Influence of Obstructive Jaundice on Acute Gastric Ulcer, Intragastric pH and Potential Difference in Rats

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The First Department of Surgery, Tohoku University School of Medicine, Sendai 980, and *the First Department of Surgery, Yamagata University School of Medicine, Yamagata 990-23

SASAKI, I., MIYAKAWA, H., KAMEYAMA, J., KAMIYAMA, Y. and SATO, T. Influence of Obstructive Jaundice on Acute Gastric Ulcer, Intragastric pH and Potential Difference in Rats. Tohoku J. exp. Med., 1986, 150 (2), 161-168 — To elucidate the influence of obstructive jaundice on the process of acute ulceration of the stomach under stress loading and to investigate the preventative effect of vagotomy, a series of experimental studies were carried out using SD rats. Animals were divided into four groups: Control, jaundice, vagotomy and jaundice with vagotomy. Each group was subjected to the water immersion-restraint stress and changes in the potential difference of gastric mucosa (PD), the intragastric pH (pH) and the score of ulcer index at sacrifice (UI) were measured. The process of acute ulceration under the stress loading was shown to be accelerated by the weakening of defensive factors in the case of obstructive jaundice. To monitor changes of pH and PD was found to be useful to predict the manifestation of gastric lesion. Vagotomy seemed to be partly effective to prevent the ulceration evidenced by lowering aggressive factor (an increase of pH), but it may also decrease the defensive factor because the vagotomy produced a significant lowering of PD. —— obstructive jaundice; stress ulcer; gastric mucosal potential difference; intragastric pH

It is known that fatal upper gastrointestinal bleeding often occurs clinically in critically ill or postoperative patients and that its incidence becomes even higher in patients with profound obstructive jaundice (Skillman et al. 1969; Kanayama 1973; Kameyama et al. 1982). In view of these facts, early prediction of acute ulcer, the effect of obstructive jaundice on it, and the efficacy of vagotomy were investigated from the view point of aggressive-defensive factors of the gastric mucosa.

MATERIALS AND METHODS

One hundred and seventy male SD rats, weighing around 250 g, were laparotomied under ether anesthesia. These animals were grouped as follows: 1) Control group (lapar-
otomy alone), 2) jaundice group (ligation and division of the bile duct), 3) vagotomy group (truncal vagotomy and pyloroplasty) and 4) jaundice and vagotomy group. Two weeks after the operation, the rats were subjected to water immersion-restraint stress and intragastric pH (pH), gastric transmucosal electrical potential difference (PD) and ulcer index were determined as follows:

**Determination of pH and PD.** Two weeks after the operation, animals of all 4 groups were starved for 18 hr (water was given ad libidum) before they were laparotomied again under ether anesthesia. Glass microelectrode (MI-506, Microelectrode, Inc., Londonderry, NH, USA) and Ag-AgCl electrode (MT Giken, Tokyo) for determination of pH and PD, respectively, were inserted into the stomach from the fore stomach. The tips of both electrodes were placed at the major curvature of the corpus. Both electrodes were brought through the abdominal wall, while the reference electrodes were fixed on the peritoneum.

Rats awakened from anesthesia after laparotomy were restrained in a metal wire box according to the method described by Takagi and Okabe (1968) and immersed in water in a thermostat at 22°C. Electrodes for determination of pH and PD were connected to a recorder (TI-102, Tokai Irika Dept., Tokyo) through a pH meter (TD-08, Tokai Irika Dept., Tokyo) for the former and directly for the latter (Fig. 1). Recordings were made continuously for 10 hr after the commencement of stress.

During the stress, rats were deprived of drinking water and food and the thermostat was fixed in a quiet place protected from light. Before and after each experiment the glass microelectrode for pH was adjusted using standard solutions of pH 4.01 and 6.86 (Wako Junyaku, Tokyo), while the electrode for PD determinations was checked against the reference electrode in vitro.

**Determination of ulcer index.** At 0, 2, 4, 6, 8 and 10 after the stress, the animals were sacrificed and the stomachs were removed. Then the longer diameter (mm) of each ulcer was measured and the sum of the measurements was used as ulcer index.

In each group, blood samples were collected by cardiac puncture before stress and serum total bilirubin, GOT, GPT and ALP were determined.

The observed values were expressed as mean±s.E. The significance of the differences was analyzed using Student's t-test and differences of p<0.05 were taken as statistically significant.

**Results**

**Post-stress changes in ulcer index, pH and PD in the control group.** The values of ulcer index increased progressively during stress and the values at 2, 4,
6, 8 and 10 hr were 4.2±1.4, 14.0±1.9, 14.8±2.9, 32.0±4.7 and 28.0±3.4, respectively. The pH was 4.8±0.3 before stress, but decreased progressively during stress. The pH value reached a statistically significant low level at the 4th hr onward, with the value at 10 hr being 2.6±0.5. On the other hand, PD value was −29.7±2.7 mV before stress. After stress the absolute value of PD decreased progressively showing significant reduction from the 5th hr onward. The PD value observed at 10 hr was −16.9±2.2 mV (Fig. 2).

Effect of obstructive jaundice on ulcer index, pH and PD. As compared to the control group, ulcer index values in the jaundice group were always high, with significant differences after 6 and 10 hr. The value of ulcer index recorded 10 hr after stress was 83.1±10.7. The value of pH showed changes quite similar to those observed for the control group, with no significant difference at any time. The values of PD in the jaundice group were insignificantly lower than those in the control group before stress was commenced. During stress they lowered remarkably, with statistically significant difference from the control group from the 5th hr onward. The value recorded at 10 hr was −8.0±2.9 mV (Fig. 2).

Effect of vagotomy on ulcer index, pH and PD in the absence of obstructive jaundice. The value of ulcer index in the vagotomy group was always lower than that in the control group, the difference reaching the statistically significant level at 2, 4 and 10 hr. The value recorded for the vagotomy group at 10 hr was 13.0±2.2. The inhibition rate of the ulceration for 10 hr, (control group−vagotomy group)/control group, was 58.7%. The value of pH decreased significantly from 6.5±0.3 before stress to 4.2±0.8 at 4 hr. Subsequently, the value of pH increased to reach 5.4±0.8 at 10 hr. Statistically significant difference from the control group was seen before stress and at 1, 6, 8, 9 and 10 hr. The value of PD recorded

Fig. 2. Post-stress changes in ulcer index (UI), intragastric pH (PH) and potential difference (PD) in the control group and jaundice group.

Data points are means±s.E.

*p < 0.05 against control values.

(): number of experiments.

○—○, control group; ●—●, jaundice group.
for the vagotomy group was $-24.2 \pm 3.8 \text{ mV}$ before stress and it remained lower than the value for the control group during stress. The difference between these two groups was significant, the value for the vagotomy group at 10 hr being $-9.8 \pm 2.3 \text{ mV}$ (Fig. 3).

**Effect of vagotomy on ulcer index, pH and PD in the presence of obstructive jaundice.** When compared to the jaundice group, the jaundice and vagotomy group gave lower values of ulcer index from the 4th hr onward. The difference between these two groups was statistically significant at 6 and 10 hr. The value of ulcer index recorded for the jaundice and vagotomy group was 28.0 ± 6.6 at 10 hr. The inhibition rate of the ulceration for 10 hr, (jaundice group - jaundice and vagotomy group)/jaundice group, was 48.5%. The value of pH for this group decreased from 5.6 ± 0.5 before stress to 3.8 ± 0.9 at 5 hr after stress, with no changes in the subsequent period. The difference from the jaundice group was significant at 8 and 10 hr. The value of PD for the jaundice and vagotomy group was $-20.7 \pm 3.5 \text{ mV}$ before stress, which was lower than that for the jaundice group. In the subsequent period the values of PD were always lower for the former group than for the latter, although the difference was not statistically significant.

**Liver function in the 4 groups.** The total serum bilirubin, GOT, GPT and Alp values for the jaundice group, and jaundice and vagotomy group significantly higher than the values recorded for the control group and the vagotomy group (Table 1).

**DISCUSSION**

In critically ill or postoperative patients, fatal upper gastrointestinal bleeding often occurs clinically. At present it is difficult to predict such bleeding. Most
such patients are not examined for bleeding until after the onset of sudden bleeding. Therefore, treatment is also begun late. Since most of these patients suffer from serious illness, their operations are frequently postponed or abandoned as being too risky (Skillman et al. 1969; Kanayama 1973; Kameyama et al. 1982). In view of these facts, the author conducted this experimental study of gastric mucosal aggressive and defensive factors in order to find a method of early prediction and prevention of acute gastric ulceration, especially in the presence of obstructive jaundice. The pH was used as an index of the aggressive factor. The PD which has been reported to reflect severity of damage to the gastric mucosal barrier was used as an index of the defensive factor (Chvasta and Cook 1972; Kameyama et al. 1983). Conventionally, ionic net flux of Na⁺, Cl⁻, and H⁺, and H⁺ back diffusion are used as the index of gastric mucosal barrier (Davenport et al. 1964). However, they were considered unsuitable, since laboratory tests required for them are too complex to be performed in critically ill patients and much time is required for obtaining data. Therefore, we chose PD because data on PD can be obtained simply and rapidly, continuous monitoring is possible and it is as accurate as ionic net flux (Davenport et al. 1964; Kameyama et al. 1983).

As to ulcer index, pH and PD values for the control group, it was found that ulcer index increased progressively with time to reach the peak value after 8 hr of stress. Both pH and PD began to decrease from the beginning of stress, with statistically significant reduction observed after 4 hr for pH and 5 hr for PD. Subsequently, relatively stable values were obtained for both parameters. It appeared that gastric secretion, the aggressive factor, increased and the defensive factor was weakened progressively during stress. These changes reflected the progress of ulceration. These results indicate that early prediction of acute gastric ulcer may be possible by continuous monitoring of intragastric pH and PD simultaneously. Stothert et al. (1980) insisted on the necessity of continuous monitoring of pH routinely in patients assumed to be loaded with serious stress such as critically ill patients or following major operations. However, we consider it necessary to monitor PD in addition to pH in these patients.

According to the results reported by various investigators (Skillman et al. 1969; Kameyama et al. 1982) as well as our results, cases associated with profound obstructive jaundice have a higher incidence of acute gastric ulcer, with poorer prognosis. This phenomenon has been explained by gastric acid hypersecretion related to obstructive jaundice and liver disturbances, which contributed to inefficient inactivation of gastric secretagogue due to hepatocellular damage (Silen et al. 1962), release of gastric secretagogue from the damaged liver (Silen et al. 1962, 1963), decrease in gastric inhibitory hormone induced by biliary diversion (Silen et al. 1962) and hyperbilirubinemia (Still and Carlson 1929; Silen et al. 1962; Kanayama 1973). However, some observers report that obstructive jaundice is not always associated with gastric acid hypersecretion (Menguy et al. 1969;
In our experience also (Kameyama et al. 1982), gastric acid hypersecretion has not been a constant finding in patients with obstructive jaundice. From these findings we postulated that in the presence of obstructive jaundice the gastric mucosal defensive factor is weakened. In the present study, changes in pH in the jaundice group were similar to those in the control group. However, PD used as the indicator for defensive factor continued to show marked decrease in the jaundice group. Marked elevation of value of the ulcer index was seen from the 4th hr after stress. Therefore, it appears that differences in the incidence of acute gastric ulcer is related to deterioration of the defensive factor in cases associated with obstructive jaundice. Our results also indicate that no changes occur in either aggressive or defensive factors, in the presence of obstructive jaundice.

![Graph showing effect of vagotomy on ulcer index (UI), intragastric pH (PH) and potential difference (PD) in the presence of jaundice.](image)

**Fig. 4.** Effect of vagotomy on ulcer index (UI), intragastric pH (PH) and potential difference (PD) in the presence of jaundice. Data points are means ± S.E.

* *p < 0.05 against jaundice group.

- ●, jaundice group; ▲—▲, jaundice with vagotomy group.

**Table 1. Liver function in the 4 groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Total bilirubin (mg/100 ml)</th>
<th>GOT (KU)</th>
<th>GPT (KU)</th>
<th>Alp (KAU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>0.3 ± 0.0</td>
<td>120.3 ± 5.5</td>
<td>35.1 ± 1.6</td>
<td>27.6 ± 1.4</td>
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<tr>
<td>Jaundice (n = 4)</td>
<td>14.1* ± 1.2</td>
<td>581.5 ± 94.5</td>
<td>59.1* ± 6.7</td>
<td>35.1* ± 1.5</td>
</tr>
<tr>
<td>Vagotomy (n = 4)</td>
<td>0.2 ± 0.0</td>
<td>133.5 ± 3.1</td>
<td>8.4 ± 0.2</td>
<td>17.8 ± 1.2</td>
</tr>
<tr>
<td>Jaundice and vagotomy (n = 4)</td>
<td>12.5* ± 1.0</td>
<td>433.5* ± 178.4</td>
<td>93.6* ± 8.4</td>
<td>40.5* ± 4.1</td>
</tr>
</tbody>
</table>

Data are given as means ± S.E.

* *p < 0.01 against control values.

Skillman et al. 1969). In our experience also (Kameyama et al. 1982), gastric acid hypersecretion has not been a constant finding in patients with obstructive jaundice.

From these findings we postulated that in the presence of obstructive jaundice the gastric mucosal defensive factor is weakened. In the present study, changes in pH in the jaundice group were similar to those in the control group. However, PD used as the indicator for defensive factor continued to show marked decrease in the jaundice group. Marked elevation of value of the ulcer index was seen from the 4th hr after stress. Therefore, it appears that differences in the incidence of acute gastric ulcer is related to deterioration of the defensive factor in cases associated with obstructive jaundice. Our results also indicate that no changes occur in either aggressive or defensive factors, in the presence of obstructive jaundice.
jaundice, provided there is no other stress. Once additional stress is commenced, however, the incidence of acute gastric ulcer increases sharply.

For prevention of acute gastric ulcer, conservative therapy such as pharmacotherapy is used and at present surgical therapy is scarcely employed for this purpose. Even in the treatment of established acute gastric ulcer, surgical therapy is used quite rarely because of poor prognosis and poor general condition in these cases. In our patients with postoperative acute gastric ulcer, operations were possible in only 7.2%. None of the patients with obstructive jaundice could be operated (Kameyama et al. 1982). Then, the efficacy of vagotomy for prevention of acute gastric ulcer was assessed experimentally since it is known to be relatively free from operative insult. In the vagotomy group, pH decreased to the level of 4 during the first 4 hr, but it did not show a decrease below 4 throughout the experimental period. However, PD value recorded for this group was always lower than that of the control group. From these results it is considered that vagotomy inhibits the aggressive factor but, on the other hand, it weakens the defensive factor simultaneously. Olsen et al. (1970) and Halvorsen et al. (1975) observed a decrease in gastric mucosal blood flow following vagotomy. From these reports of various investigators, coupled with our results on PD, it may be justifiable to say that vagotomy has an undesirable effect on the defensive factor while it inhibits the aggressive factor. In the present study acute gastric ulceration was inhibited significantly in the vagotomy group as compared to the control group.

Next, efficacy of vagotomy in cases with obstructive jaundice was assessed. In the jaundice and vagotomy group the value of pH decreased until the 5th hr after stress but remained at the high level of about pH 4 throughout the experimental periods. The values of PD were lower than those obtained for the jaundice group and they were the lowest among the four groups from the 3rd hr onward. From these results it is surmised that weakening of the defensive factor due to jaundice may be enhanced in the jaundice and vagotomy group. The value of ulcer index was lower than that in the jaundice group.

The inhibition rate of the ulceration due to vagotomy was 58.7% for cases without jaundice and 48.5% for those with jaundice. These results suggest that vagotomy brings about some improvement in the imbalance of aggressive-defensive factors, but it causes some problems, especially in terms of damage to the gastric mucosal barrier.

For the prevention of acute gastric ulcer, irrespective of the presence or absence of obstructive jaundice, vagotomy alone is not effective enough. It is recommended that some other measures be combined with vagotomy, such as administration of prostaglandin or H2-receptor antagonists to maintain the integrity of the gastric mucosal defense mechanism.
References