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PEPTIC ULCER: A REVIEW ON EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS AND MANAGEMENT STRATEGIES

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ABSTRACT

Peptic ulcer (PU) is a disease of the gastrointestinal tract resulting from an imbalance between endogenous aggressive factors and defensive factors. Peptic ulcer embraces both gastric and duodenal ulcers and has been a major threat to the world's population with a high morbidity and substantial mortality. Discovery of gastric mucosa infection with Helicobacter pylori (H. pylori) and its association with chronic antral gastritis and peptic ulcer revolutionized the treatment of ulcer illness. H. pylori are causally related to a majority of cases of both duodenal and gastric ulcer, in the west and developing countries. Despite extensive scientific advancements, this disease remains an important clinical setback, largely because of H. pylori infection and widespread use of non-steroidal anti-inflammatory drugs (NSAIDs). Management of peptic ulcer disease generally involves the practice of H2 receptor antagonists, use of proton pump inhibitors, antacids and different H. pylori eradication regimens. This review article outlines the epidemiology, etiology, pathogenesis and treatment strategies of peptic ulcer disease.

KEYWORDS: Peptic ulcer, Helicobacter pylori, Management strategies.

INTRODUCTION

Peptic ulcer disease is one of the common gastrointestinal disorders in clinical Practice.[1] Peptic ulcer occurs due to an imbalance between the aggressive (acid, pepsin, bile and Helicobacter pylori) and the defensive (gastric mucus and bicarbonate secretion, nitric oxide, prostaglandins, innate resistance of the mucosal cells) factors.[2] A localised loss of gastric as well as duodenal mucosa leads to the formation of peptic ulcer, a term that includes both gastric as well as duodenal ulcer.[3] Diverse factors such as alcohol consumption, stressful life, use of non-steroidal anti inflammatory drugs, Helicobacter pylori infections and smoking contribute to the pathogenesis of gastric ulcer.[4] Drug treatment of peptic ulcer is targeted at either counteracting aggressive factors (acid, pepsin, platelet aggravating factor, leukotrienes, endothelins, bile or exogenous factors including NSAIDs) or stimulating the mucosal defences (mucus, bicarbonate, normal blood flow, prostaglandins, nitric oxide).[5] The goals of antiulcer include relief pain, promotion of ulcer healing, prevention of complications and replace.[3] There are different chemical drugs for gastric ulcer prevention and treatment.

EPIDEMIOLOGY:

Peptic ulcer affects about 5% of the global population. About 70-90% of patients with gastric ulcer and 80-95% with duodenal ulcers are infected with H. pylori. Peptic ulcer bleeding is a medical emergency condition causing more than 300,000 hospital admissions annually in the US. An estimated 15,000 deaths occur each year as a consequence of peptic ulcer diseases. The share of antacids and antiulcer drugs is 6.2 billion rupees and occupy 4.3% of market share in Indian pharmaceutical Industry. By the use of antisecretory drugs and endoscopy methods the prevalence of peptic ulcer decreases in India.The prevalence of H. pylori infection rises with age: 29.7% in those less than 30 years old and 63% at age 55-65. Rather a decline in the incidence of gastric cancer, it remains the fourth most common cancer and second leading cause of cancer-related deaths. The worldwide incidences of stomach cancer are (7.8%), mortality rate (9.7%) and 5 year prevalence is (5.5%). Nearly 20-40% of ulcers in North America are not associated with NSAIDs use or H. pylori infection, while in Asian populations, the reported frequencies of non-NSAID ulcers and non-H.pylori ulcers are very lower: only 1.3% in Japan and 4.1% in Hong Kong. [6]

ETIOLOGY AND RISK FACTORS:

(A) HELICOBACTER PYLORI:

Chronic infection of gastric mucosa with H. pylori is generally associated with gastric lesions. H. pylori are a prevalent human pathogen with an incidence of 90% in some developing countries. H.pylori undergoes asymptomatic gastric colonization in approximately 70% of the population, with a 10%-20% susceptibility of developing into peptic ulcer. The pathogenesis and pattern of H. pylori-induced gastritis is intensely associated with the morbidity of mucosal atrophy and duodenal/gastric ulcers. Eradication of H. pylori from the gastric mucosa of infected patients is considered to be the best therapeutic approach for complete remission of H. pylori associated gastritis and its consequent ulcers. [7]

(B) NON - STEROIDAL ANTI – INFLAMMATORY DRUGS (NSAIDs):

Various studies indicates that NSAIDs helps in the progression of ulceration by overcoming the expression of enzyme cyclo-oxygenase (COX) which has been documented to inhibit the conversion of AA (Arachidonic acid) to Prostaglandins, that impairs the mucosal barrier and results in corrosive action with pepsin and results in the progression of peptic ulcers. NSAIDs causes marked reduction in mucosal blood flow, mucus bicarbonate secretions, reduced epithelial cell renewal that are responsible for pathogenesis of ulceration. [8]

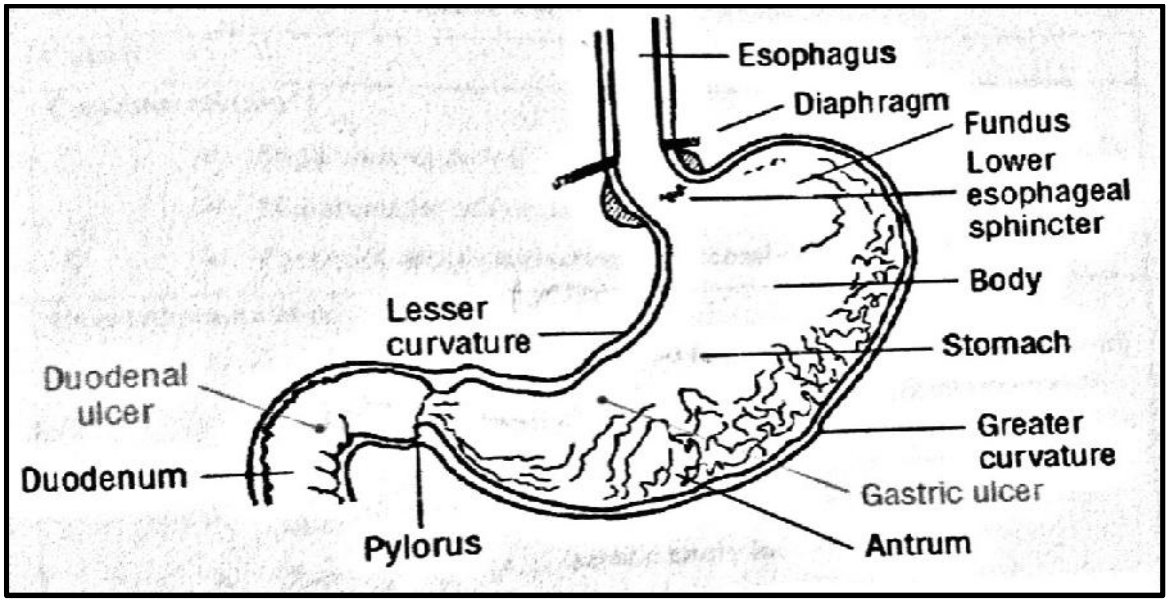

Figure 1: Anatomic structure of the stomach and duodenum and most common locations of gastric and duodenal ulcers.

(C) CIGARETTE SMOKING:

Smoking is associated with a higher prevalence of peptic ulcer disease and may be associated with impaired healing of duodenal and gastric ulcer disease. Also, death rates from peptic ulcer disease are higher in individuals who smoke.Smoking increases a person's risk of getting an ulcer because the nicotine in cigarettes causes the stomach to produce more acid. Smoking increases both the incidence and replase rate of peptic ulcer diseases and also delays ulcer. [9]

(D) PSYCHOLOGICAL STRESS:

Stress ulceration of the stomach is associated with clinical like trauma, head injury, burns, shock, sepsis and neurological disorders, and is now regarded as multifactorial phenomenon. It is reported to result from interactions between mucosal, vascular and neuro-humoral factors and the autonomic nervous system plays a crucial role. [10]

(E) ACID – PEPSIN SECRETIONS:

There is conclusive evidence that some level of acid – pepsin secretion is essential for the development of duodenal as well as gastric ulcer. Peptic ulcer never occur in association with pernicious anaemia in which there are no acid and pepsin secreting parietal and chief cells respectively. [11]

(F) DIETARY FACTORS:

Nutritional deficiencies have been regarded as etiologic factors in peptic ulcers e.g. occurrence of gastric ulcer in poor socioeconomic strata, higher incidence of duodenal ulcer in parts of

South India. However, malnutrition does not appear to have any causative role in peptic ulceration in European countries and the U.S. [11]

(G) LOCAL IRRIANTS:

Pyrolic antrum and lesser curvature of the stomach are the sites most exposed for longer periods to local irriants and thus are the common sires for occurrence of gastric ulcers. Some of the local irriants substances implicated in the etiology of peptic ulcers are heavily spiced foods, alcohol consumption, cigarette smoking, non-steroidal anti-inflammatory drugs etc. [11]

PATHOPHYSIOLOGY: [12]

Gastric and duodenal ulcers occur because of an imbalance between aggressive factors (gastric acid and pepsin) and mechanisms that maintain mucosal integrity (mucosal defense and repair).

GASTRIC ACID AND PEPSIN:

The potential for producing mucosal damage is related to the secretion of gastric (hydrochloric) acid and pepsin. Hydrochloric acid is secreted by the parietal cells, which contain receptors for histamine, gastrin, and acetylcholine. Acid (as well as HP infection and NSAID use) is an independent factor that contributes to the disruption of mucosal integrity. Increased acid secretion has been observed in patients with duodenal ulcers and may be a consequence of HP infection. Patients with ZES have gastric acid hyper secretion resulting from a gastrin-producing tumor. Patients with gastric ulcer usually have normal or reduced rates of acid secretion (hypochlorhydria). Pepsinogen, the inactive precursor of pepsin, is secreted by the chief cells located in the gastric fundus (see Fig.1.1). Pepsin is activated by acid pH (optimal pH of 1.8 to 3.5), inactivated reversibly at pH 4, and irreversibly destroyed at pH 7. Pepsin appears to play a role in the proteolytic activity involved in ulcer formation.

MUCOSAL DEFENSE AND REPAIR:

Mucosal defense and repair mechanisms protect the gastroduodenal mucosa from noxious endogenous and exogenous substances. Mucosal defense mechanisms include mucus and bicarbonate secretion, intrinsic epithelial cell defense, and mucosal blood flow. The viscous nature and near-neutral pH of the mucus-bicarbonate barrier protect the stomach from the acidic contents in the gastric lumen. Mucosal repair after injury is related to epithelial cell restitution, growth, and regeneration. The maintenance of mucosal integrity and repair is mediated by the production of endogenous prostaglandins. The term cytoprotection is often used to describe this process, but mucosal defense and mucosal protection are more accurate terms, as prostaglandins prevent deep mucosal injury and not superficial damage to individual cells.

HELICOBACTER PYLORI:

Helicobacter pylorus is a spiral-shaped, pH-sensitive, gram-negative, microaerophilic bacterium that resides between the mucus layer and surface epithelial cells in the stomach, or any location where gastrictype epithelium is found. The combination of its spiral shape and flagellum permits it to move from the lumen of the stomach, where the pH is low, to the mucus layer, where the local pH is neutral. The acute infection is accompanied by transient hypochlorhydria, which permits the organism to survive in the acidic gastric juice. The exact method by which HP initially induces hypochlorhydria is unclear. One theory is that HP produces large amounts of urease, which hydrolyzes urea in the gastric juice and converts it to ammonia and carbon dioxide. The local buffering effect of ammonia creates a neutral micro environment within and surrounding the bacterium, which protects it from the lethal effect of acid. HP also produces acid-inhibitory proteins, which allows it to adapt to the low-pH environment of the stomach. HP attaches to gastric-type epithelium by adherence pedestals, which prevent the organism from being shed during cell turnover and mucus secretion. Colonization of the corpus (body) of the stomach is associated with gastric ulcer.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS:

Non selective NSAIDs including aspirin cause gastric mucosal damage by two important mechanisms: (a) direct or topical irritation of the gastric epithelium and (b) systemic inhibition of endogenous mucosal prostaglandin synthesis. Although the initial injury is initiated topically by the acidic properties of many of the NSAIDs, systemic inhibition of the protective prostaglandins plays the predominant role in the development of gastric ulcer. Topical irritant properties are predominantly associated with acidic NSAIDs (e.g., aspirin) and their ability to decrease the hydrophobicity of the mucous gel layer in the gastric mucosa.Most non aspirin NSAIDs have topical irritant effects, but aspirin appears to be the most damaging. Although NSAIDs prodrugs, enteric-coated aspirin tablets, salicylate derivatives, and parenteral or rectal preparations are associated with less-acute topical gastric mucosal injury, they can cause ulcers and related GI complications as a result of their systemic inhibition of endogenous PGs.

COMPLICATIONS: [12]

As the epidemiology of peptic ulcer has led to decreased incidence of this disease, it remains an important surgical problem because of the severity of its complications. Upper GI bleeding, perforation, and obstruction occur with HP associated and NSAID-induced ulcers and constitute the most serious, life-threatening complications of chronic PUD.

(I) Gastrointestinal bleeding

(II) Perforation

(III) Gastric outlet obstruction

MANAGEMENT STRATEGIES: [13-14]

[A] Non-pharmacological management:

Smoking should be discontinued, and alcohol consumption discontinued or limited to small amounts of dilute alcohol. Stress reduction counseling may be helpful in individual cases but is not needed routinely.There is limited or no evidence that changing the diet (the so-called “ulcer diets”) speeds ulcer healing or prevents recurrence.However, many medical practitioners recommend eliminating those foods only that cause distress.The following are precautionary dietary measures that can be taken:

- Eat small meals at regular times, and include snacks between meals.
- Eat slowly and chew thoroughly.
- Adjust the diet to the severity of the condition.During an acute phase, the following should be avoided :
    - Strong, excessively hot tea or coffee, alcohol and caffeine (especially on an empty stomach).
    - Spices, such as curries, and blue cheese.
    - Roasts and fatty foods, for example sausage, oily fish and pasta.
    - Green and dried fruits as well as fibrous vegetables, for example onions, radishes and celery.
- Ensure that sufficient vitamin C in the form of fruit, vegetables and fresh juices is taken.
- Prevent anaemia by eating foods rich in iron, such as liver.
- Rest for 15 minutes after each meal.
- If possible, avoid emotional stress.

[B] Pharmacological treatment:

Pharmacological treatment of both gastric and duodenal ulcer involves acid suppression, eradication of H pylori (if present) and the avoidance of NSAIDs. For duodenal ulcers, it is particularly important to suppress nocturnal acid secretion. A number of medicines are effective in reducing acid secretion but vary in cost, duration of therapy and convenience of dosing. In addition, mucosal protective medicine (for example, sucralfate) may be used. Current approaches towards the treatment of peptic ulcer are as follows:

(A) Drugs which neutralise gastric acid – Antacids:

Antacids neutralise gastric acid and reduce pepsin activity. In addition, some antacids adsorb pepsin. Antacids relieve symptoms, promote ulcer healing and reduce recurrence. The efficacy of

antacids compares well with some of the other ulcer-healing drugs. Antacids remain safe, simple and effective agents for the symptomatic treatment of gastricrelated symptoms.Studies have shown that lower doses may be as effective as the high doses formerly recommended. In practice, antacids have been superseded by H. pylori eradication strategies in peptic ulcer disease and are used only for short-term symptom relief. There are two types of antacids: absorbable and nonabsorbable.

- **Absorbable antacids:** Sodium bicarbonate and Calcium carbonate provide rapid, complete neutralisation but may cause alkalosis and should only be used for one to two days.
- **Non-absorbable antacids:** Aluminium or Magnesium hydroxide cause fewer systemic side effects and are preferred.

(B) Drugs which reduce gastric acid secretion:

(I) H2-receptor antagonists:

Gastric acid secretion in response to other secretagogues (for example, acetylcholine and gastrin) is also reduced. Examples include. H2-blockers are well absorbed from the gastrointestinal tract, and duration of action is proportional to the dose (ranging from 6 to 20 hours).

- Cimetidine
- Ranitidine
- Famotidine

Mechanism of Action: The H2-receptor antagonists reduce gastric secretion by blocking the action of histamine at the H2-receptors in the parietal cells of the stomach.

(II) Proton pump inhibitors: The proton pump inhibitors (PPIs) are the most potent suppressors of gastric acid secretion. They promote ulcer healing and are key components of H. pylori eradication regimens. PPIs have replaced H2-blockers in most clinical situations because of greater rapidity of action and efficacy.

- Omeprazole
- Esomeprazole
- Pantoprazole
- Rabeprazole
- Lansoprazole

Mechanism of Action: They act by inhibiting the H+/K+-ATPase enzyme of the gastric parietal cell and inhibit acid secretion.

(III) Prostaglandins:

The production of protective prostaglandins is inhibited by NSAIDs. This is thought to be the mechanism of NSAID induced ulceration. Misoprostol, a synthetic prostaglandin E1 analogue, is indicated for protection against NSAID-associated gastric and duodenal ulceration. Misoprostol was found to decrease the incidence of serious gastrointestinal events (relative risk 0.57, 95% confidence interval 0.36-0.91).

- Misoprostol

Mechanism of Action: Inhibit acid secretion and enhance mucosal defense.

(C) Mucosal Protective Drugs:

- Sucralfate: It is a aluminium salt of sulphated sucrose. Stimulates mucosal synthesis and bicarbonate secretion.

(D) Ulcer Healing Drugs:

- Carbenoxolone: It increases the production of mucus and decreases the pepsin output by inactivating Pepsinogen.

CONCLUSION

Peptic ulcer is a common disease of digestive system. NSAIDs use and H. pylori infection are main cause of peptic ulcer. NSAIDs and Helicobacter pylori induce oxidative stress, initiate and aggravate peptic ulcer and gastric carcinoma. Mechanical devices are more successful in treatment of bleeding ulcers in comparison to injection therapy and thermal devices. However, a combination of pharmacological and endoscopic approach is best used for the treatment of ulcers. Although there is better management of H. pylori infection an increase in the both non-H. pylori and non-NSAID peptic ulcer bleeding was observed.

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