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Clinical Study of Helicobacter Pylori Infection in Operated Patients of Perforated Duodenal Ulcer During Post-Operative Period of 6 Weeks with Endoscopic Cup Mucosal Biopsy and Rapid Urease Test

[1]Jaiwant Mahurkar and [2]S.M. Veerendraswamy

[1,2]Department of General Surgery Basaveshwara Medical College and hospital, Chitradurga, Karnataka, India

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Corresponding Author
Jaiwant Mahurkar,
Department of General Surgery Basaveshwara Medical College and hospital, Chitradurga, Karnataka, India
jaichinn@gmail.com

Author Designation
[1]PG Student
[2]Professor and Unit Chief

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ABSTRACT
Perforation is one of the complications of duodenal ulcer. Its causative factors include Helicobacter pylori, NSAIDs and others. The treatment for perforated duodenal ulcer is simple closure of the perforation with an mental patch (Graham's/Modified Graham's patch repair). Yet even after surgery, few patients can have persistence of Helicobacter pylori in their post-op follow up period. This clinical study was done to investigate the prevalence and etiological role of Helicobacter pylori infection in patients who have undergone surgery for perforated duodenal ulcers. Objectives were to determine the prevalence of Helicobacter pylori infection in post-operative patients with perforated duodenal ulcer after duration of at least 6 weeks and to assess the role of Helicobacter pylori in the etiology of duodenal ulcers. A prospective study comprising of 30 patients, (who met inclusion criteria) from the period of July 2022 to December 2023, was done, who have undergone surgery for perforated duodenal ulcer and got discharged and later came for post-op follow up in surgery OPD, 6 weeks post surgery. All 30 patients were advised Upper Gastro-intestinal endoscopy followed by Rapid Urease test. The results were observed, analysed and compared with similar other studies. Our study involved 30 patients both males and females, age between 18-75 years, who have undergone surgery for perforated duodenal ulcer and got discharged and later came for post-op follow up in surgery OPD , 6 weeks after surgery. Upper gastro-intestinal endoscopy was done for them. Out of those 30 patients, 18 patients' rapid urease test was positive (60%) and 12 patients' rapid urease test was negative (40%). This showed significant prevalence of H.pylori in post-op follow up patients of perforated duodenal ulcer. Association of H.pylori in patients of post-op follow up cases with perforated duodenal ulcer is significant (60%). Alcohol, smoking and NSAIDs were significant risk factors, associated with perforated duodenal ulcer. Patients presenting with a perforated peptic ulcer should simple closure of the perforation. Additionally, they should receive treatment to promote healing of the ulcer and eliminate the H. pylori infection. The eradication of this organism is important as it reduces the likelihood of ulcer recurrence and perforation following the closure of the ulcer.

INTRODUCTION

A duodenal ulcer is defined by a disruption of the mucosal layer on the surface of the duodenum (a constituent of Peptic ulcer disease). Peptic ulcer disease (PUD) involves the bottom part of the esophagus, the stomach and the first part of the duodenum[1]. The etiology of this disorder encompasses several factors, including Helicobacter pylori (H. pylori) infection, nonsteroidal anti-inflammatory medicines (NSAIDs), psychological stress, dietary habits, alcohol use, tobacco use, as well as other contributory elements like metabolic abnormalities, Zollinger-Ellison syndrome, malignancy and vascular insufficiency and a history of chemotherapy[1,2]. The stomach and duodenal surfaces each include a defense system consisting of pre-epithelial, epithelial and subepithelial components. Ulceration occurs as a result of damage to the mucosal surface, which extends beyond its outermost layer. Dyspepsia is the primary symptom linked to duodenal ulcers., however the severity of the condition might differ and may involve gastrointestinal hemorrhage, gastric outlet blockage and perforation or fistula development[3]. While the involvement of H. pylori in the development of peptic ulcer disease (PUD) is widely recognized, its contribution to perforated peptic ulcer (PPU) is not firmly established. The literature has contradictory findings about its correlation[4]. Some studies show a strong link between H. pylori infection and peptic ulcer disease (PPU), suggesting that getting rid of this infection can prevent ulcers from recurring. However, other research indicates a weak or no connection at all, suggesting that there may be different causes for the development of PPU. This study is being conducted to evaluate the involvement of H. pylori in patients with PPU due to the inconsistent results and lack of data available[5-7].

Epidemiology: The epidemiology of PUD epidemiology has experienced significant transformations throughout the last two centuries. The incidence of duodenal ulcer began increasing in the second half of 19th century. The incidence of PUD varies from 0.12% to 4.7% for cases identified by physicians and from 0.1-2.6% for those diagnosed in hospitals. The yearly worldwide incidence is documented to be between 0.1% and 1.5%, while the occurrence rate is stated to be between 0.03% and 0.19% and the lifetime occurrence rate is claimed to be between 5% and 10%. Bleeding is the most common consequence of PUD esp. duodenal ulcer, with an annual incidence ranging from 19 to 57 per 100,000 patients (about 0.02% to 0.06%). The incidence of peptic ulcer perforation is less common compared to bleeding, with reported rates ranging from 4-14 per 100,000 individuals (0.004-0.014%)[8-24].

Etiology and Pathogenesis: Peptic ulcers arise from a combination of reduced protective factors, heightened aggressive factors, or a combination of both. Protective elements that contribute to defence against harm include the secretion of bicarbonate in the mucosal lining, the formation of mucus, sufficient blood flow, the presence of growth factors, the renewal of cells and the generation of prostaglandin within the body. The detrimental aspects that can cause harm include the release of hydrochloric acid, pepsins, ingestion of ethanol, smoking, duodenal reflux of bile, ischemia, NSAIDs, hypoxia and, most notably, the presence of Helicobacter pylori infectio[8-24].

Helicobacter Pylori Infection: Approximately 50% of the global population is impacted by H. Pylori. Previously, a significant majority of duodenal ulcers (ranging from 80% to 95%) and around 75% of gastric ulcers were found to be linked to the presence of H. pylori bacteria. The prevalence of pylori infection in peptic ulcers has decreased to 50-75% in industrialized nations due to advancements in diagnosis, treatment, and prevention. Contracting an infection caused by the bacterium H. Studies have demonstrated that pylori infection occurs before the development of ulcers and when this bacterium is eliminated during ulcer treatment, the chances of ulcer recurrence are quite low. These observations have firmly established the position of H. Helicobacter pylori is considered a main factor responsible for the development of peptic ulcer disease. H. pylori is a highly effective generator of urease, an enzyme that can break down urea into ammonia and bicarbonate. This process creates an alkaline environment within the acidic stomach, enabling the bacteria to survive. The bacteria adhere to the stomach epithelial cells by attaching to surface adhesions. H. pylori bacteria are adapted to exist in environments with low levels of oxygen and can only survive in the lining of the stomach. Therefore, H. pylori can also be present in ectopic gastric mucosa in the upper part of the oesophagus, in Barrett's oesophagus, in gastric metaplasia in the duodenum, within a Meckel's diverticulum and in ectopic gastric mucosa in the rectum[8-24]. The precise mechanisms underlying pylori-induced gastrointestinal (GI) injury remain incompletely known. However, four putative mechanisms have been hypothesised, which are believed to interact with one other, resulting in a disruption of normal gastric and duodenal physiology and ultimately leading to the formation of ulcers.

- **Production of Toxic Products that Cause Local Tissue Injury:** Locally generated harmful substances consist of byproducts resulting from the activity of urease (such as ammonia), cytotoxins, mucinase (which breaks down mucus

and glycoproteins), phospholipases that harm both epithelial and mucus cells and platelet-activating factor (which is recognised for causing damage to the mucous membrane and blood clot formation in the small blood vessels).

- **Induction of a Local Mucosal Immune Response:** H. pylori can induce a localised inflammatory response in the stomach mucosa, drawing in neutrophils and monocytes, which then generate a multitude of proinflammatory cytokines and reactive oxygen metabolites.
- **Elevated Amounts of Gastrin and Alterations in the Secretion of Acid:** For individuals diagnosed with antral H. pylori infection, there is a notable increase in baseline and stimulated gastrin levels. This is likely caused by a decrease in somatostatin production from antral D cells. Pylori. During the initial stage of H. In the case of pylori infection, there is a reduction in acid secretion. In cases of persistent infection, the bacterium H. Helicobacter pylori stimulates the growth of ECL and G cells, leading to excessive production of stomach acid. The gastric hyperacidity could be influenced by a reduction in the serum levels of somatostatin. Nevertheless, in the event that the oxyntic glands are impaired due to the persistent illness, it would lead to a decrease in stomach acid production, known as hypoacidity.
- **Gastric Metaplasia Occurring in the Duodenum:** Metaplastic replacement of certain regions of the duodenal mucosa with gastric epithelium is likely a defensive reaction to the reduced acidity in the duodenum caused by excessive acid production. This adaptation enables the release of hydrochloric acid (HCl). H. pylori colonises various regions of the duodenum, leading to duodenitis and increasing the likelihood of developing duodenal ulcers. The presence of H.pylori bacteria in the duodenum is more prevalent in patients who develop ulcers compared to people who have asymptomatic infections confined to the stomach. Antral gastritis is closely linked to the development of peptic ulcers[8-24].
- **Other Causes:** Of perforated duodenal ulcer include; Iatrogenic causes, trauma, foreign bodies, spontaneous perforations (in neonates)[8-24].

Clinical Features: From an anatomical perspective, both the surfaces of the stomach and duodenum possess a defence system that consists of pre-epithelial, epithelial and subepithelial components. Epigastric pain is the primary symptom observed in patients with uncomplicated peptic ulcer disease (PUD). The pain is usually tolerable and frequently relieved by consuming food. The pain may manifest intermittently, usually throughout the spring and autumn seasons and escalate during episodes of emotional stress. When the discomfort becomes chronic, it signifies that the ulcer has infiltrated further. Back pain is usually a sign that something has penetrated the pancreas, while widespread irritation in the peritoneum is produced by a perforation that is not contained. (Free perforation). The severity of the presentation can vary and may include gastrointestinal bleeding, gastric outlet obstruction, perforation, or fistula development[25,26,27].

Diagnosis:

Testing for Helicobacter Pylori:

Invasive Tests:

- Urease analysis via upper gastro-intestinal endoscopy.
- Histology via upper gastro-intestinal endoscopy
- Culture[8-24].
- Post-treatment endoscopy with biopsy is only necessary if a repeat procedure is clinically indicated. In such patients, sampling multiple areas of the stomach/duodenum is important to avoid missing persistent infection due to alteration of the bacterial density and distribution by prior antibiotics and antisecretory medications. These tests should not be performed sooner than 6-8 weeks after completion of treatment, because earlier testing might yield false-negative results[29].

Non Invasive Tests:

- The urea breath test.
- Stool antigen testing.
- Serology.
- Upper gastrointestinal radiography.
- Erect X-ray of abdomen in case of suspected perforated duodenal ulcer (gas under diaphragm is the pathognomic feature)[8-24].

Box 1 shows indications the indications for H.pylori testing.

Standard

Active PUD (gastric or duodenal ulcers)
History of PUD without prior treatment for H.pylori
Low grade gastric MALT lymphoma
Following endoscopic resection of early gastric cancer
Uninvesting dyspepsia (if population prevalence is <20%

Controversial

Functional dyspepsia (if population prevalence is <20%
Chronic PPI use
Chronic NSAID use
Unexplained Iron deficiency anemia or immune thrombocytopenic purpura
First degree relative with gastric cancer
First generation immigrant from a region of high incidence of gastric cancer (e.g., eastern Asia, Latin America

Treatment:

Conservative Management: It is reserved for stable patients with contained perforation. Patients are resuscitated with IV fluids, broad spectrum antibiotics, PPI's, anti-emetics , close monitoring. Main aim should be on H.pylori eradication[11-25].

Endoscopic Management: It is reserved for those with minor non contained perforations. Endoscopic management is a desirable treatment approach due to its minimally invasive nature. Endoscopic closure within 24 hours is believed to be technically simpler due to the reduced severity of inflammatory alterations.

The options are as follows:

TTSC (Through the Scope Clips):TTSCs are a useful tool for closing tiny perforations in the duodenum during endoscopic procedures. TTSC is particularly ideal for linear perforations that are less than 1cm in size. OTSC (over the scope clips). OTSCs, unlike traditional endoscopic clips, have the capacity to compress greater amounts of tissue. The OTSC system is specifically constructed in the configuration of a bear trap to facilitate the complete closure of the tissue. The OTSC method is applicable for holes with dimensions ranging from 1-3 cm. The efficacy of OTSC therapy for peptic ulcer perforations has been demonstrated, with few negative consequences.

Endoloop Combined with Clips: If the OTSC approach is not accessible, a combination of TTSC and an endoloop can be utilized.

SEMS (Self-Expandable Metal Stents): Self-expandable metal stents (SEMS) are a viable another options to endoscopic therapy for duodenal perforations[9-25].

Surgical Management of Perforated Duodenal Ulcer: The surgical procedure for this specific condition should focus on sealing the perforation and removing any debris from the abdomen. This can be accomplished with either an open operation or laparoscopically[9-25]. The suggested strategy to a ruptured duodenal ulcer can be summarized in (fig. 1) below.

Fig. 1: Displays the Treatment Protocol for Surgical Intervention in Cases with Perforated Duodenal Ulcers. HSV: Highly Selective Vagotomy

Named surgeries for treatment of perforated duodenal ulcer include **Graham's patch** or **Modified Graham's patch repair** done either using open (laparotomy) or laparoscopic approach[10-26].

Source of Data: This study was conducted comprising 30 patients of post-op patients with perforated duodenal ulcer, both male and female patients attending the General Surgery outpatient department and in patients at Basaveshwara Medical college hospital and research centre, Chitradurga in the period of July 2022 to December 2023.

Sample Size and Study Population: Sample size: 4pq/L2, p:83, q:17, L:16.6 ,which equals: 20.48 rounded off to 30.

Inclusion Criteria: Patients diagnosed with perforated peptic ulcer of ages 18-75 years, reporting to Basaveshwara Medical college and Hospital, Chitradurga, Karnataka, who had undergone emergency laparotomy for perforated duodenal ulcer repair 6 weeks ago and followed up for Upper gastro-intestinal endoscopy, after 6 weeks post surgery.

Exclusion Criteria:

- Patients who were on triple drug therapy for H. pylori for acute gastritis or any other disease.
  Patients who had respiratory failure, renal failure and congestive heart failure were excluded.
  Patients with perforations due to malignancy.
  Patients who gave negative consent.
- Patients with traumatic perforations.

Method of Data Collection: All patients have been traced for and evaluated by regular follow ups and symptoms post surgical repair of perforated duodenal ulcers. The criteria which were taken into consideration are given below. These criteria were then matched against certain criteria which are also given below. Each criteria was compared against a criteria and individual p values were calculated for each of them. All patients were subjected to surgical intervention initially followed by endoscopic cup mucosal biopsy, histo-pathological examination and rapid urease test in post-op period of 6 weeks after surgery, after routine investigations and informed consent. Patients were also informed about the possibility of occurrence of bleeding and recurrence of ulcer. The pre surgical and endoscopic criteria which were taken into consideration were:

- Chief complaints.
- History of presenting illness.
  Past and family history (including coagulation disorders).
- Past surgical history for perforated duodenal ulcer.
- Habits.

Upper gastro-intestinal endoscopy was done for all

patients, followed by mucosal biopsy taken to look for presence of Helicobacter pylori. Those reported positive were given 2 weeks therapy of oral esomeprazole, clarithromycin and amoxicillin and those negative were counselled and then discharged.

RESULTS AND DISCUSSIONS

Statistical Analysis: Data was entered into Microsoft excel data sheet and was analysed using SPSS ver. 22 software. Categorical data was represented in the form of bar diagrams and pie charts. Chi square test (X2), (for 2x2 tables only) was used as test of significance for qualitative data, in case of risk factors associated with the disease.

Graphical Representation of the Data: MS Excel and MS Word were used to obtain various types of graphs and charts such as bar diagrams and pie charts. p value (probability that the risk factor is associated with the disease) of <0.005 was considered as statistically significant after assuming all the rules of statistical tests.

Statical Software: MS Excel, SPSS ver.22, was used to analyze data. EPI info (CDC Atlanta), Open epi, med calc. and Mendeley's desktop were used to estimate sample size, odds ratio and reference management in the study.

Age Distribution: Age distribution of 30 cases, of which the age of the youngest patient was 18 years and the age of the eldest patient, was 70 years. The highest number of cases was found in the age group of 46-60 years of age. The average age of presentation of patient is 41.86 years (Table 1).

Of the total number of participants, 22 were males (73.33 %), 8 were females (26.67%) and male: female ratio was 2.75 (Table 2).

Out of 30 participants , 18 were positive for H.pylori (60 %) and the rest were negative for H.pylori (40 %). This signifies that H.pylori is prevalent even after surgery for perforated duodenal ulcer in majority of patients (Table 3).

Of the 30 participants, 12 were alcoholic. Of the 12, 10 turned out to be H.pylori positive with p value 0.033 and odds ratio 6.25, which tells us that alcohol consumption plays a significant role as as risk factor in H.pylori infection.

6 participants had a h/o chronic smoking, of which 4 turned out to be H.pylori positive , where p value was 0.709 and odds ratio as 1.43 , which signifies that role of smoking as risk factor is somewhat insignificant (Table 4). 4 participants had a h/o taking non prescribed NSAIDs, of which 2 were H.pylori positive, where p value was 0.661 and odds ratio was 0.625, which tells that in this study, NSAIDS had no significant role as a risk factor in H.pylori infection.

All female, 8 participants had no habits of any sort, where only 2 were positive for H.pylori infection, with the p value being 0.018and odds ratio being 0.125, which tells us through this study, that refraining from such habits, leads to decreased/nil prevalence of H.pylori infection. Duodenal ulcer arises when there is a disruption in the integrity of the duodenal mucosa. It is a component of peptic ulcer disease (PUD), which also encompasses stomach ulcers. The causes of this condition include H.pylori infection, NSAIDS, alcohol consumption, smoking, stress, dietary factors, as well as additional reasons such as metabolic abnormalities, Zollinger Ellison syndrome, cancer, vascular insufficiency and a history of cchemotherapy[9]. The stomach and duodenal surfaces each include a defense system that consists of pre-epithelial, epithelium, and subepithelial components. Ulceration occurs when the mucosal surface is disrupted, extending beyond the outermost layer. Dyspepsia is the primary symptom of duodenal ulcers, although the severity of the condition can vary and may lead to complications such as gastrointestinal bleeding, gastric outlet blockage, perforation, or fistula formation[9]. Although the role of H. pylori in the formation of peptic ulcer disease (PUD) is generally acknowledged, its impact on perforated peptic ulcer (PPU) is still unclear. The literature has conflicting conclusions about its correlation. Some studies show a strong link between H. pylori infection and peptic ulcer disease (PPU), suggesting that eliminating this infection can prevent ulcers from recurring. However, other research indicates a weak or no correlation, suggesting that there may be different causes for the development of PPU. The purpose of this study is to assess the role of H. pylori in patients with PPU, as there is a scarcity of data and conflicting research findings[10]. In this study, the number of patients enrolled was 30, (who were operated for perforated peptic ulcer around 5-6 weeks ago), prior to endoscopy, where males were 22 (73.33%) and females were 8 (26.67%) and the male to female ratio constitutes to 2.75%. This was similar to the study done by K.Thirupathiah[14], John[11], Ugochukwu[30] and Dogra[31] where males were most commonly affected with a ratio of 15:1, 4.38:1, 3.2:1 and 3:1 respectively, which shows that males are more commonly affected. Regarding age, majority of the patients fell under the age group of 46 years to 60 years (30 %) and the mean age were found to be 41.86 years. This is in similarity seen in studies done by K.Thirupathaiah[7](46.5 yrs), John[11](52.81 yrs), Dogra[31](49.2 yrs), Ugochukwu *et al* (39.5 yrs). Out of the 30 patients, 18 tested positive for Helicobacter pylori and 12 tested negative. This shows a prevalence rate of 60% in patients who had surgery for a perforated duodenal ulcer. The occurrence of H.pylori in patients undergoing post-operative follow-up is noteworthy and confirmed by the fast urease test conducted during upper gastrointestinal endoscopy.

Table 1: Tests for H.Pylori Infection Ig, Immunoglobulin., NPV, Negative Predictive Value., PPI: Proton Pump Inhibitor., PPV, Positive Predictive Value

Nonendoscopic tests	Advantages	Disadvantages
Serology (qualitative or quantitative lgG)	Widely available, inexpensive good NPV	Poor PPV if Hp prevelnces is
Urea breath test ("Cor Tc)	Identifies active infection accuracy (PPV, NPV) not affected by Hp prevalence. Useful both before and after treatment	low not useful treatment Availability and Reimuresement inconsistent Accuracy affected by PPI and Antibiotic use. Small radiation Does with C test
Stool Antigen Tests	Identifies active infection accuracy (PPV, NPV) not affected by Hp prevalence Useful both before and after treatment (Monoclonal test).	Fever data available for polyclonal test. Accuracy affected by PPI and
Endoscopic Tests	**Advantages**	**Disadvantages**
Histology	Excellent sensitivity and specificity. Especially with special and immune	Expensive (endoscopic and pathology costs). Some Stains.
Provides additional information	interobserve variability	About gastric mucosa. Accuracy affected by PPI and Antibiotic use.
Rapid urease test (e.g.," CLO test")	Rapid results. Accurate in patient not using PPIs or antibiotics. No added pathology cost.	Requires endoscopy. Less accurate after treatment or in Patient using PPIs.
Culture specificity	Specificity 100%. Allows antibiotic sensitivity testing.	Difficult culture protocol Expensive. Not widely available
PCR assay	Excellent sensitivity and specificity. Permits detection of antibiotic resistance.	Not widely available Techniques not standardized Expensive.

Table 2: Age Distribution of Participants

Age of participants	Total no. of participants (n=30)	Percentage (%)
18-25 years	6	20 %
26-35 years	7	23.33%
36-45 years	5	16.67%
46-60 years	9	30%
>60 years	3	10%
Total	30	100 %

Table 3: Sex Distribution

	Total no. of participants (n=30)	Percentage (%)
Males	22	73.33
Females	8	26.67

Table 4 : Test Results (Rapid Urease Test: RUT)

Result	Participants (n=30)	Percentage (%)
Positive	18	60
Negative	12	40
Total	30	100

Table 5: Risk Factors

Factors	No. of participants	RUT* positive	RUT* negative	p value	Odds ratio	X2, df	Significance
Alcohol	12	10	2	0.033	6.25	4.56, 1	yes
Smoking	6	4	2	0.709	1.43	0.1347, 1	no
NSAIDs	4	2	2	0.661	0.625	0.1926, 1	no
No habits	8	2	6	0.018	0.125	5.58, 1	yes
Total	30	18	12				

X2 : Chi square test., df: degree of freedom.

Table 6: Depicting Various Characteristics of Different Studies Done in the Recent Past.

Author	Year	Mean age (yrs)	Male:female	H.pylori prevalence(%)	Result
K.Thirupathaiah[7].	2020	46.5	15:1	12.5	Not significant
John[11]	2017	52.8	4.38:1	47	Significant
Dogra[31]	2014	49.2	3.2:1	92	Significant
Ugochukwu[30]	2013	39.5	3:1	65-70	Significant

Other studies results were as follows:
K.Thirupathaiah *et al*: 12.5 % (2020).
John B *et al*: 47% (2017)
Dogra B *et al*: 92% (2014).
Ugochukwu *et al*: 65-70% (2013).

Among the **30** patients, **12** patients had habit consuming alcohol prior to surgery of which **10** turned out to be H.pylori positive. **6** patients had a chronic history of smoking, prior to surgery, of which 4 turned out to be H.pylori positive. Another 4 patients had a habit consuming self medicated NSAIDS, prior to surgery of which 2 turned out to be H.pylori Positive. All 8 females had not habits, of which 2 were H.pylori positive by Rapid Urease test via Upper GI endoscopy (Table 5).

CONCLUSION

Association of H.pylori in patients of post-op follow up cases with perforated duodenal ulcer is significant (60%). Alcohol, smoking and NSAIDs were significant risk factors, associated with perforated peptic ulcer. Patients presenting with a perforated peptic ulcer should simple closure of the perforation. Additionally, they should receive treatment to promote healing of the ulcer and eliminate the H. pylori infection. The eradication of this organism is important as it reduces

the likelihood of ulcer recurrence and perforation following the closure of the ulcer.

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