Peptic Ulcer Diseases: Genetics, Mechanism, and Therapies

Guest Editors: Seng-Kee Chuah, Deng-Chyang Wu, Hidekazu Suzuki, Khean-Lee Goh, John Kao, and Jian-Lin Ren
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Peptic ulcer disease is a very common disease which is mainly relevant to Helicobacter pylori (H. pylori) and nonsteroid anti-inflammatory drugs (NSAIDs) [1,2]. Recent advances in biology and medicine have introduced new technologies to study the genetics of and the mechanisms underlying its pathology. Knowledge and understanding of these conditions have led to the development of animal models, successful therapies, and novel tools to characterize these clinical conditions and provide better care to patients. In this special issue, we invite investigators to contribute original research articles as well as review articles that will stimulate the continuing efforts to understand the underlying molecular issue, the development of strategies to treat these conditions, and the evaluation of outcomes. We are particularly interested in articles describing the new modalities for clinical characterization of this disease and measuring outcomes from treatment trials, advances in molecular genetics and molecular diagnostics, and current concepts in the treatment issues such as (1) recent genetic developments in peptic ulcer disease research such as genetic polymorphism and peptic ulcer disease, (2) recent advances in genetics and treatment of H. pylori, (3) latest technologies for clinical evaluation and measuring outcomes of peptic ulcer disease, (4) peptic ulcer disease mechanism using model systems such as H. pylori, (5) recent advances in peptic ulcer disease bleeding, (6) recent advances in peptic ulcer disease perforation and stenosis, and (7) recent advances in the relevant motility issue. Eventually, we published 11 papers overall.

Upper gastrointestinal bleeding (UGIB) guidelines improve patient care and outcomes [3–5]. This issue highlights the paper entitled “Consensus on control of risky nonvariceal upper gastrointestinal bleeding in Taiwan with national health insurance” which highlighted the consensus report of Taiwan UGIB consensus meeting. It comprised recommendations from a nationwide scale to improve the control of UGIB, especially for the high-risk comorbidity group. The consensus included 17 statements, including 3 on preendoscopy, 5 on endoscopy, 6 on postendoscopy assessment, and 3 on Taiwan NHIRD regarding UGIB. The consensus highlighted that patients with comorbidities, including liver cirrhosis, end-stage renal disease, probable chronic obstructive pulmonary disease, and diabetes, are at high risk of peptic ulcer bleeding and rebleeding. Special considerations are recommended for such risky patients,
including raising hematocrit to 30% in uremia or acute myocardial infarction, aggressive acid secretory control in high Rockall scores, monitoring delayed rebleeding in uremia or cirrhosis, considering cyclooxygenase-2 inhibitors plus proton-pump inhibitors (PPI) for pain control, and early resumption of antiplatelets plus PPI in coronary artery disease or stroke. The consensus comprises practical recommendations to improve patient care of UGIB, especially for those with comorbidities. The most essential point of the Taiwan consensus is that it focuses more on comorbid patients. This is very important because peptic ulcer bleeding in comorbid patients is an emerging issue [6–8].

Low-dose aspirin is widely used in the prevention of cardiovascular disorders [9]. The genetic factors predicting the development of peptic ulcer in low-dose aspirin users remain unclear. The paper entitled “Impact of blood type, functional polymorphism (T-1676C) of the COX-1 gene promoter and clinical factors on the development of peptic ulcer in low-dose aspirin users” reported that warfarin was associated with a significant incidence of GIB in Taiwanese patients. The incidence of GIB was 3.9% per patient-years. Multivariate analysis with Cox regression showed that age >65 years old, a mean international normalized ratio >2.1, a history of GIB, and cirrhosis were independent factors predicting GIB. 27.3% of the GIB patients had rebleeding after restarting warfarin while thromboembolic events were found in 16.7% of the patients discontinuing warfarin therapy.

Reports regarding outcomes for different management regimens for peptic ulcer bleeding patients during holidays are inconsistent. Some described increased adverse outcomes on holidays [13, 14] while others did not [15, 16]. The paper entitled “Outcome of holiday and nonholiday admission patients with acute peptic ulcer bleeding: a real-world report from Southern Taiwan” observed that patients who presented with peptic ulcer bleeding on holidays did not experience delayed endoscopy or increased adverse outcomes. In fact, patients who received endoscopic hemostasis on the holiday had shorter waiting times, needed less transfused blood, switched to oral PPIs quicker, and experienced shorter hospital stays.

The paper entitled “Comparison of hemostatic efficacy of argon plasma coagulation with and without distilled water injection in treating high-risk bleeding ulcers” observed that endoscopic therapy with argon plasma coagulation (APC) plus distilled water injection was no more effective than APC alone in treating high-risk bleeding ulcers, whereas combined therapy was potentially superior for patients with poor overall outcomes.

UGIB is the most frequently encountered complication of peptic ulcer disease. 

H. pylori
evolution and nonsteroidal anti-inflammatory drug (NSAID) administration are two independent risk factors for UGIB [17–19]. The paper entitled “Diagnosis, treatment, and outcome in patients with bleeding peptic ulcers and Helicobacter pylori infections” reviewed and elucidated the relationship between bleeding peptic ulcers and 

H. pylori
infection from the chronological perspective with an emphasis on diagnosis, treatments, and outcomes. They summarized that sufficient evidence supports the concept that 

H. pylori
infection eradication can heal the ulcer and reduce the likelihood of rebleeding. With increased awareness of the effects of 

H. pylori
infection, the etiologies of bleeding peptic ulcers have shifted to NSAID use, old age, and disease comorbidity.

It is urgent to find alternative agents due to increasing failure rate of 

H. pylori
eradication [20, 21]. The paper entitled “Does long-term use of silver nanoparticles have persistent inhibitory effect on 

H. pylori
based on mongolian gerbil’s model?” surveyed the long-term effect of silver nanoparticles (AgNP) on 

H. pylori
based on Mongolian gerbil’s model. They concluded that AgNP/clay would be a potential and safe agent for inhibiting 

H. pylori.
It should be helpful for eradication of 

H. pylori.

Helicobacter pylori infection leads to chronic inflammation of gastric mucosa and peptic ulcer disease. It may influence the absorption of essential trace elements. The association between trace elements and 

H. pylori
infection has been reported [22]. The paper entitled “The effect of Helicobacter pylori eradication on the levels of essential trace elements” is designed to compare the effects of 

H. pylori
infection treatment on serum zinc, copper, and selenium levels. They concluded that 

H. pylori
eradication regimen appears to influence the serum selenium concentration. 

H. pylori
were linked with several extragastrointestinal diseases, including preeclampsia and intrauterine growth restriction of fetus. There are several methods to detect 

H. pylori
infection. One of them is the urease test using gastric mucosal tissue obtained during gastroendoscopy. Despite being proven that procedure is safe when performing on the pregnant women [23], the general unwillingness, the high cost, the invasiveness of the procedure, and the possible sampling error make it not the ideal choice for screening the 

H. pylori
infection during pregnancy. The noninvasive tests include the urea breath test (UBT), the stool antigen test, and the serum 

H. pylori
IgG antibody test. The latest one is easy to perform during antenatal examination and the existence of the antibody was found to be associated with the intrauterine growth restriction [24]. How the maternal 

H. pylori
antibody influences the growth of the fetus is still elusive, but, interestingly, the antibody can be transmitted placentaly to the fetus [25, 26]. However, the detection of the serological antibody was frustrated because of the
inconsistent accuracy caused by several factors, including the different antigen extracts, the kit uses, and variable *H. pylori* strain in different regions [27, 28]. The paper entitled “The utilization of a new immunochromatographic test in detection of *Helicobacter pylori* antibody from maternal and umbilical cord serum” utilized a commercial immunochromatographic kit to detect the antibody in maternal and cord serum. The authors found out that *H. pylori* IgG antibody can be transferred through the placenta into the fetal circulation. However, accuracy of the test kit needs to be evaluated before utilization in screening.

Patients who have experienced severe caustic injury to the gastrointestinal tract are at high risk of luminal strictures [29]. Early endoscopy is usually routinely recommended in patients after gastroesophageal caustic injuries and should be performed to prevent unnecessary hospitalization and to plan future treatment after carefully assessing the severity of the initial digestive lesions [30]. The paper entitled “Predicting the progress of caustic injury to complicated gastric outlet obstruction and esophageal stricture, using modified endoscopic mucosal injury grading scale” indicates that patients over 60 years have a higher mortality rate after corrosive injury of gastrointestinal tract and, therefore, require attentive care in acute stage. And, early endoscopy to grade the extent of mucosal injury is useful to predict the incidence of subsequent stricture of GI tract and provide valuable information on clinical follow-up.

Gastrointestinal tract disorders are common in diabetic patients [31, 32]. More than 75% of patients visiting diabetes mellitus clinics reported significant gastrointestinal symptoms [31] such as dysphasia, early satiety, reflux, abdominal pain, nausea, vomiting, constipation, and diarrhea. In the paper entitled “Decreased gastric motility in type II diabetic patients,” the authors hypothesized that diabetic patients had lower motilin and ghrelin or higher glucagon-like peptide-1 (GLP-1) and hence inhibited gastric motility and induced gastrointestinal symptoms. They compared gastric motility and sensation between type II diabetic patients and normal controls and explored the roles of different gastric motility peptides in this motility effect. Type II diabetic patients have delayed gastric emptying and less antral contractions than normal controls and may be associated with less postprandial sensation. They concluded the observation that less serum GLP-1 in type II diabetic patients could offer a clue to understand that delayed gastric emptying in diabetic patients is not mainly regulated by GLP-1.

**References**


Research Article

Impact of Blood Type, Functional Polymorphism (T-1676C) of the COX-1 Gene Promoter and Clinical Factors on the Development of Peptic Ulcer during Cardiovascular Prophylaxis with Low-Dose Aspirin

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Aims. To investigate the impact of blood type, functional polymorphism (T-1676C) of the COX-1 gene promoter, and clinical factors on the development of peptic ulcer during cardiovascular prophylaxis with low-dose aspirin. Methods. In a case-control study including 111 low-dose aspirin users with peptic ulcers and 109 controls (asymptomatic aspirin users), the polymorphism (T-1676C) of the COX-1 gene promoter was genotyped, and blood type, H pylori status, and clinical factors were assessed. Results. Univariate analysis showed no significant differences in genotype frequencies of the COX-1 gene at position -1676 between the peptic ulcer group and control group. Multivariate analysis revealed that blood type O, advanced age, history of peptic ulcer, and concomitant use of NSAID were the independent risk factors for the development of peptic ulcer with the odds ratios of the 2.1, 3.1, 27.6, and 2.9, respectively. Conclusion. The C-1676T polymorphism in the COX-1 gene promoter is not a risk factor for ulcer formation during treatment with low-dose aspirin. Blood type O, advanced age, history of peptic ulcer, and concomitant use of NSAID are of independent significance in predicting peptic ulcer development during treatment with low-dose aspirin.

1. Introduction

Low-dose aspirin (75–325 mg/day) is widely used in the prevention of myocardial infarction or ischemic stroke [1]. Besides the patients requiring secondary prevention of cardiovascular events, the American Heart Association recommends prophylactic aspirin for the subjects who have a 10-year cardiovascular risk equal to or more than 10% [2]. Currently, approximately 36% of the adult US population—more than 50 million people—is estimated to take aspirin regularly for cardiovascular disease prevention [3]. However, due to its inhibition of prostaglandin synthesis, direct cytotoxicity, and microvascular injury, aspirin is associated with upper gastrointestinal side effects, which range from mild dyspepsia to life-threatening bleeding and perforation from peptic ulcers [4]. Even at doses as low as 10 mg, aspirin
has been shown to cause gastrointestinal damage and is associated with a greater risk of gastroduodenal ulcers and life-threatening ulcer complications [5].

Previous studies revealed that a history of ulcer, advanced age (>70 years), concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), use of dual antiplatelet therapy, Helicobacter pylori (H. pylori) infection, and history of alcohol abuse were risk factors for gastroduodenal ulcer in low-dose aspirin users [6,7]. However, the genetic risk factors for the development of peptic ulcer in aspirin users remain unclear. A recent 35-year cohort study from Sweden also showed that individuals with blood group O had a higher risk of peptic ulcer development than those with other blood groups and blood group A was associated with the risk of developing gastric cancer [8]. Nonetheless, whether blood group O is also a risk factor for ulcer development in low-dose aspirin users remains to be clarified.

Cyclooxygenase-1 (COX-1) is a constitutively expressed enzyme that generates prostaglanids for gastrointestinal integrity. Aspirin can inhibit COX-1 enzyme and decrease prostaglandin synthesis of gastrointestinal tract. Recently, functional polymorphism (T-1676C) in the COX-1 gene promoter has been identified and was reported to alter putative transcription factor (GATA-1, CdxA) binding sites [9,10]. Arisawa et al. revealed that the number of -1676T alleles of the COX-1 gene promoter was a significant risk factor for the NSAID-induced ulcer in Japan [11]. However, whether the COX-1 genetic polymorphism also plays an important role in the development of peptic ulcer in low-dose aspirin users remains unclear.

The aim of this case-control study was to investigate the clinical risk factors and genetic markers for the development of peptic ulcer during cardiovascular prophylaxis with low-dose aspirin.

2. Patients and Methods

2.1. Patients. A total of 111 consecutive low-dose (75–325 mg/day) aspirin users with peptic ulcer, who attended the Kaohsiung Veterans General Hospital or Kaohsiung Medical University Hospital, were included in this study. The reason for choosing this dosage range of aspirin is because the common dose of aspirin used for the prevention of cardiovascular diseases varies between 75 and 325 mg daily [1–3]. The diagnosis of peptic ulcer was confirmed by endoscopic examination. One hundred and nine consecutive asymptomatic low-dose aspirin users who underwent upper gastrointestinal endoscopy for endoscopic surveillance and had normal endoscopic appearance or gastritis only served as controls. The exclusion criteria included (1) consumption of proton pump inhibitor (PPI) or histamine-2 receptor antagonist within 2 weeks before endoscopy, (2) coexistence of gastrointestinal malignancies, (3) serious medical illness (e.g., decompensated liver cirrhosis, uremia, septic shock, acute stroke, and acute myocardial infection within 2 weeks), and (4) receiving low-dose aspirin less than 2 weeks. The study was approved by the Medical Research Committee of the Kaohsiung Veterans General Hospital and Kaohsiung Medical University Hospital. All patients and controls gave informed consent.

2.2. Methods. Endoscopies were performed with the Olympus GIF X10 and GIF XQ200 (Olympus Corp., Tokyo, Japan). During endoscopy, biopsies over antrum and body were performed for rapid urease test (with one specimen from the antrum and another one from the body). The rapid urease test was performed according to our previous studies [12]. Rapid urease tests were assessed by a technician, blind as to the endoscopic features. The diagnosis of H. pylori infection was based on the result of rapid urease test. An ulcer was defined as a circumscribed mucosal break 3 mm or more in diameter, with a well-defined ulcer crater in the stomach or duodenum [13]. The size of ulceration was measured by opening a pair of biopsy forceps of known span in front of the ulcer.

Before endoscopy, venous blood was drawn for COX-1 genotyping. To assess the significance of clinical characteristics, the following data were recorded for each patient: age, sex, blood type, smoking, alcohol consumption, coffee consumption, tea consumption, previous history of peptic ulcer, and use of thienopyridine, coumadin, steroid, or NSAIDs within 2 weeks prior to endoscopy. Coffee or tea consumption was defined as drinking 1 cup or more per day.

2.2.1. COX-1 Genotyping. Genomic DNA was extracted from 3 mL of whole blood by the use of a QIAamp DNA Extraction Mini Kit (QIAGEN Inc., Valencia, CA). The COX-1 genotype (T-1676C) was determined using the restriction fragment length polymorphism (RFLP). The primer set (COX-1R, 5'-TGGACCAGTCCTCAGAGACC-3' and COX-1F, 5'-CCCCATC AAGTCAACCACCT-3') [14] was used to amplify DNA fragments, of which the fragments of 243 base pairs were obtained. The PCR reactions were performed using 2.5 U of Taq DNA polymerase together with the corresponding Taq buffer supplemented with 2 mM MgCl₂ (Invitrogen, Life Technologies, California, USA), 2.5 mM each of the 4 deoxynucleotide triphosphates (dNTP, 100 mM, Amersham, UK), 0.5 M of each amplification primer, and 40–100 ng of genomic DNA mixed up to a final volume of 25 μL. The PCR analyses were performed on a PCR thermal cycler (model 2400, Perkin Elmer, Foster City, CA) with the following profile: 5 min of denaturation at 94°C, followed by 35 cycles of 30 s at 94°C, 30 s at 64°C, and 60 s at 72°C, with a final extension at 72°C for 7 min. The amplified DNA fragments (243 base pairs) contained two TspRI restriction sites. After TspR I digestion, fragments with 172 base pairs and 71 base pairs were observed for genotype TT; fragments with 172 base pairs, 88 base pairs, 84 base pairs, and 71 base pairs were observed for genotype TC; and fragments with 88 base pairs, 84 base pairs, and 71 base pairs were observed for genotype CC. Then the PCR products were digested by TspR I restriction enzymes in a reaction mixture (20 μL) containing PCR products (15 μL), 1X Buffer 4, 1X BSA, and TspR I (0.5 U/μL) at 65°C for 16 hours. The digested fragments were separated and analyzed by electrophoresis using 3% agarose gel. Genotypes of COX-1
Table 1: Clinical characteristics of aspirin users with and without peptic ulcer.

<table>
<thead>
<tr>
<th></th>
<th>Gastritis/normal (N = 109)</th>
<th>Peptic ulcer (N = 111)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.0 ± 12.1</td>
<td>72.0 ± 10.3</td>
<td>0.001*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.501</td>
</tr>
<tr>
<td>Female</td>
<td>40 (36.7%)</td>
<td>31 (27.9%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69 (63.3%)</td>
<td>80 (72.1%)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>13 (11.9%)</td>
<td>19 (17.1%)</td>
<td>0.275</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>7 (6.4%)</td>
<td>9 (8.1%)</td>
<td>0.630</td>
</tr>
<tr>
<td>Coffee consumption</td>
<td>22 (20.2%)</td>
<td>11 (9.9%)</td>
<td>0.033*</td>
</tr>
<tr>
<td>Tea consumption</td>
<td>36 (33.0%)</td>
<td>27 (24.3%)</td>
<td>0.153</td>
</tr>
<tr>
<td>History of peptic ulcer</td>
<td>4 (3.7%)</td>
<td>56 (50.5%)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Dual antiplatelet therapy</td>
<td>10 (9.2%)</td>
<td>10 (9.0%)</td>
<td>0.966</td>
</tr>
<tr>
<td>Coumadin use</td>
<td>1 (0.9%)</td>
<td>3 (2.7%)</td>
<td>0.622</td>
</tr>
<tr>
<td>Nonaspirin NSAID use</td>
<td>7 (6.4%)</td>
<td>18 (16.2%)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Steroid use</td>
<td>2 (1.8%)</td>
<td>2 (1.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>H. pylori infection</td>
<td>52 (47.7%)</td>
<td>29 (26.1%)</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

* denotes P < 0.05.

Gene promoter were classified into the following three groups: T/T, T/C, and C/C.

2.2.2. Statistical Analysis. Statistical evaluations were performed using the SPSS/Windows computer software package (Chicago, IL, USA). Two-sample t-tests were used to compare the mean values of the variables considered continuous in the peptic ulcer patients and controls. The chi-square test with or without the Yates correction for continuity and Fisher’s exact test when appropriate were applied to analyze the categorized variables. Differences were considered to be significant at P < 0.05. A stepwise forward conditional method was used to identify the independent risk factors for the development of peptic ulcer in low-dose aspirin users.

According to a previous study [11], the frequency of -1676T allele in the COX-1 gene promoter in healthy subjects was 47%. We estimated that a 20% difference in the allele frequency could be present in low-dose aspirin users with peptic ulcer. Based on this assumption, 93 subjects had to be studied in each group to yield a statistical power of 0.80 and an α value of 0.05.

3. Results

3.1. Clinical Characteristics of Aspirin Users with or without Peptic Ulcer. Two hundred and twenty aspirin users (126 from the Kaohsiung Veterans General Hospital and 94 from the Kaohsiung Medical University Hospital) were recruited for the study. They included 111 subjects with peptic ulcer disease (gastric ulcer: n = 90; duodenal ulcer: n = 10; both gastric and duodenal ulcers: n = 11) and 114 controls.

Table 1 shows the demographic characteristics of peptic ulcer subjects and controls. The subjects with peptic ulcer were significantly older than the controls (67.0 ± 12.1 versus 72.0 ± 10.3; P = 0.001). In addition, the rates of peptic ulcer history and the use of NSAID of peptic ulcer subjects were significantly higher than the controls (50.5% versus 3.7% and 16.2% versus 6.4%, resp.; P = 0.000 and P = 0.022, resp.). However, the peptic ulcer group had a lower rate of coffee drinking than the control group (9.9% versus 22.2%; P = 0.033). H. pylori infection was detected in 26.2% of peptic ulcer subjects and in 47.5% of the controls. The infection rate was significantly lower in the peptic ulcer group than in the control group (P = 0.005). The two groups were similar with respect to gender, tea consumption, alcohol consumption, dual antiplatelet therapy with thienopyridine, and use of steroids.

3.2. Genetic Factors Related to Peptic Ulcer Development in Aspirin Users. Table 2 shows the blood group and genotype polymorphisms at position -1676 of the COX-1 gene promoter in aspirin users with and without peptic ulcer. The distributions of blood groups between aspirin users with and without peptic ulcer were different (P = 0.047). Peptic ulcer group had a higher rate of blood type O than the control group (45.9% versus 29.4%, resp.). The T/T, C/T, and C/C genotypes at position -1676 of the COX-1 gene promoter in aspirin users with peptic ulcer were 24.7%, 66.3%, and 9.0%, respectively. No significant differences in genotype frequencies of the COX-1 gene were found between the peptic ulcer group and control group (P = 0.245).

3.2.1. Independent Risk Factors for the Development of Peptic Ulcer in Aspirin Users. A stepwise forward logistic regression analysis for clinical and genetic variables was performed to search for the independent risk factors of peptic ulcer development in low-dose aspirin users. Multivariate analysis indicated that the advanced age, history of peptic ulcer, use of...
Table 2: Blood group and COX-1 genotype in low-dose aspirin users with and without peptic ulcer.

<table>
<thead>
<tr>
<th></th>
<th>Gastritis/normal (n = 109)</th>
<th>Peptic ulcer (n = 111)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>36 (33.0%)</td>
<td>29 (26.1%)</td>
<td>0.047</td>
</tr>
<tr>
<td>B</td>
<td>38 (34.9%)</td>
<td>25 (22.5%)</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>32 (29.4%)</td>
<td>51 (45.9%)</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>5 (4.6%)</td>
<td>6 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>COX-1 genotype*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>15 (19.5%)</td>
<td>22 (24.7%)</td>
<td>0.245</td>
</tr>
<tr>
<td>C/T</td>
<td>59 (76.6%)</td>
<td>59 (66.3%)</td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>3 (3.9%)</td>
<td>8 (9.0%)</td>
<td></td>
</tr>
</tbody>
</table>

* One hundred and eighty six DNA samples were available.

Table 3: Multivariate analysis for clinical and genetic factors related to the development of peptic ulcer in aspirin users.

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>1.248</td>
<td>0.464</td>
<td>3.1 (1.4–8.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Peptic ulcer history</td>
<td>3.320</td>
<td>0.576</td>
<td>27.6 (8.9–85.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonaspirin NSAID use</td>
<td>1.154</td>
<td>0.525</td>
<td>2.9 (1.1–8.0)</td>
<td>0.045</td>
</tr>
<tr>
<td>Blood type O</td>
<td>0.751</td>
<td>0.351</td>
<td>2.1 (1.1–4.2)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

NSAID, and blood type O were the independent risk factors for the development of peptic ulcer (Table 3). The odds ratios of the four parameters were 3.1, 27.6, 2.9, and 2.1, respectively (95% confidence intervals, 1.4–8.6, 8.9–85.5, 1.1–8.0, and 1.1–4.2, resp.).

4. Discussion

Aspirin, usually available as an over-the-counter drug, is one of the most used drugs worldwide. In Western countries, 6 to 12% of the general population is exposed to low-dose aspirin [15, 16]. It is well known that aspirin use is associated with upper gastrointestinal adverse effects [17]. However, only a small proportion of low-dose aspirin users develop peptic ulcer or life-threatening ulcer bleeding. Currently, the main genetic risk factors determining the development of peptic ulcer in low-dose aspirin remain unclear and pose a fascinating challenge in gastroenterology. In the current study, we investigate the clinical and genetic factors related to the development of peptic ulcer in low-dose aspirin users. The data indicated that the blood type O, advanced age, history of peptic ulcer, and use of NSAID were independent factors predictive of ulcer development in low-dose aspirin users. The C-1676T polymorphism in the COX-1 gene promoter is not a risk factor for ulcer formation during treatment with low-dose aspirin.

Blood group O has traditionally been associated with the risk of developing peptic ulcer [18, 19]. However, it remains unclear whether a subject with blood group O is a genetic marker for ulcer development during low-dose aspirin use. In this study, peptic ulcer group had a higher rate of blood type O than that of the control group (45.9% versus 29.4%). Multivariate analysis with logistic regression documented that blood type O was an independent factor for ulcer development in low-dose aspirin users with an odds ratio of 2.1 (95% CI: 1.1–4.2). Our study is the first in identifying blood group O as a genetic risk factor of peptic ulcer formation during treatment with low-dose aspirin.

Cyclooxygenases catalyze the conversion of arachidonic acid to prostaglandins. As a corollary, COX gene polymorphisms could be important in the pathogenesis of peptic ulcer disease because the function of cyclooxygenases affects prostaglandin formation and its protective effect at the level of the gastric mucosa. A previous study showed that the A-842G polymorphism did not play a significant role in the development of ulcer in NSAID users in the Japanese population [11]. In this study, we investigated the association between genetic polymorphisms in the COX-1 gene promoter and peptic ulcer development in low-dose aspirin users. Our data indicated that no significant differences in genotype frequencies of the C-1676T polymorphism in the COX-1 gene promoter were found between the peptic ulcer group and control group. However, Arisawa et al. reported that the C-1676T functional polymorphism in the COX-1 gene promoter was related to the development of NSAID-induced ulcer [11]. The reasons for the contradictory results are unclear, but different doses of NSAIDs (low-dose aspirin for cardiovascular protection versus regular-dose NSAIDs for various neuromuscular diseases) or different ethnic populations are possible explanations.

In this study, we confirmed that advanced age, history of peptic ulcer, and use of NSAID were independent factors predictive of ulcer development in low-dose aspirin users. History of peptic ulcer is the most important clinical risk factor for ulcer development in low-dose aspirin use with an odds ratio of 27.6. The finding was consistent with previous studies that also identified a history of peptic ulcer as a clinical risk factor for peptic ulcer in low-dose aspirin users [20, 21]. PPI has been shown to effectively reduce the risk of developing peptic ulcers associated with the continuous use...
of low-dose aspirin [22, 23]. Therefore, cotherapy with a PPI to prevent the development of ulcers and ulcer complications could be considered in the aged patients with a previous history of peptic ulcer [24, 25].

Several other independent studies [26, 27] have also highlighted the importance of age factor in ulcer formation. García-Rodríguez and Jick [26] proved that advanced age increases risk of ulcer complications in an NSAID user. Lanas and Scheiman [4] also demonstrated that advanced age was an independent risk factor of ulcer formation in low-dose aspirin users. The reason why the aged stomach is more vulnerable to injury remains unclear. However, aging-related changes in gastric mucosa defense are possible explanations. Two human studies [28, 29] have demonstrated that gastric mucosal prostaglandin content declines with age. Feldman and Cryer [28] have also disclosed that advanced age is associated with a significant decline in gastric bicarbonate, sodium ion, and nonparietal fluid secretion. Thus, aging is associated with selective and specific changes in the gastric mucosal defenses that may predispose aged aspirin users to develop peptic ulceration.

In the current study, _H. pylori_ infection was detected in 26.2% of peptic ulcer subjects and in 47.5% of the controls. The infection rate was significantly lower in the peptic ulcer group than in the control group. The reason for the lower _H. pylori_ infection rate in the peptic ulcer group was probably due to prior anti- _H. pylori_ therapy in many aspirin users in this patient group. Among the patients in peptic ulcer group, 50.5% of the subjects had a history of prior peptic ulcer. Multivariate analysis indicated that the history of peptic ulcer was the independent risk factor for the development of peptic ulcer and _H. pylori_ status was removed from independent factors related to peptic ulcer development following logistic regression analysis.

The strengths of this study included investigating both clinical and genetic risk factors for ulcer development in low-dose aspirin users and prospective assessment of clinical data of the recruited subjects. However, it has several limitations. First, the sample size was moderate and possibly unable to detect minor independent risk factors for the development of peptic ulcer in low-dose aspirin users. Secondly, aspirin users who took PPIs or histamine-2 receptor antagonists before endoscopy were excluded. We therefore could not identify some protective factors for ulcer development in low-dose aspirin users. Thirdly, it was a case-control study and selection bias of recruited cases could not be completely ruled out. A large-scale, long-term cohort study is therefore merited to clarify the risk factors identified in this work.

In conclusion, blood type O, advanced age, history of peptic ulcer, and use of nonaspirin NSAID are independent risk factors for development of peptic ulcer in low-dose aspirin users. The C-1676T polymorphism in the _COX-1_ gene promoter is not a risk factor for ulcer formation during treatment with low-dose aspirin.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**Acknowledgments**

The study was partly supported by a research grant from the Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan (VGHKS100-094). The authors are indebted to Drs. H. M. Wang and J. L. Ou for recruiting the patients and performing the endoscopies and study nurse L. Y. Wang at the Kaohsiung Veterans General Hospital.

**References**


Clinical Study

Comparison of Hemostatic Efficacy of Argon Plasma Coagulation with and without Distilled Water Injection in Treating High-Risk Bleeding Ulcers

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Background. Argon plasma coagulation (APC) is useful to treat upper gastrointestinal bleeding, but its hemostatic efficacy has received little attention. Aims. This investigation attempted to determine whether additional endoscopic injection before APC could improve hemostatic efficacy in treating high-risk bleeding ulcers. Methods. From January 2007 to April 2011, adult patients with high-risk bleeding ulcers were included. This investigation compared APC plus distilled water injection (combined group) to APC alone for treating high-risk bleeding ulcers. Outcomes were assessed based on initial hemostasis, surgery, blood transfusion, hospital stay, rebleeding, and mortality at 30 days posttreatment. Results. Totally 120 selected patients were analyzed. Initial hemostasis was accomplished in 59 patients treated with combined therapy and 57 patients treated with APC alone. No significant differences were noted between these groups in rebleeding, emergency surgery, 30-day mortality, hospital stay, or transfusion requirements. Comparing the combined endpoint of mortality plus the failure of initial hemostasis, rebleeding, and the need for surgery revealed an advantage for the combined group \(P = 0.040\). Conclusions. Endoscopic therapy with APC plus distilled water injection was no more effective than APC alone in treating high-risk bleeding ulcers, whereas combined therapy was potentially superior for patients with poor overall outcomes.

1. Introduction

Acute upper gastrointestinal bleeding (UGIB) is common and has significant associated mortality and morbidity. Up to 5–10% mortality of upper gastrointestinal bleeding results from bleeding event or worsening of concurrent medical illness [1, 2]. Severe upper gastrointestinal bleeding typically results from peptic ulcer bleeding, and endoscopic treatment can effectively reduce the rate of rebleeding, the need for surgery, and the mortality [3].

Effective endoscopic therapies for bleeding ulcers include injection with sclerosants/epinephrine/normal saline, contact thermal coagulation, and hemoclips [4]. Endoscopic injection therapy is recommended by studies owing to the tamponade effect in hemostasis [5]. Injection therapy is clearly effective, easy to administer, and relatively inexpensive. Additionally, injection therapy can slow bleeding and facilitate other treatments. Thermal coagulation uses heat probe or argon plasma coagulation (APC) device for hemostasis. Heat probe coagulation uses a device that directly contacts the point where bleeding is occurring to achieve thrombosis and coagulation. Meanwhile, APC is a noncontact method that uses high-frequency monopolar current associated with ionized and electrically conductive argon gas [6].

Combination therapy outperforms single therapy for hemostasis. For example, hemoclips combined with injection therapy outperform either hemoclips or injection therapy alone [7, 8]. Injection therapy combined with heat probe treatment outperforms injection therapy alone but does not
differ significantly from heater probe therapy alone [9]. This is probably because heat probe coagulation exerts a tamponade effect via direct contact [9].

Theoretically, no tamponade effect exists for APC alone. This study aimed to determine whether additional endoscopic injection before APC could increase hemostatic efficacy in treating high-risk bleeding ulcers.

2. Methodology

2.1. Patient. From January 2007 to April 2011, a retrospective analysis was performed of patients hospitalized due to upper gastrointestinal bleeding. Inclusion criteria were as follows: (1) patients with melena or hematemesis and (2) patients in which the emergent upper endoscopy revealed high-risk bleeding ulcers within 24 hours upon admission to the emergency units. Exclusion criteria included (1) another possible bleeding site, (2) coexistence of severe illness (e.g., acute stroke, acute surgical abdomen, acute myocardial infarction, or sepsis), (3) pregnancy, (4) patient age under 20 years old, and (5) tendency to systemic bleeding (e.g., prothrombin time > 3 sec, platelet count < 50,000/mm³, or treatment with an anticoagulant agent).

High-risk bleeding ulcers were defined as those with stigmata of an actively bleeding visible vessel (i.e., spurting or oozing), a nonbleeding visible vessel (NBVV), or adherent clots [10]. A NBVV was defined as a raised red or bluish-red hemispheric vessel protruding from the ulcer base, without active bleeding. Meanwhile, an adherent clot was defined as an overlying clot that was wash-resistant.

2.2. Endoscopic Treatment. All patients were admitted to our emergency department with nonvarices upper gastrointestinal bleeding. They received an intravenous bolus of 40 mg pantoprazole, followed by penameandose within 24 hours upon admission. Local pharyngeal anesthesia was used by 8% xylocaine spray, gastric lavage before endoscopy to enhance the visual field, and intramuscular injection with hyoscine butyrate 20 mg for premedication. Patients with high risk of bleeding ulcers nonrandomly received either APC plus distilled water injection (combined group) or APC alone (APC group).

Therapeutic endoscopies were performed by four experienced endoscopists with more than 3 years of experience, using Olympus GIF XV10, GIF XQ200, and GIF IT20 (Olympus Corporation, Tokyo, Japan) devices. Stigmata of active bleeding ulcer or adherent blood clots were irrigated with distilled water via the accessory channel of the endoscope [11]. A large blood clot that covered the ulcerative lesion was removed using a 3-prong device, snare catheter, or water irrigation. Distilled water was then injected in aliquots of 0.5 to 2.0 mL, at and around the suspected site of bleeding, up to 20.0 mL if needed. The injections were placed in the 4 quadrants surrounding the bleeding site or the vessel. No bleeding was noted after injection for at least 3 minutes. Injection amount was determined by endoscopists. APC was performed by an Olympus electroendoscopist unit/APC unit (PSD-60/Endoplasma, Olympus Corp., Tokyo, Japan), and its catheters were 2.3 mm and 3.5 mm and were equipped with endoscope channels with corresponding diameters [12]. APC used a coagulation mode at a gas flow/power setting of 1.5 L/min and 40–60 watts (40 watt for duodenal ulcer; 40–60 watt for gastric ulcer). Operative distance between the probe and suspected site of bleeding ranged from 2 to 8 mm. Helicobacter pylori status was not verified during acute bleeding episodes since, according to several studies, the biopsy-based test must have a low sensitivity to detect H. pylori in bleeding ulcers [12].

Initial hemostasis was defined as following the first endoscopic treatment (index endoscopy) and endoscopically verified to have stopped bleeding for at least 5 minutes. If the initial hemostasis failed owing to uncontrollable profusion, patients received subsequent endoscopic modality or emergency surgery, as determined by a gastroenterologist. Recurrent hemorrhaging during a 30-day observation period, defined herein as rebleeding, includes one or more of the following factors: aspiration of fresh blood from a nasogastric tube, new hemostasis event, pulse rate over 100 beats/min with unstable vital signs, drop in systolic blood pressure exceeding 30 mmHg, or continuous melena with drop in Hb of at least 2 g/dL. Upper endoscopy was performed immediately if rebleeding occurred, followed by second hemostasis. Both treated groups with recurrent bleeding underwent endoscopic combination therapy, either APC plus distilled water injection or hemoclipping plus distilled water injection as a rescue therapy. If the second endoscopic therapy failed to achieve hemostasis, emergency surgery was performed.

2.3. Medication Treatment and Follow-Up. Medical treatments included partial parenteral nutrition and intravenous administration of pantoprazole (40 mg every 24 h) and the patients continued to fast [13, 14]. Following two days of observation, the patients consumed a soft diet for 2 to 3 days, followed by a regular diet; pantoprazole was shifted to an oral form (40 mg daily). For the first three days, daily hemoglobin (Hb) levels were monitored routinely for following the index endoscopy. Blood transfusion criteria included the following: (1) persistent hematemesis or melena, with a systolic blood pressure below 100 mm Hg or a pulse rate exceeding 100 beats/min, and (2) Hb levels lower than 8 g/dL.

Patients received oral pantoprazole (40 mg daily) for up to 8 weeks following discharge and were instructed to undergo follow-up through our outpatient department on days 14, 28, and 56 after the initial hemostasis was achieved.

2.4. Analysis. Qualitative variables, similar to the baseline characteristics and treatment outcomes, were compared via the X² and Fisher exact tests. Quantitative variables were also compared using Student’s t-test, and the data were expressed as mean ± SD. Next, the risk factors for the development of rebleeding on univariate and/or multivariate analysis were evaluated using the Cox regression model. Those variables significant at P < 0.20 in the univariate models were subsequently subjected to multivariate analysis in order to identify the most significant predictors. All hypothesis
tests were compared with a two-sided alternative, whenever deemed appropriate. The level of statistical significance was set at \( P < 0.05 \). Analyses were performed using SPSS software (SAS, SPSS Inc., Chicago, IL).

### 3. Results

One hundred thirty-five patients were included in the study between January 2007 and April 2011 and were recruited through the Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital. Fifteen patients were excluded owing to gastric cancer (\( n = 2 \)), acute severe illness (\( n = 10 \)), and bleeding tendency (\( n = 3 \)). Finally, 60 patients underwent combination therapy (APC plus distilled water injection) and 60 patients received APC alone.

Among the 120 patients with ulcers who had a high risk of bleeding, most of them are male (79.1%) or over 60 years old (69.1%). The sample included 70 cases of bleeding duodenal ulcer (34 who received combined therapy and 36 who received APC alone) and 41 cases of bleeding gastric ulcer (23 who received combined therapy and 18 who received APC alone) and nine cases of bleeding stump ulcer (three who received combined therapy and six who received APC alone) were included. Table 1 lists the clinical data of the patient on study entry. The two treatment groups were similar in terms of all baseline characteristics.

Initial hemostasis was achieved in 98.3% (59/60) and 95.0% (57/60) of the combined group and APC alone group, respectively, with similar initial hemostasis rates (\( P = 0.619 \)). Bleeding recurred in two patients (3.4%) treated with combined therapy and in seven (12.3%) treated with APC alone. Subsequently, one patient underwent APC plus distilled water injection and the other received hemoclipping plus distilled water injection in the combined group. In the APC group, two patients underwent APC plus distilled water injection and five patients received hemoclipping plus distilled water injection. Despite a higher rebleeding rate in the APC alone group, the two groups did not differ significantly (\( P = 0.092 \)). Table 2 lists the data on clinical outcomes for the patients in this study. Next, possible reasons for recurrent bleeding were examined. According to those results, NSAID use (\( P = 0.046 \)) and previous bleeding (\( P = 0.045 \)) may predict the possibility of rebleeding, based on Cox regression multivariate analysis (Table 3). One patient (1.7%) in the combined group and five (8.3%) in the APC group underwent emergency surgery (\( P = 0.207 \)). The two treatment groups exhibited no significant differences in 30-day mortality (1.7% versus 3.3%, \( P = 1.000 \)), hospital stay (6.6 + 4.5 versus 5.7 + 2.9 days, \( P = 0.219 \)), or transfusion requirements (4.3 + 4.2 versus 3.6 + 2.7 units, \( P = 0.306 \)). Moreover, both groups were free of major complications. The combined treatment group only exhibited an advantage (5.0% versus 16.7%, \( P = 0.040 \)) in the combined end point of mortality, as well as the failure of initial hemostasis, rebleeding, and the need for surgery.

Two of the three deaths occurred in patients with uncontrollable bleeding, with both of those patients belonging to the APC group. The other one occurred in the patient with progressive pneumonia and septic shock. No life-threatening procedure-related complications were observed in either group at index endoscopy. However, three patients with NBVV (3/23, 13%) in the APC group and none (0/25, 0%) in the combined treatment group experienced procedure-induced bleeding. Fortunately, these adverse events were subsequently controlled through repeated APC therapy.

### 4. Discussion

Thus far, despite the effectiveness of endoscopic injection therapies, the rebleeding rate remained around 20% [22]. Recurrent bleeding has been reported to be the most important factor in predicting mortality [23]. Thus, several endoscopic methods for hemostasis of gastrointestinal bleeding

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**Table 1: Baseline characteristics of the study group.**

<table>
<thead>
<tr>
<th></th>
<th>Combined group (( n = 60 ))</th>
<th>APC group (( n = 60 ))</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year (SD)</td>
<td>65.7 ± 17.2</td>
<td>68.0 ± 14.7</td>
<td>0.433</td>
</tr>
<tr>
<td>Age ≥ 60 yrs</td>
<td>40 (66.7%)</td>
<td>43 (71.7%)</td>
<td>0.553</td>
</tr>
<tr>
<td>Male gender</td>
<td>48 (80.0%)</td>
<td>47 (48.3%)</td>
<td>0.822</td>
</tr>
<tr>
<td>Cigarette consumption</td>
<td>13 (21.7%)</td>
<td>13 (21.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>11 (18.3%)</td>
<td>7 (11.7%)</td>
<td>0.306</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>3 (5.0%)</td>
<td>4 (6.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>NSAID use</td>
<td>27 (45.0%)</td>
<td>19 (31.7%)</td>
<td>0.113</td>
</tr>
<tr>
<td>Steroid use</td>
<td>1 (1.7%)</td>
<td>4 (6.7%)</td>
<td>0.364</td>
</tr>
<tr>
<td>Previous ulcer bleeding</td>
<td>19 (31.7%)</td>
<td>16 (26.7)</td>
<td>0.547</td>
</tr>
<tr>
<td>Hypovolemic shock</td>
<td>11 (18.3%)</td>
<td>14 (23.3%)</td>
<td>0.500</td>
</tr>
<tr>
<td>Hemoglobin, g/dL (SD)</td>
<td>10 (16.7%)</td>
<td>12 (20.0%)</td>
<td>0.637</td>
</tr>
<tr>
<td>Platelet count, k/cumm (SD)</td>
<td>200.5 ± 87.6</td>
<td>194.0 ± 63.8</td>
<td>0.644</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>16 (26.7%)</td>
<td>17 (28.3%)</td>
<td>0.838</td>
</tr>
<tr>
<td>PT/APTT prolongation</td>
<td>9 (15.0%)</td>
<td>6 (10.0%)</td>
<td>0.408</td>
</tr>
<tr>
<td>Comorbid disease**</td>
<td>17 (28.3%)</td>
<td>18 (30.0%)</td>
<td>0.841</td>
</tr>
<tr>
<td>Ulcer size, mm (SD)</td>
<td>15.0 ± 7.1</td>
<td>16.0 ± 8.7</td>
<td>0.514</td>
</tr>
<tr>
<td>Ulcer ≥ 20 mm</td>
<td>18 (30.0%)</td>
<td>21 (35.0%)</td>
<td>0.559</td>
</tr>
<tr>
<td>Ulcer location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>23 (38.3%)</td>
<td>18 (30.0%)</td>
<td>0.336</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>34 (56.7%)</td>
<td>36 (60.0%)</td>
<td>0.711</td>
</tr>
<tr>
<td>Stump ulcer</td>
<td>3 (5.0%)</td>
<td>6 (10.0%)</td>
<td>0.491</td>
</tr>
<tr>
<td>Bleeding type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spurring</td>
<td>3 (5.0%)</td>
<td>5 (8.3%)</td>
<td>0.717</td>
</tr>
<tr>
<td>Oozing</td>
<td>19 (31.7%)</td>
<td>26 (43.3%)</td>
<td>0.187</td>
</tr>
<tr>
<td>NBVV</td>
<td>25 (41.7%)</td>
<td>23 (38.3%)</td>
<td>0.709</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>13 (21.7%)</td>
<td>6 (10.0%)</td>
<td>0.080</td>
</tr>
<tr>
<td>Injection volume, mL (SD)</td>
<td>8.4 ± 4.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APTT: activated partial thromboplastin time; NBVV: nonbleeding visible vessel; PT: prothrombin time; and SD: standard deviation.

*Thrombocytopenia is defined as platelet count <150000/mm³.

** Comorbid disease included old stroke, diabetes mellitus, liver cirrhosis, uremia, congestive heart failure, chronic pulmonary obstructive disease, and poststatus chemotherapy [15–21].
have been developed, including heat probe coagulation, mechanical devices like hemoclips, and APC.

Injection therapy is frequently used as an endoscopic treatment for ulcer bleeding, with 1:10000 diluted epinephrine as the injected solution. Because mechanical compression of injected solution is the most significant factor for initial bleeding control, some studies have demonstrated that large volume endoscopic injection therapy can help prevent rebleeding via the same mechanism as compression effect [24, 25]. Regarding the reason for using distilled water rather than epinephrine injection, some scholars agreed that epinephrine injection may result in increased risk of cardiovascular event. Sung and his colleagues [26] found that plasma epinephrine concentration increased significantly for 10 minutes following endoscopic injection and increased the likelihood of adverse cardiovascular events. Distilled water is used rather than epinephrine injection because epinephrine injection may increase the risk of a cardiovascular event. Meanwhile, Lai et al. [5] found injection therapy with distilled water or 1:10000 diluted epinephrine did not significantly differ from each other upon initial hemostasis. Endoscopic therapy with distilled water injection has traditionally been the most popular approach and continues to be considered safe and effective. Severe complications (e.g., perforation, worsening of bleeding) have not been reported in association with distilled water injection [5, 27]. Due to the above reason, we choose endoscopic injection with distilled water for tamponade effect.

Combination therapy is accepted to be better than single therapy in hemostasis. For example, the combination of injection therapy with another method of hemostasis (e.g., hemoclips or heat probe) outperforms injection alone for controlling bleeding, particularly high-risk bleeding [7, 8]. However, therapeutic gain of contact thermal therapy and injection therapies may display no more hemostatic benefits than contact thermal monotherapy does [9]. Because contact thermal therapy, such as heat probe, exerts a tamponade effect on the artery, coaptivity coagulates the tissue, activates arterial coagulation, and causes edema that compresses the artery, and it has similar hemostatic efficacy to combined therapy [28, 29].

APC, a noncontact thermal therapy, can more easily target the sites of bleeding than can hemoclips, particularly those in the posterior wall of lesser curvature of the upper gastric body or the posterior wall of the duodenal bulb [30, 31]. In spite of its efficient treatment of radiation proctitis, angiodysplasia, and gastric antral vascular ectasia, some trials have been published on the efficacy of APC for treating bleeding peptic ulcer. APC had similar efficacy to heat probe in terms of initial hemostasis and the prevention of recurrent bleeding [32, 33]. APC also achieved a lower rebleeding rate than distilled water injection therapy [11]. Moreover, APC had the same effects as contact thermal therapy, including tissue coagulation, arterial coagulation, and tissue edema, except the direct compression effect. The risk of perforation following APC is estimated at approximately 0.3% [33]. Although this potential risk can be considered a disadvantage of APC, both groups in the present were free of perforation, probably because of the noncontact method.

This investigation was specifically designed to test the hypothesis that outcomes differ between patients treated by APC monotherapy and combined APC therapy with distilled water injection. Combined therapy was expected to increase the local tamponade effect since APC lacks a direct compression effect. The results showed that both treatment arms were equally effective in terms of initial hemostasis (98.3% versus 95.0%). Notably, a trend existed toward lower recurrent bleeding (3.4% versus 12.3%, $P = 0.092$) in the combined group yet does not reach statistical significance. The tamponade effect with noncontact thermal therapy may affect recurrent bleeding rate. In the current study, the rate of peptic ulcer rebleeding was relatively low (3.4%) in the combined group, even though those patients did not receive high-dose PPI therapy. A lower incidence of Forrest grades Ia and Ib than other clinical trials may contribute to this phenomenon [7–9, 11]. No significant difference existed between the two treatment groups in terms of need for surgery, need for blood transfusion, hospital stay, and mortality. The combined group exhibited an advantage in the combined end point of mortality plus the failure of initial hemostasis, rebleeding, and the need for surgery (5.0% versus 16.7%, $P = 0.040$). In the future, larger randomized studies may be able to clarify the differences between these two treatment methods.

This investigation suffers some limitations. First, it includes possible selection bias. Volunteer participants for endoscopy may have a reason to suspect that they have other coexisting bleeding sites. Second, examiner subjectivity may influence endoscopic estimation of ulcer size. Third, this study excluded some patients unable to undergo endoscopy.
Table 3: Probable effects of variables on recurrent bleeding.

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Treatment method</td>
<td>0.30 (0.06–1.57)</td>
<td>0.155</td>
</tr>
<tr>
<td>NSAIDs use*</td>
<td>5.03 (0.97–26.10)</td>
<td>0.055</td>
</tr>
<tr>
<td>Steroid use*</td>
<td>4.95 (0.45–53.99)</td>
<td>0.189</td>
</tr>
<tr>
<td>Previous bleeding</td>
<td>4.48 (1.01–19.96)</td>
<td>0.049</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.35 (1.00–18.98)</td>
<td>0.050</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10.38 (1.97–54.76)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

CI: confidence interval; OR: odds ratio.
*NSAIDs use or steroid use was defined as medication ended in 30 days before the index endoscopy.

owing to acute critical illness or tendency of systemic bleeding. Finally, this study is not a randomized controlled study. However, all study participants were followed up using standard protocols administered by experienced gastroenterologists and trained assistants. Notably, this study was the first to investigate the effectiveness and safety of APC as an additional endoscopic treatment compared to APC alone in treating high-risk bleeding ulcers.

5. Conclusions

In conclusion, endoscopic therapy with APC plus distilled water injection failed to prove more effective than APC alone in treating high-risk bleeding ulcers, while APC plus injection therapy may be superior for patients with poor overall outcomes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Yuan-Rung Li and Ping-I Hsu contributed equally to the work.

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References


Background and Aims. To compose upper gastrointestinal bleeding (UGIB) consensus from a nationwide scale to improve the control of UGIB, especially for the high-risk comorbidity group.

Methods. The steering committee defined the consensus scope to cover preendoscopy, endoscopy, postendoscopy, and overview from Taiwan National Health Insurance Research Database (NHIRD) assessments for UGIB. The expert group comprised thirty-two Taiwan experts of UGIB to conduct the consensus conference by a modified Delphi process through two separate iterations to modify the draft statements and to vote anonymously to reach consensus with an agreement ≥80% for each statement and to set the recommendation grade.

Results. The consensus included 17 statements to highlight that patients with comorbidities, including liver cirrhosis, end-stage renal disease, probable chronic obstructive pulmonary disease, and diabetes, are at high risk of peptic ulcer bleeding and rebleeding. Special considerations are recommended for such risky patients, including raising hematocrit to 30% in uremia or acute myocardial infarction, aggressive acid secretory control in high Rockall scores, monitoring delayed rebleeding in uremia or cirrhosis, considering cyclooxygenase-2 inhibitors plus PPI for pain control, and early resumption of antiplatelets plus PPI in coronary artery disease or stroke. Conclusions. The consensus comprises recommendations to improve care of UGIB, especially for high-risk comorbidities.

1. Introduction

Upper gastrointestinal bleeding (UGIB) is a highly prevalent and potentially fatal condition worldwide [1, 2]. The incidence of UGIB has an increasing trend in elderly people with comorbid illnesses and in users of nonsteroid anti-inflammatory drugs (NSAIDs) [1, 2]. The recommendations from previous UGIB guidelines and reviews have resulted in improvements in patients care and outcomes [3–5]. The international consensus recommendations on the management of patients with nonvariceal UGIB were updated in 2010 with a substantial expansion [1]. Due to concerns about Asia-Pacific regional differences in patient characteristics and healthcare systems as compared to developed Western countries, some
specific strategies have been revised [2]. However, there remains evident diversity in the availability of medications and endoscopy facilities within the Asia-Pacific region.

In Taiwan, endoscopy and the therapeutic modalities are readily available on a nationwide scale. Moreover, the National Health Insurance program, which covers more than 99% of the entire population of Taiwan, provides full support for medication and endoscopy for UGIB. Therefore, there is a need to refresh the current consensus for patient care of peptic ulcer bleeding. Although some recommendations in this consensus are based on local data extracted from the National Health Insurance program, these recommendations address many important issues, for example, comorbidity, also emerging in other countries [6]. Because patients are now older and sicker than before, the consensus statements can be applied in general to improve evolution in health care due to the aging population worldwide.

Owing to the National Health Insurance Research Database (NHIRD) which covers more than 23 million residents over more than 15 years, the current consensus has provided strong evidence of its validity in a nationwide cohort setting for UGIB. To collect recommendations from a nationwide scale to improve the outcomes of UGIB, especially to improve the care for the high-risk group, is a novel project.

2. Methods

2.1. Scope Setting and Preparation Structure of Consensus by a Steering Committee. To establish the expert consensus of UGIB in Taiwan, the steering committee was initiated by J. T. Lin, chaired by B. S. Sheu, and cochaired by C. Y. Wu along with seven other opinion leaders from the Gastroenterological Society of Taiwan (M. S. Wu, C. T. Chiu, C. J. Lin, P. I. Hsu, H. C. Cheng, T. Y. Lee, and H. P. Wang). The steering committee defined the scope sessions of the consensus, searched for and reviewed the literature, formulated the draft statements, and defined the statement evidence level.

2.2. Literature Search and Review to Address the Draft Statements with Evidence Level Grading. The literature searches included Medline, Embase, the Cochrane Central Register of Controlled Trial, and ISI Web of Knowledge, with manual searches of bibliographies of key articles and proceedings of abstracts of major gastroenterology conferences held over the past 7 years. The keywords used in the search included gastrointestinal bleeding, peptic ulcer, proton pump inhibitor, upper gastrointestinal endoscopy, rebleeding, and mortality.

The members of the steering committee summarized the findings into the four scope sessions of this consensus: the first three sessions were ranked in order by patient-centric time-framed allocations from preendoscopy, endoscopy, and postendoscopy assessments, and the last session commented on the particular scenario of an overview of UGIB from the Taiwan NHIRD. Based on the review of the literature, the draft statements of the consensus were established by the session leader(s) of each scope session. For each statement, the level of evidence was defined according to modified grading of the Oxford Centre for Evidence-Based Medicine Levels of Evidence (March, 2009) [7]. The draft statements were refined at the steering committee meeting held in Tainan during May 2013.

2.3. Expert Group Process to Achieve Agreement of Statement and Grading of Recommendation. The expert group of the Taiwan UGIB consensus comprised a total of 32 experts, including 10 members in the steering committee and 22 members who accepted the invitation of the steering committee. The draft statements from the four session groups were sent to all experts, together with pertinent literature before the consensus meeting in Taichung in July 2013.

During the two-day consensus meeting, for each draft statement from the four scope sessions, the supporting evidence from the keynote literature summary by the steering committee was presented serially in order from preendoscopy, endoscopy, and postendoscopy to NHIRD assessments. Based on a modified Delphi process through two separate iterations, all participants voted anonymously for the first round of statements and modified the statements by discussion. The modified statements were followed by a second round of voting with electronic keypads until a consensus was reached at the agreement percentage of ≥80%. If the agreement was less than 80%, the statement was rejected.

The expert members also discussed the level of evidence suggested by the steering committee and then provided grading of the recommendation level by voting for each statement. The grading of recommendation into 4 grades from A to D was applied as in the Asia-Pacific working group consensus for UGIB [2]. The level of recommendation was defined as the grade with the highest number of votes of the expert group members. The conferences were underwritten by unrestricted grants from the Gastroenterological Society of Taiwan. Mandatory written disclosures of financial conflict of interests within the period of three years before the meetings were obtained from all experts before voting.

3. Consensus Statements

3.1. Section I: Preendoscopy Assessment

Statement I-1. For specific comorbid patients with uremia or coronary artery diseases, to raise hematocrit at least 30% shall be beneficial (agreement: 94%, level of evidence: Ib, and recommendation: A).

For patients who present with acute bleeding, hemoglobin (Hb) concentration < 7 g/dL is an indication for blood transfusion. For those with Hb concentration > 10 g/dL, blood transfusion is rarely indicated [1]. Among patients with bleeding from a peptic ulcer, further bleeding risk is lower in the strategy with threshold transfusion of Hb < 7 g/dL than in the strategy with Hb < 9 g/dL [8].

Special consideration should be given for blood transfusions in UGIB patients with comorbid diseases including uremia and acute myocardial infarction to keep the hematocrit level above 30% [9, 10]. The platelet-mediated hemorrhagic
tendency in uremia may be managed successfully by raising hematocrit to above 30% [11].

Statement I-2. The preendoscopy Rockall score is a useful tool to identify high-risk patients who need further endoscopic therapy and radiologic and surgical interventions (agreement: 90%, level of evidence: 2b, and recommendation: B).

Rockall scoring system combining both clinical and endoscopic variables may identify patients who are given early discharge or outpatient management who are in need of more aggressive treatment interventions, including endoscopy, and who have further bleeding or death [12]. In predicting the need for endoscopic therapy, the Glasgow-Blatchford score may be more useful in detecting which patients need clinical intervention than the preendoscopic Rockall score [13, 14]. However, only 1% to 5% of cohort cases have Glasgow-Blatchford score of 0 to indicate that they are at low risk and intervention is not required [14, 15]. So the expert discussions preserve the statement to be more focused on Rockall score and suggest there should be a need of local validations for the Glasgow-Blatchford score in future.

Statement I-3. Preendoscopic intravenous proton pump inhibitor can enhance resolution of stigmata of bleeding and decrease the need of endoscopic therapy, though it cannot replace the urgent endoscopy (agreement: 97%, level of evidence: 1a, and recommendation: A).

The use of intravenous proton pump inhibitors (PPI) before endoscopy can reduce endoscopic therapy at index endoscopy, but it does not improve the clinical outcome of UGIB including rebleeding, surgery, or mortality [16, 17]. Nevertheless, endoscopy should generally be conducted within 24 hours for UGIB [18, 19], and the preendoscopy administration of PPI should not delay or replace urgent endoscopy for UGIB.

3.2. Section II: Endoscopy Assessment

Statement II-1. Stigmata of recent hemorrhage (SRH) of bleeding peptic ulcer can predict the risk of rebleeding and guide management decisions. Forrest classification is commonly used to describe SRH (agreement: 100%, level of evidence: 2b, and recommendation: A).

The stigmata of recent hemorrhage (SRH) are now widely used to record the endoscopic finding of bleeding peptic ulcers with the classification of Forrest et al., to disclose recurrent bleeding rates [20, 21], and to guide endoscopic hemostasis [22–25] and time to discharge [26–28]. For example, a visible vessel has average 43% rebleeding risk [21], needs endoscopic hemostatic therapies [24], and takes four days to disappear [26].

Statement II-2. Endoscopic therapy is recommended to be provided for patients with high-risk lesions, such as active spurting, oozing bleeding, or a nonbleeding visible vessel (Forrest Ia, Ib, or Ila) (agreement: 100%, level of evidence: 1a, and recommendation: A).

Meta-analyses of randomized controlled trials confirmed the benefits of endoscopic hemostatic therapies to arrest active bleeding or decrease recurrent bleeding for high-risk bleeding peptic ulcers (such as Forrest Ia, Ib, or Ila lesions) [22–25]. Endoscopic hemostatic therapies including injection, thermal therapy, and a combination are better than pharmacotherapy only to control peptic ulcer recurrent bleeding [24, 25].

Statement II-3. Endoscopic therapy may be considered for ulcers with adherent clots (Forrest IIb) (agreement: 100%, level of evidence: 1a, and recommendation: A).

A meta-analysis suggested that endoscopic therapy is superior to medical therapy and to decrease recurrent bleeding and surgery but without improvement in mortality [29]. However, another meta-analysis did not show significant benefit in any clinical outcomes [24]. Because these studies had the variable definition of adherent clots and different results, what to do with clots remains inconclusive.

Statement II-4. Endoscopic therapy is not routinely recommended to ulcers with a flat pigmented spot or a clean base (Forrest IIc or III) (agreement: 93%, level of evidence: 2b, and recommendation: A).

The rates of recurrent bleeding may be as low as 5%~10% in bleeding ulcers with a clean base and flat pigment spot without endoscopic therapy [21], and they are thus not in need of endoscopic therapy.

Statement II-5. Epinephrine injection therapy is recommended to be combined with a second modality (agreement: 90%, level of evidence: 1a, and recommendation: A).

Endoscopic injection of epinephrine is less effective than other monotherapies to prevent recurrent ulcer bleeding [24, 25]. By combining epinephrine injections with a second modality (such as thermal coagulation, fibrin glue, or hemoclip), the outcome of UGIB, including further bleeding and the need for surgery, may be much improved [22–25, 30].

3.3. Section III: Postendoscopy Assessment

Statement III-1. Patients with bleeding peptic ulcers are recommended to be treated with intravenous high dose or nonhigh dose of proton pump inhibitors, as bolus or continuous infusion for 72 hours after successful endoscopic therapy (agreement: 97%, level of evidence: 1a, and recommendation: A).

An intravenous PPI administration can improve control of peptic ulcer bleeding after endoscopic therapy [31, 32]. A nonhigh dose regimen can still be as efficacious as a high dose regimen of PPI (such as esomeprazole at least 8 mg/hr intravenous infusion for 72 hr) to control recurrent peptic ulcer bleeding [32–34]. Nevertheless, a recent Cochrane review showed that low quality evidence did not exclude either a potential reduction or an increase in outcomes including rebleeding, surgery, mortality, and repeated endoscopic hemostatic treatment, with high dose compared to nonhigh dose proton pump inhibitor regimens [35].

Statement III-2. Oral proton pump inhibitors could be an alternative treatment to intravenous infusion after successful
endoscopic hemostasis for low-risk peptic ulcer bleeding (agreement: 87%, level of evidence: Ib, and recommendation: B).

The hospital stay, need for blood transfusion, recurrent bleeding, and mortality are similar for oral high dose PPI and intravenous PPI infusion after endoscopic hemostasis among low-risk patients, whose Rockall scores <6 or American Society of Anesthesiologists class I or II [36, 37].

Statement III-3. For NSAID users with previous peptic ulcer bleeding, either nonselective NSAID to plus PPI or COX-2 inhibitor alone can reduce the recurrent peptic bleeding. Otherwise, COX-2 inhibitor plus PPI may offer better gastrointestinal protection (agreement: 97%, level of evidence: Ib, and recommendation: A).

For the users of nonsteroid anti-inflammatory drugs (NSAIDs) with a previous history of peptic ulcer bleeding, either a cyclooxygenase-2 (COX-2) inhibitor or a nonselective NSAID plus PPI can reduce the recurrent bleeding [38]. The combination of a COX-2 inhibitor and PPI can achieve nearly no recurrence rate of peptic ulcer bleeding [39].

Statement III-4. Patients with comorbidities or poor nutrition status have higher incidence of peptic ulcer diseases and recurrent bleeding (agreement: 100%, level of evidence: 2b, and recommendation: B).

Nosocomial bleeding [40] and the presence of comorbidities [12, 41] including uremia [34, 42, 43], liver cirrhosis [41, 44], chronic obstructive pulmonary disease [34], and poor nutrition status as hypoalbuminemia [45] are the significant factors to have a higher incidence of peptic ulcer disease or recurrent bleeding. The domestic data suggested the effect of 3-day PPI infusion after therapeutic endoscopy was limited to prevent recurrence bleeding in patients with comorbidities [45, 46]. Extending the duration of intravenous PPI infusion to 7 days or doubling the dose of oral PPI as twice daily after 3-day intravenous infusion can improve the control of recurrent bleeding in such high-risk populations [47, 48]. This implies that more aggressive acid control is necessary for high-risk patients who are defined by Rockall score ≥6 [48].

Statement III-5. In bleeding ulcer patients who require low-dose aspirin therapy for cardiovascular prophylaxis, aspirin plus PPI should be restarted as soon as possible, once hemostasis can be achieved or cardiovascular risks outweigh gastrointestinal risks (agreement: 97%, level of evidence: Ib, and recommendation: A).

It is reasonable to stop the antiplatelet therapy during acute ulcer bleeding [49]. Once hemostasis is achieved, early resumption of antiplatelet agents with PPI at 3-5 days after the last dose can be suitable [50, 51]. For the long-term prevention of peptic ulcer bleeding, cotherapy with PPI is suggested for aspirin or clopidogrel users [52–55]. The COGENT trail confirmed a reduction in gastrointestinal bleeding risk without increase in cardiovascular events when clopidogrel was coprescribed with omeprazole [56].

Statement III-6. The second-look endoscopy is not routine for all patients but can be reserved for the high-risk patients (agreement: 100%, level of evidence: 1a, and recommendation: B).

There are no proven benefits by second-look endoscopy and, considering the availability of high dose PPIs, the second-look endoscopy may be reserved for high-risk patients [57, 58]. A meta-analysis showed that routine second-look endoscopy in peptic ulcer bleeding might be effective in high-risk patients, including those with hemodynamic instability, active bleeding, large ulcers, ulcer of posterior wall of bulb, and more or active comorbidities [1, 58]. Therefore, there is a pressing need for further studies to elucidate the role and, moreover, the selection criteria of second-look endoscopy. This is the reason why the expert members had 100% agreement but only B recommendation.

3.4. Section IV: Special Scenario of an Overview of UGIB from the NHIRD

Statement IV-1. Taiwan NHIRD researches identify the high-risk populations of peptic ulcer bleeding and recurrent bleeding, including liver cirrhosis, end stage renal disease, probably chronic obstructive pulmonary disease, and type II diabetes (agreement: 100%, level of evidence: 2b, and recommendation: B).

A number of nationwide studies using the NHIRD in Taiwan have identified several populations at risk of peptic ulcer bleeding, including those with liver cirrhosis, end stage renal disease, type II diabetes, chronic obstructive pulmonary disease, age > 65 years, male gender, hypertension, heart failure, history of peptic ulcer disease, and chronic users of NSAIDs [59–63]. These underlying comorbidities may serve as independent risk factors of the recurrent ulcer bleeding [46, 64, 65]. The effect of life-long antisecretory medications in prevention of peptic ulcer recurrence in high-risk populations represents an important topic for future research.

Statement IV-2. Taiwan NHIRD researches identify NSAID and high-affinity serotonin reuptake inhibitors increase the risk of peptic ulcer bleeding (agreement: 97%, level of evidence: 3b, and recommendation: B).

The nonselective NSAIDs are significantly associated with a higher risk of UGIB [66, 67]. Selective serotonin reuptake inhibitors also predispose to recurrent bleeding of UGIB [68, 69]. Concomitant use of antisecretory medications may therefore be suggested.

Statement IV-3. Taiwan NHIRD researches support the fact that H. pylori eradication reduces peptic ulcer diseases and the risk of gastric cancer for patients with peptic ulcer diseases (agreement: 90%, level of evidence: 2b, and recommendation: B).

Anti-H. pylori therapy given within 6 months of ulcer diagnosis can reduce the ulcer events [70, 71] and prevent bleeding recurrence [72]. An increased risk of gastric cancer correlates with a late eradication beyond one year in patients with peptic ulcer. Early H. pylori eradication is therefore suggested as an independent protective factor to reduce the risk of gastric cancer [73]. This result is compatible with a large-scale study and meta-analysis, showing that eradication
of *H. pylori* decreases the development of gastric cancer only among those without precancerous lesion [74,75].

4. Dissemination Strategies and Legal Issues

These statements are based on the best available evidence to pursue better quality of care and will be updated per 5 years. They are not suitable for deciding standard of care in specific cases. This consensus statement will be disseminated by (1) presentations given at the annual society meeting of Taiwan Digestive Week in 2013; (2) possible release of copies of these statements in electronic and paper format to national societies/associations of gastroenterologists for their iterations; (3) release on the website of our society link.

Abbreviations

- **COX-2**: Cyclooxygenase-2
- **NHIRD**: National Health Insurance Research Database
- **NSAIDs**: Nonsteroid anti-inflammatory drugs
- **NTT**: Number needed for treatment
- **PPI**: Proton pump inhibitor
- **RR**: Relative risk
- **SRH**: Stigmata of recent hemorrhage
- **UGIB**: Upper gastrointestinal bleeding.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Bor-Shyang Sheu and Chun-Ying Wu contributed equally to this study. Dr. B. S. Sheu coordinated as the chairman of the Taiwan expert group to compose the draft of the paper. Dr. C. Y. Wu served as the cochairman and Drs. M. S. Wu, C. T. Chiu, C. C. Lin, P. I. Hsu, H. C. Cheng, T. Y. Lee, and H. P. Wang reviewed the literatures and statements. Dr. J. T. Lin applied the funding for the expert meeting and critically reviewed the paper.

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References


Research Article

The Utilization of a New Immunochromatographic Test in Detection of Helicobacter pylori Antibody from Maternal and Umbilical Cord Serum

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Background. Helicobacter pylori (H. pylori) was linked with several extragastrointestinal diseases, including preeclampsia and intrauterine growth restriction of fetus. One of the signals which can be transferred from mother to fetus is the H. pylori IgG antibody. Aims. We utilized a commercial immunochromatographic kit to detect the antibody in maternal and cord serum. Methods. Three hundred and forty-six females were enrolled and the blood samples were collected on antenatal examination and on delivery. The maternal H. pylori infection was determined by stool H. pylori antigen test. Results. One hundred and five females (30.3%) were H. pylori-infected, and the prevalence was higher in immigrants (43.5%) than in Taiwanese (28.7%, \( P = 0.058 \)). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the kit were 77.1%, 88.0%, 73.6%, 89.8%, and 84.7%, respectively. This kit also had similar performance in cord serum. Comparing to the maternal result on delivery, this kit offered a consistent performance in antenatal maternal serum (kappa coefficient 0.92) and in cord serum (kappa coefficient 0.88). Conclusions. H. pylori IgG antibody can be transferred through the placenta into the fetal circulation. However, accuracy of the test kit needs to be evaluated before utilization in screening.

1. Introduction

Helicobacter pylori (H. pylori), a Gram-negative bacteria existing in the stomach, has been linked with many gastrointestinal diseases, such as peptic ulcer disease, gastric adenocarcinoma, and gastric mucosal-associated lymphoid tissue lymphoma [1]. Following the observation from public health studies, however, H. pylori was thought to be associated with several extragastrointestinal diseases [2], such as hematological disease (idiopathic thrombocytopenic purpura, unexplained iron deficiency anemia) [3, 4], cardiovascular disease [5], and neurological disorders [6]. Recently, studies focusing on the obstetric field mentioned the possible influence of H. pylori infection in pregnant female. The high prevalence of the H. pylori was observed in population who had preeclampsia during pregnancy [7]. The specific
gastrointestinal symptom, hyperemesis gravidarum, was also linked with this bacterium [8], although the other study showed conflicting result [9]. These observations raise a concern about the necessity of knowing the \( H. pylori \) infection status for female in gestational age.

There are several methods to detect of \( H. pylori \) infection. One of them is the urease test using gastric mucosal tissue obtained during endoscopy. Despite being proven that procedure is safe when performing on the pregnant women [10], the general unwillingness, the high cost, the invasiveness of the procedure, and the possible sampling error make it not the ideal choice for screening the \( H. pylori \) infection during pregnancy. The noninvasive tests include the urea breath test (UBT), the stool antigen test and the serum \( H. pylori \) IgG antibody test. The latest one is easy to perform during antenatal examination and the existence of the antibody was found to be associated with the intrauterine growth restriction [11]. How the maternal \( H. pylori \) antibody influences the growth of the fetus is still elusive, but, interestingly, the antibody can be transmitted transplacently to the fetus [12, 13]. However, the detection of the serological antibody was frustrated because of the inconsistent accuracy caused by several factors, including the different antigen extracts the kit uses and variable \( H. pylori \) strain in different region [14, 15]. In the present study, we will evaluate the performance of a new immunochromatographic test kit and detect the existence of the \( H. pylori \) IgG antibody in both maternal and cord serum.

2. Materials and Methods

2.1. Subjects and Data Collection. This study was carried out according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of E-Da Hospital (EMRP-096-092 and EMRP-099-052). Subjects were recruited from mothers who received regular antenatal examinations and/or delivered their babies at department of Gynecology and Obstetrics of E-Da Hospital in southern Taiwan between April 2008 and September 2011. Participation was voluntary. Informed consent was obtained from each subject and personal data regarding demographic characteristics and obstetric history was collected via questionnaire after interviewing with trained interviewers on participation and/or after baby delivery. Those who have history of gastric surgery, peptic ulcer, \( H. pylori \)-eradication treatment, or antibiotics or proton pump inhibitor prescription within two month before delivery were excluded. Blood samples from mothers were collected on receiving antenatal examination and/or on admission for delivery. After delivery, blood samples were also collected from umbilical cord vessels representing the existence of \( H. pylori \) antibody in baby's circulation. The heparinized whole blood was centrifuged at 2,000 rpm for 10 min to isolate plasma supernatant. Stool samples from mothers were supplied during hospitalization for baby delivery. Both stool and serum samples were stored under −20°C until utilized.

2.2. Serum \( H. pylori \) IgG Detection. The IgG antibody to \( H. pylori \) in serum was detected using a commercial immunochromatographic test kit (ASSURE \( H. pylori \) Rapid Test, MP Biomedicals, USA). The procedure followed the manufacturer's protocol. In summary, 25 μL defrosted serum sample were added into the square well at the lower end of the kit. When the sample front moved upstream the viewing window and reached the pink control line labeled “A” 2 drops of chase buffer were added into the oval well at upper end of the kit. Then pull the “Hp” marked tab until resistance was felt and add 1 drop of chase buffer into the square well. The result was read after 15 minutes by two trained technicians independently. Positive and negative controls were run simultaneously. The results were determined as both technicians had the same interpretation. The one which had invalid test result or discrepant interpretation was retested using a new device.

2.3. Stool \( H. pylori \) Antigen Detection. Another commercial kit (ImmunoCard STAT! HpSA, Meridian bioscience, Cincinnati, OH, USA), based on a lateral flow chromatography technique using monoclonal antibodies, was utilized for detection of \( H. pylori \) antigens in human stool. The procedure followed the manufacturer's protocol. In summary, stool specimen (5-6 mm in diameter) was transferred into diluent vial and mixed with sample diluent. After vortexing for 15 seconds, break the tip of the vial and dispense 4 drops into the round window at the lower end of the device and read the results after 5 minutes. The results were also interpreted independently by two technicians.

2.4. Statistical Analysis. Distribution of demographic and clinical characteristics of participants by \( H. pylori \) status was reported as means (± standard deviations (SD)) or number (frequency) and was analyzed by independent t-test, Chi-square test, and Fischer's exact test, whenever appropriate. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of \( H. pylori \) status in maternal and umbilical cord serum during delivery were presented, using \( H. pylori \) status in maternal stool specimens as gold standard. The reliability of \( H. pylori \) status in maternal serum during delivery and before delivery as well as in maternal serum and umbilical cord serum during delivery was compared by Kappa coefficient. All tests were performed by SAS 9.2 statistical software (SAS Institute Inc., Cary, NC); two-sided \( P \) value less than 0.05 was considered statistically significant.

3. Results

Total 346 pregnant women were enrolled. The demographic characteristics were listed in Tables 1 and 2. Based on the result of stool \( H. pylori \) antigen detection, 105 subjects were infected with \( H. pylori \) on baby delivery, 241 subjects had negative stool test results, and the overall infection rate was 30.3%. There was no significant difference between these two groups in body mass index (BMI), education, daily habit (alcohol, smoking, and exercise), underline disease (diabetes mellitus (DM) and hypertension), and obstetric characteristics (parity, history of miscarriage, gestation age (GA), prematurity of infant, placenta weight, and gender of
infant). The only difference but without significance was the nationality (P = 0.058). Within the enrolled subjects, 39 were immigrants from Singapore (2), Thailand (2), Cambodia (3), Vietnam (14), and China (18), respectively. Seventeen (43.5%) belonged to the *H. pylori*-infected group, and the prevalence was higher than in Taiwanese (28%).

Next, we evaluated the existence of *H. pylori* IgG antibody in maternal serum. Using the immunochromatographic device to test the serum sample collected on delivery, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 77.1%, 88.0%, 73.6%, 89.8%, and 84.7%, respectively (Table 3). This commercial test also had similar performance when testing the serum collected from umbilical vein. Within 338 umbilical serum samples (100 from babies delivered from *H. pylori*-infected mothers), the sensitivity, specificity, and accuracy were 69.0%, 91.6%, and 84.9%, respectively, in comparison with maternal stool test results.

This commercial test also offers consistent results (Table 4). Within 324 participants who donated two blood samples (one collected when receiving antenatal examination and the other collected during admission for delivery), 314 had consistent result. Two participants were positive in antenatal test but negative in delivery. The situation of the other 8 cases was reversed, with negative result on antenatal but positive on delivery. The kappa coefficient was 0.92 (95% CI 0.88–0.97). Besides, when comparing between the maternal (on delivery) and the cord serum, 89 out of 105 *H. pylori*-infected mothers had positive cord serum antibody detection from their babies. On the other hand, none of the baby’s cord serum from *H. pylori*-negative mothers showed the existence of *H. pylori* antibody. The kappa coefficient was 0.88 (95% CI 0.83–0.93).

### 4. Discussion

In the present study, we evaluated the *H. pylori* IgG antibody from maternal and cord serum using a commercial immunochromatographic test kit. It has been shown that the human immune system can produce variable antibodies with different molecular weight against *H. pylori*, either in serum (IgG) or in human milk (IgA) [13]. We found that, in cord serum, there was detectable *H. pylori* IgG antibody, and all these seropositive babies were delivered from seropositive mothers. The consistency of the *H. pylori* IgG antibody detection between maternal and cord serum suggested that the antibody in cord serum was transferred transplacentally, similar to the findings reported previously [12, 13]. However, the antibody was not detected from 16 infants who were delivered from *H. pylori*-seropositive mothers, and the relatively low antibody titer in cord serum might be the reason.

We utilized the stool antigen test as the gold standard of *H. pylori* infection. In fact, both UBT and stool antigen test are acceptable noninvasive test [16]. UBT has better performance, with a sensitivity of 88–95% and a specificity of 95%–100% [17]. It has also been proven that both 13C- (nonradioactive) and 14C-UBT (radioactive) are harmless in the pregnant female [18], with the possibility of the fetal radiation dose in the latter being much lower than the dose considered teratogenic [19]. However, the high cost and the unavailability in clinic limit its utilization. In the present study, we chose the stool antigen test for determining the *H. pylori* status and this test has been shown to have equal performance to UBT, with a sensitivity of 94% and a specificity of 92% [20].

Detection of the *H. pylori* IgG antibody in serum is an alternative method. The advantage of this test is that it is not affected by local changes in the stomach, such as bleeding, that could lead to false-negative results in the other tests. For female in pregnancy, it is an option to screen when they receive the regular antenatal examinations, using commercial available test kit. In the present study, we confirmed that the results obtained antenatally were consistent with the ones checked on baby delivery. However, this method has several disadvantages. Firstly, the performance of each test kit varies in different regions [21]. This depends on the *H. pylori* strain chosen for development of the IgG antibody and the prevalence of the strain in the given region, as the *H. pylori* strain differs in different countries or area [22]. Therefore, it is necessary to know the performance of a new test kit before utilizing it for screening. In the present study performed in southern Taiwan, the sensitivity, specificity, and accuracy of this test kit were 77.1%, 88.0%, and 84.7%, respectively, relatively lower than the data in manufacturer’s instructions which was tested in the other Asian countries. Secondary,
the result cannot represent the current infection, as the antibody is still detectable months to years after successful *H. pylori* eradication [23, 24]. So it raises a concern about the interpretation of the association between disease and *H. pylori* when the infection is determined by the existence of *H. pylori* IgG antibody. All mentioned above might be the reasons to cause fluctuated association between *H. pylori* and variable disease, including preeclampsia [25–27].

**Table 2:** The distribution of demographic and clinical characteristics of participants according to the *H. pylori* status determined by stool antigen test (HpSA) on delivery (N = 346).

<table>
<thead>
<tr>
<th>Variable</th>
<th><em>H. pylori</em> (+)</th>
<th><em>H. pylori</em> (−)</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; college</td>
<td>48 (45.7)</td>
<td>90 (37.5)</td>
<td>0.152</td>
</tr>
<tr>
<td>≥ college</td>
<td>57 (54.3)</td>
<td>150 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>88 (83.8)</td>
<td>218 (90.8)</td>
<td>0.058</td>
</tr>
<tr>
<td>Immigrant</td>
<td>17 (16.2)</td>
<td>22 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (1.9)</td>
<td>8 (3.3)</td>
<td>0.729&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>103 (98.1)</td>
<td>233 (96.7)</td>
<td></td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>2 (0.8)</td>
<td>1.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>105 (100.0)</td>
<td>238 (99.2)</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 times/week</td>
<td>37 (35.2)</td>
<td>69 (28.8)</td>
<td>0.229</td>
</tr>
<tr>
<td>&lt;1 times/week</td>
<td>68 (64.8)</td>
<td>171 (71.3)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (3.8)</td>
<td>8 (3.3)</td>
<td>0.760&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>101 (96.2)</td>
<td>233 (96.7)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (2.9)</td>
<td>17 (7.1)</td>
<td>0.124</td>
</tr>
<tr>
<td>No</td>
<td>102 (97.1)</td>
<td>224 (92.9)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>51 (48.6)</td>
<td>121 (50.2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>43 (41.0)</td>
<td>100 (41.5)</td>
<td>0.806</td>
</tr>
<tr>
<td>&gt;3</td>
<td>11 (10.5)</td>
<td>20 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Miscarriage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (12.4)</td>
<td>32 (13.3)</td>
<td>0.820</td>
</tr>
<tr>
<td>No</td>
<td>92 (87.6)</td>
<td>209 (86.7)</td>
<td></td>
</tr>
<tr>
<td>Type of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSD/VED</td>
<td>72 (68.6)</td>
<td>158 (65.6)</td>
<td>0.585</td>
</tr>
<tr>
<td>C/S</td>
<td>33 (31.4)</td>
<td>83 (34.4)</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 weeks</td>
<td>4 (3.8)</td>
<td>11 (4.6)</td>
<td>1.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥37 weeks</td>
<td>101 (96.2)</td>
<td>230 (95.4)</td>
<td></td>
</tr>
<tr>
<td>Baby gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58 (55.2)</td>
<td>140 (58.1)</td>
<td>0.622</td>
</tr>
<tr>
<td>Female</td>
<td>47 (44.8)</td>
<td>101 (41.9)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Fisher’s exact test.

It has been mentioned that maternal *H. pylori* infection influences the development of the fetus [11]. The mechanism of intrauterine growth restriction is still elusive. Previous study proved that transmission of infection from mother to infant was not detected on delivery [28]. Therefore, the other factors associated with this bacterium, such as the transplacentally acquired antibody, should be taken into consideration. In fact, the human immune system responding to the *H. pylori* produces variable antibodies, and most of them can be detected in cord serum [13]. Although it has been shown that the transplacentally acquired antibody does not protect infants from colonization by *H. pylori* [12], it is necessary to further investigate its possible role during pregnancy.

Following the improvement of the hygiene condition and the comprehensive utilization of eradication, the prevalence of *H. pylori* infection is decreasing in Taiwan. The overall infection rate in the present study was 30.3%. Interestingly, when classifying the *H. pylori*-positive group, higher infection rate (43.5%) was found in immigrants who came from China and south-east Asian countries where the *H. pylori* prevalence was high [29]. It is worth observing how this situation will influence the prevalence of *H. pylori* in their next generation.

**Table 3:** The performance of the immunochromatographic test kit (ASSURE *H. pylori* Rapid Test) in detection of *H. pylori* IgG antibody in maternal serum collected on delivery and cord serum in comparison to the stool antigen test.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n/N)</td>
<td>(n/N)</td>
<td>(n/N)</td>
<td>(n/N)</td>
<td>(n/N)</td>
</tr>
<tr>
<td>Maternal serum</td>
<td>77.1</td>
<td>88.0</td>
<td>73.6</td>
<td>89.8</td>
<td>84.7</td>
</tr>
<tr>
<td>umbilical serum</td>
<td>(81/105)</td>
<td>(212/241)</td>
<td>(81/110)</td>
<td>(212/236)</td>
<td>(293/346)</td>
</tr>
</tbody>
</table>

: serum sample number; N: stool sample number.

**Table 4:** The consistent performance of the immunochromatographic test kit (ASSURE *H. pylori* Rapid Test) in detection of *H. pylori* IgG antibody in cord serum and maternal serum collected antenatally and on delivery.

<table>
<thead>
<tr>
<th></th>
<th>Maternal serum,</th>
<th>Kappa coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>on delivery</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>H. pylori</em> (+)</td>
<td><em>H. pylori</em> (−)</td>
</tr>
<tr>
<td>Maternal serum,</td>
<td>93</td>
<td>2</td>
</tr>
<tr>
<td>antenatal</td>
<td>8</td>
<td>221</td>
</tr>
<tr>
<td>Cord serum</td>
<td><em>H. pylori</em> (+)</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td><em>H. pylori</em> (−)</td>
<td>16</td>
</tr>
</tbody>
</table>
5. Conclusion

*Helicobacter pylori* is not only connected with gastrointestinal symptoms; in pregnant female, the related antibody can transfer through the placenta into the fetal circulation. The IgG antibody can be detected during antenatal examination using commercial test kit. However, accuracy of the test kit needs to be evaluated before utilization in screening. And the possible role of the *H. pylori* IgG antibody in the fetal development needs further investigation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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References


Predicting the Progress of Caustic Injury to Complicated Gastric Outlet Obstruction and Esophageal Stricture, Using Modified Endoscopic Mucosal Injury Grading Scale

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1. Introduction

Patients who have experienced severe caustic injury to the gastrointestinal (GI) tract are at high risk of luminal strictures [1]. Early endoscopy is usually routinely recommended in patients after gastroesophageal caustic injuries and should be performed to prevent unnecessary hospitalization and to plan future treatment after carefully assessing the severity of the initial digestive lesions [2]. Ingested corrosive substances are either alkalis or acids, and these produce different types of tissue damage [3]. Acids cause coagulation necrosis, whereas alkalis combine with tissue proteins to liquefy and cause necrosis to penetrate deep into tissues [4]. Alkali ingestion may lead to more serious injury and complications by penetrating tissues and leading to full-thickness damage of the esophageal/gastric wall [5].

Gastroesophageal strictures can be severely injurious for patients who survive caustic injuries. The incidence of esophageal stricture (ES) following grade IIB and grade III esophageal burns is very high, at 70–100% [6, 7]. Gastric outlet obstruction can be a late sequel to caustic stomach injury, mainly in the prepyloric area, causing gastric outlet obstruction (GOO). The reported incidence of GOO caused by caustic stomach injury is more than 60% [3, 8]. Timely evaluation and endoscopic pneumatic dilations of the stricture have been widely practiced and reported in the literature and are now one of the standard treatment options; however, different outcomes have been reported for patients with ES alone, GOO alone, or a combination of both ES and GOO [9–13]. Therefore, it is important to identify which patients could potentially progress to ES or GOO.

The aim of this retrospective study was to identify the predicting factors for the progress of caustic injury to GOO and ES, using MEMIGS.
2. Patients and Methods

2.1. Ethics Approval. This study was approved by both the Institutional Review Board and Ethics Committee of Chang Gung Memorial Hospital.

2.2. Patients. We retrospectively reviewed the medical records of patients who had ingested a corrosive substance and were admitted to our hospital between July 2003 and December 2010. These patients had received early upper GI endoscopy (GIF-Q240; Olympus Optical Co., Ltd, Tokyo, Japan) within 48 hours of ingestion. During endoscopy, air insufflation and retroflexion were carefully performed to avoid iatrogenic injury. Endoscopy was performed in all patients without sedation to minimize the risk of aspiration. Mucosal burns of the esophagus, stomach, and duodenum were graded by modifying the method previously reported by Zargar et al.: grade 0, normal examination; grade I, edema and hyperemia of the mucosa; grade II, subdivided into grade IIa (friability, hemorrhages, erosions, blisters, whitish membranes, exudates, and superficial ulcerations); grade IIb (grade IIa plus deep discrete or circumferential ulceration); and grade III, multiple ulcerations and areas of necrosis [5]. Esophageal, gastric, and duodenal injuries were graded separately. Patients with grade I and IIa burns were discharged after endoscopy, while those with grade IIb and burns remained hospitalized.

During admission, patients were treated with a proton pump inhibitor or H2 antagonist and were maintained without oral intake until their condition was considered stable. Patients received parenteral nutrition during this period. If infection was suspected, antibiotics (first-generation antibiotics, such as cephalosporin and gentamicin) were administered after blood cultures were obtained. If a patient's condition destabilized or respiratory difficulty was encountered, they were transferred to the intensive care unit for further evaluation. If the patient demonstrated symptoms of upper GI stricture, including dysphagia, easy satiety, or postprandial vomiting, endoscopy was performed in the fourth week after the corrosive injury to examine the upper GI tract. Stricture was defined as dysphagia, symptoms of regurgitation, or difficulty in swallowing, with confirmation by endoscopy and/or upper GI radiography. After discharge, patients were followed up in the outpatient clinic for at least 6 months. Exclusion criteria were (1) patients who died during the acute stage of corrosive injury and (2) patients who were unable to give informed consent for endoscopic balloon dilation (EBD).

Clinical information, including the amount and type of ingested corrosive substance, hospital course, and complications, was collected. Body weight at time of presentation and follow-up was also recorded. Presence and severity of difficulty in swallowing and/or postprandial satiety and vomiting in the follow-up period were recorded at each clinical follow-up.

2.3. Study End-Point. The end-point was the development of GOO and ES during endoscopic follow-up.

<table>
<thead>
<tr>
<th>Severity of corrosive injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>Esophagus ((n = 108))</td>
</tr>
<tr>
<td>Stomach ((n = 108))</td>
</tr>
<tr>
<td>Duodenum* ((n = 78))</td>
</tr>
</tbody>
</table>

*Operators refrained from forcing the scope through the pylorus in 30 cases because of severe gastric damage.

2.4. Statistical Analysis. Continuous variables are given as means and standard deviation. The continuous variables were analyzed by the Mann-Whitney U-test. Categorical variables are given as total and percentages and were analyzed using the χ² tests or Fisher’s exact test. Univariate and multivariate logistic regression were used to analyze the factors related to mortality and stricture development after corrosive injury. Two-sided P value of <0.05 was considered significant. All statistical operations were performed using SPSS (Statistical Package for the Social Sciences version 15, Chicago, IL, USA).

3. Results

A total of 108 medical records of patients (49 male, 59 female, mean age 50.1 years, range 18–86) with diagnosis of caustic GI tract injury were reviewed. The corrosive substance ingested was acid in 90 cases and alkali in 18. Table 1 shows the degree and extent of their injuries based on the results of endoscopic examination performed within 48 hours of ingestion. Grade III corrosive injury was noted in the esophagus in 43 (39.8%) patients, in the stomach in 58 (53.7%), and in the duodenum in 13 (12%). Tables 2 and 3 show the clinical characteristics and severity of corrosive injury in patients with and without ES and GOO. Patients with ES had more severe (at least grade III) injuries to the esophagus (58.6% versus 27.5%, \(P = 0.006\)) and stomach (65.5% versus 43.5%, \(P = 0.046\)) than those without ES. Patients who developed GOO had more severe injuries to the stomach (100% versus 38.8%, \(P < 0.001\)) and duodenum (43.8% versus 8%, \(P < 0.001\)) than those without GOO.

Of the 108 patients, 10 (9.3%) died during the acute stage as a result of esophageal perforation \((n = 2)\), hematemesis with sudden apnea \((n = 1)\) or aspiration pneumonia with respiratory failure \((n = 7)\). The average duration of hospital stay was 11.1 ± 7.6 days, with an intensive care unit (ICU) admission rate of 15.6%.

As shown in Table 4, univariate analysis of mortality rate demonstrated that age of over 60 years (O.R 6.636, \(P = 0.004\)) and grade III injury to the stomach (O.R 5.106, \(P = 0.042\)) correlated with high mortality rates. Multivariate analysis revealed that only age over 60 years (O.R 4.725, \(P = 0.029\)) was an independent risk factor of mortality for patients after corrosive injury.
Table 2: Comparison of the clinical characteristics and severity of corrosive injury between patients with and without esophageal stricture (ES).

<table>
<thead>
<tr>
<th></th>
<th>ES</th>
<th>Non-ES</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>45.1 ± 15</td>
<td>49.5 ± 17</td>
<td>0.321</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>12/17</td>
<td>34/35</td>
<td>0.475</td>
</tr>
<tr>
<td>Acid/alkali</td>
<td>25/4</td>
<td>61/8</td>
<td>0.745</td>
</tr>
<tr>
<td>Grade III esophagus injury</td>
<td>17 (58.6%)</td>
<td>19 (27.5%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Grade III stomach injury</td>
<td>19 (65.5%)</td>
<td>30 (43.5%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Grade III duodenum injury</td>
<td>6 (24%)</td>
<td>7 (10.6%)</td>
<td>0.103</td>
</tr>
</tbody>
</table>

Table 3: Comparison of the clinical characteristics and severity of corrosive injury between patients with and without gastric outlet obstruction (GOO).

<table>
<thead>
<tr>
<th></th>
<th>GOO</th>
<th>Non-GOO</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>50.9 ± 14.9</td>
<td>47.6 ± 17.8</td>
<td>0.445</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/10</td>
<td>38/42</td>
<td>0.814</td>
</tr>
<tr>
<td>Acid/alkali</td>
<td>17/1</td>
<td>69/11</td>
<td>0.457</td>
</tr>
<tr>
<td>Grade III esophagus injury</td>
<td>9 (50%)</td>
<td>27 (33.8%)</td>
<td>0.279</td>
</tr>
<tr>
<td>Grade III stomach injury</td>
<td>18 (100%)</td>
<td>31 (38.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade III duodenum injury</td>
<td>7 (43.8%)</td>
<td>6 (8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

GOO demonstrated that patients with grade III injury to the stomach (OR 33.103, \( P = 0.001 \)) and the duodenum (OR 10.182, \( P < 0.001 \)) had a significantly higher incidence of GOO than those without such extensive injury. Multivariate analysis revealed that only grade III injury to the stomach (OR 18.972, \( P = 0.007 \)) was an independent risk factor of GOO for patients after corrosive injury.

4. Discussion

The incidence of corrosive ingestion is high and largely unreported in developing countries, where prevention is lacking [3]. It is a serious public health concern worldwide [3]. The acute stage of treatment is very important and in many cases, the results of such ingestion can be very serious. The need to perform emergency surgery has a persistent long-term negative impact both on survival and functional outcome [3]. In the current study, 10 patients (9.3%) died during the acute stage as a result of esophageal perforation (\( n = 2 \)), hematemesis with sudden apnea (\( n = 1 \)), or aspiration pneumonia with respiratory failure (\( n = 7 \)). The remaining 98 (89.8%) of the 108 patients survived the acute stage of corrosive injury. The average duration of hospital stay was 11.1 ± 7.6 days with an ICU admission rate of 15.6%.

However, for those who survive the acute stage, the late complications of corrosive gastric injury include intractable pain, gastric outlet obstruction, late achlorhydria, protein-losing gastroenteropathy, mucosal metaplasia, and development of carcinoma [3, 14]. In this study, we focused on the late complication of obstructions, such as GOO and ES. EBD remains the most important treatment option for luminal stricture caused by caustic injuries [9–12], and although it has been reported to be generally safe and effective, serious complications may occur, especially when there is concomitant existence of GOO and ES [13]. Therefore, identification of clinical factors to predict the possible occurrences of GOO and ES is an important issue. In the current study, we used endoscopic parameters in an attempt to identify these predictors using modified endoscopic parameters. Our results showed that grade III injury to the stomach and esophagus were independent risk factors of GOO and ES, respectively, for patients after corrosive injury.

Some literature also found that grade 2b was also related to subsequent luminal strictures [15]. Among the 98 survived patients in our study, the incidence rates of ES were 26.7% (12/45) in grade 2b injury to esophagus and 48.6% (17/35) in grade 3 injury (\( P = 0.043 \)). And the incidence rates of GOO were 5% (1/20) in grade 2b injury to stomach and 34.7% (17/49) in grade 3 injury (\( P = 0.011 \)). No matter in esophagus or stomach, patients with grade 3 injury had a higher risk to develop lumen stricture than those with grade 2b injury.

The relative extent of esophageal and gastric involvement largely depends on the nature and volume of the corrosive ingested [16]. Acids are more likely than alkalis to affect the stomach [17]. Alkalis cause liquefaction necrosis, and as they are more viscous, most of the liquid adheres to the esophageal mucosa, with only a relatively small amount reaching the stomach [18]. Therefore, the extent of esophageal damage is...
Table 4: Univariate and multivariate analyses of mortality for individual parameters in patients with corrosive injury of gastrointestinal tract.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>6.636</td>
<td>1.824–24.143</td>
</tr>
<tr>
<td>Gender</td>
<td>0.355</td>
<td>0.090–1.393</td>
</tr>
<tr>
<td>Acid/alkali</td>
<td>1.440</td>
<td>0.169–12.261</td>
</tr>
<tr>
<td>Grade of esophagus injury</td>
<td>3.429</td>
<td>0.962–12.215</td>
</tr>
<tr>
<td>Grade of stomach injury</td>
<td>5.106</td>
<td>1.062–24.558</td>
</tr>
<tr>
<td>Grade of duodenum injury</td>
<td>3.429</td>
<td>0.879–13.379</td>
</tr>
</tbody>
</table>

* Cut-off: age: ≥60 or <60 years; gender: male or female; type of ingestion substance: acid or alkali; grade of esophagus injury: grade III or not; grade of stomach injury: grade III or not; grade of duodenum injury: grade III or not.

Table 5: Univariate and multivariate analyses of esophageal stricture for individual parameters in patients with corrosive injury of gastrointestinal tract.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O.R</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>0.421</td>
<td>0.129–1.371</td>
</tr>
<tr>
<td>Gender</td>
<td>0.727</td>
<td>0.302–1.746</td>
</tr>
<tr>
<td>Acid/alkali</td>
<td>0.762</td>
<td>0.226–2.970</td>
</tr>
<tr>
<td>Grade of esophagus injury</td>
<td>3.728</td>
<td>1.503–9.246</td>
</tr>
<tr>
<td>Grade of stomach injury</td>
<td>2.470</td>
<td>1.003–6.085</td>
</tr>
<tr>
<td>Grade of duodenum injury</td>
<td>2.797</td>
<td>0.838–2.887</td>
</tr>
</tbody>
</table>

* Cut-off: age: ≥60 or <60 years; gender: male or female; type of ingestion substance: acid or alkali; grade of esophagus injury: grade III or not; grade of stomach injury: grade III or not; grade of duodenum injury: grade III or not.

greater with alkalis than with acids. In the current study, the corrosive substance ingested was acid in 90 cases and alkali in 18. None of the 18 patients with GOO alone or with concomitant GOO and ES had ingested alkaline substances. Thus, a possible explanation for progress to GOO could be the prolonged contact of corrosive agents with the antral mucosa, as a result of pyloric spasm, causing mucosal damage by coagulation necrosis [3,19]. Sometimes, in cases of a large volume of corrosive agent being ingested, the damage may be so severe that strictures can be found in the antrum, body, or pyloroduodenal area, so that the entire stomach might be diffusely scarred [18]. As shown in Table 1, we refrained from forcing the scope through the pylorus in 30 cases because of the severe gastric damage. We also observed that all of the patients who developed GOO had at least grade III caustic injuries, compared with slightly over a third of who did not (100% versus 38.8%, \( P < 0.001 \)). Moreover, this was further confirmed by multivariate analysis, showing that severe caustic injury to the stomach of at least grade III was an independent risk factor.

Endoscopy should be avoided within 2 weeks after EBD because of the high risk of perforation, although there is no good evidence in the literature to suggest the best timing to perform this technique [20]. However it is known that EBD can be performed effectively and safely 4–6 weeks after corrosive injury and is the treatment of choice for most of these injuries [21, 22]. Surgery is carried out only in cases with severe complications, when EBD fails or when patients are unable to tolerate EBD procedures. This is because esophagectomy followed by reconstruction surgery is a laborious and invasive procedure that exposes patients to high risks of morbidity and mortality. The same appears to the surgical intervention for GOO, which usually involves subtotal gastrectomy or bypass gastrojejunostomy, although this tends to have fewer complications [23, 24]. Therefore, it is important to identify which patients might potentially progress to ES or GOO. The current study confirmed that the modified endoscopic parameter helps to assess and identify those patients with grade III caustic injuries, allowing physicians to ensure close follow-up and to instigate prompt therapy without delay. A recent study by Cheng et al. also showed that patients with grade III b burns identified by endoscopy have high rates of morbidity. The grading scale by Zargar et al. is useful for predicting immediate and long-term complications and guiding appropriate therapy [15].

Mortality can occur in patients with extensive injuries to both the stomach and the esophagus. In the current study, 10 of the 108 patients (9.3%) died during the acute stage and all of them had severe caustic injuries of at least grade III diagnosed by endoscopic examinations, and all were aged over 60 years. The average duration of hospital stay for patients was 11.1 ± 7.6 days, with an ICU admission rate of 15.6%. However, this could be an underestimate because some patients with severe acute and chronic gastric and esophageal injuries die in peripheral centers before they make it to a tertiary care referral hospital.

5. Conclusion

The results of this study indicate that patients over 60 years have a higher mortality rate after corrosive injury of GI tract
Table 6: Univariate and multivariate analyses of gastric outlet obstruction for individual parameters in patients with corrosive injury of gastrointestinal tract.

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>O.R</th>
<th>95% CI</th>
<th>P</th>
<th>O.R</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.024</td>
<td>0.329–3.185</td>
<td>0.967</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>1.305</td>
<td>0.394–2.721</td>
<td>0.944</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid/alkali</td>
<td>2.333</td>
<td>0.405–27.422</td>
<td>0.263</td>
<td>1.11</td>
<td>0.105–11.772</td>
<td>0.931</td>
</tr>
<tr>
<td>Grade of esophagus injury</td>
<td>2.944</td>
<td>1.094–7.922</td>
<td>0.320</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade of stomach injury</td>
<td>33.103</td>
<td>4.217–259.882</td>
<td>0.001</td>
<td>18.972</td>
<td>2.226–158.875</td>
<td>0.007</td>
</tr>
<tr>
<td>Grade of duodenum injury</td>
<td>10.182</td>
<td>2.815–36.863</td>
<td>&lt;0.001</td>
<td>3.805</td>
<td>0.983–14.735</td>
<td>0.053</td>
</tr>
</tbody>
</table>

* Cut-off: Age ≥60 or <60 years; gender: male or female; type of ingestion substance: acid or alkali; grade of esophagus injury: grade III or not; grade of stomach injury: grade III or not; grade of duodenum injury: grade III or not.

and, therefore, require attentive care in acute stage. And, early endoscopy to grade the extent of mucosal injury is useful to predict the incidence of subsequent stricture of GI tract and provide valuable information on clinical follow-up.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the production of this paper.

**Acknowledgment**

The authors wish to thank Ms. Mei-Chin Hsu for helping with the statistical analysis of this study.

**References**


Clinical Study

Decreased Gastric Motility in Type II Diabetic Patients

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Background. To differentiate gastric motility and sensation between type II diabetic patients and controls and explore different expressions of gastric motility peptides.

Methods. Eleven type II diabetic patients and health volunteers of similar age and body mass index were invited. All underwent transabdominal ultrasound for gastric motility and visual analogue scales. Blood samples were taken for glucose and plasma peptides (ghrelin, motilin, and glucagon-like peptides-1) by ELISA method.

Results. Gastric emptying was significantly slower in diabetic patients than controls (T50: 46.3 (28.0–52.3) min versus 20.8 (9.6–22.8) min, 𝑃 ≤ 0.05) and less antral contractions in type II diabetic patients were observed (𝑃 = 0.02). Fundus dimensions did not differ. There was a trend for less changes in gastrointestinal sensations in type II diabetic patients especially for abdomen fullness, hunger, and abdominal discomfort. Although the serum peptides between the two groups were similar a trend for less serum GLP-1 in type II diabetic patients was observed (𝑃 = 0.098).

Conclusion. Type II diabetic patients have delayed gastric emptying and less antral contractions than controls. The observation that there were lower serum GLP-1 in type II diabetic patients could offer a clue to suggest that delayed gastric emptying in diabetic patients is not mainly influenced by GLP-1.

1. Introduction

Gastrointestinal tract disorders are common in diabetic patients [1, 2]. More than 75% of patients visiting diabetes mellitus clinics reported significant gastrointestinal symptoms [1] such as dysphasia, early satiety, reflux, abdominal pain, nausea, vomiting, constipation, and diarrhea. The symptoms may be severe enough to substantially affect quality of life, induce poor sugar control, and progress with duration of diabetes mellitus. The pathogenesis of the gastrointestinal abnormalities is multifactorial complex in nature which may involve autonomic neuropathy, motor dysfunction, glycemic control, psychological factors, and so forth and is not well understood [3]. In diabetic patients with gastrointestinal symptoms, 68% were found to have delayed gastric emptying [4] that influences the quality of life and sugar control in these patients. Owing to the fact that the pathogenesis is still poorly understood, it is rational that the effective medical treatment for these patients with diabetic dyspepsia is yet unavailable. Gastric motility is regulated by gastrointestinal motility hormones such as cholecystokinin, gastric inhibitor peptide, motilin, and ghrelin. Previous publications reported that motilin [5, 6] and ghrelin [7, 8] stimulated gastric motility and glucagon-like peptide-1 (GLP-1) inhibited gastric motility [9, 10]. We hypothesized that diabetic patients had lower motilin and ghrelin or higher GLP-1 and hence inhibited gastric motility and induced gastrointestinal symptoms. Therefore, we conducted this study to compare gastric motility and sensation between type II diabetic patients and normal controls and explore the roles of different gastric motility peptides in this motility effect.

2. Methods

Eleven patients (2 female) with long-standing (>5 years) type II diabetes mellitus (DM) and 11 healthy controls (2 female)
of similar age (58 ± 2 years; 51 ± 5 years) and body mass index (25.0 ± 2.2 kg/m²; 23.7 ± 2.5) were invited to participate in current study from August 2009 to July 2010. The basic demographic data were listed in Table 1. All patients gave written, informed consent, and the protocol was approved by both the institutional Review Board and the Research Ethics Committee of Kaohsiung Chang Gung Memorial Hospital, Taiwan (IRB 96-1583B). Patients were excluded if they had a history of ketosis or dysautonomic or gastrointestinal symptoms determined by interview or from the review of medical records. All patients with type II diabetes mellitus in current study were prescribed with oral hypoglycemic agents instead of insulin therapy. Subjects were also excluded in current study were prescribed with oral hypoglycemic agents including anticholinergics, calcium channel blockers, 3-adrenergic antagonists, or hormones 48 hours before the study except oral hypoglycemic agents instead of insulin therapy. Patients were excluded if they had a history of ketosis or dysautonomic or gastrointestinal symptoms determined by interview or from the review of medical records. All patients with type II diabetes mellitus in current study were prescribed with oral hypoglycemic agents instead of insulin therapy. Subjects were also excluded if they had previous gastrointestinal disease or abdominal surgery with the exception of uncomplicated appendectomy, herniorrhaphy, or gynecologic surgery. All patients must not have had gastrointestinal symptoms of pain, nausea, abdominal discomfort, bloating, and abdominal fullness during a 25-minute interval, recorded per five minutes, and the antral contractions were defined as one time while the maximal contraction-induced reduction of the antral area (difference between relaxed and contracted area) as a fraction of the relaxed area (ΔA/A) > 50% as our previous study [11].

Each subject was studied on afternoons. Following a fast of 8 h for solids and liquids, the patients consumed 500 mL of chicken and corn soup (United Kanboo, Taipei, Taiwan), containing 118.6 kcal (2.6 g protein, 2.6 g fat, 21.2 g carbohydrate). The soup was boiled and subsequently cooled to 37°C and was consumed over 5 min (t = −5−0 min). All patients underwent transabdominal ultrasound to record antral area, fundic area, and diameter and antral contractions in regular time by using an Aloka SSD-2000 CL Ultrasound Machine (Aloka, Tokyo, Japan) with a 3.5-MHz annular array probe. The frequency of antral contractions was defined as the number of contractions during a 25-minute interval, recorded per five minutes, and the antral contractions were defined as one time while the maximal contraction-induced reduction of the antral area (difference between relaxed and contracted area) as a fraction of the relaxed area (ΔA/A) > 50% as our previous study [11].

Table 1: The basic characteristics between type II DM and normal control.

<table>
<thead>
<tr>
<th></th>
<th>Type II DM (11)</th>
<th>Normal controls (11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 2</td>
<td>51 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>2/11</td>
<td>2/11</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 ± 2.5</td>
<td>25.0 ± 2.2</td>
<td>0.000*</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td>11.1 ± 5.6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>126.0 ± 32.1</td>
<td>82.0 ± 4.9</td>
<td>0.012</td>
</tr>
<tr>
<td>HbA1C</td>
<td>9.5 ± 1.3</td>
<td>5.5 ± 0.1</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*Significant statistic difference.

3. Statistical Analysis

The curves for antral area, fundic area, diameter, antral contractions, and gastrointestinal sensation scores were compared by using repeated measures ANOVA. Linear regression analysis was used to examine relationships between gastrointestinal sensations and gastric motility (antral area, fundic area, diameter, and frequency of antral contraction). Results were shown as means ± standard deviation. P values <0.05 were considered significant. Mean values and standard deviations (SD) of each variable were calculated if not specifically noted otherwise. Statistical analysis was performed with Student’s t-test for paired comparison. The tests are two-tailed, and P < 0.05 is considered significant.

4. Results

All subjects tolerated the study well.

4.1. Antral Area and Gastric Emptying. Antral area was larger in type II diabetic patients than normal controls especially after test meal (antal area 15.6 ± 2.3 cm² versus 12.6 ± 2.4 cm²). Gastric emptying was more significant in normal controls than diabetic patients (T50: 20.8 (9.6–22.8) min versus 46.3 (28.0–52.3) min, P = 0.03). There was a statistical significance trend for smaller antral area in the normal controls between the two groups, P = 0.014 (Figure 1(a)).
4.2. **Antral Contractions.** There was a significant trend for less antral contractions in type II diabetic patients during 90 minutes after the test meal ($P = 0.02$) (Figure 1(b)).

4.3. **Fundic Area and Diameter.** Fundus dimensions did not differ between normal controls and type II diabetic patients (fundic area: $P = 0.454$; fundic diameter: $P = 0.331$) (Figures 1(c) and 1(d)).

4.4. **Gastrointestinal Sensations.** Soup ingestion was associated with increased abdominal fullness and bloating and decreased hunger and appetite scores only in control group but not in type II diabetic patients. Figure 2 demonstrated a trend for less significant changes in gastrointestinal sensations in type II diabetic patients especially abdomen fullness, hunger, and appetite in current study.

4.5. **Gastric Motility Peptides.** There were no differences in serum peptide (motilin, ghrelin, and GLP-1) between the two groups but a trend for less serum GLP-1 in patients with type II diabetes mellitus was observed ($P = 0.098$) (Figure 3).

5. **Discussion**

Faraj and colleagues reported as high as 68% of the diabetic patients with gastrointestinal symptoms were associated with delayed gastric emptying [4]. In current study, we observed that type II diabetic patients were found to have larger gastric antral area on sonography. Type II diabetic patients had delayed gastric emptying and less gastric contraction and experienced less postprandial sensation than normal volunteers probably owing to gastric atony and gastric paralyzis (gastroparesis) in diabetic patients.

As we had shown that less gastric contraction in diabetic patients were correlated with less gastric emptying, there were reports indicating that diabetic patients had postprandial antral hypomotility, decreased temporal organization of antral pressure waves, and increased small intestinal motor activity. All these gastric disorders occurred in long-term diabetic patients and were associated with peripheral neuropathy. Prolonged poor sugar control induced sympathetic nerve dysfunction. Samsom and colleagues observed a lower fasting fundal tone and a decrease in volume change of the gastric fundus after a nutrient drink in patients with
autonomic neuropathy due to type I diabetes mellitus but
the fundus dimensions between type II diabetic patients with
normal controls were not different in current study. They
used barostat to measure fundic volume and tone but we
used ultrasound to detect fundic dimensions. Kumar and
colleagues then emphasized more significant impairment in
gastric fundic volume and the accommodation response to
a test meal in diabetic patients [12] but we still did not
observe the difference in our study. The plausible explanation
could be the low nutrient test meal we used in current study.
Low volume test meal would not remain in the fundus long
enough to be detected by abdominal ultrasound. Perhaps
such drawback could be overcome if higher nutrient test
meals were used. Other than this, computer tomography
might be a better imaging study to overcome the difference.

Type II diabetic patients experienced less gastrointestinal
sensation after a test meal than normal controls in spite of
significant delaying gastric emptying and decreasing gastric
contraction. Loo and colleagues found out that approximately
50% of these patients with gastric motor disorders might be
asymptomatic [13].

It is still unclear about the actual roles of different motility
expression in diabetic patients. Motilin had been reported
to regulate the interdigestive migrating contractions (IMC),
the fasted motor pattern in the gastrointestinal tract [14], and
ghrelin stimulated GI motility. Ghrelin induced premature
phase III contractions of IMC in the human stomach [7] and
intravenous ghrelin injection could accelerate gastric emp-
tying and improve meal-related symptoms. All these reports
suggested that ghrelin could be a potential prokinetic agent.
More studies are mandatory to clarify the physiological role
of plasma ghrelin and motilin in these digestive physiological
events and stimulation of gastric emptying. However, we
observed no different motilin and ghrelin between diabetic
patients and normal controls, only a trend of less serum GLP-1 expression in type II diabetic patients in current study. This could not well explain the pathology of delayed gastric emptying in our diabetic patients. This was consistent with the findings of Pala and colleagues who reported that GLP-1 levels were significantly lower in subjects with impaired glucose tolerance and type 2 diabetes mellitus compared to those with normal glucose tolerance [15]. Shirra and Delgado-Aros and colleagues observed that GLP-1 significantly inhibited gastric emptying and vagal function [16,17]. Rosenstock and colleagues even used GLP-1 agonists to treat diabetic patients [18, 19]. There was limitation in our study, small patient number that could cause why there was no difference in motility peptides in current study.

In conclusion, Type II diabetic patients have delayed gastric emptying and less antral contractions than normal controls and may be associated to less postprandial sensation. The observation that less serum GLP-1 in type II diabetic patients could offer a clue to understand that delayed gastric emptying in diabetic patients is not mainly regulated by GLP-1.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

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References

Research Article

Outcome of Holiday and Nonholiday Admission Patients with Acute Peptic Ulcer Bleeding: A Real-World Report from Southern Taiwan

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Background. Recent findings suggest that patients admitted on the weekend with peptic ulcer bleeding might be at increased risk of adverse outcomes. However, other reports found that there was no “holiday effect.” The purpose of this study was to determine if these findings hold true for a real-life Taiwanese medical gastroenterology practice.

Materials and Methods. We reviewed the medical files of hospital admissions for patients with peptic ulcer bleeding who received initial endoscopic hemostasis between January 2009 and March 2011. A total of 744 patients were enrolled (nonholiday group, \( n = 615 \); holiday group, \( n = 129 \)) after applying strict exclusion criteria. Holidays were defined as weekends and national holidays in Taiwan.

Results. Our results showed that there was no significant difference in baseline characteristics between the two groups. We also observed that, compared to the nonholiday group, patients in the holiday group received earlier endoscopy treatment (12.20 hours versus 16.68 hours, \( P = 0.005 \)), needed less transfused blood (4.8 units versus 6.6 units, \( P = 0.02 \)), shifted from intravenous to oral proton-pump inhibitors (PPIs) more quickly (5.3 days versus 6.9 days, \( P = 0.05 \)), and had shorter hospital stays (13.05 days versus 17.36 days, \( P = 0.005 \)). In the holiday and nonholiday groups, the rebleeding rates were 17.8% and 23.41% (\( P = 0.167 \)), the mortality rates were 11.63% versus 13.66% (\( P = 0.537 \)), and surgery was required in 2.11% versus 4.66% (\( P = 0.093 \)), respectively.

Conclusions. Patients who presented with peptic ulcer bleeding on holidays did not experience delayed endoscopy or increased adverse outcomes. In fact, patients who received endoscopic hemostasis on the holiday had shorter waiting times, needed less transfused blood, switched to oral PPIs quicker, and experienced shorter hospital stays.

1. Introduction

Peptic ulcer bleeding is a common cause of hospitalization, and mortality remains at 6–8% despite advances in both pharmacologic and endoscopic therapies [1, 2]. Reports regarding outcomes for different management regimens for peptic ulcer bleeding patients during holidays are inconsistent. Some described increased adverse outcomes on holidays [3, 4] while others did not [5, 6].

It is well documented that the risk for recurrent bleeding is increased in patients with high-risk peptic ulcers after initial endoscopic hemostasis, although it can control bleeding and reduce the rebleeding, morbidity, and mortality rates [7, 8]. Theoretically, the possibility of greater risk on holidays is due to potential lower staffing levels, less senior staff, cross-cover of clinical specialties, and a lower likelihood that invasive procedures, such as endoscopy, will be performed on holidays. Peptic ulcer bleeding is a common medical emergency in Taiwan that challenges both gastroenterologists and general surgeons. The purpose of this study was to determine whether the holiday effect occurred in our hospital. We analyzed the outcomes of patients with peptic ulcer bleeding who presented on holidays compared to those admitted on nonholidays. The endpoints were rebleeding, need for surgery, and mortality.
2. Materials and Methods

2.1. Study Design. Between January 2009 and March 2011, we performed 37,019 esophagogastroduodenoscopy studies in our endoscopic center. Among them, 1,051 patients underwent endoscopic hemostasis for confirmed gastric and duodenal ulcer bleeding. All subjects received the intravenous proton-pump inhibitors (PPIs). After the medical records of these 1,051 patients were reviewed, we excluded 307 patients with malignant ulcers and nonulcerative bleeding (e.g., angiodysplasia, Mallory-Weiss tear), subjects lost to follow-up before 30 days (except those who died), and patients with incomplete chart records. Eventually, we included 744 patients in this study. We divided these patients into holiday (n = 129) and nonholiday groups (n = 615) (Figure 1). Gastric or duodenal ulcers bleeding was diagnosed by the gastroscopy (GIF-Q260; Olympus Optical Co., Ltd., Tokyo, Japan) and clinical signs of hematemesis, coffee ground vomitus, hematochezia, or melena. The time from admission to endoscopic treatment was measured, and the bleeding source was identified. Patients’ statuses were stratified according to the Rockall score system [9]. All of our patients received endoscopic interventions within 24 hours of arriving at the emergency room, and endoscopic hemostasis interventions were performed by experienced endoscopists. In our hospital, our endoscopic center provides therapeutic endoscopic services 24 hours a day. The registered clinical variables were demographic data; clinical manifestations of bleeding; time to endoscopy; the use of tobacco, alcohol, aspirin, clopidogrel, and nonsteroidal anti-inflammatory drugs (NSAIDs); and comorbidities such as diabetes mellitus, cardiovascular disease, stroke, chronic kidney disease (CKD), and chronic obstructive pulmonary disease. Other clinical characteristics, such as age, sex, and hemodynamic instability on admission, and laboratory data, including hemoglobin, platelet count, and international normalized ratio, were analyzed. The endpoints were rebleeding, need for surgery, and mortality.

This retrospective chart review study was approved by both the Institutional Review Board and the Ethics Committee of Chang Gung Memorial Hospital, Taiwan (IRBI03-1639B). All patients were at least 18 years old and provided written informed consent before undergoing endoscopic interventions.

2.2. Definitions. The holidays were defined as all national holidays and weekends in Taiwan during the study period. Patients with peptic ulcer bleeding were treated with intravenous high-dose PPIs (pantoprazole or esomeprazole 80 mg bolus followed by 200 mg continuous infusion for 3 days). Rebleeding was defined as a new onset of hematemesis, melena, fresh blood or coffee ground material in the nasogastric (NG) tube, or both associated with tachycardia or hypovolemic shock or a decrease in serum hemoglobin level >2 g/dL after successful endoscopic and pharmacological treatment, and hemodynamic stability of at least a 24-hour period of stable vital signs [10–12]. Bleeding recurrence was confirmed by endoscopy in all cases. Shock was defined as tachycardia, heart rate ≥ 100/min, or hypotension (systemic blood pressure ≤ 90 mmHg) [13–16].

2.3. Endoscopic Assessment. Endoscopic signs of high-risk ulcers were defined according to the Forrest classification [16]. In high-risk stigmata, active bleeding was defined as continuous blood spurring (Forrest IA) or oozing (Forrest IB) from the ulcer base. A nonbleeding vessel visible at endoscopy was defined as a discrete protuberance at the ulcer base (Forrest IIa). An adherent clot was resistant to forceful irrigation or suction (Forrest IIb). In low-risk stigmata, flat, pigmented spots or clean bases were defined as Forrest grade IIIc or III. We performed endoscopic hemostasis for all patients with peptic ulcers and high-risk stigmata.

2.4. Statistical Analysis. The Statistical Package for Social Sciences (SPSS22.0 for Windows, IBM Corp., Armonk, NY, USA) was used to analyze the data. The results are expressed as distributions, absolute frequencies, relative frequencies, medians and ranges, or mean ± SD. The quantitative data were compared using Student’s t-test for normally distributed variables. Differences between the proportions of categorical data were evaluated with the χ2 test or with Fisher’s exact test when the number of expected subjects was less than five. Differences were considered statistically significant at P < 0.05.

3. Results

3.1. Demographic and Clinical Characteristics. The patients’ demographics and clinical characteristics are shown in Table 1. There were no significant differences between the two groups.

3.2. Rebleeding and Receipt of Red Cell Transfusion. Univariate analysis revealed that the percentages of patients who experienced rebleeding were comparable between the nonholiday and holiday groups (23.4% versus 17.8%, P = 0.167; Table 2). The holiday group required smaller amounts of transfused blood (4.8 ± 5.2 units versus 6.6 ± 9.3 units, P = 0.02; Figure 2).

3.3. Time to Endoscopy, Length of Hospital Stay, and Time to Oral PPI. We found that patients in the holiday group received earlier endoscopy treatment (12.2 ± 15.3 h versus 16.7 ± 19.8 h, P = 0.008; Table 2). In addition, patients in the nonholiday group required longer hospital stays than the holiday group (17.4 ± 28.2 days versus 12.1 ± 12.5 days, P = 0.005) and required more time to shift from intravenous to oral PPI (6.9 ± 9.1 days versus 5.3 ± 6.1 days, P = 0.05; Table 2).

3.4. Surgical Intervention and Mortality. There was no significant difference in the number of patients who required surgeries between the two groups, but a trend toward significance was observed for the nonholiday group patients and higher rate of surgical intervention (2.1% versus 4.7%, P = 0.093; Figure 2). There was no significant difference in mortality
Patients who received endoscopic hemostasis (n = 1486)

Patients who did not receive endoscopic hemostasis (n = 35533)

Nonvariceal bleeding patients (n = 1051)

Variceal bleeding patients (n = 435)

* Patients excluded from the study (n = 307)

Patients enrolled into the study (n = 744)

Holiday group (n = 129)

Nonholiday group (n = 615)

The existing reports reached inconsistent results. Some studies describe increased rates of adverse outcomes [3, 4, 21], whereas some reported that there is no evidence of a “holiday effect” [5, 6, 22]. The present study suggests that the holiday effect was not observed for patients with peptic ulcer bleeding who were treated in our hospital. The percentages of patients who suffered from rebleeding and mortality and those who needed surgery were comparable between the nonholiday and holiday patients. In fact, the holiday group required less transfused blood, had a shorter time to endoscopy, more

**Figure 1:** Schematic flowchart of the study design and the patient numbers during follow-up.

between the two groups (13.66% versus 11.63%, \( P = 0.537 \); Figure 2).

4. Discussion

A growing body of health services research indicates that increased mortality is associated with admission to hospitals on the weekends [17–20]. This issue has raised concern over the quality care of very important medical and surgical emergencies, including peptic ulcer bleeding, on holidays.
Table 1: Baseline characteristics of nonholiday and holiday groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nonholiday group (n = 615)</th>
<th>Holiday group (n = 129)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>64.6 ± 14.1</td>
<td>66.45 ± 14.1</td>
<td>0.978</td>
</tr>
<tr>
<td><strong>Female gender, n (%)</strong></td>
<td>195 (32%)</td>
<td>48 (37%)</td>
<td>0.226</td>
</tr>
<tr>
<td><strong>Hb (g/dL)</strong></td>
<td>9.3 ± 2.8</td>
<td>9.2 ± 2.7</td>
<td>0.848</td>
</tr>
<tr>
<td><strong>Platelets (×10⁴/µL)</strong></td>
<td>190.1 ± 99.3</td>
<td>205.4 ± 120.1</td>
<td>0.244</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>1.24 ± 0.64</td>
<td>1.17 ± 0.49</td>
<td>0.116</td>
</tr>
<tr>
<td><strong>Use of NSAIDs, n (%)</strong></td>
<td>72 (12%)</td>
<td>9 (7%)</td>
<td>0.117</td>
</tr>
<tr>
<td><strong>Use of aspirin, n (%)</strong></td>
<td>93 (15%)</td>
<td>18 (14%)</td>
<td>0.735</td>
</tr>
<tr>
<td><strong>Use of clopidogrel, n (%)</strong></td>
<td>65 (11%)</td>
<td>14 (11%)</td>
<td>0.924</td>
</tr>
<tr>
<td><strong>Use of warfarin, n (%)</strong></td>
<td>32 (5%)</td>
<td>5 (4%)</td>
<td>0.528</td>
</tr>
<tr>
<td><strong>Shock at presentation</strong></td>
<td>311 (51%)</td>
<td>76 (59%)</td>
<td>0.084</td>
</tr>
<tr>
<td><strong>Coexisting illness, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD III, IV/V</td>
<td>204/83 (33%/13%)</td>
<td>49/11 (40%/9%)</td>
<td>0.245</td>
</tr>
<tr>
<td>COPD</td>
<td>44 (7%)</td>
<td>11 (9%)</td>
<td>0.588</td>
</tr>
<tr>
<td>CAD</td>
<td>110 (18%)</td>
<td>19 (15%)</td>
<td>0.389</td>
</tr>
<tr>
<td>DM</td>
<td>199 (32%)</td>
<td>36 (28%)</td>
<td>0.323</td>
</tr>
<tr>
<td>CVA</td>
<td>105 (17%)</td>
<td>24 (19%)</td>
<td>0.676</td>
</tr>
<tr>
<td>HTN</td>
<td>326 (53%)</td>
<td>63 (49%)</td>
<td>0.389</td>
</tr>
<tr>
<td>Cancer</td>
<td>116 (19%)</td>
<td>24 (19%)</td>
<td>0.946</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>115 (19%)</td>
<td>20 (16%)</td>
<td>0.392</td>
</tr>
<tr>
<td>Rockall score</td>
<td>6.2 ± 1.7</td>
<td>6.0 ± 1.8</td>
<td>0.727</td>
</tr>
<tr>
<td>Ulcer size (cm)</td>
<td>1.1 ± 0.7</td>
<td>1.2 ± 0.8</td>
<td>0.434</td>
</tr>
<tr>
<td>Forrest classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia/Ib/Ia/Ib/Iic/III</td>
<td>44/348/67/140/14/2</td>
<td>8/62/20/33/6/0</td>
<td>0.260</td>
</tr>
</tbody>
</table>


Table 2: Clinical outcomes for all patients presenting with acute upper gastrointestinal bleeding.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nonholiday group (n = 615)</th>
<th>Holiday group (n = 129)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to oral PPI (days)</strong></td>
<td>6.9 ± 9.1</td>
<td>5.3 ± 6.1</td>
<td>0.05*</td>
</tr>
<tr>
<td><strong>Rebleeding, n (%)</strong></td>
<td>144 (23.4%)</td>
<td>23 (17.8%)</td>
<td>0.167</td>
</tr>
<tr>
<td><strong>Surgery, n (%)</strong></td>
<td>13 (2.1%)</td>
<td>6 (4.7%)</td>
<td>0.997</td>
</tr>
<tr>
<td><strong>Hospital stay (days)</strong></td>
<td>17.4 ± 28.2</td>
<td>12.1 ± 12.5</td>
<td>0.005*</td>
</tr>
<tr>
<td><strong>Mortality, n (%)</strong></td>
<td>84 (13.7%)</td>
<td>15 (11.6%)</td>
<td>0.776</td>
</tr>
<tr>
<td><strong>Bleeding related/other causes</strong></td>
<td>24 (3.9%)/60 (9.8%)</td>
<td>5 (3.9%)/10 (7.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Time to endoscopy (h)</strong></td>
<td>16.7 ± 19.8</td>
<td>12.2 ± 15.3</td>
<td>0.008*</td>
</tr>
<tr>
<td><strong>PRBC BT (U)</strong></td>
<td>6.6 ± 9.3</td>
<td>4.8 ± 5.2</td>
<td>0.020*</td>
</tr>
</tbody>
</table>

* A significant value.

PRBC BT: blood transfusion of packed red blood cell; PPI: proton pump inhibitor.

quickly shifted from intravenous to oral PPI, and had shorter hospital stays.

Generally, the outcome of treatment for peptic ulcer bleeding should be much improved given the emergence of more potent medications such as PPIs, increased use of dual endoscopic therapy and endoscopic triage for risk stratification, and advances in general medical care. Shaheen et al. observed an overall 25% reduction in the odds of mortality, irrespective of the day of admission, when comparing the 2000–2005 and 1993–1999 time periods [21]. However, patients admitted to hospital on the weekend for peptic ulcer-related hemorrhage have a higher mortality rate and more frequently undergo surgery [4]. For those reports suggesting a weekend or holiday effect of peptic ulcer bleeding, the explanations included lower staffing levels, less senior staff, cross-cover of clinical specialties, and a lower likelihood that invasive procedures, such as endoscopy, will be undertaken on weekends [4, 21]. Early endoscopic interventions and the first 72 hours of hospitalization are crucial for favorable outcomes in patients with peptic ulcer bleeding, especially
the rebleeding rates. Therefore, the availability of early access to upper endoscopy and physicians with endoscopic expertise are key factors to treatment success [23–25]. A lack of staff on holidays and subsequent delays in upper endoscopy may explain the poorer outcomes. However, Ananthakrishnan et al. observed that the difference in mortality for weekend admissions was only significant among patients who did not undergo endoscopic intervention, with similar outcomes among the groups that did undergo emergency endoscopy [4]. Large population-based reports from the US, Canada, and the Netherlands describe the rates of early endoscopy as 72%, 76%, and 78%, respectively [26–28], but these data were from older publications. Recently, Haas et al. reported that >94% of patients with peptic ulcer bleeding underwent upper endoscopy within 24 hours. In the current study, 83.2% of patients with peptic ulcer bleeding underwent upper endoscopy within 24 hours.

Recent publications have suggested that the holiday effect did not influence the outcome of peptic ulcer bleeding [6, 22], which is in accordance with the present results. Those studies that did not find differences were probably performed in hospitals that were able to provide full-time therapeutic endoscopic services for early endoscopy. Therefore, the effects of lower staffing levels, less senior staff, and lower likelihood of invasive procedure on holidays were not problematic in these hospitals. Indeed, we found that patients in the holiday group received earlier endoscopy treatment than nonholiday patients (12.2 ± 15.3 h versus 16.7 ± 19.8 h, \( P = 0.008 \)).

Nevertheless, previous studies also pointed out that patients presenting on weekends might be more critically ill than those presenting on weekdays. However, we observed that patients admitted with peptic ulcer bleeding on holidays and nonholidays were comparable for coexisting illness, shock status, and Rockall scores. Nahon et al. reported similar findings in a post hoc subanalysis of a prospective study performed in 53 general nonuniversity hospitals in France [22]. They further explained that the severity of bleeding estimated by the Rockall score and the rates of endoscopic interventions for active bleeding did not differ between weekend and weekday admissions. Importantly, a senior gastrointestinal specialist was on call and available on weekends in their hospitals. In addition, we had well-trained emergency room physicians who understood and adhered to the guidelines for early risk stratification in patients with peptic ulcer bleeding [23, 24].

In Taiwan, medical care is well covered by the National Health Insurance system. Patients are allowed to seek medical care in referral hospitals, including medical centers and university hospitals, regardless of the severity of their illness. For instance, patients with peptic ulcer bleeding are allowed to go to a hospital center with full-time therapeutic endoscopic services. In our endoscopic teams, a senior gastroenterology specialist who supervises the lower level staff members is always on call, even on holidays. This is necessary to minimize the difference of endoscopist skill and reduce waiting time, regardless of whether it is a holiday or nonholiday. This could also be one reason why the patients with peptic ulcer bleeding admitted on holidays achieved good outcomes in the present study.

This study was limited by the fact that it was a retrospective chart review study performed at a single institution, which could have resulted in sampling bias. In conclusion, patients who present with peptic ulcer bleeding on holidays did not experience delayed endoscopy or increased adverse outcomes, such as recurrent bleeding or mortality. In fact, patients who received endoscopic hemostasis on holidays experienced shorter waiting times, required less transfused blood, were more quickly shifted from intravenous to oral PPI, and had shorter hospital stays.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.
References


Diagnosis, Treatment, and Outcome in Patients with Bleeding Peptic Ulcers and Helicobacter pylori Infections

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Upper gastrointestinal (UGI) bleeding is the most frequently encountered complication of peptic ulcer disease. *Helicobacter pylori* (*Hp*) infection and nonsteroidal anti-inflammatory drug (NSAID) administration are two independent risk factors for UGI bleeding. Therefore, testing for and diagnosing *Hp* infection are essential for every patient with UGI hemorrhage. The presence of the infection is usually underestimated in cases of bleeding peptic ulcers. A rapid urease test (RUT), with or without histology, is usually the first test performed during endoscopy. If the initial diagnostic test is negative, a delayed ¹³C-urea breath test (UBT) or serology should be performed. Once an infection is diagnosed, antibiotic treatment is advocated. Sufficient evidence supports the concept that *Hp* infection eradication can heal the ulcer and reduce the likelihood of rebleeding. With increased awareness of the effects of *Hp* infection, the etiologies of bleeding peptic ulcers have shifted to NSAID use, old age, and disease comorbidity.

1. Introduction

Left untreated, peptic ulcer diseases (PUD) will cause major complications, such as hemorrhage, perforation, or obstruction in 20–25% of patients. Among these complications, upper gastrointestinal (UGI) bleeding is the most frequently encountered, accounting for about 70% of cases [1, 2]. With the discovery of *Helicobacter pylori* (*Hp*) [3], the pathogenic relationship between PUD and *Hp* infection has come into focus. Worldwide consensus guidelines recommend the mandatory eradication of *Hp* in patient with PUD [4–13].

Another independent risk factor for PUD and subsequent UGI bleeding is the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) [14]. Those patients requiring long-term NSAID treatment should be screened for *Hp* status, and *Hp* eradication is suggested before administering NSAIDs [8]. Writing prescriptions for aspirin and antiplatelet agents is a common clinical scenario that creates new challenges related to UGI bleeding in gastroenterological practices [15, 16]. However, the relationship between the use of these medications and UGI bleeding is beyond the scope of this paper. Here, we will elucidate the relationship between bleeding peptic ulcers and *Hp* infection from the chronological perspective with an emphasis on diagnosis, treatments, and outcomes.

2. Materials and Methods

We searched Pubmed (to 15 March 2014). Overall, we identified 708, 526, and 120 with the following key word combinations: “bleeding peptic ulcer AND Helicobacter pylori diagnosis,” “bleeding peptic ulcer AND Helicobacter pylori treatment,” and “bleeding peptic ulcer AND Helicobacter pylori outcome,” respectively.

Medical subject headings (MeSH) terms were employed to assist the search, and the results were reviewed by the authors. We also conducted a manual search of material
from several congresses. The paper selection criteria included (1) discussion with diagnosis, treatment, or outcome of bleeding peptic ulcers and Hp infection and (2) publication in full manuscript form in English. Finally, 129 articles were selected, and their reference lists were checked for other possible studies for inclusion.

3. Results and Discussion

3.1. Diagnosis. The diagnosis of Hp infection is based on both invasive and noninvasive methods. Endoscopy is an invasive method, which includes a rapid urease test (RUT), histology, culturing, and polymerase chain reaction (PCR). The noninvasive methods include serology antibody assessment, 13C-urea breath test (UBT), and stool antigen testing. There are only minimal differences in the accuracies of the invasive tests. Among them, the RUT is the most frequently used. The UBT is the recommended noninvasive test [17]. Recently, the monoclonal stool antigen test has also been suggested [18]. The prevalence of Hp infection in noncomplicated PUD has been reported to be high in duodenal ulcer patients and moderate in gastric ulcer patients, regardless of which test is performed [19, 20]. However, there have been discrepant test results among patients with bleeding peptic ulcers. The individual diagnostic tests are discussed below.

3.1.1. RUT. The RUT is the most common examination for patients with UGI bleeding because endoscopy is always performed in such cases. An early study from Hong Kong disclosed a high false-negative rate for urease tests from antral biopsies in bleeding ulcer patients [21]. Almost simultaneously, we reported delayed positive results on the CLO test (color change after 24 hours) in our bleeding peptic ulcer patients if there was blood in the gastric antrum [22]. Another study from Greece demonstrated similar results at the same meeting [23]. These studies were further elucidated in subsequently published full articles [24–26]. Because there is always blood in the stomachs of patients with bleeding peptic ulcers, interference with RUT results by blood components is a concern. Several mechanisms have been suggested, including the bactericidal effect of serum inducing a transient decrease in bacterial density, the presence of anti-Hp antibodies inhibiting urease production, suppressed urease activity by serum enzymes or electrolytes, various buffering systems (e.g., albumin, bicarbonate, and phosphate) interfering with the pH level of the RUT reagent, and concomitant administration of NSAIDs or proton pump inhibitors (PPIs). In one in vitro study [27], a false-negative RUT result was caused by the buffering effects of serum albumin on the pH indicator but not on urease activity. Another in vitro study concluded that large gastric lavage before endoscopy can cause a false-negative RUT result [28]. However, our study found no influence on the likelihood of a false-negative result if the gastric antral biopsy specimen was cleansed by normal saline before inoculating the wells for the CLO test [29]. Similarly, another study concluded that an artificial blood-soaked antral specimen did not influence the results of two RUTs [30]. The bactericidal effect of human plasma [31, 32] and the reduction in bacterial load by PPIs [33] have been demonstrated.

In subsequent studies worldwide [34–40], RUT was further confirmed to be less sensitive than other tests in the diagnosis of Hp infection in bleeding peptic ulcers. Another consideration is that Hp bacterial density may be patchy, and only using samples from the gastric antrum may be inadequate. Inappropriate biopsy site and inadequate specimens are other explanations of false-negative results of RUT in patients with UGI bleeding. (Blood in stomach could induce Hp migration to corpus and fundus and the decrease of bacterial density in the antrum. Fewer amounts of specimens are obtained during emergent endoscopy procedure.) Simultaneous antral and body specimens or multiple biopsies have been found to produce more positive RUTs [41, 42]. Most authors concluded that the RUT cannot be the only diagnostic test in such circumstances [43]. If the initial diagnostic test is negative, a delayed test 4–8 weeks later can have up to an 80% positive rate in previously negative patients [44].

3.1.2. Histology. Different studies have reported low sensitivity with histologic methods, which is consistent with RUT sensitivity. This suggests that histology cannot reliably exclude Hp infection in patients with bleeding peptic ulcers [24, 34]. However, other studies have reported that histology is more sensitive than RUT [24, 25, 35, 36]. As previously mentioned, patchy distribution of bacterial density can be one factor, but the staining method and pathologist’s interpretations also influence the results [45]. Others have suggested that the prevalence of Hp infection is probably the same among bleeding and nonbleeding patients [46]. The sensitivity of histology also relies on the experience of the endoscopist to take the biopsy from the appropriate site. Some publications had shown that atrophic change, rugal hyperplasia, edema, and spotty erythema are valuable endoscopic findings of Hp infection. It is very important to avoid false-negative histology finding by taking the biopsy from RAC (regular arrangement of collecting venules) negative site [47]. Therefore, combination tests should be performed to achieve a more precise diagnosis [48].

3.1.3. Culturing and PCR. Culturing Hp in patients with bleeding peptic ulcers produced a low yield in several studies [24, 34]. The reasons for its infrequent use include the time-consuming nature of the process due to the microanaerobic pathogen characteristics and the lack of time to perform the procedure during endoscopy.

Mucosal PCR has been used as an invasive test to diagnose Hp infection. In one study, this test was less sensitive in patients with bleeding peptic ulcers than for those with nonbleeding peptic ulcers and chronic gastritis [49]. However, another study reported that PCR had higher sensitivity than other biopsy-based tests and similar sensitivity to noninvasive tests [50]. The authors also demonstrated that blood may reduce the sensitivities of all biopsy-based tests. A study using real-time PCR can improve Hp detection in a histology-negative, formalin-fixed, and paraffin-embedded
biopsy and is superior to immunohistochemical staining [51]. Modified PCR could improve diagnostic accuracy in patients with UGI bleeding [52].

3.1.4. UBT. Many studies have confirmed that the $^{13}$C-UBT can accurately diagnose Hp infection [53, 54]. This statement also applies to patients with UGI bleeding [24, 26, 35, 36, 38]. The test's sensitivity is not affected by blood in the stomach and is higher than those of biopsy-based methods and other noninvasive tests [55–57].

Because a subject must drink a urea-containing solution in conjunction with a test meal or citric acid, one might question whether this method is suitable for bleeding patients. Most UBTs are done when patients resume eating, or the UBT is reserved as a delayed test if the initial invasive methods are negative. However, using low-dose encapsulated $^{13}$C-urea has proven to be feasible in fasting patients or even before an endoscopy because it only takes a small amount of water to swallow a pill [58].

3.1.5. Stool Antigen Test. The stool Hp antigen test has been introduced as an accurate noninvasive test [59]. It can be performed by enzyme-linked immunosorbent assay (ELISA) with monoclonal or polyclonal antibodies or by immunochromatographic assay with monoclonal antibodies. The sensitivity of this method is reduced by UGI bleeding when polyclonal ELISA or immunochromatographic stool antigens are used [38, 60, 61]. Furthermore, it is not reliable in patients with bleeding peptic ulcers [62]. Another study reported a high number of false-positive results in patients with UGI bleeding due to a cross-reaction with the blood [63]. Therefore, the stool Hp antigen diagnostic test is not recommended for use in patients with UGI.

3.1.6. Serology. We [24] and others [34] have demonstrated that serology is more sensitive than other invasive tests in cases of bleeding peptic ulcer. It can be used as the initial invasive test, as an alternative test, or when the UBT test is negative. However, commercial serological tests must be confirmed by a local laboratory before they are used in an individual hospital [64]. Additionally, if patients have been treated for Hp infection, serological tests have revealed that serum antibodies may last for up to a year [65]. This fact must not be overlooked when interpreting the results.

3.1.7. NSAIDs, PPI, and Other Drugs with Bleeding PUD on Diagnosis Tests. No matter which diagnostic tests are employed in patients with bleeding PUD, physicians should preclude NSAID use. Many studies have confirmed the influence of NSAIDs on the sensitivities of the test results [66–68]. Hp infection and NSAID use are two independent factors related to bleeding peptic ulcers [69]. In patients who are already on long-term NSAIDs, Hp eradication does not prevent the peptic ulcer from bleeding. Nevertheless, patients who require long-term NSAID medications should be tested for Hp infection in advance. Hp eradication can decrease the incidence of peptic ulcer bleeding. But in patients with long-term NSAIDs use, the cause of peptic ulcer bleeding should be NSAIDs use, not Hp status.

Another frequently encountered scenario is that most patients are given PPIs either intravenously or orally at the initial presentation of UGI bleeding, even before an endoscopic examination. There is concern over whether the recent use of a PPI interferes with the diagnostic accuracy for Hp infection. One study with a 3-day dosage of intravenous PPI in a bleeding peptic ulcer case found that a high infusion dose significantly impacts negative histology and RUT results as compared to a regular daily dose [70]. Dose-dependent PPIs do produce short-term effects on Hp diagnosis. Recent PPI use may induce false-negative results on both invasive tests [35] and noninvasive tests, such as the UBT [71–74] and stool Hp antigen test [75]. The duration of PPI administration can vary significantly affect diagnostic accuracy. Usually, discontinuation of the drug for 2 weeks is recommended before performing any test, except serology.

Antisecretory medication is mandatory in patients with bleeding peptic ulcers. H2-receptor antagonists (H2RA) may be an alternative regimen. There are several studies evaluating H2RA and Hp diagnostic accuracy. Conflicting results exist, but most data indicate that these drugs have little influence on the Hp diagnosis [76, 77].

3.1.8. Summary. A systematic review and meta-analysis explored the accuracies of Hp diagnostic tests in patients with bleeding peptic ulcers [78]. The authors found that biopsy-based methods had low sensitivity and high specificity; UBT had high accuracy; stool antigen tests were less accurate; and serology, though not influenced by UGI bleeding, was not recommended as the first test. Pooled data on sensitivity, specificity, and positive and negative likelihood ratios are shown in Table 1. Because the positive likelihood ratio is high, positive invasive tests or UBT requires no further confirmation of Hp infection. However, the other delayed tests should not be overlooked.

A recent meta-regression study [79] suggested that the low prevalence of Hp infection in patients with bleeding peptic ulcers might be related to the methodology of the studies and to the patients’ characteristics. The authors found a higher prevalence of Hp infection when a delayed test was performed and when younger patients were included. They concluded that the prevalence of Hp infection had been underestimated in patients with bleeding peptic ulcers. They also suggested that a delayed diagnostic test should be carried out if the initial diagnostic test is negative, as recommended by the International Consensus [11].

3.2. Treatment

3.2.1. Hp Eradication. Hp infection is still an important factor in peptic ulcer development. Eradication therapy is suggested for both duodenal and gastric ulcers in patients infected with Hp [13], regardless of whether they have complications. Although there is no direct causal relationship between Hp infection and early rebleeding in patients with peptic
ulcer bleeding [80, 81], empirical *Hp* eradication as soon as patients resume eating is the most cost-effective strategy for preventing recurrent hemorrhage [82].

Many studies in the 1990s demonstrated the benefit of *Hp* eradication in decreasing peptic ulcer recurrences, as well as in bleeding cases. Using antibiotics to kill the bacteria was proven effective in preventing ulcer rebleeding in early studies [83, 84]. Other regimens using aminopentazole and amoxicillin can also reduce the recurrence of peptic ulcer bleeding as compared to omeprazole or ranitidine alone [85–88]. The results were the same when the antibiotics were changed [89].

With the introduction of the ideal eradication regimen for *Hp* infection, triple therapy has been applied worldwide [90–92]. We previously reported that triple therapy can achieve a 91.3% eradication rate and a 97.1% ulcer healing rate in bleeding peptic ulcers [93]. One study found that as long as antibiotic eradication or *Hp* infection suppression is achieved, bleeding can be reduced [94]. Subsequent studies also confirmed that *Hp* eradication improves healing and decreases rebleeding [95–97].

The current dogma is that *Hp* eradication in bleeding peptic ulcers is superior to simple ulcer healing in preventing further ulcer hemorrhages [98, 99]. Therefore, testing for the presence of *Hp* infection and eradicating it are both mandatory and cost effective [100]. While there has been concern over whether maintenance antisecretory treatment was necessary, the current position is that, as long as *Hp* is eradicated, peptic ulcer rebleeding is virtually eliminated. Therefore, antisecretory therapy is no longer required [101–104]. However, maintenance antisecretory therapy should be considered for *Hp*-eradicated patients who did not stop NSAID use.

We performed a prospective 5-year followup of patients after *Hp* eradication and assessed the healing of bleeding peptic ulcers [101]. We randomized 82 consecutive patients into 4 different groups after 1 week of triple therapy and 3 weeks of PPI treatment. Despite 4 months of different maintenance regimens among the four groups (antacid suspension, colloidal bismuth, famotidine, or a placebo treatment), all the patients remained ulcer free with no evidence of reinfection. In recent pooled data of 1000 patients from 10 Spanish university hospitals and a total of 3253 patient-years of long-term followup, maintenance antiulcer treatment was not indicated once *Hp* had been eradicated [104]. However, the recent Maastricht IV/Florence Consensus suggested that while maintenance antulcer treatment is not needed for bleeding duodenal ulcers, it should be continued for gastric ulcers [13].

PPI treatment is usually administered to patients with bleeding peptic ulcers, even before endoscopic examination. This treatment can facilitate the endoscopic hemostatic effect in reducing short-term rebleeding [105, 106]. PPI treatment also has benefits for *Hp* eradication. One study demonstrated that intravenous omeprazole can decrease the risk of peptic ulcer rebleeding and may even improve the *Hp* eradication rate of the subsequent triple therapy [107].

*Hp* eradication after peptic ulcer bleeding reduces recurrence. Is confirmation of eradication of *Hp* worthwhile? One study using the Markov model proved that confirmation of *Hp* eradication after completion of antibiotic treatment in peptic ulcer bleeding is cost effective [108].

### 3.2.2. Summary

Eradication therapy is suggested in *Hp*-infected bleeding peptic ulcers. Triple therapy including a PPI and two antibiotics is the primary regimen. However, the rising antibiotic resistance rate should be taken into consideration in specific regions. Concomitant triple therapy, sequential therapy, bismuth- or non-bismuth-based quadruple therapy, and levofloxacin-based regimens are appropriate alternatives. After eradication, prolonged acid-suppressive therapy for duodenal ulcers is unnecessary, but gastric ulcers may require additional acid-suppressive therapy for 4–8 weeks due to their slow healing time and larger size.

### 3.3. Outcome

#### 3.3.1. Outcome with/without *Hp* Eradication

Among patients with peptic ulcer diseases, 20–25% develop bleeding, perforation, or obstruction. In patients with bleeding peptic ulcers, approximately 33% develop recurrent bleeding within 1–2 years if left untreated after the ulcer heals [117]. Consequently, *Hp* eradication reduces the recurrence rate of peptic ulcers [118]. As mentioned previously, several studies have also reported a low rebleeding rate after *Hp* eradication, even without acid-suppressive drug maintenance [83–89, 95, 96, 101, 109, 111–116]. A multicenter Spanish cohort study with similar findings was published recently, and comparative results with other studies are shown in Table 2.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Number of studies</th>
<th>Pooled patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive LR</th>
<th>Negative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUT</td>
<td>16</td>
<td>1,417</td>
<td>0.67</td>
<td>0.93</td>
<td>9.6</td>
<td>0.31</td>
</tr>
<tr>
<td>Histology</td>
<td>10</td>
<td>827</td>
<td>0.70</td>
<td>0.90</td>
<td>6.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Culture</td>
<td>3</td>
<td>314</td>
<td>0.45</td>
<td>0.98</td>
<td>19.6</td>
<td>0.31</td>
</tr>
<tr>
<td>UBT</td>
<td>8</td>
<td>520</td>
<td>0.93</td>
<td>0.92</td>
<td>9.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Stool Ag</td>
<td>6</td>
<td>377</td>
<td>0.87</td>
<td>0.70</td>
<td>2.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Serology</td>
<td>9</td>
<td>803</td>
<td>0.88</td>
<td>0.69</td>
<td>2.5</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Ag: antigen; LR: likelihood ratio; RUT: rapid urease test; UBT: urea breath test.

Table 1: Accuracies of different diagnostic tests based on pooled data of different studies of patients with bleeding peptic ulcers [78].
Table 2: Incidence of rebleeding in Hp-eradicated patients with no maintenance acid-suppressive therapy among different studies [104].

<table>
<thead>
<tr>
<th>Author</th>
<th>Year and area</th>
<th>Ulcer type</th>
<th>Regimen</th>
<th>ER number</th>
<th>Mean F/U (M)</th>
<th>Rebleeding number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham et al. [83]</td>
<td>1993, USA</td>
<td>PU</td>
<td>Triple</td>
<td>17</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Labenz and Borsch [84]</td>
<td>1994, Germany</td>
<td>PU</td>
<td>7 different protocols</td>
<td>42</td>
<td>17</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Jaspersen et al. [86]</td>
<td>1995, Germany</td>
<td>PU</td>
<td>Dual</td>
<td>24</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Jaspersen et al. [109]</td>
<td>1995, Germany</td>
<td>DU</td>
<td>Dual</td>
<td>29</td>
<td>12</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Rokkas et al. [85]</td>
<td>1995, Greece</td>
<td>DU</td>
<td>Dual</td>
<td>13</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Santander et al. [87]</td>
<td>1996, Spain</td>
<td>PU</td>
<td>Dual or triple</td>
<td>84</td>
<td>12</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Riemann et al. [88]</td>
<td>1997, Germany</td>
<td>PU</td>
<td>Dual</td>
<td>42</td>
<td>19</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>Sung et al. [89]</td>
<td>1997, Hong Kong</td>
<td>PU</td>
<td>Triple</td>
<td>108</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Macri et al. [110]</td>
<td>1998, Italy</td>
<td>DU</td>
<td>Quadruple</td>
<td>21</td>
<td>48</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Amendola et al. [111]</td>
<td>1999, Argentina</td>
<td>PU</td>
<td>PPI 1-week regimen</td>
<td>42</td>
<td>24</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gisbert et al. [112]</td>
<td>1999, Spain</td>
<td>DU</td>
<td>Triple or dual</td>
<td>111</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lai et al. [113]</td>
<td>2000, Hong Kong</td>
<td>DU</td>
<td>Triple</td>
<td>41</td>
<td>53</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>Vergara et al. [95]</td>
<td>2000, Spain</td>
<td>PU</td>
<td>Triple or quadruple</td>
<td>93</td>
<td>27</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pellicano et al. [114]</td>
<td>2001, Italy</td>
<td>DU</td>
<td>Antibiotics</td>
<td>46</td>
<td>47</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Capuro et al. [115]</td>
<td>2001, Italy</td>
<td>DU</td>
<td>Dual</td>
<td>83</td>
<td>36</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td>Arkkila et al. [96]</td>
<td>2003, Finland</td>
<td>PU</td>
<td>Quadruple or dual</td>
<td>176</td>
<td>12</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Liu et al. [101]</td>
<td>2003, Taiwan</td>
<td>PU</td>
<td>Triple</td>
<td>26</td>
<td>56</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Horvat et al. [116]</td>
<td>2005, Croatia</td>
<td>GU</td>
<td>Triple</td>
<td>43</td>
<td>12</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Gisbert et al. [104]</td>
<td>2012, Spain</td>
<td>PU</td>
<td>Triple*</td>
<td>1000</td>
<td>39</td>
<td>5 (0.5%)</td>
</tr>
</tbody>
</table>

DU: duodenal ulcer; ER: eradication; F/U: followup; GU: gastric ulcer; PU: peptic ulcer (gastric or duodenal ulcer).
*Triple therapy first followed by 2nd-, 3rd-, or 4th-line treatment.

Posttreatment Hp status has been found to be an independent predictor of duodenal ulcer bleeding recurrence [113]. Followup Hp testing after eradication in cases of bleeding peptic ulcers is therefore beneficial [108]. Because recurrence is more common than reinfection [119], physicians should use combined tests or select a much lower cut-off value for 13C-UBT to verify eradication success.

Is there a trend toward decreasing Hp-related bleeding peptic ulcers today? The answer is yes. After the global implementation of Hp eradication for PUDs, the incidence of Hp-infected UGI hemorrhage has decreased. A 10-year nationwide database from Taiwan also demonstrated 42–48% and 41–71% decreases in the incidence of hospitalization for gastric ulcers and duodenal ulcers, respectively, and these rates included uncomplicated and complicated cases [120]. Similar results have also been reported in other countries [121].

Nevertheless, bleeding peptic ulcers remain a worldwide problem. The increasing use of NSAIDs is considered to be an important underlying cause. Many studies have confirmed that current UGI bleeding in patients can be attributed to NSAID usage [122–126]. One study from the United States found that admission for PUD-related complications has not decreased despite decreasing Hp prevalence and increasing Hp eradication [127], and the authors proposed that this could be due to NSAID use. Meanwhile, Hp eradication...
can decrease the long-term incidence of recurrent ulcer bleeding in low-dose aspirin users [128]. Eliminating one independent risk factor can attenuate the effect of another independent factor on inducing peptic ulcer bleeding. A recent study found that patients with bleeding peptic ulcers and concurrent \( H. pylori \) infection have a more favorable outcome than those without [129].

3.3.2. Summary. \( H. pylori \) infection is an independent risk factor for bleeding duodenal ulcers. \( H. pylori \)-infected gastric ulcers in combination with old age and NSAID or aspirin therapy may increase the bleeding risk. Eradication treatment can decrease the likelihood of peptic ulcer rebleeding and associated complications. Admissions for bleeding peptic ulcers have not decreased despite the eradication of \( H. pylori \) infections. Concomitant administration of NSAIDs, old age, and comorbidities are currently considered as risk factors for UGI bleeding.

4. Conclusions

Three decades after the discovery of \( H. pylori \), the etiologies of bleeding peptic ulcers are changing. However, diagnosis of \( H. pylori \) infection is still the first priority in these patients. Invasive RUT is most frequently used, but this methodology is hampered by a high rate of false-negative results, especially in patients with UGI bleeding. Other delayed tests should be performed if the initial diagnostic test is negative. Eradication of \( H. pylori \) infection can reduce the risk of rebleeding and should be started as soon as patients resume eating. Concomitant use of NSAIDs, aspirin, or other antiplatelet drugs associated with old age and comorbidities is the most likely etiology for current bleeding peptic ulcers. \( H. pylori \) eradication is beneficial for patients who require the long-term administration of these drugs.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

The authors thank Dr. Martin Meng-Lin Lee from Hsinchu Mackay Memorial Hospital for assistance with the paper.

References


[80] D. Schilling, A. Demel, T. Nüsse, E. Weidmann, and J. F. Riemann, "Helicobacter pylori infection does not affect the


Clinical Study

The Effect of Helicobacter pylori Eradication on the Levels of Essential Trace Elements

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Objective. This study was designed to compare the effect of Helicobacter pylori (H. pylori) infection treatment on serum zinc, copper, and selenium levels. Patients and Methods. We measured the serum zinc, copper, and selenium levels in H. pylori-positive and H. pylori-negative patients. We also evaluated the serum levels of these trace elements after H. pylori eradication. These serum copper, zinc, and selenium levels were determined by inductively coupled plasma mass spectrometry. Results. Sixty-three H. pylori-positive patients and thirty H. pylori-negative patients were studied. Serum copper, zinc, and selenium levels had no significant difference between H. pylori-positive and H. pylori-negative groups. There were 49 patients with successful H. pylori eradication. The serum selenium levels were lower after successful H. pylori eradication, but not significantly (P = 0.06). There were 14 patients with failed H. pylori eradication. In this failed group, the serum selenium level after H. pylori eradication therapy was significantly lower than that before H. pylori eradication therapy (P < 0.05). The serum zinc and copper levels had no significant difference between before and after H. pylori eradication therapies. Conclusion. H pylori eradication regimen appears to influence the serum selenium concentration (IRB number: KMUH-IRB-20120327).

1. Introduction

Helicobacter pylori (H. pylori), a spiral-shaped pathogenic bacterium found on the human gastric mucosa, was first isolated by Warren and Marshall in 1982. It is one of the most common worldwide human infections [1]. H. pylori plays an important role in the development of chronic gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Established indications for H. pylori eradication include gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue lymphoma, atrophic gastritis, after gastric cancer resection, uninvestigated dyspepsia, patients who are first degree relatives of patients with gastric cancer, and patient’s wishes [2, 3]. Therefore, there are many studies concerning the treatment of H. pylori infection.

Copper is an essential nutrient in human physiology and is an essential constituent of numerous enzymes. Copper deficiency may result in microcytic anemia, leukopenia, osteoporosis, new subperiosteal bone formation, and fibrosis of epiphysis [4]. Zinc is also an important micronutrient in the human body and plays a vital role in homeostasis, immune function, oxidative stress, apoptosis, and aging. Zinc deficiency is related to atherosclerosis, several malignancies,
neurological disorders, autoimmune diseases, aging, age-related degenerative diseases, and Wilson's disease [5]. Zinc is also a key component of proteins in adult humans [6]. Selenium is an important antioxidant and anticancer nutrient [7]. In the study of Steevens et al. selenium status has an inverse association with gastric and esophageal cancer [8]. Helicobacter pylori infection leads to chronic inflammation of gastric mucosa and peptic ulcer disease. It may influence the absorption of essential trace elements. The association between trace elements and H. pylori infection has been reported [9]. The aim of this study is to explore the effect of H. pylori eradication on the essential trace elements of zinc, copper, and selenium.

2. Method

2.1. Patients and Study Design. Patients, who were older than 18 years and complained of dyspepsia or epigastralgia, were evaluated in our gastroenterology outpatient clinic. The exclusion criteria included (a) age less than 18 years; (b) patients who had had previous H. pylori eradication; (c) patients with allergy history to PPI, or antibiotics; (d) patients who had ever taken PPI, antibiotics, and bismuth; (e) patients with severe systemic diseases (e.g., decompensated liver cirrhosis and uremia); (f) patients with previous gastric surgery; and (g) pregnant women. All of the clinical diagnoses were documented by endoscopic examination. The patients with H. pylori infection were classified as the study group, and the patients without H. pylori infection were the control group.

The status of H. pylori infection was diagnosed by histology, culture, and rapid urease test. Patients who were infected with H. pylori were treated with lansoprazole 30 mg bid, amoxicillin 1g bid, and clarithromycin 500 mg bid or levofloxacin 500 mg qd for 7–10 days. After 6–12 weeks of triple combination therapy, repeated gastroendoscopy with rapid urease test, histology, and culture was performed. If the patient refused repeated gastroendoscopy, 13C-urea breath tests were conducted to assess the status of H. pylori infection.

This study conformed to the Helsinki Declaration and was approved by the Institutional Review Board (IRB) of Kaohsiung Medical University Hospital (IRB number: KMUH-IRB-20120327). The written informed consents were collected from all participating patients.

2.2. Diagnosis of H. Pylori Infection

2.2.1. Culture Examination. Biopsy specimens were rubbed on the surface of a Columbia blood agar plate and then incubated at 35°C under microaerobic conditions for 4-5 days. Culture of H. pylori was considered positive if one or more colonies showed gram negativity, oxidase (+), catalase (+), urease (+), and spiral or curved rods in morphology.

2.2.2. Histological Examination. The biopsy specimens were fixed with formalin, embedded in paraffin, and stained with hematoxylin and eosin. The result for the gram's stain was considered positive when curvy, gram-negative bacteria were found on the slide. They were interpreted and reported by the same pathologist.

2.2.3. Rapid Urease Test. The results of the rapid urease test (CLO test, Delta West, Bentley, WA, Australia) were interpreted as positive if the color of the gel became pink or red after 6 hours at room temperature.

2.2.4. 13C-Urea Breath Test. The 13C-urea was manufactured by the Institute of Nuclear Energy Research, Taiwan. One hundred milliliters of fresh whole milk was used as the test meal. This detailed procedure was reported in our previous study [10]. For patients who received endoscopy, H. pylori infection was established if the culture was positive or both CLO test and histology were positive.

2.3. The Methods of Trace Element Assay. Blood samples were drawn from the median cubital vein in individuals and collected in vacutainer plain tubes. The centrifuge was set at a speed of 3000 rpm for 15 minutes under room temperature. After centrifugation, the supernatant was pipetted into an unused vial for −20°C preservation without any additives. The serum copper, zinc, and selenium levels were determined by inductively coupled plasma mass spectrometry (ICP-MS). At present, ICP-MS is the most sensitive analytical technique for the determination of trace elements in various matrices.

2.4. Statistical Analysis. All data were analyzed using Statistical Package for Social Sciences Version 14.0 software (SPSS Inc., Chicago, Ill, USA). Statistical differences between mean values were tested with Student's t-test. The difference between the two groups was tested with paired t-test. A P value of <0.05 was considered statistically significant.

3. Results

There were 93 patients in our study: 63 patients infected with H. pylori in the study group and 30 patients without H. pylori infection in the control group. The mean age was 53.87 ± 13.18 years in the study group and 48.00 ± 12.22 years in the control group. The endoscopic diagnosis in the study group was 11 patients with gastric ulcers, 28 patients with duodenal ulcers, 3 patients with gastritis, and 21 patients with reflux esophagitis. The control group had 30 patients with primary endoscopic finding of gastritis (Table 1).

Table 2 shows that serum copper, zinc, and selenium levels had no significant differences between study and control groups (all P values > 0.05). Forty-nine patients had successful H. pylori eradication with a rate of 77.78% (49/63). After successful H. pylori eradication, the serum levels of copper, zinc, and selenium had no significant difference compared with before treatment (Table 3; all P values > 0.05). Among the patients with failure of H. pylori eradication, the serum copper and zinc levels were not significantly different between before and after treatments (Table 4, P = 0.26 and 0.25, resp.). However, the serum selenium level
Table 1: The demography of studied patients including healthy control group and Helicobacter pylori-infected group.

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 30)</th>
<th>Study (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Helicobacter pylori</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.00 ± 12.22</td>
<td>53.87 ± 13.18</td>
</tr>
<tr>
<td>Male/female</td>
<td>16/14</td>
<td>36/27</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Gastritis</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Reflux esophagitis</td>
<td>0</td>
<td>21</td>
</tr>
</tbody>
</table>

Control: H. pylori-negative patients. Study: H. pylori-positive patients.

Table 2: The comparison of serum copper, zinc, and selenium levels between control and study groups.

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 30)</th>
<th>Study (n = 63)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu (mg/L)</td>
<td>1.11 ± 0.27</td>
<td>1.05 ± 0.31</td>
<td>0.40</td>
</tr>
<tr>
<td>Zn (mg/L)</td>
<td>1.92 ± 0.37</td>
<td>1.79 ± 0.45</td>
<td>0.19</td>
</tr>
<tr>
<td>Se (µg/L)</td>
<td>142.03 ± 25.61</td>
<td>155.05 ± 47.77</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Control: H. pylori-negative patients. Study: H. pylori-positive patients.

Table 3: The comparison of serum copper, zinc, and selenium levels in Helicobacter pylori- (Hp-) infected patients before and after successful eradication therapy (n = 49).

<table>
<thead>
<tr>
<th></th>
<th>Before Hp eradication</th>
<th>After Hp successful eradication</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu (mg/L)</td>
<td>1.01 ± 0.25</td>
<td>1.02 ± 0.28</td>
<td>0.66</td>
</tr>
<tr>
<td>Zn (mg/L)</td>
<td>1.78 ± 0.42</td>
<td>1.67 ± 0.44</td>
<td>0.17</td>
</tr>
<tr>
<td>Se (µg/L)</td>
<td>154.24 ± 37.51</td>
<td>141.72 ± 39.01</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 4: The comparison of serum copper, zinc, and selenium levels in Helicobacter pylori- (Hp-) infected patients before and after failure of eradication therapy (n = 14).

<table>
<thead>
<tr>
<th></th>
<th>Before Hp eradication</th>
<th>After Hp failed eradication</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu (mg/L)</td>
<td>1.23 ± 0.40</td>
<td>1.16 ± 0.29</td>
<td>0.26</td>
</tr>
<tr>
<td>Zn (mg/L)</td>
<td>1.84 ± 0.54</td>
<td>1.62 ± 0.51</td>
<td>0.25</td>
</tr>
<tr>
<td>Se (µg/L)</td>
<td>157.24 ± 37.51</td>
<td>127.20 ± 33.92</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

was significantly lower after failure of H. pylori eradication therapy (Table 4, P < 0.05).

4. Discussion

H. pylori infection may result in stomach inflammation. H. pylori, when having altered gastric secretion coupled with tissue injury, leads to peptic ulcer disease and gastritis, and maybe progresses to atrophy, intestinal metaplasia, and eventually gastric carcinoma. H. pylori also leads to hypochlorhydria in H. pylori-related gastritis [11]. The change of gastric environment may affect the absorption of trace elements.

Copper is an essential mineral in the human body, which is required as a catalytic cofactor in different enzyme reactions, such as an allosteric enzyme component and a potent antioxidant with a critical role in the oxidant defense system [12]. For children, Janjetic et al. reported that serum copper level was associated with gastric H. pylori infection [13]. For adults, previous reports have shown that serum copper level had no significant difference between gastric H. pylori infection and noninfection [14, 15]. These results are compatible with our study, which revealed that there was no significant difference between H. pylori- positive and H. pylori-negative patients (Table 2). Even after H. pylori eradication therapy, the serum copper levels had no significant changes between successful and failed H. pylori eradication groups (Tables 3 and 4).

Zinc is an important trace element in the organism, with catalytic, structural, and regulatory roles. Zinc is also related to some diseases, including Alzheimer’s disease, cancer, aging, diabetes, depression, and Wilson’s disease [5]. For children, Janjetic et al. have reported that serum zinc level was not associated with gastric H. pylori infection [13, 16]. The role of zinc in adults seems to modulate the oxidative stress in gastric mucosa. Zinc deficiency results in an increased susceptibility to oxidative stress and higher risk of mucosal damage in inflammation [17]. It has been reported that serum zinc level was an indicator of protecting gastric mucosa against damage, and it appears significantly reduced in patients with gastritis, peptic ulcer, and gastric cancer [18]. The degree of inflammation in H. pylori-induced gastritis seems to be modulated by gastric tissue zinc concentration. The more severe the H. pylori infection is, the lower concentration of zinc in gastric mucosa is noted [19]. In our study, the serum zinc level was lower in H. pylori-infected patients compared with H. pylori-negative cases. However, the difference was not statistically significant (Table 2). Besides, our study demonstrated the H. pylori eradication regimen had no effect on the serum zinc levels in both successful and failed H. pylori eradication groups (Tables 3 and 4).

Selenium has long been noted as an integral component of glutathione peroxidase, which is an important antioxidant against oxidative damage in human body [20]. It is also involved in maintaining structure and functional efficiency of mitochondria [21]. Selenium deficiency is associated with cancer formation, immune dysfunction, cardiovascular disease, and reproductive disorder [8, 22]. Previous reports showed that serum selenium level was not associated with H. pylori-infected subjects [15]. However, the report of Ustündağ et al. indicated that selenium accumulated obviously in gastric tissue in the cases of H. pylori-related antral inflammation and then significantly decreased in tissue after successful H. pylori eradication [23]. Furthermore, this reactive increase in gastric mucosal selenium also disappeared in atrophic gastritis, a status of H. pylori-related precancerous lesion. So, the authors suggested that decreased gastric mucosal selenium during a long-lasting mucosal inflammation may be a part of the gastric microenvironmental changes in gastric...
carcinogenesis [23]. This is why the relationship between serum selenium level and H. pylori-infected subjects has been studied in this paper. It shows that serum selenium level has no significant difference between H. pylori-positive and H. pylori-negative groups (Table 2). However, the serum selenium levels decrease after H. pylori eradication therapy (Tables 3 and 4), especially decreasing significantly in failed H. pylori eradication group (Table 4, P < 0.05). The definite mechanism responsible for decreasing serum selenium level after H. pylori eradication therapy is not clearly defined. However, the changes of microbiota in small intestine may play an important role in determining serum selenium level because it is mainly absorbed in the duodenum and cecum by active transport through a sodium pump [22]. Previous report showed that short-term antibiotics use, such as H. pylori eradication regimen, may have a long-term impact on the native microbiota in the intestine for up to 4 years posttreatment [24]. Besides, proton pump inhibitor used in H. pylori eradication regimen also results in bacterial and fungal overgrowth in small intestine [25]. The changes of microenvironmental microbiota in small intestine may explain the effect of H. pylori eradication therapy on decreasing serum selenium level, but the detailed mechanism needs to be further elucidated.

Our study aims to explore the association of serum copper and zinc levels with H. pylori infection, although the relationship is not significant in statistics. However, the serum selenium level decreases after H. pylori eradication therapy in both successful and failed eradication groups, and it achieves significantly lower levels of selenium after eradication therapy in the failed group. Our study shows that the H. pylori eradication regimen may influence the serum selenium level.

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

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References


Gastrointestinal Hemorrhage in Warfarin Anticoagulated Patients: Incidence, Risk Factor, Management, and Outcome

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Background. Warfarin reduces the incidence of thromboembolism but increases the risk of gastrointestinal bleeding (GIB). GIB during warfarin anticoagulation is rarely evaluated in Asian patients.

Aims. This study aimed at investigating the incidence, risk factors, management, and outcome of GIB in Taiwanese patients treated with warfarin.

Methods. We analyzed a cohort of warfarin anticoagulated patients between July 1993 and May 2012. Clinical data were retrieved in a chart-reviewing manner.

Results. A total of 401 warfarin anticoagulated patients were enrolled. The incidence of GIB was 3.9% per patient-years. Multivariate analysis with Cox regression showed that age > 65 years old (RR: 2.5, 95% CI: 1.2–5.5), a mean international normalized ratio > 2.1 (RR: 2.1, 95% CI: 1.0–4.2), a history of GIB (RR: 5.1, 95% CI: 1.9–13.5), and cirrhosis (RR: 6.9, 95% CI: 2.0–24.5) were independent factors predicting GIB. 27.3% of the GIB patients had rebleeding after restarting warfarin while thromboembolic events were found in 16.7% of the patients discontinuing warfarin therapy.

Conclusions. Warfarin was associated with a significant incidence of GIB in Taiwanese patients. The intensity of anticoagulation should be monitored closely during warfarin therapy, especially in patients with risk factors of GIB.

1. Introduction

Warfarin is currently the most commonly used oral anticoagulant worldwide. It produces an anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3-epoxide (vitamin K epoxide) [1]. The indications of warfarin include prevention of venous thromboembolism, prevention of systemic thromboembolism and stroke in patients with prosthetic heart valves and atrial fibrillation, primary prevention of myocardial infarction, and prevention of stroke, recurrent infarction, and death in the management of acute myocardial infarction [2]. However, warfarin has a narrow therapeutic window, wide variability in dose-response across individuals, and a significant number of drug and dietary interactions and requires close laboratory monitoring with frequent dose adjustment [1, 2].

Gastrointestinal bleeding (GIB) is one of the severe bleeding complications of warfarin anticoagulation and occurs in up to 12% of cases [3]. Several factors that influence the source and severity of GIB in patients taking warfarin are identified including prolonged prothrombin time, concomitant use of aspirin, advanced age, previous GIB, atrial fibrillation, and coexisting conditions such as renal insufficiency and anemia [4]. However, the correlation between some of these factors, for instance, advanced age, and GIB is controversial [5].

New oral anticoagulant agents are direct and selective inhibitors of a specific step or enzyme of the coagulation cascade. They have been shown to be effective in the prevention and treatment of various thromboembolic diseases with more predictable anticoagulant response and no need for close laboratory monitoring. However, new oral anticoagulants still have some limitations. Drug-drug
interactions, difficulty in monitoring the anticoagulant effect in patients with severe renal and liver failure, the much more expensive prices compared with warfarin, and, most importantly, lack of a specific antidote are the major drawbacks of these agents [6]. A recent meta-analysis reveals that new generation of oral anticoagulants results in a significantly higher risk of GIB compared with warfarin [7]. Besides, new oral anticoagulants are not cost-effective when compared with warfarin in patients with atrial fibrillation [8]. Taking these together, warfarin remains a widely used anticoagulant before more promising agents are available. As a result, a more detailed understanding of the use of warfarin and its bleeding complication is necessary while managing the patients.

Average warfarin dose required to maintain the international normalized ratio (INR) between 2.0 and 3.0 is affected by ethnicity [9]. The maintenance doses of warfarin for the Japanese and the Chinese are about 30% and 40% lower than those of Caucasians, respectively [10]. Actually, genetic determinants of warfarin dosing may affect the effect of warfarin [11, 12]. Several studies evaluated GIB complications associated with warfarin in Western countries but the data of Asian population was rarely reported. This study investigated the incidence, characteristics, risk factors, management, and outcome of GIB in Taiwanese patients treated with warfarin anticoagulation therapy.

2. Materials and Methods

2.1. Study Design. This was a retrospective study of a cohort of warfarin anticoagulated patients in Kaohsiung Veterans General Hospital. We searched the electronic medical records of all patients with prescriptions of warfarin between July 1993 and May 2012. Patients were enrolled if they met the following criteria: (1) age equal to or more than 20 years old and (2) taking warfarin for more than 6 weeks. We reviewed the medical records and retrieved the information including age, gender, the indications and duration of warfarin therapy, concomitant medication during anticoagulation such as antiplatelet agents, nonsteroid anti-inflammatory drugs, and steroids, comorbidity, and INR values during anticoagulation. We further divided all patients into GIB group and non-GIB group. For patients with GIB, the symptoms and signs of GIB at presentation, needs of transfusion, endoscopic findings and therapies, duration of discontinuation of warfarin, and outcome of the patients were recorded. This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS12-CT11-01).

2.2. Definition. The average INR value was determined as the mean of all INR values measured during anticoagulation and before GIB, if present. GIB was defined as (1) clinically evident hematemesis, melena, and hematochezia, or positive for occult blood test, and (2) needs of transfusion of two or more units of packed red blood cells, or a decline in hemoglobin level of 2 g/dL or greater, or a systolic blood pressure < 100 mmHg in patients negative for evident signs of GIB or occult blood test.

2.3. Statistical Analysis. The primary aim of this study was the incidence of GIB in patients treated with warfarin. The secondary aims were the risk factors of GIB and the outcome of the patients with GIB. The incidence of GIB was calculated as values per patient-year in this cohort. Demographic data were compared between patients of GIB group and non-GIB group. Categorical data were compared using chi-square or Fisher’s exact tests as appropriate. Continuous variables with normal distributions were compared using independent Student’s t-test. Continuous variables without normal distributions were compared using Mann-Whitney U test. A receiver operating characteristic (ROC) curve was used to determine the cut-off value of the mean INR which best discriminated GIB patients from non-GIB patients. Risk factors of GIB were examined by univariate and multivariate Cox regression analysis. Significance was defined as P < 0.05 for all two-tailed tests. All analyses were conducted by using SPSS software (version 12; SPSS Inc., Chicago, IL).

3. Results

A total of 401 warfarin anticoagulated patients were enrolled into this study. There were 234 males and 167 females. The mean age of the patients was 65.2 ± 16.6 years. The indications of warfarin were as follows: valvular replacement in 148 patients (36.9%), atrial fibrillation in 89 patients (22.1%), deep vein thrombosis in 71 patients (17.7%), pulmonary embolism in 31 patients (7.7%), and other conditions in 62 patients (15.4%). There were 36 patients in GIB group and 365 patients in non-GIB group. Demographic data of both groups were shown in Table 1. Patients with GIB were older (P < 0.001) and had a higher mean INR value (P = 0.01) than patients without GIB. Besides, the proportion of a history of GIB (P = 0.003), concomitant cirrhosis (P < 0.001), and septic shock (P < 0.001) was also significantly higher in GIB group patients than in non-GIB group patients.

3.1. Incidence and Characteristics of GIB. Thirty-six patients had at least one episode of GIB. The incidence of GIB was 3.9% per patient-year. There were totally 43 bleeding episodes in this cohort and the average episode of GIB was 1.1 per patient. The time between the use of warfarin and the first onset of GIB was 41.0 ± 58.4 months. Twelve patients (36.0%) had the first episode of bleeding within the first month after the start of warfarin anticoagulation. The presenting symptoms and signs of GIB included melena (15 patients, 41.7%), hematemesis (9 patients, 25.0%), hematemesis with melena (6 patients, 16.7%), hematochezia (3 patients, 8.3%), and a decrease of hemoglobin level more than 2 g/dL but negative for evident signs of GIB or occult blood test (3 patients, 8.3%).

Twenty-five of the 36 GIB patients underwent esophagogastroduodenoscopy (EGD) or colonoscopy according to the presentation of GIB. The causes of GIB included esophageal ulcer (1 patient, 4.0%), gastric ulcer (1 patient, 4.0%), duodenal ulcer (16 patients, 64.0%), gastric polyp (1 patient, 4.0%), rectal cancer (2 patients, 8.0%), and pseudomembranous colitis (1 patient, 4.0%) (Table 2). However,
Table 1: Demographic data of patients treated with warfarin.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients without GIB* (n = 365)</th>
<th>Patients with GIB* (n = 36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>64.1 ± 17.0</td>
<td>74.3 ± 12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>215</td>
<td>19</td>
<td>0.5</td>
</tr>
<tr>
<td>Smoking</td>
<td>101 (27.6%)</td>
<td>10 (27.7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol</td>
<td>73 (20.0%)</td>
<td>6 (16.6%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Indications for warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>63 (17.2%)</td>
<td>8 (22.2%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>28 (7.6%)</td>
<td>3 (8.3%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Valvular replacement</td>
<td>138 (37.8%)</td>
<td>10 (27.7%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>81 (22.1%)</td>
<td>8 (22.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Others</td>
<td>55 (15.0%)</td>
<td>7 (19.4%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Platelet count (K/cumm)</td>
<td>201.6 ± 139.2</td>
<td>206.8 ± 144.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean INR* value</td>
<td>1.8 ± 1.2</td>
<td>2.2 ± 1.7</td>
<td>0.01</td>
</tr>
<tr>
<td>History of GIB†</td>
<td>12 (3.2%)</td>
<td>5 (13.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>200 (54.8%)</td>
<td>22 (61.1%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>62 (16.9%)</td>
<td>6 (16.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>32 (8.7%)</td>
<td>6 (16.6%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1 (0.2%)</td>
<td>3 (8.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>27 (7.3%)</td>
<td>4 (11.1%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Malignancy</td>
<td>38 (10.4%)</td>
<td>5 (13.9%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Septic shock</td>
<td>2 (0.5%)</td>
<td>3 (8.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID†</td>
<td>6 (1.6%)</td>
<td>2 (5.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Aspirin</td>
<td>46 (12.6%)</td>
<td>4 (11.1%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>30 (8.2%)</td>
<td>1 (2.7%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>22 (6.0%)</td>
<td>5 (13.8%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Steroids</td>
<td>25 (6.8%)</td>
<td>4 (11.1%)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*INR: international normalization ratio.
†GIB: gastrointestinal bleeding.
‡NSAID: nonsteroidal anti-inflammatory drug.

Table 2: Endoscopic findings of warfarin anticoagulated patients with gastrointestinal bleeding.

<table>
<thead>
<tr>
<th>Source of bleeding</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper gastrointestinal bleeding</td>
<td></td>
</tr>
<tr>
<td>Esophageal ulcer</td>
<td>1 (4.0%)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1 (4.0%)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>16 (64.0%)</td>
</tr>
<tr>
<td>Gastric polyp</td>
<td>1 (4.0%)</td>
</tr>
<tr>
<td>Lower gastrointestinal bleeding</td>
<td></td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>2 (8.0%)</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>1 (4.0%)</td>
</tr>
<tr>
<td>No identifiable source</td>
<td>3 (12.0%)</td>
</tr>
</tbody>
</table>

no identifiable source of bleeding could be found in 3 patients (12.0%). One of these patients received both EGD and colonoscopy and the other two patients underwent EGD only because they refused colonoscopy. No enteroscopy or angiography was performed in these patients.

3.2. Risk Factors of GIB. We further stratified the patients according to the mean INR values and found that the incidence of GIB increased with higher intensity of anticoagulation (Table 3). A ROC curve found that a mean INR of 2.1 was the cut-off value which best discriminated patients with GIB from patients without GIB. Patients with advanced age also had a trend towards a higher incidence of GIB, especially in patients aged more than 70 years old (Table 4).

Univariate analysis with Cox regression showed that GIB was significantly related to age >65 years old (relative risk (RR): 2.5, 95% confidence interval (CI): 1.3–5.3, P = 0.02), a mean INR value > 2.1 (RR: 2.4, 95% CI: 1.2–4.5, P = 0.01), a history of GIB (RR: 4.6, 95% CI: 1.8–11.9, P = 0.002), and cirrhosis (RR: 8.9, 95% CI: 2.7–29.9, P < 0.001) (Table 5). Multivariate analysis with Cox regression revealed that age >65 years old (RR: 2.5, 95% CI: 1.2–5.5; P = 0.02), a mean
### Table 3: Incidence of gastrointestinal bleeding in relation to international normalization ratio.

<table>
<thead>
<tr>
<th>INR*</th>
<th>Events</th>
<th>Patients</th>
<th>Follow-up (months)</th>
<th>Events/patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.0</td>
<td>0</td>
<td>0</td>
<td>112</td>
<td>0</td>
</tr>
<tr>
<td>1.0–1.5</td>
<td>6</td>
<td>5</td>
<td>3278</td>
<td>2.1</td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>18</td>
<td>14</td>
<td>5412.5</td>
<td>3.9</td>
</tr>
<tr>
<td>2.1–2.5</td>
<td>11</td>
<td>9</td>
<td>2874</td>
<td>4.5</td>
</tr>
<tr>
<td>2.5–3.0</td>
<td>2</td>
<td>2</td>
<td>887</td>
<td>4.5</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>6</td>
<td>6</td>
<td>503.1</td>
<td>14.3</td>
</tr>
</tbody>
</table>

*INR: international normalization ratio.

### Table 4: Incidence of gastrointestinal bleeding in relation to age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Events</th>
<th>Patients</th>
<th>Follow-up (months)</th>
<th>Events/patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40</td>
<td>0</td>
<td>0</td>
<td>869</td>
<td>0</td>
</tr>
<tr>
<td>41–50</td>
<td>2</td>
<td>2</td>
<td>1273</td>
<td>1.8</td>
</tr>
<tr>
<td>51–60</td>
<td>6</td>
<td>5</td>
<td>2336</td>
<td>3.0</td>
</tr>
<tr>
<td>61–70</td>
<td>5</td>
<td>4</td>
<td>2115.5</td>
<td>2.8</td>
</tr>
<tr>
<td>71–80</td>
<td>13</td>
<td>10</td>
<td>3667</td>
<td>4.2</td>
</tr>
<tr>
<td>&gt;80</td>
<td>17</td>
<td>15</td>
<td>2806.1</td>
<td>7.2</td>
</tr>
</tbody>
</table>

### 3.3. Management of GIB and Outcome.

Intravenous vitamin K was administered in all GIB patients. Patients were transfused with 2.8 ± 5.0 units of packed red cells and 2.7 ± 6.3 units of fresh frozen plasma. Eight patients underwent endoscopic treatments including hemoclipping (4 patients), endoscopic injection therapy (3 patients), and argon plasma coagulation (1 patient). Uncontrolled bleeding was noticed in 2 patients with a history of GIB and cirrhosis. Warfarin was restarted in 22 patients (61.1%) in 7.9 ± 6.5 days after the GIB was controlled and none of these patients had thromboembolic events. However, recurrent GIB was found in 6 patients (27.3%). Of these patients, 1 patient presented with recurrent gastric ulcer bleeding, 2 patients presented with recurrent duodenal ulcer bleeding, and 2 patients presented with gastric cancer bleeding. One patient was among the patients with a decrease of hemoglobin level of more than 2 g/dL but negative for evident signs of GIB or occult blood test at the first bleeding episode and no bleeder could be identified at the rebleeding episode either. Warfarin was not restarted in 12 patients and none of them had recurrent GIB while cerebrovascular accident was noticed in 2 patients (16.7%). Fourteen GIB patients died. The causes of mortality included sepsis (6 patients), pneumonia (2 patients), subdural hemorrhage (1 patient), heart failure (2 patients), acute myocardial infarction (1 patient), and uncontrolled GIB (2 patients). In all 401 patients, the incidence of cerebral vascular accident and myocardial infarction was 1.2% (5 patients) and 0.7% (3 patients), respectively.

### 4. Discussion

We investigated the incidence, risk factors, management, and outcome of GIB in a cohort of warfarin anticoagulated Taiwanese patients. GIB occurred at an incidence of 3.9% per patient-year in this study. Age > 65 years old, a mean INR value > 2.1, a history of GIB, and cirrhosis were found to be independent risk factors of GIB. Warfarin was restarted in 61.1% of the GIB patients and 27.3% of them had recurrent GIB. Thromboembolic events were found in 16.7% of the patients who discontinued treatment of warfarin because of GIB.

GIB occurs at a rate ranging from 0% to 67% with an average bleeding rate of 3% in patients treated with warfarin [5]. The incidence of life-threatening and fatal hemorrhage episodes is around 5% and 1%, respectively [5]. Among our GIB patients, up to 33.3% of them had the first bleeding episodes within the first month of anticoagulation and 61.1% of the GIB occurred within the first year, which was consistent with the results of a meta-analysis [5]. This might be due to unstable intensity of anticoagulation during the early dosage adjustment period. As the INR values reach a stable therapeutic range, the bleeding incidence might decrease thereafter.

Polymorphisms in VKORC1 and CYP2C9 genes are associated with reduced doses of warfarin [12, 13]. The effect of warfarin is affected by genetic determinants of warfarin dosage, which may vary between different races. In our study, the bleeding incidence was similar to those of Western studies. It is possible that the genetic polymorphisms are similar between different races so the dosing of warfarin may only play a partial role in addition to anticoagulation intensity, drug interactions, and underlying diseases. Recently, two large randomized controlled trials compared clinically
guided dosing with genotype-guided dosing of warfarin in patients initiating anticoagulant therapy, and genotype-guided dosing strategy did not result in a better outcome in both studies [14, 15]. Therefore, close monitoring of INR testing is still the most important issue in patients initiating warfarin anticoagulation.

Several risk factors were found to be associated with GIB in this study. The incidence of GIB increased with the increment of the mean INR values, and a mean INR of 2.1 best discriminated the patients with and without GIB and patients with a mean INR of 3.0 or more carried the highest risk of GIB. This was not surprising because intensity of anticoagulation highly correlates with the risk of bleeding in warfarin anticoagulated patients in most studies [4, 5, 16]. Age > 65 years old was found to be significantly associated with GIB. Slow metabolized rate of warfarin, an elevated risk of drug interactions because of polypharmacy, and chronic illness were proposed to increase the risk of bleeding in elderly patients [17]. Whether older age increases the risk of bleeding in patients treated with warfarin is controversial [5]. However, it is well known that persons older than 80 or 85 years of age do carry a significant risk of bleeding [17, 18]. Therefore, warfarin should be cautiously used in elderly patients, especially in extremely old patients. Chronic liver disease had been shown to increase bleeding risks in hospitalized patients [19]. Although the mechanism is unclear, the relative deficiency in vitamin K dependent clotting factors causing bleeding tendency as seen in cirrhotic patients may play a role. We also found that a history of GIB increased the risk of GIB. Actually, concurrent use of proton pump inhibitors significantly reduces risk of GIB in patients treated with warfarin [20]. Therefore, acid suppressants may be considered in patients with a history of GIB during warfarin anticoagulation.

Most of the GIB events were controlled by vitamin K administration, blood transfusion, acid suppression, or endoscopic therapies. However, two fatal GIB events were noticed within the first month of warfarin anticoagulation. Both patients had a history of GIB and underlying liver cirrhosis. This suggested that patients with multiple risk factors of GIB might need more frequent testing of INR values, especially in the early stage of warfarin anticoagulation.

The pros and cons of restarting warfarin in the patients with GIB are rarely evaluated. It was noteworthy that warfarin was restarted in only 61.1% of our GIB patients and 27.3% of them experienced recurrent GIB while thromboembolic
events were noticed in 16.7% of the patients who did not continue warfarin therapy. The chance of rebleeding after successful hemostasis depends on the cause of bleeding [4], and patients with independent risk factors for GIB should be thoroughly evaluated before restarting warfarin. Long-term acid suppressants may be considered in patients with peptic ulcer bleeding. Besides, a policy of lower-intensity anticoagulation may be beneficial in most of the cases. A warfarin dose adjusted to maintain an INR of 1.4 or more was found to be effective in the primary prevention of coronary heart disease [21]. Recent guidelines also recommended using lower-intensity anticoagulation in patients older than 75 years of age [22]. To prevent the thromboembolic event while minimizing the risk of GIB, an anticoagulation intensity at an INR of 2.0 or less could be an alternative anticoagulation strategy to traditional range, that is, 2.0 to 3.0.

Some limitations do exist in this study. First, it was a retrospective study and the GIB rate may be underestimated because some GIB patients might not present to this hospital. Second, the pharmacogenetics information such as polymorphisms in VKORC1 and CYP2C9 genes was not available in this study. Third, only 70% of our GIB patients underwent endoscopy, which was similar to a previous study [3]. Besides, the bleeding source was not identified in 12% of the patients undergoing endoscopic examination. Excessive anticoagulation intensity may contribute to the low diagnostic rate of endoscopy [23]. Fourth, some patients were missing the information of the status of Helicobacter pylori (H. pylori) infection. Patients with H. pylori infection are well known to be at a higher risk of GIB. Whether eradication of H. pylori can decrease the risk of GIB in warfarin anticoagulated patients needs to be studied in the future. Finally, although cirrhosis and a history of GIB were found to be independent risk factors for GIB, the possibility of overinterpretation could not be overlooked because the numbers of these patients were relatively small and the confidence intervals were wide during subgroup analysis.

5. Conclusions

Our study found that warfarin therapy carried a similar risk of GIB in Taiwanese patients as compared with most Western studies. Old age, intensity of anticoagulation, a history of GIB, and advanced liver disease were associated with GIB. To decrease the risk of GIB while maintaining the effect of anticoagulation, frequent testing of INR values and a strategy of low to moderate intensity of anticoagulation could be considered in patients with risk factors of GIB. In terms of restarting warfarin following hemostasis in patients with GIB, long-term acid suppressants could be used in addition to more close monitoring of INR values and low to moderate intensity of anticoagulation.

Conflict of Interests

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interests.

References


Background. It is urgent to find alternative agents due to increasing failure rate of Helicobacter pylori (H. pylori) eradication. The study surveyed the long-term effect of silver nanoparticles (AgNP) on H. pylori based on Mongolian gerbil’s model.

Methods. Fifty gerbils were randomly allocated to six groups (A–F). Group (Gr) A: the gerbils were fed with broth; Gr B and D: the gerbils were fed with AgNP/clay complex (0.1% of weight); Gr C and E: the gerbils were fed with AgNP/clay complex (1% of weight); and Gr D, E, and F: the gerbils were inoculated with H. pylori. At the 20th experimental week, the gerbils were sacrificed. Histology was evaluated according to the classification of the Sydney system. P < 0.05 was considered to be statistically significant.

Results. The AgNP/clay has more obvious inhibitory effect on H. pylori in vitro. There was a trend of higher concentrations of AgNP with stronger inhibitory effect on H. pylori growth (P = 0.071). There were no significant differences of inflammation among groups D, E, and F (P = 0.688).

Conclusion. AgNP/clay would be a potential and safe agent for inhibiting H. pylori. It should be helpful for eradication of H. pylori infection.

1. Introduction

Helicobacter pylori (H. pylori) infection is an important factor of many gastrointestinal diseases such as chronic gastritis, peptic ulcer, and gastric cancer. Eradication of H. pylori is the most important strategy for treatment of these diseases. However, the failure rate of currently used first-line therapies has increased up to 30% [1–4]. Therefore, there is an urgent need to find alternative agents to improve the efficacy.

The potential side effects of bismuth decrease the compliance of second-line eradication therapies. For the conventional antimicrobial treatments, some metals including silver in large quantities are applied to control skin infection [5], so previous studies applied silver to be the alternative treatment.
for gastrointestinal symptoms and infections (including *H. pylori*) [6]. Besides this, silver compounds have been used as antiulcer agents [7]. Because *H. pylori* is a major peptic-ulcer cause, it is logical that the antiulcer activity of silver might be related to its effects on *H. pylori*.

Currently, metal-based nanopreparations have become more and more important in their applications in various fields including antimicrobial abilities [8–14]. The synthesis of silver nanoparticles (AgNP) has aroused more interest because of the broad applications including wound dressings and medical devices [10, 11, 13, 15, 16]. The possible mechanism of action of metallic agents is the inhibition of *H. pylori* urease [17–19]. However, previous studies were mostly in vivo studies, so we need an ideal animal model to survey the long-term effects of AgNP exposure on human physiology and *H. pylori*. Watanabe et al. [20] demonstrated that *H. pylori* infection could induce well-differentiated adenocarcinoma based on a Mongolian gerbil’s model. The Mongolian gerbils provide a suitable experimental animal model, so the aim of our study was to survey the long-term effect of AgNP on *H. pylori* based on a Mongolian gerbil’s model.

2. Materials and Methods

Experiments were performed according to the experimental guidelines of the Ethics Committee of Kaohsiung Medical University Laboratory Animal Center.

2.1. Animals and Housing. Eight-week-old gerbils with body weight of 30–40 g were purchased from the Kaohsiung Medical University Experimental Animals Center, Kaohsiung, Taiwan. In usual time, 4 to 5 gerbils per cage were housed and maintained under standard laboratory conditions (room temperature, 23°C–26°C; relative humidity, 55%–65%; 12/12-hour light/dark cycle) with free access to a commercial rodent diet and tap water.

2.2. Synthesis of AgNP/Clay Nanohybrid. The AgNP/clay complex was prepared via the reduction of silver ions in solution (3.4 g, 1.0 wt% in water; J.T. Baker, USA) was added to this slurry. The reducing agent was prepared by swelling in deionized water at 80°C. In usual time, 4 to 5 gerbils per cage were housed and maintained under standard laboratory conditions (room temperature, 23°C–26°C; relative humidity, 55%–65%; 12/12-hour light/dark cycle) with free access to a commercial rodent diet and tap water.

2.3. Dose Escalation of AgNP. Part I: the optimal concentration of the antibacterial activity of AgNP/clay: AgNP/clay (0.06%, 0.08%, 0.1%, 0.2%, and 0.3% of weight) was added into the Brucella broth containing bacteria $1 \times 10^3$ CFU/mL and then they were incubated at 37°C. The incubation time was 12 hours. Then 100 μL of these cultured broths were spread on CDC Anaerobe 5% Sheep Blood Agar (BD, USA) and incubated at 37°C with 5% O$_2$ conditions. The colony numbers were counted after 48 hours of incubation. Part II: the time course of the antibacterial activity of AgNP/clay: AgNP/clay (0.01%, 0.05%, and 0.1% of weight) was added into the Brucella broth containing bacteria $1 \times 10^3$ CFU/mL and then they were incubated at 37°C. The incubation time was 0, 0.5, 1, 2, 4, 12, and 24 hours, respectively. Then 100 μL of these cultured broths was spread on CDC Anaerobe 5% Sheep Blood Agar (BD, USA) and incubated at 37°C with 5% O$_2$ conditions. The colony numbers were counted after 48 hours of incubation.

2.4. *H. pylori* Inoculation. The gerbils were randomly allocated to six groups according to a randomized number (A–F): group A: the gerbils were fed with broth only; group B: the gerbils were fed with AgNP/clay complex (0.1% of weight) in the 8th to 20th week; group C: the gerbils were fed with AgNP/clay complex (1% of weight) in the 8th to 20th week; group D: the gerbils were inoculated with *H. pylori* (CagA (+)/VacA (+)) during the 1st to 4th week and then they were fed with AgNP/clay complex (0.1% of weight) in the 8th to 20th week; group E: the gerbils were inoculated with *H. pylori* (CagA (+)/VacA (+)) during the 1st to 4th week and then they were fed with AgNP/clay complex (1% of weight) in the 8th to 20th week; group F: the gerbils were inoculated with *H. pylori* (CagA (+)/VacA (+)) during the 1st to 4th week. At the end of the 20th experimental week, the animals were fasted for 24 hours before being sacrificed (Figure 1).

2.5. Histological Evaluation of the Gastric Mucosa in Gerbils. Samples of the gastric mucosa were excised from each gerbil stomach for the assessment of the presence of *H. pylori* and gastric inflammation using Giemsa and hematoxylin-eosin (HE) staining for histological examination, respectively. The samples were fixed in 10% buffered formalin and embedded in paraffin [II–34]. The paraffin sections were cut at a thickness of 5 mm and stained. Two experienced pathologists, blinded to the treatment given, performed histological examinations. Histological features of mucosal inflammation and intestinal metaplasia were evaluated for each specimen under a light microscope according to the classification of the Sydney
Figure 1: The timing of AgNP/clay and H. pylori given. Group (Gr) A: the gerbils were fed with broth only. Gr B and D: the gerbils were fed with AgNP/clay (0.1% of weight) in the 8th to 20th week. Gr C and E: the gerbils were fed with AgNP/clay (1% of weight) in the 8th to 20th week. Gr D, E, and F: the gerbils were inoculated with H. pylori [CagA (+)/VacA (+)] in the 1st to 4th week. At the end of the 20th experimental week, the animals were fasted for 24 hours before being sacrificed.

system. The degree of inflammatory cell infiltration and the area of intestinal metaplasia were scored as follows: 0, normal; 1, mild; 2, moderate; 3, marked.

2.6. Statistical Analyses. We analyzed the collected data using the statistical software package SPSS. Kruskal-Wallis test was used for comparing histological change of mucosa. \( P < 0.05 \) was considered to be statistically significant.

3. Results

The inhibitory effects of different materials on H. pylori were surveyed. The results revealed that AgNP/clay has more obvious inhibitory effect on H. pylori. This inhibitory effect became more obvious when the concentration of AgNP/clay was more than 0.08% of weight. However, the clay did not show any inhibitory effect in any concentration. The AgNP had mild inhibitory effect only at high concentration (0.3% of weight) (Figure 2).

We surveyed the reaction time of inhibiting H. pylori in different concentrations of AgNP/clay. We found that the higher the concentration of AgNP/clay, the shorter the reaction time. In concentration of 0.1% weight of AgNP/clay, H. pylori would be completely inhibited since the 12th hour and this effect would persist up to the 24th hour (Figure 3). So the optimal frequency of feeding AgNP/clay might be daily.

Fifty gerbils were used in this study. The numbers of gerbils in each group were 6 (Gr A), 6 (Gr B), 6 (Gr C), 11 (Gr D), 15 (Gr E), and 6 (Gr F), respectively. The study design is shown in Figure 1. In our study, all gerbils were alive till the end of this experiment, and there was no significant difference in the survival rates among the various groups. On the 13th week, the positive rates of H. pylori were all 100% in groups D, E, and F.

Figure 2: The inhibitory effects of different materials on H. pylori were surveyed. The results revealed that AgNP/clay has more obvious inhibitory effect on H. pylori (concentration more than 0.08% of weight). However, clay did not have the inhibitory effect and the AgNP had mild inhibitory effect only at high concentrations. H. pylori: Helicobacter pylori; AgNP: silver nanoparticles.

We surveyed the densities of H. pylori in groups D, E, and F. We wanted to survey the inhibitory effect of AgNP on H. pylori. The average densities of H. pylori (according to Sydney classification) were 1.45±0.52, 1.27±0.70, and 1.83±0.41 in Gr D, E, and F, respectively. It did not show significant difference between the three groups (\( P = 0.071 \)); however, we found the trend that higher concentrations of AgNP had stronger effect on inhibiting H. pylori (Figures 4 and 6).

The possible toxic effect of AgNP on gastric mucosa and its interaction with H. pylori were also surveyed. We showed the severity of inflammation of gerbil’s mucosa according to
4. Discussion

The approaches to overcoming drug resistance include increasing the dosage and treatment duration of drugs and using multiple drugs or pretreatment with agents to reduce bacterial load. The agents used to decrease H. pylori load include probiotics, bismuth, or some herbs. Our study was designed to survey whether AgNP could reduce the H. pylori load in gerbils.

To the best of our understanding, the present investigation can be considered to be the first report of the anti-H. pylori activity of silver nanoparticles based on a gerbil model. A previous study showed that silver nanoparticles may have the effect of inhibiting urease activity of H. pylori [19]. However, these previous studies were under the evidence of in vitro studies. We chose 13 weeks as the intervention's duration according to our previous preliminary data (not published) of Mongolian gerbil's model. We found that H. pylori would induce obvious inflammation since this time point. So we expected that there might be obvious difference in different groups at this time point.

According to our results, AgNP could not completely inhibit the growth of H. pylori neither in low nor high concentrations of AgNP. But AgNP showed the potential effect of decreasing densities of H. pylori and also had dose-dependent response. This supported the notion that AgNP might be a bacteriostatic agent for H. pylori. Our results supported the finding of a previous study [19]. The effect of inhibition was directly related to AgNP/clay itself but not free silver ion in solution, because the synthesized AgNP/clay was nearly free of Ag⁺ leaching from the nanohybrid, even after a storage period of six months at room temperature.

Multiple investigations have been performed to show the antibacterial activity of metals and metals chelated with some ligands against H. pylori [22, 23]. According to a previous report, the charged clay could trap bacteria and the close interfacial interaction between bacteria and AgNP plays a cardinal role in inhibiting bacteria [15]. The contact and interaction between the AgNP/clay and the cell wall of bacterium is important to trigger a cytotoxic signal; unfortunately, H. pylori was colonized within the gel layer of gastric mucosa and we thought that the gel layer might interfere with the contact between H. pylori and AgNP/clay. This should be one of the reasons in which H. pylori was not inhibited obviously in our gerbil's model.

A previous study found that under anaerobic conditions, newly synthesized AgNP/clay still enabled suppression of cell growth as efficiently as under aerobic conditions [15]. So its effect would not be influenced by the microanaerobic environment in which H. pylori lives. Another possible challenge is the acidic environment in the stomach; one study revealed that the bactericidal effect would diminish in an acidic environment [24]. This might be one of the reasons that AgNP/clay only had bacteriostatic effect in the gerbil's stomach.

The bacterial load is an important factor for eradication of H. pylori. Previous studies demonstrated that decreasing the amount of H. pylori would increase the success rate of eradication [25]. They usually used bismuth as the agent for...
inhibiting \textit{H. pylori}, but the side effects of bismuth were obvious and would decrease the compliance and success rates. Another method might use more complex regimens, such as sequential therapies, to achieve successful eradication by lowering bacterial load. In our study, we found that AgNP had the effect of inhibiting \textit{H. pylori}. Our study might provide another reliable way to help us eradicate \textit{H. pylori}.

A previous study in vitro demonstrated that urease inhibitory activity increased linearly with increased concentration of AgNP. So we tried two different doses of AgNP/clay...
to previous study [6], the paper clearly demonstrated that mucosal damage was found in groups B and C. According to toxic effect on gastric mucosa. In our results, no obvious mucosal damage was found in groups B and C. According to previous study [6], the paper clearly demonstrated that fed silver nanoparticles were not absorbed by animal. In our study, we did not find any evidence about AgNP absorbed by gastrointestinal mucosa. However, further survey and longer observation period would be needed for application of AgNP in human.

There were some limitations of our study. One was the duration of feeding AgNP. To our best knowledge, there is no previous similar design reported in Mongolian gerbil’s model, so we did not know the optimal intervention period. It might need longer therapeutic period for obtaining obvious inhibitory effect. Another limitation was the unequal number of gerbils used in these groups. However, we used more gerbils in groups D and E (fed both H. pylori and AgNP). The number per group of gerbils used in previous studies was around six to ten, so the number of gerbils used in our study groups A, B, C, and F was enough for analysis. Besides this, we kept feeding gerbils during the experiment and the various ions in the food might have interaction with AgNP/clay. So the effect of AgNP/clay on H. pylori was possibly diminished.

In summary, our study showed that AgNP/clay would be a potential and safe agent for decreasing the amount of H. pylori infection and needs further survey on the method given.

Conflict of Interests

All the authors have no conflict of interests to declare.

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References


