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Randomized Controlled Trial Comparing Standard Triple and Sequential Regimens for *Helicobacter pylori* Eradication

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Objectives: The aim of this study was to compare effectiveness of sequential therapy to the standard triple therapy to eradicate *Helicobacter pylori (H. pylori)* in Mongolia. **Methods:** From September 2014 to February 2016, 140 patients with confirmed *H. pylori* infection (upper gastrointestinal tract (GI) endoscopy, rapid urease test, histology, *H. pylori* stool antigen test (HpStAg)) randomly received 10 days standard triple therapy (20 mg pantoprazole, 1 g amoxicillin, 500 mg clarithromycin, all twice daily for 10 days; STT group, n = 70), and sequential therapy (20 mg pantoprazole, 1 g amoxicillin twice daily for 5 days followed by 20 mg pantoprazole, 500 mg clarithromycin, 500 mg metronidazole twice daily for 5 days; SQT group, n = 70). Successful eradication therapy for *H. pylori* infection was defined as a negative HpStAg test 4 weeks after the end of eradication treatment. **Results:** The eradication rates by intention to treat (ITT) analysis were 71.4% (50/70) and 50% (35/70) in the STT and SQT groups, respectively (p = 0.033). The eradication rates by per-protocol (PP) analysis were 72.5% (50/69) and 51.5% (35/68) in the STT and SQT groups, respectively (p = 0.018). The adverse event rates were 7.6% (5/70) and 18.6% (13/70) in the STT and SQT groups, respectively (p = 0.043). **Conclusion:** The eradication rate was significantly higher in the STT group compared with the SQT group. But the eradication efficacies of both STT and SQT for *H. pylori* infection in Mongolia are unacceptable.

Keywords: *Helicobacter pylori,* Disease Eradication

Introduction

Helicobacter pylori (H. pylori) infects approximately 50% of the population worldwide [1]. As in other developing countries, prevalence of *H. pylori* infection is reported to be high in Mongolia, which is thought to be related to poor sanitary conditions [2]. The prevalence was 69-76% among adults [3, 4], 64% among adolescents, 65-100% among pediatric patients with gastric comorbidity [5], and 65.7% among patients diagnosed with gastric ulcer [6].

Treatment of *H. pylori* infection is paramount for the management of prevalent gastrointestinal disorders including

peptic ulcer disease and gastric cancer [7, 8]. Until now, the gold standard of *H. pylori* eradication regimen has been triple therapy, consisting of proton-pump inhibitor (PPI), amoxicillin (AMX), clarithromycin (CAM) or metronidazole (MNZ) with a duration of 7-14 days [9, 10]. However, successful *H. pylori* eradication rates with standard triple therapy (STT) have been plummeting down due to increasing antibiotic resistance, having declined to as low as below 70% in many countries [10, 11]. Therefore, many investigators have attempted to introduce regimens with higher efficacy for *H. pylori* eradication. Several strategies, including sequential therapy (SQT), concomitant therapy, and bismuth-containing quadruple therapy have therefore been proposed to increase the eradication rate [12-15]. SQT consists of a PPI and AMX for the first 5 days, followed by a PPI plus CAM and MNZ for another 5 days. SQT has been shown to be more effective than STT in multiple randomized controlled trials and several meta-analyses, although several studies have also demonstrated conflicting results [14-16]. In Mongolia, no previous studies investigating the *H. pylori* eradication rate exist. The purpose of this study was to compare the efficacy of SQT to that of STT in eradicating *H. pylori*.

Materials and Methods

1. Subjects

The open-labeled randomized trial was conducted at the Department of Gastroenterology, Mongolian National University of Medical Sciences in accordance with the principles of good clinical practice according to the Declaration of Helsinki. Written informed consent was obtained from all participants, and the study protocol was approved by the Medical Committee of the Mongolian National University of Medical Sciences (Ulaanbaatar, Mongolia).

Consecutive outpatients complaining of dyspeptic symptoms referred for upper GI endoscopy in the participating center in Ulaanbaatar, Mongolia were considered for recruitment to the study. Exclusion criteria were: age <18 years; previous *H. pylori* eradication therapy; consumption of PPI, histamine H_2-receptor antagonists, bismuth and/or antibiotics, concomitant anticoagulant, nonsteroidal anti-inflammatory drugs, or ketoconazole within the previous 4 weeks; patients with allergic history to the medications used; previous surgery of the stomach, including endoscopic mucosal or submucosal resection for adenoma or early gastric cancer; patients with peptic ulcer disease and gastric cancer; the coexistence of serious concomitant illness (for example, decompensated liver cirrhosis or kidney failure); alcohol abuse; pregnancy or lactation; Zollinger- Ellison syndrome; hematological disorders; and severe psychiatric or neurological disorders.

2. Endoscopy and *H. pylori* detection

All patients underwent upper GI endoscopy and gastric biopsy was taken according to the updated Sydney System [17]. Before enrollment, the status of *H. pylori* infection was determined by a rapid urease test (Mon HP), histology (Eosin & Hematoxylin staining and modified Giemsa staining), and *H. pylori* stool antigen test (SD BIOLINE *H. pylori* Ag Enzyme-Linked Immunosorbent Assay (ELISA) kit, Korea). Patients with positive results in at least two of these tests were eligible for enrollment. *H. pylori* eradication was checked 6-8 weeks following therapy by using the SD BIOLINE *H. pylori* stool antigen test according to the manufacturer's directions.

3. Randomization and treatment

Using a computer-generated number sequence, the eligible *H. pylori*-infected patients were randomly assigned to the STT group (20 mg pantoprazole twice daily, 1 g amoxicillin twice daily and 500 mg clarithromycin twice daily for 10 days) and the SQT group (20 mg pantoprazole twice daily and 1 g amoxicillin twice daily for 5 days, followed by 20 mg pantoprazole twice daily, 500 mg clarithromycin twice daily and 500 mg metronidazole twice daily for 5 additional days). An independent research assistant generated the computerized random number sequence. PPIs were given a half-hour before breakfast and dinner while antibiotics were given following these meals. All patients received 2 weeks monotherapy with 20 mg pantoprazole orally once daily following eradication therapy. At the end of the treatment, both side effects and therapeutic compliance were assessed by personal interview.

The patients were informed of the common adverse events from the study drugs before treatment and were asked to record these symptoms during treatment in provided diaries. The adverse events were assessed according to a 4-point scale system: 1 = none, 2 = mild (discomfort annoying but not interfering with daily life), 3 = moderate (discomfort sufficient to interfere with daily life), and 4 = severe (discomfort resulting in

discontinuation of eradication therapy).

Compliance to treatment was considered excellent if the patient took more than 90% of the medication, moderate if he/she took 70-90% of the medication, and poor if the patient took less than 70% of medications.

4. Statistical analysis

All statistical analyses were performed using the SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA). Comparisons between patient groups were performed by using the t-test for unpaired data and the Chi-squared test, as appropriate. The eradication rates with their 95% confidence intervals (CI) were calculated at both 'intention-to-treat' (ITT) and at 'per protocol' (PP) analyses. At ITT, all the enrolled patients were included, whilst at PP only compliant patients who had done HpStAg test control were considered. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

A total of 140 *H. pylori*-infected patients were randomly assigned to receive STT (n = 70) or SQT (n = 70). Patients were enrolled from September 2014 to February 2016. The data regarding the clinical characteristics of the patients are summarized in Table 1.

The subjects were all included in the ITT analysis for *H. pylori* eradication. A total of 137 patients completed the study. One patient in the STT group and one patient in the SQT group did not perform the control HpStAg ELISA test. One patient in the SQT group had interrupted therapy because of severe adverse effects. Therefore, the STT and SQT groups had 69 and 68 patients at PP analysis, respectively (Figure 1).

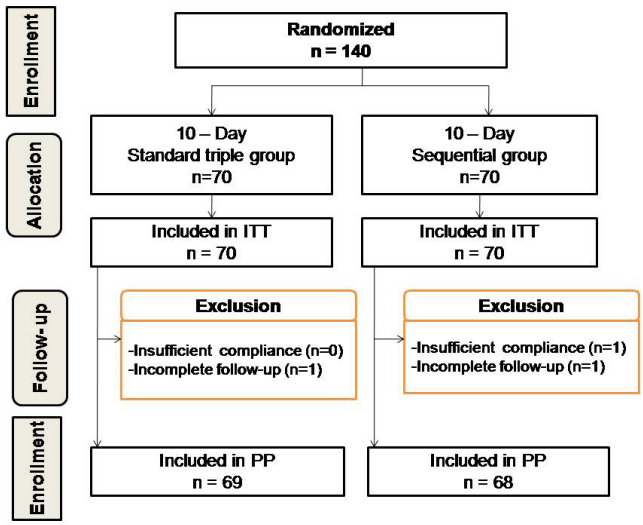

Figure 1. Flowchart of patients in the study.

Compliance to treatment was excellent in 70 patients (100%) of the STT group. In the SQT group, compliance to treatment was excellent in 69 patients (98.5%) and poor in 1 patient (1.5%) (p = 0.78).

Overall 5 (7.6%) and 13 (18.6%) patients in the STT and SQT complained of side effects. The rate of side effects of the SQT was more than the STT (p = 0.04). One of the patients in the SQT group stopped the medication due to moderate vomiting and severe nausea (Table 2).

According to ITT analysis, the eradication rates were 71.4% and 50.0% in the STT and SQT groups, respectively (p = 0.033). PP eradication rates were 72.5% and 51.5%, respectively (p = 0.018, Table 3).

Table 1. Demographic and clinical characteristics of the enrolled patients

Characteristic	Standard triple (n)	Sequential (n)	p-value
Total patients	70	70	-
Age (years)	38.7 ±15.6[a]	37.1 ±12.7[a]	0.64
Sex (male/female)	32/38	36/34	0.03
Smoking habit (yes/no)	11/59	13/57	0.82

[a]Mean ±SD

Table 2. Adverse effects reported by the patients during treatment

Adverse event	Total number of patients (number of patients with mild/ moderate/ severe adverse events)	
	Standard triple (n = 70)	Sequential (n = 70)
Nausea	0 (0/0/0)	6 (0/5/1)
Vomiting	0 (0/0/0)	4 (0/4/0)
Taste perversion	0 (0/0/0)	1 (0/2/0)
Diarrhea	1 (1/0/0)	1 (1/0/0)
Headache	1 (1/0/0)	0 (0/0/0)
Weakness	1 (1/0/0)	0 (0/0/0)
Skin rash	2 (2/0/0)	0 (0/0/0)
Other	0 (0/0/0)	1 (1/0/0)

Table 3. Major outcomes of the two therapies

Outcome characteristic	Rate % (number/total number)		p-value
	Standard triple therapy (n = 70)	Sequential therapy (n = 70)	
Eradication rate			
Intention-to-treat	71.4 (50/70)	50.0 (35/70)	0.033
Per-protocol	72.5 (50/69)	51.5 (35/68)	0.018
Adverse events	7.6 (5/70)	18.6 (13/70)	0.043

Discussion

If we consider *H. pylori* infection as an infectious disease, an ideal regimen would be the one that can eradicate *H. pylori* in more than 95% of cases, with less than 5% severe adverse effects. According to Graham's classification, the efficacy of *H. pylori* eradication regimens are considered as: A = excellent (>95% PP eradication rate), B = good (90-95%), C = fair (85-89%), D = poor (81-84%), and F = unacceptable (≤80% PP eradication rate) [18]. Therefore in our study, STT and SQT regimens are classified as unacceptable regimens since the eradication rates were 72.5% and 51.5%, respectively. The rate of side effects is also an important issue. Incidence of adverse events was significantly higher in the SQT group compared with the STT group.

In Mongolia, no study had previously evaluated *H. pylori* eradication rate. Therefore we cannot compare our results with the studies in our country. But, in other countries, STT and SQT have mostly achieved poor and unacceptable *H. pylori* eradication rates. Since 1982, many investigations have been performed to introduce a regimen with an ideal *H. pylori* eradication rate. The efficacy of STT is constantly decreasing worldwide recently. Two meta-analyses including more than 53,000 patients have shown that the ITT cure rate is less than 80%. The most important explanation for the decrease in efficacy of the STT is the increase in *H. pylori* resistance to CAM [19-21].

Sequential therapy was introduced as a novel therapeutic approach for *H. pylori* eradication by Zullo et al. in 2000 [22]. This regimen is strictly an innovative approach rather than a new strategy because it is based on a different combination of well-known drugs with an approved indication for *H. pylori* eradication. Meta-analyses conducted between 2007 and 2009, pooling mostly Italian evidence, confirmed the advantage of 10-day SQT (cure rates >90%) over 7- or 10-day STT [15, 16, 23, 24]. In 2012 and 2013, two updated meta-analyses [25, 26] and two systematic reviews [27, 28], including studies on sequential therapy from Asia, Europe, and Latin America, showed that the mean eradication rates were dramatically lower (79-84%) than those reported in the early Italian trials [15, 16, 23, 24]. These poor results were confirmed in a global meta-analyses in 2013

when overall cure rates were found to be 84% [29].

Some studies reported that CAM resistance decreased the efficacies of both SQT and STT, and that MNZ resistance decreased the efficacy of SQT. In 2014, Zhou et al. reported no significant difference between the eradication rates achieved with STT (66.4%) and SQT (72.1%) in either the ITT analysis or the PP analysis (72.7% and 76.5%, respectively) [30]. Patients in the SQT group with dual CAM-resistance and MNZ-resistance had a low eradication rate (43.9%) [30]. Therefore, the results of our study may be partly due to the increasing prevalence of antibiotic resistance.

The most commonly used antibiotics in the first line treatment of *H. pylori* in Mongolia include AMX, CAM, or MNZ. The unpublished result from our group reported that the antibiotic resistant strains of *H. pylori* were common in the Mongolian population (the resistance rate for AMX, CAM and MNZ were 17.6%, 37.4% and 72.5%, respectively). The current recommendations from the Maastricht IV guidelines showed that in an area where the resistance rate of CAM is more than 15-20%, it would be not recommended to use the STT [10]. Therefore, regimens including CAM are also not suitable and should not be chosen as first-line treatments in Mongolia. *H. pylori* resistance to MNZ was very high (72.5%) in Mongolia. This finding was consistent with other studies from developing countries, possibly due to the common use of MNZ to treat parasitic infections, periodontal, and gynecological diseases in developing countries, including Mongolia. Considering the high prevalence of MNZ resistance, the question arises whether we should continue to use MNZ widely in the first-line treatment of *H. pylori* in Mongolia.

Black market drugs and the over the counter availability of antibiotics to the general population is a major problem in Mongolia. This fact could be partly responsible for such a high prevalence of *H. pylori* resistance to the three antibiotics tested. Here, our results provide more evidence for enforcing stricter drug regulation policy in Mongolia in the long term. In the near future, it is necessary to continuously monitor *H. pylori* resistance to drugs used in eradication therapies, especially information on resistance to CAM and MNZ is most valuable. This knowledge should be organized into suggested first- and second-line treatment guidelines by the professional bodies and communicated to the medical community on a periodic basis to optimize therapy.

The main limitations of this study were the fact that it was a single-center study conducted on a small sample size, taken from a geographically limited population in Ulaanbaatar, Mongolia. Furthermore, due to the nature of design of the study, treatment was provided in an open-label manner with inadequate blinding. The strong point of this study is it being the first study that is evaluating the effect of STT and SQT on *H. pylori* eradication in Mongolia.

In conclusion, the eradication rate was significantly higher in the STT group compared with the SQT group. But the eradication efficacies of both STT and SQT for *H. pylori* infection in Mongolia were unacceptable. We suggest more evidence-based search and adoption of alternative standard treatment regimens with good efficacy and safety. In the case of failing first line therapy, an individual antibiotic resistance study-led approach should be undertaken. Therapy duration is one of the factors that increased therapeutic efficacy. Future studies into alternative treatment should also include head-to-head comparison of the same regimens with 10- and 14-day therapy durations to increase efficacy.

Conflict of Interest

The authors state no conflict of interest.

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