A Clinicopathological Study of Peptic Ulcer Perforation, Recurrence and its \textit{H. pylori} Association

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\textbf{ABSTRACT}

\textbf{BACKGROUND}

The causes for complications of peptic ulcer disease, like perforation, hematemesis and gastric outlet obstruction are multifactorial. Of these causes, the presence of \textit{H. pylori} infection, injudicious use of NSAIDs, smoking, etc. are well established. This study aims to find the association of \textit{H. pylori} with peptic ulcer perforation and peptic ulcer recurrence.

\textbf{METHODS}

One hundred and fifty patients operated for peptic ulcer perforation were observed in the study and their results analysed. A thorough clinical examination, proper investigative work up along with adequate preoperative resuscitative measures were undertaken. All patients were then operated, two biopsies were taken and sent for \textit{H. pylori} histopathological examination and rapid urease test. Upper G1 endoscopy was done in follow up period to evaluate ulcer recurrence. Biopsy was sent to confirm \textit{H. pylori} eradication. Collected data was then analysed.

\textbf{RESULTS}

Out of 150 cases, rapid urease test was positive in 65 patients and in histology \textit{H. pylori} was seen in 54 patients (total \textit{H. pylori} cases 65). 120 (80\%) were taking NSAIDs, 90 (60\%) were smokers, 75 (50\%) were taking alcohol, 105 (70\%) of the patients were tobacco chewers. Sixty five (urease +ve) patients were randomly divided into the triple therapy group (34 patients) and the control group (31 patients). Eradication of \textit{H. pylori} and initial ulcer healing were significantly higher in the triple therapy group than the pantoprazole alone group. After 1 year, ulcer recurrence was 6.1\% in the eradication group vs. 33.3\% in the control group (p value=0.001).

\textbf{CONCLUSIONS}

\textit{H. pylori} (urease+ 65, histology+ 54) and non-steroidal anti-inflammatory drugs (120 cases) are two main culprits causing peptic ulcer perforation. Peptic ulcer perforation is second highest in \textit{H. pylori} +ve group. So, \textit{H. pylori} is also a major causative agent for peptic ulcer perforation. Eradication of \textit{H. pylori} was significantly higher in the triple therapy group and ulcer healing was significantly better in the eradication group. Eradication of \textit{H. pylori} reduced the incidence of recurrent ulcer (p value= 0.001)

\textbf{KEYWORDS}

Peptic Ulcer, \textit{H. pylori}, Perforation, Recurrence
Peptic ulcer is characterized by mucosal damage secondary to pepsin and gastric acid secretion. It usually occurs in the stomach and proximal duodenum; less commonly, it occurs in the lower oesophagus, the distal duodenum, or the jejunum, as in unopposed hypersecretory states such as Zollinger–Ellison syndrome, in hiatal hernias, or in ectopic gastric mucosa (e.g., in Meckel’s diverticulum). Acid peptic disease has some of complications which can be fatal as perforation, haematemesis and gastric outlet obstruction. There are multifactorial causes for the acute perforation of peptic ulcer disease. Helicobacter pylori, a curved Gram negative, microaerophilic bacteria has its Godwin et al.1 (1990), normal habitat is in the stomach of human and other primates where it survives closely opposed to the gastric mucus secreting cells. Lee, 19912 The bacterial urease creates a neutral pH ecological niche and the (Blaser 1992)3 ammonia generated buffers the acidic juice; and provides an source of nitrogen for H. pylori. NIH Consensus Conference (1994)4 Although H. pylori is present in most patients with duodenal ulcers, only 10 to 15 percent of them develop peptic ulcer disease. Nilsson C, Sillén A, Eriksson L, Strand ML, Enroth H. Normark S, et al5 (2003) Patients with H. pylori infection have increased resting and meal-stimulated gastric levels and decreased gastric mucus production and duodenal mucosal bicarbonate secretion, all of which favor ulcer formation.

Hopkins RJ, Girardi LS, Turney EA (1996)6 Eradication of H. pylori greatly reduces the incidence of duodenal ulcer recurrence from 67 to 6 percent and gastric ulcer recurrence from 59 to 4 percent. Whether H. pylori is the cause or effect of gastric mucosal disease remain controversial. Bytzer P, Teglbjaerg PS (2001)7 NSAIDs are the most common cause of peptic ulcer disease in patients without H. pylori infection. NSAIDs cause submucosal erosions and inhibit the formation of prostaglandins and their protective effects of stimulating mucus and bicarbonate secretion and epithelial cell proliferation. Huang JQ, Sridhar S, Hunt RH (2002)8 Coexisting H. pylori infection increases the likelihood and intensity of NSAID-induced damage.

Collier DS, Pain JA (1985)9 & Lanas A, Serrano P, Bajador E, Esteva F, Benito R, Sainz R (1997)10 NSAID use is responsible for approximately one half of perforated ulcers, which occur most commonly in older patients taking aspirin or other NSAIDs for cardiovascular disease or arthropathy. Proton pump inhibitors and misoprostol (Cytotec) minimize the ulcerogenic potential of NSAIDs and reduce NSAID-related ulcer recurrence. NSAIDs are proved causes of acute peptic ulcer perforation alone or in combination with corticosteroids. Epidemiological studies have also identified tobacco use, alcohol abuse, smoking etc. as contributors to peptic ulcer perforation. These products prevent ulcer healing thereby causing recurrence. Our main aim is to find association with H. pylori, peptic ulcer perforation and peptic ulcer recurrence

We wanted to study the incidence of H. pylori infection in patients with peptic ulcer perforation and evaluate the effect of helicobacter pylori eradication on ulcer recurrence after repair of peptic ulcer perforation.

METHODS

We prospectively studied one hundred fifty patients admitted for perforation peritonitis, who were operated and gastroduodenal perforation confirmed at laparotomy in G.S.V.M. Medical College & LLR & Associated Hospital, Kanpur. Upon admission the details of the identification data, clinical history and examination findings were recorded according to a set proforma with particular emphasis on the past history of ulcer symptoms, its duration, history of taking non-steroidal anti-inflammatory drugs, steroids or H2 blockers, tuberculosis, hypertension ischaemic heart disease, chronic obstructive airway disease etc. Exact time of the onset of pain was recorded as far as possible. Detailed clinical examination of the patient was done immediately upon admission especially looking for the evidence of circulatory shock, septicemia and peritonitis. Routine haematological and urine investigations were sent in all patients and a sample was collected for grouping and cross matching investigations included Hb%, total leukocyte count, differential leukocyte count, serum creatinine, random blood sugar, serum potassium, sodium concentrations and urine examination for presence of albumin, sugar and microscopic picture. Where ever possible serum amylase, packed cell volume and arterial blood gas estimation was done; and an electrocardiogram was taken. Resuscitation measures were started immediately upon admission with placement of an intravenous line and administration of necessary fluids and electrolytes. Blood was arranged and transfused whenever required. Oral intake was suspended and a 16G nasogastric tube was passed in the stomach and the contents evacuated completely. Urinary catheter was inserted to monitor the urine output.

An antero-posterior erect abdominal skiagram showing both domes of the diaphragm was taken in all patients after maintaining the patient in an up-right position for ten minutes. Postero-anterior chest film in inspiratory and expiratory phase was also taken. All patients were operated under general anaesthesia.

Two biopsies were taken from the ulcer margin. One was sent for the histopathological examination and other sample was immediately tested by rapid urease test. For this pre-prepared refrigerated urease broth was used. In H. pylori positive cases the colour of media changed from yellow to red. In most of the cases colour change occurred within 2 hrs, but it was observed up to 24 hrs. Preserved fixed and paraffin embedded biopsy pieces from 150 patients were evaluated. Histological slides
were stained with haematoxylin, Giemsa and the new H. pylori silver stain (AgNOR stain). H. pylori silver stain method showed these bacteria brown black and they could be detected easily in most cases at low magnification. Simple closure of the perforation was done by Cellan-Jones technique. Urease positive cases were randomised in two group (triple therapy and pantoprazole alone). Upper GI endoscopy and biopsy done in follow-up period 12 weeks, 6 months and 1yr to evaluate ulcer persistence and recurrence (equal or greater than 5 mm in size).

**Inclusion Criteria**

All patients of peptic ulcer with gastroduodenal perforation and > 20 years of age were included.

**Exclusion Criteria**

Patients of peptic ulcer with large bowel perforation, patients of renal failure, liver failure, severe comorbid conditions like diabetes mellitus and tuberculosis, coagulopathy and patients not willing to participate in the study were excluded.

### RESULTS

#### Table 1. Age and Sex Distribution

<table>
<thead>
<tr>
<th>Age (Yrs.)</th>
<th>Male</th>
<th>Female</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 30</td>
<td>3</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>30 – 40</td>
<td>12</td>
<td>12</td>
<td>88</td>
</tr>
<tr>
<td>40 – 50</td>
<td>76</td>
<td>72</td>
<td>96</td>
</tr>
<tr>
<td>50 – 60</td>
<td>39</td>
<td>36</td>
<td>84</td>
</tr>
<tr>
<td>&gt;60</td>
<td>18</td>
<td>18</td>
<td>100</td>
</tr>
</tbody>
</table>

#### Table 2. Predisposing Factors

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Occasional users</th>
<th>Acute users</th>
<th>Chronic users</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>27</td>
<td>81</td>
<td>12</td>
<td>120</td>
</tr>
<tr>
<td>Percentage</td>
<td>50</td>
<td>60</td>
<td>8</td>
<td>80</td>
</tr>
</tbody>
</table>

**Table 3. Acute and Chronic Users of NSAIDs**

**Occasional Users** - Patients who took NSAIDs sporadically on and as needed basis.

**Chronic Users** - Patients who had taken NSAIDs regularly for more than one month.

#### Table 4. Chronic Smoker and Alcoholic

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Tobacco chewing</th>
<th>Alcohol</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 yr</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>1-5 yrs</td>
<td>24</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>&gt;5 yrs</td>
<td>6</td>
<td>99</td>
<td>105</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>105</td>
<td>141</td>
</tr>
</tbody>
</table>

#### Table 5. Blood Group Distribution

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>No. of pts.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>84</td>
<td>60</td>
</tr>
<tr>
<td>A</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>B</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>AB</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

Age was categorized at interval of 10 yrs. Peptic ulcer perforation was most common in age group between 40-50 yrs. of age, 78(52%) or more than half cases out of 150 belonging to this age group, least number of cases were present between age group 20-30 yrs. Overall peptic ulcer perforation was most common, both in males and females of this age (40-50 yrs.) group. Out of 150 patients 120 were taking NSAIDs (occasional, acute or chronic abusers), 90 were smokers, 75 were taking alcohol and 105 were tobacco chewer. 60 patients took the treatment in combination with corticosteroids. Most of the patients 66(44%) were chronic smokers. 66% of the patients were chronic tobacco chewers. 10% of patients were taking alcohol from more than 5 years. 90 (60%) patients had blood group O (84 positive and 6 negative), peptic ulcer perforation was least common in blood group AB. Most common site of peptic ulcer perforation was found to be Gastric (prepyloric). Duodenal perforation (1st part) was present only in 6(4%) cases. In all the patients two biopsies were taken. One biopsy sample was utilized for urease examination and the other for histology. Urease test was found to be positive in 65 patients and in histology H. pylori was seen in 54 patients. By statistical data, it is proved that the incidence of H. pylori infection in peptic ulcer perforation is high, p value- 0.001,
which is highly significant or in other words the *H. pylori* is a major causative agent for peptic ulcer perforation

**Follow Up after 12 Weeks & 6 Months**

*H. pylori* positive patients were randomized into the eradication group (34) who received amoxicillin 750 mg bd for 2 weeks, clarithromycin 500 mg bd for 2 week and pantoprazole 40 mg bd for 4 weeks and control group (31) was given pantoprazole 40 mg bd for 4 weeks. *H Pylori* eradication was significantly higher in the triple therapy group than the omeprazole alone group (at 12 weeks 94.1% vs. 17.6% and at 6 months 97.6% vs. 51.6%). Initial healing of ulcer at 12 week's follow-up endoscopies was significantly better in the eradication group. There were 88.2% healed ulcers in the triple therapy group and 41.1% in the omeprazole alone group (p=0.05). At 6 month's endoscopy the healed ulcer rates increased to 97.6% in the triple therapy group and 87.1% in the omeprazole group (p=0.48).

**Follow Up after 1 Yr.**

After 1 yr, ulcer recurrence was 6.1% in the eradication group vs 33.3% in control group (p value=0.001). Eradication of *H. pylori* reduced the incidence of recurrent ulcer.

**DISCUSSION**

**Age and Sex-** In this study most common age group affected in peptic ulcer perforation was found to be between 40-50 years and least common age group was found to be between 20-30 years and the mean age was 50 years. In all age group male population was dominant as compared with female population, ratio was almost 21:1 (male: female).

**Socioeconomic Status-** Socio economic status was determined by family income. It was found that population of lower socioeconomic status were mostly affected 108 out of 150 (72%), and the least number was in higher socioeconomic group 4(3%). This result may be influenced by lower income group patient's inability to afford services of private hospitals due to financial reasons. Less influential reason is that in higher socio economic status, people are aware and take treatment for their symptoms of epigastric pain and burning in the form of acid suppressive drugs, resulting in less chances of peptic ulcer perforation.

**NSAIDs-** History of NSAIDs intake was positive in 120 (80%) of patients. Occasional users (those who take off and on as per need basis) 18%, acute users (who took regularly for month) 54% and chronic users (who took regularly for more than one month) 8%. NSAIDs abuse causes peptic ulcer perforation alone and also in combination with corticosteroids. NSAIDs are believed to damage mucosa by several mechanisms including local irritation, reduction of mucosal blood flow, inhibiting local production of prostaglandins and interference in repair of injury.

**Smoking, Alcohol and Tobacco-** Tobacco chewing was found in 105 cases (70%), smoking was positive in 90 cases (60%) and alcohol intake was present in 75 cases (50%). Smokers are more likely to develop ulcers. Ulcers in smokers are more difficult to heal and ulcer relapse is more likely in smokers. Smoking has adverse effects on mucosal aggressive and protective factors, of the aggressive factors it appears to have no consistent effect on acid secretion. However, smoking, alcohol and tobacco impairs the therapeutic effect of histamine-2 antagonists; may stimulate pepsin secretion; promote reflux of duodenal contents into the stomach; increase the risk for harmful effect of *H. pylori*; increase production of free radicals; increased secretion of endothelin by the gastric mucosa; increased production of platelet activating factor; decreases gastric mucosal blood flow; inhibits gastric mucosal secretion; inhibits gastric prostaglandins generation; inhibit salivary epidermal growth factor secretion.

**Helicobacter pylori-** In biopsy samples rapid urease test was positive in 65case (43.3%) & histology for helicobacter pylori was positive in 54 cases (36%). This was found that *H. pylori* is an important causative organism for peptic ulcer perforation in patients who were not taking NSAIDs. Eradication of *H. pylori* was significantly higher in the triple therapy group and initial ulcer healing was significantly better in the eradication group. After 1year, ulcer recurrence was 6.1% in the eradication group vs 33.3% in control group. *H. pylori* infection was also present in higher proportion with peptic ulcer perforation.

**Genetic Factors-** Ninety patients (60%) have blood group O, 84 'O' positive and 6 `O' negative. Peptic ulcer disease is 3 times more common in patients having blood group 'O'. A study was carried out by Ahmed in 1990 he concluded that "O" blood group was present in thirty percent cases of peptic ulcer perforation, genetic influence may be due to large parietal cell mass.

**CONCLUSIONS**

Peptic ulcer perforation is most common between the age group 40-50 yrs. and least in 20-30 yrs. Males were predominantly affected. Gastric perforation is more common than duodenal perforation in India. NSAID use is the most important contributing factor in peptic ulcer perforation. Tobacco abuse is also a contributing factor in peptic ulcer perforation. Together alcohol and smoking have synergistic action to irritate the mucosa of stomach and duodenum. Dominant blood group was found to be O. It indicates that there is a definite correlation between blood group O and peptic ulcer perforation. The incidence of *H. pylori* infection is high in peptic ulcer perforation patients. Eradication of *H. pylori* was significantly higher in the triple therapy group and ulcer healing was significantly better in the eradication group.
REFERENCES


