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Peptic Ulcer: A Review on Epidemiology, Molecular Mechanism of Pathogenesis and Management

Adarsh Choudhary*[1], Amarjeet Singh[2]

*[1]*Department of Pharmaceutical Sciences, Lovely Professional University, Punjab, India*
[2]*Shakti College of Pharmacy, Balrampur, Uttar Pradesh, India*

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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. The former includes factors such as hydrochloric acid, pepsin, refluxed bile, leukotrienes, reactive oxygen species (ROS), while the later includes surface active phospholipids, nitric oxide (NO), bicarbonate barrier, mucosal blood flow, prostaglandins (PGs), cell migration and renewal, nonenzymatic and enzymatic antioxidants like catalase, and some growth factors. Reactive oxygen species play a key role in the pathogenesis of gastric inflammation and ulcerogenesis in H. pylori infections via increased expression of IL-8. Although there is better management of H. pylori infection but still the cases of idiopathic ulcers are increasing. Therefore, a combination of pharmacological and endoscopic approaches is used for the management of ulcers.

Keywords: Peptic ulcer, H. pylori, ROS, inflammatory mediators

Contents

***Corresponding author**
Adarsh Choudhary
E-mail: adarsh66677@yahoo.com
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1. Introduction

Peptic ulcer (PU) is the disease of gastrointestinal tract affecting primarily the stomach and duodenum. It results due to lack of equilibrium between some endogenous aggressive factors and cytoprotective or defensive factors. The former includes factors such as hydrochloric acid, pepsin, refluxed bile, leukotrienes, reactive oxygen species (ROS), while the later includes surface active phospholipids, nitric oxide (NO), bicarbonate barrier, mucosal blood flow, prostaglandins (PGs), cell migration and renewal, enzymatic and non enzymatic antioxidants like catalase, and some growth factors[1]. The etiological factors behind the disease are inadequate dietary habits, prolonged use of NSAIDs, stress, *H. pylori* infection and some genetic factors[2]. Stress either psychological or physical (surgery or microbial infection by H. *pylori)* leads to oxidative stress in stomach i.e production of reactive oxygen species[3]. Reactive oxygen species play a key role the pathogenesis of gastric inflammation, ulcerogenesis, and carcinogenesis in *H. pylori* infection[4].A combination of pharmacological and endoscopic therapy offers the best method of

hemostasis to those with active bleeding ulcers. In case of recurrent bleeding a new dose regimen or second-look endoscopy can be used[5]. Although there is better management of *H. pylori* infection but still the cases of idiopathic ulcers are increasing. The reason for non *H. pylori* and non-NSAID peptic ulcer may be that the mucosa after NSAID attack or after *H. pylori* infection may not recover properly even after NSAID withdrawal or after antibacterial treatment[6].

2. Epidemiology of Peptic Ulcer

Peptic ulcer affects about 5% of the global population[7]. About 70-90% of patients with gastric ulcer and 80-95% with duodenal ulcers are infected with *H. pylori*[8]. Peptic ulcer bleeding is a medical emergency condition causing more than 300,000 hospital admissions annually in the US[9]. An estimated 15,000 deaths occur each year as a consequence of peptic ulcer diseases[10]. 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[11]. 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 988602 (7.8%), mortality rate 737419 (9.7%) and 5 year prevalence is 1598440 (5.5%)[12]. 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[13] and 4.1% in Hong Kong[14].

3. Pathogenesis of Ulcer

3.1 *Helicobacter pylori* induced ulcer

H. pylori infect the gastric mucosa of approximately half of the world population and cause chronic gastritis[15]. *H. pylori* is highly heterogeneous; comprising a genome of approximately 1,600 genes[16,17]. Genes most commonly associated with the virulence are *CagA*, *VacA*, *OipA* and *dupA*.

3.1.1 Virulence genes

A. *CagA* (Cytotoxin-Associated Gene A Product)

CagA (40 kbp region) is located at one end of the *cag* pathogenicity island[18]. It is transferred to host cell via type IV secretary system[19] which forms a syringe-like pilus that penetrates gastric epithelial cells and facilitates the translocation of *CagA*, peptidoglycan, and possibly other bacterial components into host epithelial cells[20].

B. *VacA* (Vacuolating Cytotoxin)

VacA gene encodes a vacuolating cytotoxin. This gene is involved in the membrane channel formation, Cytochrome c (cyt c) release from mitochondria leading to apoptosis, and binding to cell membrane receptors, which is followed by the initiation of a pro-inflammatory responses[21].

C. *OipA* (Outer Inflammatory Protein)

OipA is an outer membrane protein involved in adhesion. *OipA* is a better marker of severe clinical outcomes than *Cag* A[22].

D. *DupA* (Duodenal Ulcer Promoting)

DupA pathogenesis appears to involve the induction of IL-8 production in the antrum, leading to antrum-predominant gastritis, which is a well-recognized characteristic of duodenal ulcer. It has been also reported that *H. pylori* containing intact *DupA* induces the IL-12 production in monocytes[23].

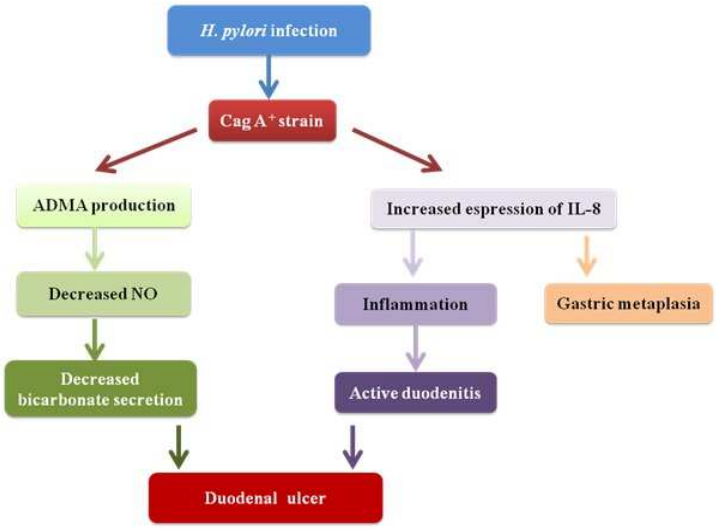

Figure 1. *H. pylori* induced duodenal ulcer and gastric metaplasia

Active duodenitis, an infection of duodenum, occurs only in patients with duodenal ulcer (DU) mostly with $CagA^+$ strains in the duodenal bulb[24,25]. The prevalence of the East Asian-type CagA genotype is 64.0% in duodenal ulcer (*P*=0.001 and 0.02)[26]. Gastric metaplasia (GM) has been found at a high frequency in *H. pylori* infected subjects, with a prevalence of about 90% in DU patients and about 60% in non-DU subjects. In duodenal ulcer, the concentration of asymmetric dimethyl arginine (ADMA) has been found to be increased in the duodenal tissue. ADMA is an endogenous nitric oxide inhibitor which causes a decrease in concentration of NO. This leads to suppression of the bicarbonate secretion and ultimately more acidification as represented in figure1[25].

H. pylori CagA+ strain induces ADMA production leading into decreased synthesis of NO. This suppresses the bicarbonate secretion and causes more acidification. H. pylori also induces IL-8 production. IL-8 has pro-angiogenic and carcinogenic factor which causes gastric metaplasia and inflammation in the duodenum.

3.2 Oxidative stress and peptic ulcer

NSAIDs and *Helicobacter pylori* induced oxidative stress is believed to initiate and aggravate many diseases including peptic ulcers and gastric carcinoma. In clinical peptic ulceration and gastric carcinoma patients, an increase in serum LPO and a decrease in SOD and CAT levels have been observed indicating a positive correlation between oxidative stress in gastric and duodenal ulcers and gastric carcinoma[27]. Glutathione (GSH), an antioxidant, prevents cellular damage caused by reactive oxygen species such as free radicals and peroxides[28]. *H. pylori* directly stimulate the ROS production from gastric epithelial cells, and reduce cellular GSH levels[29]. ROS production in the gastric mucosa is enhanced by the infection of $cagA^+$ *H. pylori* species with an extensive accumulation of neutrophils in patients with gastric ulcer[30]. This excessive ROS production induces oxidative stress to the gastric mucosa, and may damage cellular components, including polyunsaturated fatty acids, proteins, and DNA. *H. pylori* contains urease enzyme, which produces ammonia (NH_3) in the the stomach protecting the bacteria from the acidic environment. This ammonia (NH_3) reacts with HOCl to yield monochloramine (NH_2Cl). Being highly lipophilic, it freely penetrates the biological membrane and oxidizes the intracellular components[31]. Gastric epithelial pit cells contains isozyme of gp91-phox, mitogen oxidase 1 (Mox1), and essential components for the phagocyte NADPH oxidase (p67-, p47-, p40-, and p22-phox). These pit cells produce ROS via activation of non phagocytic NADPH oxidase in response to *H. pylori*[32]. In activated neutrophils, NADPH oxidase becomes activated causing an electron transfer from NADPH to oxygen inside and outside of the cells. This leads to the formation of superoxide radicals (O_2^-), which may be converted into: a) hydrogen peroxide (H_2O_2) by spontaneous dismutation or by enzyme superoxide dismutase (SOD); and b) hydroxyl radicals (•OH) non enzymatically in the presence of Fe^{2-} as a secondary reaction. Moreover, myeloperoxidase, present in neutrophils, has also resulted in the formation of potent oxidant hypochlorous acid (HOCl) from H_2O_2 in the presence of chloride ions[33]. These ROS can oxidize the lipid membrane and cause lipid peroxidation forming thiobarbituric acid reactive substances (TBARS) as by-product, which can be detected by the TBARS assay using the thiobarbituric acid as a reagent[34].

Prostaglandins (PGs) have a beneficial effect on ulcer healing. The level of essential fatty acids (EFA), linoleic acid (LA) and α- linolenic acid (ALA) decreases in DU patients resulting in decreased synthesis of PGs. This results in decreased mucosal defence and increased susceptibility to ulcers[35]. Nitric oxide (NO) is also a defence factor for mucosa. It is a potent vasodilator which maintains the mucosal blood flow providing protection against ischemic injury[36]. Manjari and Das found that the concentration of SOD, catalase, GSH, arachidonic acid, α-linolenic acid and decosahexaenoic acid were low and level of lipid peroxidation and NO were high in patients with duodenal ulcer (DU). Following treatment with proton pump inhibitor, lansoprozole, these biochemical abnormalities became normal. This study suggested that polyunsaturated fatty acids (PUFAs) can inhibit the growth of *H. pylori*, hence, can be used as anti ulcer drugs[37].

NSAIDs inhibit the enzyme cyclooxygenase (COX) decreasing production of prostaglandins. NSAIDs induce mucosal damage via recruitment of leukocytes and then by production of ROS **(figure 2).** ROS mediated mitochondrial damage as well as lipid, protein, and DNA oxidation leads to apoptosis and mucosal injury. A study demonstrated that antiulcer activity of a lansoprazole appears to be mediated by preventing NSAID-induced reductions in anti-apoptotic genes (e.g., Bcl and Bcl2) while inhibiting increased Fas and Fas ligand as well as pro-apoptotic genes (e.g., Bax and Bak)[38]. Apirin disrupts the membrane permeability causing activation of p38 MAPK pathway and downregulation of claudin-7, a protein component of tight junctions[39].

H. pylori produces a γ-glutamyltranspeptidase (GGT) in the periplasm which catalyzes the trans-peptidation and hydrolysis of the γ-glutamyl groups of glutamine and glutathione. These both are antioxidant enzymes of the host cell so the *H. pylori* GGT perform 2 functions. First, *H. pylori* unable to take up extracellular glutamine and glutathione directly so GGT hydrolyzes these substances to glutamate. The glutamate is then transported into *H. pylori* cells via a Na^+ dependent reaction and is mainly incorporated into the TCA cycle. Second, GGT acts as a

virulence factor by disrupting the antioxidant ability of host cells. So the *H. pylori* GGT reduces the ROS resistance of the host cells and induces apoptosis or necrosis[40,41].

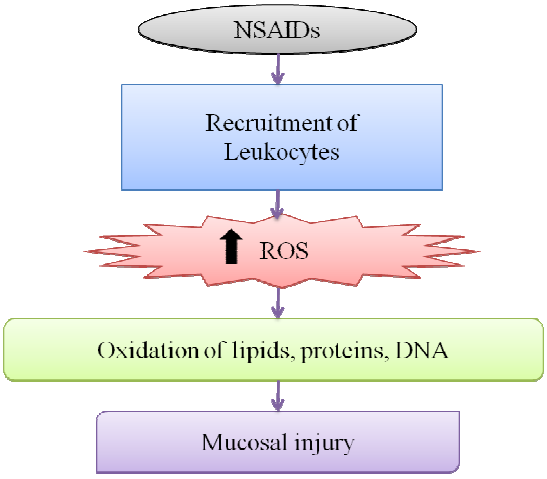

Figure 2. NSAIDs induced oxidative stress.

NSAIDs induce mucosal injury by recruitment of leukocytes which causes increased production of reactive oxygen species. These reactive species oxidises the DNA, lipids and proteins and induces mucosal injury.

3.3 Role of Inflammatory cytokines in pathogenesis of peptic ulcer

H. pylori induces infiltration of polymorphonuclear (PMN) and mononuclear leukocytes and enhances the production of various pro-inflammatory cytokines in gastric mucosa like interleukin-8 (IL-8), interleukin-1β and tumour necrosis factor-α[42]. Holck et al. found that expression of various inflammatory cytokines (IL-8, IL-10 and Interferon-Q) was increased during *H. pylori* infection. They also found a significant association between the cytokines and parameters like: bacteria load, chronic inflammation and activity [43]. IL-8 has been found as pro-angiogenic and carcinogenic factor as it is over expressed in gastric cancer cells in comparison to normal mucosa cells[44]. Transfection of IL-8 increases the angiogenesis and tumorigenesis of human gastric carcinoma cells in nude mice[45]. *H. pylori* water extract activates the neutrophils. The adhesion occurs between ICAM-1 on endothelial cells and CD11b/CD18 on neutrophils. This is responsible for the attachment of neutrophils to endothelial cells[46]. In *H. pylori* infection induction in the expression of ICAM-1 on gastric epithelial cells is dependent on NF-κB pathway[47]. ICAM causes the recruitment of inflammatory cell at the site of inflammation. *H. pylori* neutrophil-activating protein (HP-NAP), a bacterial cytosil protein promotes the neutrophil adhesion to endothelial cells. HP-NAP act as a chemotactic factor for both monocytes and neutrophils as it acts as an antigen to the human immune system, activates NADPH oxidase[48] and also stimulates the synthesis of tissue factors and plasminogen activator inhibitor-2 (PAI-2)[49].

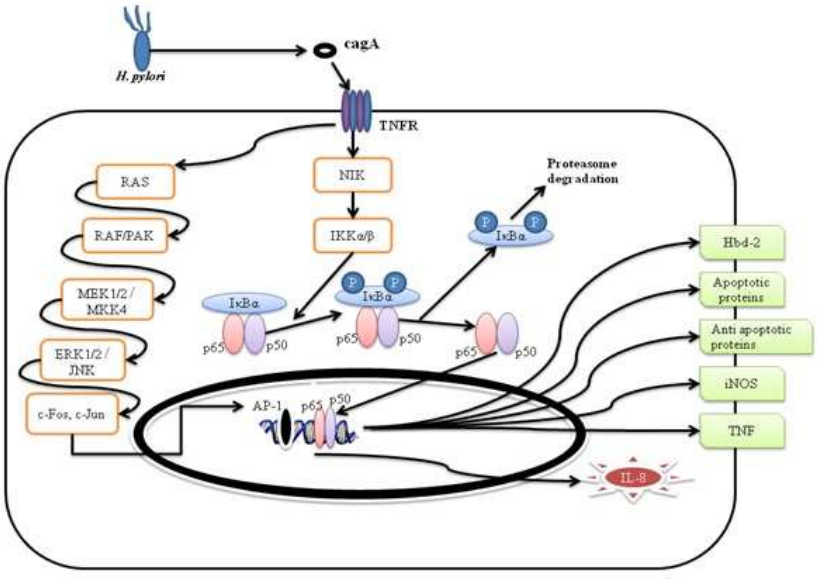

Figure 3. H. pylori induced inflammatory mediators

In a study, *cag* PAI-positive *H. pylori* significantly upregulated mRNA expression in 8, 2304 genes tested among these 8 upregulated genes; IL-8 showed the greatest increase (11.8-fold)[50]. Induction of epithelial IL-8 by live bacteria involves tyrosine phosphorylation and NF-κB activation[51]. *H. pylori* activates NF-κB-inducing kinase (NIK) via TNF receptor associated factor 2 (TRAF2) and TRAF6 and this activated NIK in turn phosphorylates and activates IKK-α and IKK-β, which then phosphorylate IkBα, leading to its proteosomal degradation. Then, the homo or heterodimer of NF-κB translocates into the nucleus inducing expression of IL-8 by binding to the promoting region of IL-8 gene[52]. Induction of NF-κB cause activation of inducible Nitric oxide synthase (iNOS) (role in apoptosis), increase the expression of apoptotic and anti apoptotic proteins (Bcl-2), cause Tumour necrosis factor α (TNF-α) mediated apoptosis, induction of human β defensin-2 (hBD-2)[33] (role in the epithelial innate host defence, act as anti microbial) ***(Figure 3).***

H. pylori cagA$^+$ strain activates NF-κB-inducing kinase (NIK) via TRAF2 and TRAF6. The activated NIK phosphorylates and activates IKK-α and IKK-β causing proteosomal degradation of IkBα. The homo- or heterodimer of NF-κB translocates into the nucleus and induce expression of IL-8 gene. Induction of NF-κB cause activation of iNOS, increase the expression of apoptotic and anti apoptotic proteins (Bcl-2), cause Tumour necrosis factor α (TNF-α) mediated apoptosis, induction of human β defensin-2 (hBD-2). *H. pylori* (Cag PAI) co cultured with gastric cancer cells shows transactivation of SRE and AP1 through the ERK1/2 and JNK/SAPK cascade. *Helicobacter pylori* infection induces expression of proinflammatory cytokines such as interleukin-8 (IL-8) and tumour necrosis factor α (TNF-α) in gastric mucosa, and their genes have AP-1 binding sites in the promoter region. c-Fos is important for transactivation of AP-1 which has SRE in the promoter region[53].

In *Helicobacter pylori* (cag PAI) infection the activation of AP-1 is mediated by SAPK cascade involving JNK, MKK4, PAK, and Rho-GTPases[54] and via p38 MAP Kinase[55]. *H. pylori* induced mucosal inflammation results in high production of interleukin 17 (IL-17), a potent inducer of IL-8 in gastric epithelial cells. The experiments show on treatment of MKN28 cells by IL-17 increased AP-1 and NF-κB DNA-binding activity. ERK 1/2 activity and IL-8 are expressed at high levels in freshly isolated *H. pylori*-colonized gastric epithelial cells. Moreover, the study demonstrates that IL-17, independently of *H. pylori*, increases ERK 1/2 phosphorylation and IL-8 transcripts in isolated gastric epithelial cells and that neutralization of IL-17 results in a significant suppression of ERK 1/2 activity and IL-8 synthesis in gastric biopsy cultures. However, the activation of ERK 1/2 was required to mediate AP-1, but not NF-κB, transcriptional activation. This finding confirms that the MAP kinase and NF-κB pathways may exert independent regulatory effects on gastric epithelial cell IL-8 production following *H. pylori* infection[56].

4. Management of peptic ulcer (need more focus-include preventive measures)

For the management of peptic ulcer, the most effective treatment approaches are: pharmacological treatment and endoscopy.

4.1 Pharmacological treatment

Different pharmacological classes of drugs which are used for the treatment of ulcer[57,58] are shown in **table1.**

Table 1. Different classes of drugs used for treatment of ulcers and their side effects

Class	Example	Side effects
Ant acids	Sodium bicarbonate Calcium carbonate Aluminium hydroxide Magnesium hydroxide / Combination	Rebound acid secretion
H_2 receptor antagonist	Cimetidine, Ranitidine Famotidine, Nizatidine Roxatidine, Lafutidine	Diarrhoea, Headache Drowsiness, Fatigue Muscle pain
Anti cholinergic	Propantheline Benactidine methobromide Pirenzepine, Terenzepine (selective M_1R antagonist)	Dry mouth, blurred vision, tachycardia, bladder dysfunction
Acid pump (H^+/K^+ATPase) inhibitor	Omiprazole, Lansoprozole Pantaprozole, Rabeprazole	Nausea, Abdominal pain, Constipation, diarrhoea
Cholecystokinin-2-receptor antagonist	Proglumide, L 365260 YM 022, YF476 S 0509, Z 360, PD 136450	Under clinical trial
Mucosal defensive agents	Prostaglandin analogue (Misoprostal) Sucralfate	Diarrhoea, contraindicated in pregnancy, Constipation

The antibiotics which are used specifically as a treatment therapy for *H. pylori* induced ulcer[59] are summarised in table 2.

Table 2. Treatment therapy for *H. pylori*

Class	Example	Dose
Proton pump inhibitors	Omiprazole	20 mg twice daily
	Esomeprazole	40 mg once or 20 mg twice daily
	Lansoprozole	30 mg once or twice daily
	Rabeprazole	20 mg once or twice daily
	Pantoprazole	40 mg once or twice daily
Bismuth compounds	Bismuth subcitrate (BSC)	120 mg four times daily
	Bismuth subsalicylate (BSS)	524 mg four times daily
	Ranitidine bismuth citrate (RBC)	400 mg twice daily
Antimicrobial agents	Amoxicillin	1,000 mg twice daily
	Clarithromycin	250 mg or 500 mg twice daily
	Metronidazole	500 mg twice or 250 mg four times daily
	Tinidazole	500 mg twice daily
	Tetracycline	500 mg four times daily
	Rifabutine	300 mg once or 150 mg twice daily
	Levofl oxacin	250 mg or 500 mg once or twice daily
	Furazolidone	200 mg twice daily

4.2 Endoscopy

Upper GI endoscopy has largely replaced upper GI barium X-ray series for the evaluation of upper GI tract disease or symptoms because it allows direct visualization, tissue acquisition, and therapeutic interventions[60,61].

Categories of endoscopic therapy

- **Injection therapy**
- **Thermal devices**
- **Mechanical devices**
- **Combined therapy**

4.2.1 Injection therapy

Hypertonic saline, dextrose, sclerosant (absolute alcohol, polidoconol), tissue adhesives: cyanoacyralate, thrombin/fibrin glue, epinephrine are used for therapy. Injection with solutions of diluted epinephrine (1:10,000) is widely used. In a recent study, a large volume (35-45 ml) epinephrine injection appeared to be more effective than a standard volume (15-25 ml) injection.

4.2.2 Thermal devices

Thermal devices can be divided into contact type- heater probe, monopolar and bipolar electrocoagulation and non-contact type- laser treatment, argon plasma coagulation -APC). A prospective, randomized study was performed by Llach et. al. to compare the hemostatic effect of injection therapy and heater probe thermocoagulation in the treatment of peptic ulcer bleeding. 104 patients were under study. Patients were randomly assigned during endoscopy to receive injection therapy (adrenaline and polidocanol) (n=51) or heater probe thermocoagulation (10F probe, at setting of 30J (n=53). No significant difference in effectiveness between injection therapy and thermocoagulation was found (recurrent hemorrhage- 4% vs 6% or minor rebleeding- 16% vs 17%, need for emergency surgery- two patients from each group, transfusion requirement- 0.45 ± 0.9 units vs 0.51 ± 1.1 units, the mean number of hospitalization days- 7.1 ± 4.2 vs 6.9 ± 4.9, and mortality- one patient from each group died)[62].

4.2.3 Mechanical devices

Hemoclips or endoscopic band ligation are mechanical devices have been used for the treatment of variceal haemorrhage, but rarely in the treatment of peptic ulcer disease[60,61]. A meta-analysis was performed to compare the efficacy of hemoclips versus injection or thermocoagulation in endoscopic hemostasis by pooling data from the literature. Out of 1156 patients recruited in the 15 studies, 390 were randomly assigned to receive clips alone, 242 received clips combined with injection, 359 received injection alone, and 165 received thermocoagulation with or without injection. Definitive hemostasis was higher with hemoclips (86.5%) than injection (75.4%; RR 1.14, 95% CI 1.00–1.30), or endoscopic clips with injection (88.5%) compared with injections alone (78.1%; RR 1.13, 95% CI 1.03–1.23), leading to a reduced requirement for surgery but no difference in mortality. Compared with thermocoagulation, there was no improvement in definitive hemostasis with clips (81.5% versus 81.2%; RR 1.00, 95% CI 0.77–1.31). Conclusion was that a Successful application of hemoclips is superior to injection alone but comparable to thermocoagulation in producing definitive hemostasis. There was no difference in all-cause mortality irrespective of the modalities of endoscopic treatment[63].

4.2.4 Combined therapy

Injection therapy and thermal coagulation are combined for the treatment of ulcer bleeding. This combination therapy has better outcome. Even the better management of ulcers bleeding with endoscopy, rebleeding occurs in 10-15% of cases. So in these cases second look endoscopy or surgery is done. Transarterial embolization (TAE) has been proposed as an alternative to surgery in patients with bleeding peptic ulcers in whom endoscopic hemostasis fails. TAE reduces the need for surgery without increasing the overall mortality and is associated with fewer complications[64].

5. 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. The reason for non-*H. pylori* and non-NSAID peptic ulcer may be that the mucosa after NSAID attack or after *H. pylori* infection may not recover properly even after NSAID withdrawal or after antibacterial treatment.

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