrictor which can cause a mucosal damage[(8)]. As shown, different mechanisms can cause mucosal damage, but they are insufficient to cause overt mucosal ulceration and bleeding. An important component that lead to the occurrence of taken from Lukas **Buendgens *et al.*** [(9)] Overt bleeding is the presence of gastric acid. **Michida *et al.*[(8)]** mentioned that the addition of gastric acid with the presence of gastric ischemia in the animal models increased the damage by factor of ten[(8)]. As a result of this finding, we can see the rationale for the use of antaacids as a stress ulcer prophylaxis.

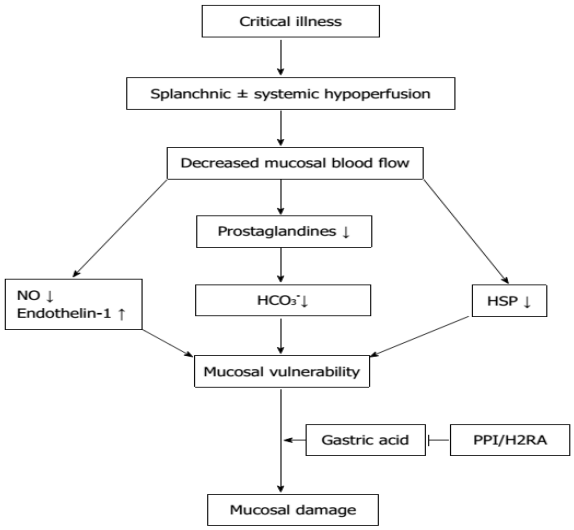

Figure (1): Pathophysiology of stress-related mucosal disease and rationale for the routine use of proton pump inhibitor/histamine 2 receptor antagonists at the intensive care unit. No: Nitric oxide; PPI: Proton pump inhibitor(s); H2RA: Histamine 2 receptor antagonists; HSP: heat-shock proteins; $HCO3^-$: Bicarbonate.

Stress ulcer related bleeding risk factors:

Several literatures have been done to assess the risk factors that can lead to stress ulcer related bleeding. **Cook *et al.*** [(3)] did a large multicenter trial that enrolled 2252 ICU patients, two main risk factors were identified: mechanical ventilation (OR = 15.6; P< 0.001) and coagulopathy (OR = 4.3; P< 0.001) [(3)]. They concluded that in the absence of these risk

factors the risk of stress ulcer related bleeding rate was < 0.1%[3].

A small earlier study agreed with the same findings [11]. In a recent study, **Krag *et al.*** [12] identified that the presence of three or more comorbidities rise the risk of stress ulcer related bleeding (OR = 8.9; 95%CI: 2.7-28.8), liver failure (OR = 7.6; 95%CI: 3.3-17.6), use of renal replacement therapy (OR = 6.9; 95%CI: 2.7-17.5), and coagulopathy (OR = 4.2; 95%CI: 1.7-10.2). Interestingly, **Krag *et al.*** [12] results showed that mechanical ventilation was not associated with increased risk of stress ulcer related bleeding [12]. A lot of other risk factors were identified but with low degree of evidence to assess in the development if stress ulcer related bleeding such as, head trauma, extended operations with time more than 4 h, sepsis, hypotension, advance age and male sex [10]. Figure 2 shows a summary of these various risk factors.

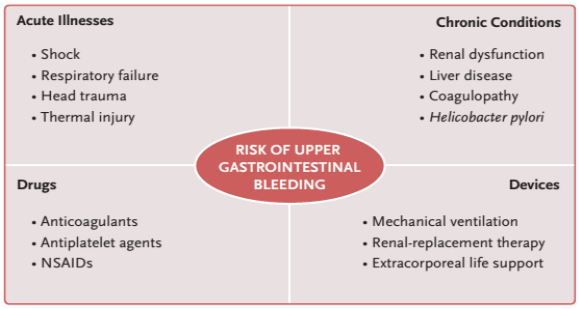

Figure (2): Risks of clinically important gastrointestinal bleeding. Data on risk factors for bleeding are derived from large epidemiologic studies and from many smaller studies of mixed populations or specific subgroups of patient cared for in medical and surgical wards and intensive care units. The severity of acute and chronic illnesses, along with certain drugs and devices used in the hospital, form the basis for population-specific risk profiles.

Prevention of stress ulcer:

As mentioned early, stress ulcer infrequently can cause significant gastrointestinal bleeding, which can be associated with poor outcomes for the acutely ill hospitalised patients. As a result of this, a lot of measures have been investigated to assess their role in stress ulcer prevention, including sucralfate, histamine-2 receptor blockers (H2RBs) and proton pump inhibitors (PPIs). Sucralfate act by forming a physical cytoprotective barrier at the ulcer site which help in protection of gastric mucosa from the effects of acid and pepsin[6]. According to the literatures, Sucralfate use in reduction of clinically significant bleeding is inferior to (H2RBs) and (PPIs), since it can be associated with impairment in the absorption of enteral feeds and co-administered oral medication [13].

H2RBs act by blocking of histamine binding to its G-protein coupled receptor on the gastric parietal cells, which will lead to reduction in acid production and an overall decrease in gastric secretions. **Netzer *et al.*** [14] mentioned that continuous use of (H2RBs) infusion is associated with reduction in its effect. With intragastric pH monitoring, studies in health have demonstrated that 70 % of patients have an intragastric pH > 4 in the first 24 hours of ranitidine intravenous infusion which falls to 26 % on the third day of continuous infusion.

PPI acts by inhibition of H^+/K^+ ATPase enzyme at the secretory surface of the parietal cell, which cause inhibition of H^+ ions and thereby increasing the pH of the gastric contents. In contrast to H2RBs, **Netzer *et al.*** [14] found that the use of PPIs is not associated with the development of tolerance. Also, the recent studies found that PPIs more effective in reduction of clinically significant gastrointestinal bleeding than other drugs [14]. The Surviving Sepsis Campaign guidelines recommend the use of PPIs rather than H2RBs for stress ulcer prophylaxis citing level 2C evidence [13].

Krag *et al.* [12] evaluated the effect of stress ulcer prophylaxis against placebo in prevention of significant overt gastrointestinal bleeding. They enrolled a total of 20 randomize clinical trials (Numbers of patients= 1971) that compare between PPIs or H2RBs with ether placebo or no prophylaxis according to specific inclusion and exclusion criteria. They found that gastrointestinal bleeding was low in patients treated with stress ulcer prophylaxis compared with patients treated with placebo or no prophylaxis [12]. Also, the Surviving Sepsis Campaign guidelines recommend the use of stress ulcer prophylaxis in patients with severe sepsis who have a risk factor, one of which is need for mechanical ventilation > 48 hours [15]. According to the recent interventional studies the use of prophylaxis helped in reduction of the incidence of stress ulcer, but did not have any effect on either mortality or length of stay [4]. **Plummer *et al.*** [16], explained the lack of effect of the prophylaxis measures by the following[16]: a) A demonstrable proportion of clinically significant

bleeding is not attributable to SRMD and will not respond to acid suppressive therapy, b) Previous studies were underpowered; the interventions studied have adverse effects that negate any benefit from a reduction in stress ulceration, c) The association between development of clinically significant bleeding and mortality may not be causal, and that clinically significant bleeding may just be heralding a poor outcome.

Adverse effects of stress ulcer prophylaxis:

Stress ulcer prophylaxis act by reduction of gastric acidity environment, which has a role in host defense mechanism, with an intragastric PH< 4 being suitable for bactericidal activity. As a result of this reduction in acidity, a lot of literatures discussed the role of stress ulcer prophylaxis in infection development, mainly infection-related ventilator-associated complications (IVAC) and Clostridium difficile.

- ***Stress ulcer prophylaxis and infection-related ventilator associated complications (IVAC):***

Plummer *et al.* [16], explained the relation between stress ulcer prophylaxis and infection-related ventilator by contamination of the oropharyngeal area by reflux of gastric fluid, with subsequent aspiration of the oropharyngeal bacteria to the lower airways[16]. With introduction of drugs that reduce gastric acidity and increase intragastric PH, there will be increase in the chances of gastric colonization with pathogenic organisms and predispose to respiratory infections. **Laheij *et al.*** [20]. Found that the use of PPIs is associated with significant increase in the risk of community acquired pneumonia development. Also, **Cook *et al.*** [18] reported a trend towards increased rates of pneumonia with the routine use of H2RBs[18]. According to **Alhazzani *et al.*** [4] the rate of IVAC associated with PPI use is likely to be at least similar to that observed with H2RBs. Regardless of whether H2RBs or PPIs is associated more with providing an optimal environment for bacterial colonization, this problem is more likely to be related for enteral fed patients, as enteral feeding *per se* may be a risk factor for IVAC.

- ***Stress ulcer prophylaxis and Clostridium difficile infection:***

Zilberberg *et al.* [21] evaluated the data of 65000 patients whom required prolong mechanically ventilation in the ICU. They found that C. difficile infection developed in > 5% of the patients. Also, they comment that C. difficile infection was associated with prolongation of patients hospital stay. The reduction in the acidic environment might be a risk factor for increasing the risk of acquiring a C. difficile infection, because intragastric acidity is considered as natural body defense mechanism. **Yearsley *et al.*** [22] evaluated a case-control study of 303 patients admitted to a general medical ward; they found that there was a significant increase in the risk of acquiring C. difficile infection in patients using PPIs [22]. **David *et al.*** [23] evaluated the relation between PPIs and healthcare facility–onset C. difficile infection in intensive care unit patients (ICU). They found that the use of antibiotics was the most important risk factor for development of C. difficile infection in ICU patients (adjusted HR (aHR) 2.79; 95% confidence interval (CI), 1.50–5.19). Also, there was no escalating in the risk of acquiring C. difficile infection in ICU patients whom only received PPIs without antibiotics, and PPIs use were actually associated with reduction in the risk of C. difficile infection development in the patients whom received antibiotics. Further case prospective studies are needed to assess this relation and to weight the benefits of PPIs use in ICU patients against the harm.

- ***Long term complications associated with anti-acid use:***

A lot of people are using anta-acids without any prescription to relive heartburn symptoms. Also, there are medical conditions including, Gastroeseophageal reflux disease, Barrets oesophagus, and prolong Nonsteroidal anti-inflammatory drugs in which physicians prescribe the use of anta- acid for longtime. **Khalili *et al.*** [24] mentioned that long use of PPIs is associated with osteoporosis and fractures [24]. As a result physicians should evaluate their patients periodically and assess their need for anta- acid use.

The role of enteral feeding in stress ulcer prevention:

Intensive studies have been done to assess the role of enteral feeding in prevention of stress ulcers, over the last 20 years a lot of progress has been done. **Ephgrave *et al.*** [25] mentioned that liquid nutrient help in prevention of stress ulcers, liquid nutrient work as a buffer for the gastric acid,

increasing the mucosal blood flow, and enhancement of prostaglandin and mucus secreations [(25)]. **Bonten *et al.*** [(26)] also found that continuous enteral nutrition is more effective in increasing intragastric PH than PPIs and H2RBs [(26)]. In rats **Harju E *et al.*** [(27)] found that enteral nutrition have a better outcomes in stress ulcer prevention than do intravenous H2RBs[(27)]. Still this area needs further evaluation to assess how enteral feeding helps in rising the intragastric PH, and assessment the benefits of using enteral feeding with the use of low dose of intravenous PPIs in critical ill patients.

CONCLUSION

Stress related mucosal disease is associated with increase in the risk of clinically overt gastrointestinal bleeding. As a result, patients who require mechanically ventilation for more than 48 h and those with a manifest of coagulopathy are highly recommended for having stress ulcer prophylaxis (SUP). Anta- acid such as Proton Pump Inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA) help in prevention of gastrointestinal bleeding, but did not have any effect on mortality risk reduction. Still further prospective randomizes trials needs to be done to evaluate our scientific research survey to guide the physicians in making a decision about the use of SUP in ICU patients.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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