High-Dose Dual Therapy versus Triple Therapy for Treatment of *H. Pylori* Infection: A Parallel Randomized Study

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**ABSTRACT**

The prevalence of antibiotic resistance has considerably increased and as a result, the elimination pace of Helicobacter pylori (*H. pylori*) infection have decreased significantly to an unacceptable level. High dose dual therapy (HDDT) has been suggested as an alternative to standard triple therapy (TT) for the first-line treatment of *H. pylori* infection. The aim of the present work was to compare the effectiveness and tolerability of HDDT with standard TT, for treatment of *H. pylori* infection. This randomized parallel interventional study was carried out on 130 treatment naïve *H. pylori* infected patients, selected from outpatient clinic of Hepatology and Gastroenterology department of Zagazig University Hospitals, in the duration between November 2017 and December 2018. All patients were *H. pylori* positive as was evidenced by stool antigen test. Patients were divided into two groups; group A (n=65) received a 14-day HDDT (esomeprazole 40 mg twice daily and amoxicillin 1 g three times daily) whereas group B (n=65) received a 14-day TT (esomeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg, each administered twice daily). Eradication rates, side effects and drug compliance were compared among both groups. The eradication rate between the two regimens was not significantly different. The eradication rates were 80% for TT and 72.3% for HDDT (P= 0.3). No significant differences were observed between both groups regarding the side effects or patient adherence. HDDT is as effective and safe as TT as empiric first-line therapy for *H pylori* infection.

**INTRODUCTION**

Helicobacter pylori (*H. pylori*) is one of the most common infections worldwide (Carrasco and Corvalan, 2013). *H. pylori* has been linked to a wide spectrum of gastrointestinal diseases including duodenal or gastric ulcers, gastric cancer and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma (Mccoll, 2010). The use of traditional triple therapy (TT) consisting of amoxicillin or metronidazole, clarithromycin and proton pump inhibitor (PPI) is recommended by many guidelines as the first treatment line (Chey et al., 2017; Fock et al., 2009; Malfertheiner et al., 2012). High rate of treatment failure for *H. pylori* infection due to increas-
ing antibiotic resistance is a growing universal concern (Graham and Fischbach, 2010; Malfertheiner et al., 2012). The failure of the first treatment line can significantly let secondary antibiotic resistance evolve (Heep et al., 2000; Peitz et al., 2002). In regions with H. pylori antibiotic resistance with a consequent failure of treatment protocol, antimicrobial susceptibility testing is recommended. However, such testing is not readily accessible in the majority of regions, and it depends on the techniques available (Graham and Fischbach, 2010; Malfertheiner et al., 2012). Therefore, designing a treatment protocol of high efficacy, high tolerability, cost-effective as well as being empirically applied without the need for microbial susceptibility testing is becoming a pivotal necessity (Yang et al., 2015).

Unfortunately, the prevalence of H. pylori resistance to clarithromycin and metronidazole has increased greatly in recent years (Francesco et al., 2010; Megraud et al., 2013). On the contrary, the resistance of H. pylori to amoxicillin is extremely low, whether primary resistance or acquired resistance (Glupczynski et al., 2001; Heep et al., 2000). Amoxicillin has a characteristic property as it depends on pH and on time in exerting its bactericidal effect against H. pylori (Berry et al., 1995). Amoxicillin is effective when the intragastric pH is high (> 5.5) (Safari et al., 2016), so giving the PPI simultaneously is compulsory (Goddard et al., 1996). Also, H. pylori are reproducible and so become susceptible to amoxicillin in an intragastric pH of more than 6, and the bacteria are in a viable state but turn into a non-reproducible state when the intragastric pH is less than 6 (Safari et al., 2016). PPI at a higher doses than the used in standard treatment regimens can be more effective in decreasing gastric acidity and maintaining the pH at a high level, which can also, enhance both the oral bio availability and the stability of amoxicillin in the stomach (Gao et al., 2016).

The efficacy of amoxicillin depends on time rather than plasma concentration and therefore its effect is dependent on the period in which the concentration remains higher than the minimum inhibitory concentration (MIC) (Marcus et al., 2016). So, small and more frequent administration of amoxicillin is more effective compared to less frequent high dose regimen (Yang et al., 2014). The amoxicillin is absorbed rapidly from gastrointestinal tract (GIT) into the blood stream and it is excreted after 6 to 8 hours of administration. So, Administration of 500 – 750 mg three or four times a day will probably lead to a higher amoxicillin blood concentration than if it is administered as 1000 mg twice daily (Gao et al., 2016). Moreover, previous in-vitro studies on esomeprazole showed higher antibacterial activity against H. pylori as compared to other PPIs members like omeprazole, and an improvement of the eradication rate against H. pylori was suggested (Gatta et al., 2003). A combination of high-dose esomeprazole, which has the advantage of raising the pH of the stomach as well a direct activity against the bacteria, and high-dose amoxicillin, that is characterized by very low primary resistance, may therefore be an ideal first-line therapy for H. pylori induced gastric disorders (Zullo et al., 2015).

**Aim of the study**

- To compare the effectiveness of high dose dual therapy (HDDT) with the currently recommended standard TT, for H. pylori eradication.
- To compare the tolerability of these two regimens regarding the gastric upset and other expected side effects such as (diarrhea, Nausea and bad taste).

**MATERIALS AND METHODS**

This randomized parallel interventional study was carried out at the outpatient clinic of Hepatology and Gastroenterology Department of Zagazig University Hospitals, Zagazig, Egypt, during the period between November 2017 and December 2018. All consecutive patients were included (130) treatment between November 2017 and December 2018. All consecutive patients were included (130) treatment naive H. pylori infected patients; whose ages ranged from 18 to 65 years. They were proved to be H. pylori infected as evidenced by using H.pylori stool antigen test (Foresight® H. pylori Antigen EIA Test Kit, ACON Laboratories, Inc., Mesa Rim Road, San Diego, CA, USA) according to the manufacturer’s instructions. Exclusion criteria included pregnant and lactating patients, patients with a history of severe ulcer bleeding, malignant tumors, serious concomitant diseases, hypersensitivity to any of the administered drugs, previous treatment of H. pylori infection, taking PPIs or antibiotics in the previous month and previous gastric surgeries. Patient’s demographic information including age, gender, weight, height, smoking history, occupation and address was obtained. All patients in the current study were subjected to intricate medical history with symptoms collection and clinical examination. This study was approved by the committee of medical ethics of Zagazig university (IRB number: 5234). A written informed consent was taken from each participant to take part in the study.

**Study design**

Using a computer generated randomization software, we divided the patients in the current work randomly into two equal groups (1:1) ratio.
• **Group A**: The patients in this group (n = 65) received HDDT consisting of esomeprazole (40 mg b.i.d) and amoxicillin (1 g t.i.d) for 14 days. While the proton pump inhibitor was given half an hour before breakfast and dinner, the amoxicillin prescribed dose was given after breakfast, lunch and dinner.

After 14 days of treatment in both groups, the patients were interviewed in the clinic to investigate their compliance and the adverse effects of treatment. Patients were instructed to return empty packs and all unused medications. Compliance was estimated using pill counting method. Adherence was described as the use of over 90% of the prescribed drugs. Adverse effects were reported; any experienced symptoms after ingesting the drugs were considered as adverse effects. Any symptom that caused patients to discontinue treatment was considered severe Figure 1.

**Eradication assessment**

All patients returned 4 weeks after treatment cessation to assess eradication of *H. pylori* infection through stool antigen test. PPI use was prohibited during the two weeks period before the test. And the use of any antibiotics was also prohibited during the four weeks period prior to assessment of therapeutic efficacy.
Table 1: Demographic data distribution between studied groups.

|                          | HDDT group | TT group | t/ X2 | P     |
|--------------------------|------------|----------|-------|-------|
| Age (mean±SD, years)     | 32.96±7.98 | 32.4±7.59| 0.417 | 0.678 |
| Weight (mean±SD, Kg)     | 80.01±7.25 | 80.21±6.16| -0.169| 0.866 |
| Height (mean±SD, cm)     | 166.72±4.17| 167.64±3.96| -1.292| 0.199 |
| BMI (mean±SD)            | 28.8±2.65  | 28.53±1.92| 0.665 | 0.507 |
| Sex                      |            |          |       |       |
| Female                   | 36 (55.4%) | 38 (58.5%)| 0.12  | 0.72  |
| Male                     | 29 (44.6%) | 27 (41.5%)|       |       |
| Smoking                   |            |          |       |       |
| No smoking               | 47 (72.3%) | 47 (72.3%)| 0.0   | 1.0   |
| Smoke                    | 18 (27.7%) | 18 (27.7%)|       |       |

Table 2: Differences in clinical presentations between studied groups.

|                  | Group | Total | X² | P |
|------------------|-------|-------|----|---|
|                  | HDDT | TT    |    |   |
| Abdominal pain   |       |       |    |   |
| Abdominal pain   | N(%)  | 38(58.5%) | 43(66.2%) | 81(62.3%) |
| Non              | N(%)  | 27(41.5%) | 22(33.8%) | 49(37.7%) |
| Nausea           |       |       |    |   |
| Nausea           | N(%)  | 16(24.6%) | 12(18.5%) | 28(21.5%) |
| No               | N(%)  | 49(75.4%) | 53(81.5%) | 102(78.5%) |
| Vomiting         |       |       |    |   |
| Vomiting         | N(%)  | 13(20.0%) | 10(15.4%) | 23(17.7%) |
| Non              | N(%)  | 52(80.0%) | 55(84.6%) | 107(82.3%) |
| Heart burn       |       |       |    |   |
| Heart burn       | N(%)  | 18(27.7%) | 20(30.8%) | 38(29.2%) |
| Non              | N(%)  | 47(72.3%) | 45(69.2%) | 92(70.8%) |

Table 3: Differences in H. pylori eradication rates between studied groups.

|                  | Group | Total | X² | P |
|------------------|-------|-------|----|---|
|                  | HDDT | TT    |    |   |
| Eradication      |       |       |    |   |
| Not responding   | N(%)  | 18(27.7%) | 13(20.0%) | 31(23.8%) |
| Responding       | N(%)  | 47(72.3%) | 52(80.0%) | 99(76.2%) |

Statistical Analysis

Data collected included medical history, baseline physical examination, lab results and outcome measures. Microsoft Excel software 2010 was used to analyze these data after coding. Further statistical analysis was performed after importing the data into Statistical Package for the Social Sciences (SPSS version 25.0) software. Qualitative variables were represented as numbers and percentages, on the other hand continuous variables were expressed as mean ± standard deviation (SD).

Chi square test (X²) was used to test for significant difference in case of qualitative variable while an independent t-test was used for quantitative variables. P value of less than 0.05 was considered as a significant difference between the two groups while P value of less than 0.001 indicated a highly significant difference between the groups.

RESULTS AND DISCUSSION

Age was distributed as 32.96±7.98 years and 32.4±7.59 years between HDDT group and TT group, respectively, with no significant difference between them. Also, there were no significant differences regarding anthropometric measures, sex or smoking between both groups Table 1. There was no significant difference between groups regarding pre-treatment clinical presentation and the most frequent symptom was abdominal pain Table 2.

There was no significant difference between both groups as regards the one-month post-treatment H. pylori eradication rate (p=0.3). In HDDT group, eradication was achieved in 72.3% of patients (47/65). Whereas, 80% (52/65) of patients in TT group were cured (Table 3 & Figure 2). Side effects in all participants were generally mild. Five patients out of the 65 patients in the HDDT group (7.7%) and
Table 4: Complications and adverse effects distribution between groups.

|                  | Group   | Total | X^2  | P   |
|------------------|---------|-------|------|-----|
|                  | HDDT    | TT    |      |     |
| Diarrhea         |         |       |      |     |
| Non              | N(%)    | 62(95.4%) | 63(96.9%) | 125(96.2%) | 0.208 | 0.64 |
| Abdominal        |         |       |      |     |
| distresse        |         |       |      |     |
| Non              | N(%)    | 62(95.4%) | 61(93.8%) | 123(94.6%) | 0.15  | 0.69 |
| Nausea           |         |       |      |     |
| Non              | N(%)    | 62(95.4%) | 62(95.4%) | 124(95.4%) | 0.208 | 0.64 |
| Bad taste        |         |       |      |     |
| Non              | N(%)    | 64(98.5%) | 62(95.4%) | 126(96.9%) | 1.02  | 0.310 |
| Overall          |         |       |      |     |
| Complicated      | N(%)    | 60(92.3%) | 61(93.8%) | 121(93.1%) | 0.11  | 0.73 |
| Not              | N(%)    | 5(7.7%)   | 4(6.2%)   | 9(6.9%)   |

Table 5: Compliance distribution between groups.

|                  | Group   | Total | X^2  | P   |
|------------------|---------|-------|------|-----|
|                  | HDDT    | TT    |      |     |
| Compliance       |         |       |      |     |
| No               | N(%)    | 1(1.5%)   | 2(3.1%)   | 3(2.3%)   | 0.34  | 0.55 |
| Yes              | N(%)    | 64(98.5%) | 63(96.9%) | 127(97.7%) |

four patients out of the 65 in the TT group (6.2%) had treatment-related adverse events. The most frequently encountered complication was abdominal distress (4.6% in HDDT group versus 6.2% in TT group), followed by diarrhea in HDDT group and nausea in TT group. However, no significant differences were observed between the groups regarding the adverse effects. No patients stopped treatment because of side effects (Table 4 & Figure 3). There was no significant difference between groups regarding the compliance. A total of 64 (98.5%) patients in the HDDT group and 63 (96.9%) patients in the TT group adhered to the treatment Table 5. The Maastricht I Consensus Report concerning management of *H. pylori* infection, proposed that treatment regimens should accomplish a minimum eradication rate of 80%, and this has remained a standard for the Maastricht consensus group through subsequent conferences (Malfertheiner et al., 1997).

A report card format was suggested by Graham et al. to evaluate the outcome of novel treatment regimens for *H. pylori* infection. According to their proposal, the effectiveness of treatment regimen is classified as following:

- Excellent or A when the elimination rate is more than 95%
- Good or B when the elimination rate is 90%-95%
- Fair or C when the elimination rate is 85%-89%
- Poor or D when the elimination rate is 81%-84%
- Unacceptable or F when the elimination rate is ≤ 80% (Graham et al., 2007).

The results in this study showed that HDDT cured 72.3% of treatment-naive patients.

This result is comparable to that reported previously by (Graham et al., 2010) whereas, they used a high dose dual therapy with a PPI (esomeprazole) at a dose of 40 mg and amoxicillin at a dose of 750 mg, each given three times daily for 14 days for treatment naive patients, and they achieved an eradication rate of 72.2%. In another study done by Schwartz et al. it was shown that when 30 mg of lansoprazole was administered twice daily with 1 g of amoxicillin 3 times daily, the eradication rate was 53%, while when lansoprazole was given 30 mg three times daily with amoxicillin 1g 3 times daily the eradication rate increased to 77% (Schwartz et al., 1998). (Kim et al., 2012) also showed that when lansoprazole 30 mg and amoxicillin at a dose of 750 mg was administered three times daily the eradication rate of *H. pylori* was 67.3% in treatment naive patients.

On the other hand, using high-dose dual therapy regime in other studies was able to achieve higher
eradication rates between 85% and 89% as these reported by (Zullo et al., 2015; Bayerdörffer et al., 1995) and more than 90% as those reported by (Bayerdörffer et al., 1995; Hu et al., 2017). The frequency of PPI administration was suggested to be one of the reasons as why different studies had variable eradication rates against H. pylori. Giving the PPI three times a day had a better result than giving it twice (Schwartz et al., 1998), and giving it four times had a much better result (Yang et al., 2014).

In the present study, to promote high compliance, the PPI dose was intensified by using a double strength dose twice daily, but not by increasing the frequency of administration. CYP2C19 is the main enzyme responsible for the metabolism of PPIs. CYP2C19 is highly polymorphic and the genetic variability may contribute to reduced efficacy of high dose dual therapy. Esomeprazole was less affected by CYP2C19 genotype than omeprazole and was therefore chosen for use in the treatment regimen (Yang et al., 2011).

The most recent data show low eradication rates with standard triple therapy and often allows the cure of less than 80% of patients (Graham and Fischbach, 2010). This study confirms these data, as the triple therapy in this study achieved an eradication rate of only 80%. Both treatments were well tolerated and there was no difference between them regarding patient compliance. However, it worth mentioning that the relatively small sample size in the current experiment as well as that the lacking of CYP2C19 genotyping are among the work limitation.

CONCLUSIONS

In patients with active cases of H. pylori in stool, using a standard TT protocol of a combination of amoxicillin, clarithromycin, and esomeprazole showed an eradication rate against H. pylori of 80%. This rate was non significantly different from that obtained by using a HDDT regimen consisting of amoxicillin (1 g; three times daily) and esomeprazole (40 mg; twice daily). Similar safety profiles and tolerability was obtained, in both treatment protocols, mild diarrhea and abdominal pain were observed as common side effects of the given medication. HDDT is recommended as an empiric first-line therapy for H pylori infection being the one that avoids the using of clarithromycin with high potential growing resistance. Further large studies are needed to establish the efficacy and safety of HDDT.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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