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Gastric Ulcer: An overview

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Gastric ulcers are breaks in the mucosa of the stomach lining that penetrate through the muscularis mucosa and extend more than 5 mm in diameter. When alterations occur to the defense mechanisms of the stomach, it can cause changes in the gastric mucosa, eventually resulting in erosion and then ulceration. Non-steroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori (H. pylori) infection are the two major factors disrupting mucosal resistance to injury. Gastric ulcers are characterized by discontinuation in the inner lining of the gastrointestinal (GI) tract because of gastric acid secretion or pepsin. It extends into the muscularis propria layer of the gastric epithelium. It usually occurs in the stomach and proximal duodenum. It may involve the lower esophagus, distal duodenum, or jejunum. Epigastric pain usually occurs within 15–30 minutes following a meal in patients with a gastric ulcer. Conversely, the pain with a duodenal ulcer tends to occur 2–3 hours after a meal. The treatments for gastric ulcers, such as proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, have demonstrated adverse effects, relapses, and various drug interactions. On the other hand, medicinal plants and their chemical compounds are useful in preventing and treating numerous diseases.

Keywords: gastric ulcer, NSAIDs, epigastric pain, pathophysiology

Introduction

Gastric ulcer is a common disease that affects millions of people worldwide. Considering its global prevalence finding, a new approach to treating it is important. According to WHO, Gastric ulcer disease death in India reached 85487 or 0.96% of total death. The age-adjusted death rate is 9.12%, i.e. one lac of the population suffers from Gastric ulcer, so India is ranked 26th in the world [1-5]. Ulcers are open sores in the upper part of the digestive tract that can cause stomach pain and upset stomach, leading to internal bleeding. There are two types of Gastric ulcer (1) Gastric ulcer and (2) Duodenal ulcer. Gastric ulcer disease is a multicausal and complex disease that occurs when the biological balance between defensive and aggressive factors in the gastrointestinal tract is disturbed. The aggressive factors are endogenous factors like gastric acid, endothelins and pepsin secretion, active free radicals and oxidants, leukotrienes, and exogenous factors like ethanol or nonsteroidal anti-inflammatory drugs (NSAIDs). On the other side, gastric mucus, bicarbonate, normal blood flow, prostaglandins (PGs), nitric oxide (NO), and antioxidant enzymes like catalase (CAT), or antioxidant peptides like glutathione (GSH) work as a defensive barrier, Mucosal cell death results from an increase in H^+ concentration in its immediate environment due to this pH decreases. There are many drugs that are used in the treatment of Gastric ulcers. Until now, no drug without a side effect gives a 100% curative rate or complete cure of the disease [3, 6-8].

Anatomy of the normal stomach: On the top left side of the abdomen is a muscular organ called the stomach. Food travels down the oesophagus and into the stomach. The lower esophageal sphincter, a muscle valve, allows food to exit the oesophagus and enter the stomach. The stomach secretes acid and digestive enzymes to help with meal digestion. The muscular tissue ridges that border the stomach are called ruae. Regular contractions of the stomach muscles help with digestion by churning the meal. A muscle valve called the pyloric sphincter opens to let food pass from the stomach into the small intestine [9-11].

Pathophysiology

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and Indomethacin are the most commonly prescribed drugs for arthritis, inflammation, and cardiovascular protection. However, they cause gastrointestinal complications such as ulcers and erosion. The pathophysiology of these complications has mostly been ascribed to NSAID's action on the cyclooxygenase (COX) inhibition and the subsequent prostaglandin (PG) deficiency [10, 12, 13]. Due to their high chemical reactivity and the existence of uncoupled electrons inside their molecules, reactive oxygen species (ROS) play a role in the pathophysiology of gastric mucosal injury. As a result, there is tissue damage, which is mostly caused by increased lipid peroxidation. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are the products of the metabolism of lipid peroxides. The local rise in MDA and 4-HNE levels indicate ROS-dependent tissue damage. The primary enzyme that converts ROS into less harmful hydrogen peroxide is called superoxide dismutase (SOD). The protective system is impaired when SOD activity declines, which also greatly increases cell damage. In the presence of reduced glutathione, hydrogen peroxide is further metabolised to water. (GSH). In order to neutralise ROS, GSH can also operate in concert with SOD [12, 14, 15]. GSH and ROS react to form glutathione free radicals (GS•), which then react with GSH to form glutathione disulfide free radicals (GSSG•). The oxygen molecule can then accept an electron from this free radical of GSSG, creating O_2•-. O_2•- is then removed by SOD. Reduced GSH levels are harmful to the cellular components that provide an antioxidative defense [14, 16, 17]. When under stress, the gastric mucosa shows increased lipid peroxidation (an increase in MDA and 4-HNE) and a decline in SOD activity and GSH content. Understanding the aetiology of NSAIDs-induces functional abnormalities in the gastric mucosa leading to ulcerogenesis appears to depend on this cascade of ROS production that is brought on by NSAIDs and stress [16, 18, 19].

Other types of ulcers :

(1) Gastric ulcer

When a Gastric ulcer occurs in the stomach, it is called a gastric ulcer. The bacterium called *H. pylori* cause this type of ulcer. Antacids are used as a treatment option for gastric ulcers; the patient usually starts to feel well after two or three weeks of using antacids. Also, ulcer patients are advised not to use too much oily and greasy food and also asked to limit the consumption of acidic foods [12, 20, 21].

(2) Duodenal ulcer:

When a Gastric ulcer is in the duodenum, it is called a duodenal ulcer. The initial section of the small intestine is where this kind of gastric ulcer forms. Interesting contrasts exist between some duodenal ulcer symptoms and those of stomach ulcers. In the Western world, duodenal ulcers are the most typical kind of ulcers. [12, 20, 22].

(3) Esophageal Ulcers:

Esophageal ulcers are lesions that occur in the esophagus (food pipe). These are most commonly formed at the end of the food pipe and can be felt as a pain right below the breastbone, in the same area where symptoms of heartburn are felt. Oesophageal ulcers are associated with acid reflux or GERD, prolonged use of drugs like NSAIDs and smoking [20,23].

(4) Bleeding Ulcer:

Internal bleeding is caused by a Gastric ulcer that has been left untreated. When this happens, it is referred to as a bleeding ulcer, this is the most dangerous type of ulcer and it requires immediate treatment [20,24,25].

(5) Refractory Ulcer:

Simple Gastric ulcers that have not healed after at least 3 months of treatment are called refractory ulcers [20].

(6) Stress Ulcer:

A series of lesions (or lacerations) known as stress ulcers can develop in the esophagus, stomach, or duodenum. These are typically only seen in people who are seriously unwell or under a lot of stress [20,25-27].

Common cause of Gastric ulcer:

Helicobacter Pylori (*H. pylori*): H. pylori (initially named as Campylobacter pyloridis) is a gram-negative bacillus, motile, microaerophilic flagellated and spiral-shaped bacteria. It was identified by two Australian scientists, Barry Marshall and Robin Warrens 1982 discovered that bacteria are the primary cause of stomach and duodenal ulcers, excluding those caused by aspirins or arthritis. The bacteria are probably acquired from contaminated food or from infected drinking water. Type one stain of *H. pylori* possess a pathogenic activity that encodes the effectors protein cytotoxin-associated gene A (cag A), further translocation into the host cell [28-30]. Cag A affects cell shape, increase cell motility disturbs cell junctional activity and this is responsible for gastric carcinomas and gastric ulcer. H. pylori- mediated pathogenesis and colonization such as the outer membrane protein (Hop protein) Urease and the vacuolating cytotoxin (Vac A). Infection by bacteria is dependent on the bacteria's mortality and its ability to produce Urease. Urease produces ammonia and carbon dioxide from urea which is secreted from the stomach and this CO_2 interact with environmental water producing H_2CO_3 in the presence of carbonic anhydrase, an essential step in alkalinizing the surrounding pH. The H_2CO_3 converts into the H^+ & HCO_3^- and the resulting H^+ ion reacts with NH_3 to form NH_4^+, which can damage epithelial cells [28, 29, 31].

H. Pylori Transmission and Spread of Infection

Transmission

H. pylori is typically spread from person to person via saliva and faecal contamination of food or water. Untreated water, congested living circumstances, and inadequate hygiene all lead to higher H. pylori prevalence in poorer nations. The majority of persons become infected as youngsters, and parents and siblings appear to play a significant role in transmission [29, 32-34].

Spread of Infection

H. pylori enter the body through the mouth, moves through the digestive system, and infects the stomach or the first part of the small intestine. The spiral-shaped bacterium uses its tail-like flagella to move around and burrow into the stomach lining, which causes inflammation [32,35]. Unlike other bacteria, H. pylori bacteria can survive in the stomach's harsh acidic environment because they produce a substance that neutralizes stomach acid. This substance, Urease, reacts with urea to form ammonia, which is toxic to human cells. Depending on where the infection occurs in the stomach, H. pylori can also cause the overproduction of stomach acid [32, 36, 37].

NSAIDs (Non-steroidal anti-inflammatory drugs): Nonsteroidal anti-inflammatory medications (NSAIDs) are the most well-known pharmaceuticals for the treatment of pain, inflammation, and fever globally. NSAIDs are often used to treat inflammatory conditions such as rheumatoid arthritis, osteoarthritis, dysmenorrhea, and ischemic cerebrovascular disorders. The use of these medications in some types of cancer treatment has also lately been documented. These medications work by inhibiting prostaglandin biosynthesis and thereby producing a therapeutic effect. On the other hand, long-term use of NSAIDs causes unpleasant gastrointestinal (GI) symptoms such as mucosal lesions, bleeding, gastric ulcer, and inflammation in the intestine leading to perforation, strictures in the small and large intestines, and chronic difficulties. Some of the side effects of NSAIDs may be transitory, but there have been numerous reports of life-threatening situations [36, 38, 39].

NSAIDs include Ibuprofen, Fenoprofen, Aspirin, Diclofenac, Sulindac, Naproxen, Indomethacin, Tolmetin and many others. These are valuable therapeutics that act not only as an anti-inflammatory but also as analgesics and antipyretics. They are used in a wide variety of clinical conditions, including arthritis and other musculoskeletal disorders. Nearly 25% of chronic users of these drugs develop gastric ulcer disease. Various studies indicate that NSAIDs help in the progression of ulceration by overcoming the expression of the enzyme cyclooxygenase (COX), which has been documented to inhibit the conversion of Arachidonic acid to PG's that impairs the mucosal barrier and results in corrosive action with pepsin and results in the progression of Gastric ulcer [38, 40, 41]. Further, COX-1 inhibition by the NSAIDs leads to the significant release of endothelin-1 (ET-1), which is a potent vasoconstriction that has been shown to induce mucosal injury. NSAIDs, by inhibiting the prostaglandin synthesis, cause the activation of neutrophils and the local release of reactive oxygen species (ROS), thus initiating the gastric injury [40, 42, 43]. NSAIDs also cause a marked reduction in mucosal blood flow, mucus-bicarbonate secretions, impaired platelet aggregation, reduced epithelial cell renewal and increased leukocyte adherence, which are responsible for the pathogenesis of ulceration. Gastric acid worsens the NSAID effects by deepening superficial lesions interfering with platelet aggregation and impairing the ulcer healing process [40, 42, 44].

Mechanism of action of NSAIDs: The principle of action of nonsteroidal anti-inflammatory drugs (NSAIDs) was initially established in the early 1970s and is based on the inhibition of prostaglandin (PG) synthesis.PG, which is synthesised from arachidonic acid, is a major mediator of inflammation, pain, and fever. The enzyme cyclooxygenase (COX), also known as PGH synthase, catalyses the reaction. By binding to and inhibiting COX, NSAIDs prevent the PG production [45-47].COX has two isoforms, COX-1 and COX-2, each with a distinct function. COX-1 is expressed constitutively and responsible for the stomach mucosa's normal physiological protection. It is in charge of the manufacture of prostaglandins, which protect the stomach lining from acid secretion, keep blood flowing in the gastric mucosa, and create bicarbonate. COX-2, the other isoform, is activated by cell injury, proinflammatory cytokines, and tumor-derived substances. NSAIDs primarily cause NSAID-induced gastropathy by inhibiting COX-1 [45, 46, 48].NSAIDs are also directly cytotoxic to stomach mucosal cells, causing lesions and damage. One study discovered that direct cytotoxicity is unaffected by COX inhibition. This type of topical damage has been reported in the case of acidic NSAIDs such as aspirin, resulting in an accumulation of ionised NSAID, a phenomenon known as "ion trapping." NSAIDs are thought to produce membrane permeabilization, which disrupts the epithelial barrier. NSAIDs could also cause necrosis and apoptosis in gastric mucosal cells [49-51].

Conclusion

Gastric ulcer disease remains a frequent clinical problem in our environment, predominantly affecting people of all ages. As the prevalence of Gastric ulcer disease increases with advancing age, it is expected that this common disease will continue to have a significant global impact on healthcare delivery, health economics and the quality of life of patients. The standard anti-gastric ulcer drugs might present a synergistic effect against H. pylori and gastric ulcer disease and improve the outcome for patients with gastric ulcers. With only a few human studies, conducting further clinical studies with larger sample sizes on the efficacy and safety of medicinal plants with

antiulcer activity is recommended. Finally concluded that timely diagnosis and treatment of Gastric ulcer disease and its sequelae are crucial in order to minimize associated morbidity and mortality, as is the prevention of Gastric ulcer disease among patients at high risk, including those infected with H. Pylori and users of NSAIDs.

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