

The cost-effectiveness of sequential versus standard triple therapy for *Helicobacter pylori* eradication in Saudi Arabia

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Abstract

Background: The utilization rate of different treatment regimens for *Helicobacter pylori* infection is believed to be high; however, the cost-effectiveness of these regimens has not been examined before. Therefore, the aim of this study was to examine the cost-effectiveness of the two commonly prescribed treatments for *H. pylori* infection.

Methods: The data of an open-label, single-center, randomized trial that compared the efficacy of sequential therapy (SQT) (i.e., esomeprazole 20 mg twice daily for 10 days, amoxicillin 1000 mg twice daily for 5 days, then clarithromycin 500 mg and tinidazole 500 mg twice daily for 5 days) to standard triple therapy (STT) (i.e., esomeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg twice daily for 14 days) in the eradication of *H. pylori*, as confirmed by the negative urea breath test (UBT), were used. Propensity score matching bin bootstrapping, with 10,000 replications and bias correction was conducted to generate the 95% confidence limits. Moreover, probabilistic sensitivity analysis was conducted by varying both the eradication rates and the costs of treatment regimens.

Results: There were 82 and 88 patients who were on SQT and STT, respectively. Patients' mean age was 47 years, and approximately 55% of them were females. The mean treatment costs were SAR 2,075.51 (USD 553.47) and SAR 2,629.26 (USD 701.14) for SQT and STT, respectively. The mean eradication rates for SQT and STT were 63.41% and 67.05%, respectively. The mean difference in costs and eradication rates for SQT versus STT were SAR – 550.75 (95% CI: –563.84 –537.69) and – 3.64% (95% CI: –6.98– 5.88). The use of SQT was more likely to be cost saving and more effective with 56.25% confidence level, in comparison to STT.

Conclusion: The use of SQT in the treatment of *H. pylori* seems to be more cost-effective than STT.

Keywords: Cost-effectiveness, *Helicobacter pylori*, Saudi Arabia, sequential therapy, triple therapy

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INTRODUCTION

Helicobacter pylori is a gram-negative, spiral-shaped bacterium, commonly found in the gastrointestinal tract in over 50% of the world's population.^[1] This microbe is known to be the leading cause of peptic ulcer disease, gastritis, mucosa-associated lymphoid tissue lymphoma, or gastric cancer.^[2,3] Its prevalence in Saudi Arabia has been reported to range from 23% to 67% among healthy adults, and can be as high as 50% among symptomatic patients with dyspepsia.^[4] Several factors have been associated with higher risk of infection, such as low socioeconomic status, older age, and African and Hispanic ethnic groups.^[5]

Due to the high prevalence of *H. pylori* infection and its impact on patients' health related quality of life (HRQoL), effective short-term treatment is recommended.^[6] Currently, there are multiple treatment regimens that can be used in the management of *H. pylori*, with variable rates of eradication (i.e., successful treatment) and recurrence, such as the triple, sequential, quadruple, concomitant, and hybrid treatment regimens. However, the most commonly prescribed treatment regimens are the Standard Triple Therapy (STT) and Sequential Therapy (SQT).^[7,8] The STT regimen is considered the first-line therapy in the management of *H. pylori* and consists of a proton pump inhibitor (PPI), clarithromycin (CLR) 500 mg and either amoxicillin (AMX) 1 g or metronidazole 500 mg for 7-14 days.^[9] In a meta-analysis that examined the optimal duration of different *H. pylori* treatment regimens, the 14-day therapy had a significantly higher eradication rate in comparison to the 7-day therapy (e.g., 81.9% versus 72.9%).^[10] However, the increasing rate of antibiotic resistance over the past decade has rendered the STT less efficacious in eradicating *H. pylori*, especially in European and Western countries.^[11,12] In Saudi Arabia, 69.5% and 21% of 46 *H. pylori* isolates for patients with gastritis or duodenal ulcers were resistant to metronidazole and clarithromycin, respectively.^[13] Therefore, new treatment regimens have been recently introduced to improve the eradication rate (i.e., successful treatment) of *H. pylori* infection.^[14]

The SQT is an *H. pylori* eradicating regimen that is widely used as an alternative to STT, and consists of a 10-day treatment with a PPI, such as esomeprazole 20 mg twice daily, AMX 1 g twice daily for five days, followed by another 5-day treatment with CLR 500 mg and metronidazole 500 mg (or tinidazole) each taken twice daily.^[14] The efficacy of SQT in eradicating *H. pylori* is believed to be comparable to STT. In a single-center, randomized open-label clinical trial that compared the eradication rates among adult patients with *H. pylori* infection, the eradication rates

ranged from 50.7% to 70.6% and 54.8% to 69.0% for SQT and STT, respectively. However, this difference in eradication rates between SQT and STT did not reach a statistically significant level in both intention to treat (ITT) and per protocol (PP) analyses.^[15] Furthermore, in another single-center, randomized open-label trial that examined the efficacy of SQT versus STT in eradicating *H. pylori* in Saudi Arabia, the ITT eradication rates or treatment success rates as confirmed by the negative urea breath test (UBT) were 50.4% and 59% for SQT and STT, respectively; and, the PP eradication rates were 62.4% and 67.6% for SQT and STT, respectively. However, neither ITT nor PP eradication rates were significantly different between the two treatment regimens (i.e., SQT and STT).^[16] On the other hand, the SQT has shown to be better than STT in eradicating *H. pylori*, based on the findings of 10 out of 13 randomized controlled trials that were included in a systematic review.^[17] Similarly, in a randomized open-label trial that compared the eradication rate of *H. pylori* by SQT and STT in the United Arab Emirates, the eradication rate was significantly higher among patients treated with SQT in comparison to their counterparts who were treated with STT (i.e., 84.6% vs. 68%).^[18] Additionally, in a randomized open-label, multicenter, clinical trial in Taiwan, the SQT was superior than STT in eradicating *H. pylori* when used for 14 days instead of a 10-day therapy (i.e. 90.7% vs. 82.3%). However, this difference was not statistically significant when the *H. pylori* eradication rate of the 10-day SQT was compared to the eradication rate of 14-day STT, despite the fact that the eradication rate of the 10-day SQT was higher (e.g., 87% vs. 82.3%).^[19] Consequently, the 10-day SQT can be used as a first-line viable alternative treatment to STT in the management of *H. pylori* infection.

From a cost-effectiveness perspective, few studies have examined both the efficacy and cost of STT and SQT. The findings of these studies were inconsistent, however, they were mostly in favor of the SQT.^[20-22] In Saudi Arabia, the cost-effectiveness of different *H. pylori* treatment regimens was not examined. Therefore, the aim of this study was to examine the cost-effectiveness of the two most commonly prescribed *H. pylori* treatment regimens in Saudi Arabia (10-day SQT versus 14-day STT) using local data from the healthcare payer's perspective.

PATIENTS AND METHODS

Study design and data sources

The data of a single-center, randomized open-label clinical trial, that was conducted between October 2011 and February 2014, were utilized. The study compared the *H. pylori* eradication rates between patients who were

randomized to receive either a 10-day SQT, which consisted of esomeprazole 20 mg twice daily for 10 days, AMX 1 g twice daily for 5 days, then CLA 500 mg and tinidazole 500 mg twice daily for 5 days, or a 14-day STT that consisted of esomeprazole 20 mg, AMX 1000 mg, and CLA 500 mg twice daily for 14 days. *H. pylori* treatment naïve adults aged ≥ 18 years with a confirmed diagnosis of *H. pylori* infection by esophago-gastro-duodenoscopy (EGD) were included in the study. Patients were tested after six weeks of treatment to check whether *H. pylori* was eradicated or not. Pregnant or lactating women and patients with compromised renal, hepatic, and/or respiratory functions as well as those with cardiovascular disease, and those who are allergic to AMX, CLA, or tinidazole, were excluded from the study. In addition, patients who were lost to follow-up or those with missing data on the adherence to treatment protocols and eradication status at week six, were excluded from the analysis, since per protocol analysis was used.

In order to estimate the non-drug costs, two scenarios of *H. pylori* infection management were considered. The first scenario was when an EGD is indicated for the presence of any alarm features and included performing an EGD and a CLO test once to confirm the diagnosis of *H. pylori* prior to the initiation of therapy, a UBT at the end of therapy to ensure *H. pylori* eradication, and two clinic visits (e.g., one visit before and after therapy); whereas the second scenario included two clinic visits (e.g., one visit before and after therapy) that involved performing a UBT on each visit. The non-drug costs were retrieved from the Ministry of Health cost center, and the cost of drug regimens were retrieved from the Saudi Food and Drug Authority (SFDA)

public drug prices database. The non-drug costs for each scenario as well as the costs of drug regimens for the two treatment groups are presented in Table 1.

Statistics

The differences in sociodemographic and medical characteristics between patients who were randomized to the 10-day SQT and 14-day STT were examined using Chi-square test, Fisher's exact test, and Student's *t*-test, as appropriate. The mean total cost for the 10-day SQT and 14-day STT treatment groups were estimated alongside their standard deviations. On the other hand, the mean *H. pylori* eradication rates for the two treatment groups were estimated alongside their ranges of lowest and highest values. Non-parametric bootstrapping with 10,000 replications was conducted to generate the 95% confidence intervals (e.g., 95% CI) for the mean total costs for the two treatment regimens, as well as their eradication rates, with bias correction. Probabilistic sensitivity analysis was conducted using propensity score matching bin bootstrapping with 10,000 replications in which the patients in the two treatment groups were matched based on their age, gender, presence of gastritis, duodenitis, gastric ulcer, duodenal ulcer and GERD. In addition, the total cost was varied based on the two aforementioned scenarios of *H. pylori* infection management as well as the treatment regimen acquisition costs, in which the cost per unit for each drug in the two treatment groups was varied from 50% of the cost of the lowest registered generic version of drug by the SFDA to the most expensive registered brand-name version of the same drug. The decision to vary the drugs' acquisition costs from 50% of their cheapest registered generic versions by the SFDA was made based

Table 1: Direct medical cost breakdown

Item	First scenario		
	Cost per unit in SAR	Quantity	Total
Esophago-gastro-duodenoscopy (EGD)	1000	1	1000
Clinic visit	350	2	700
CLO Test	120	1	120
Urea breath test (UBT)	640	1	640
Total cost for non-drug items			2,460
Second scenario			
Urea breath test (UBT)	640	2	1280
Clinic visit	350	2	700
Total cost for non-drug items			1,980
Cost of drug regimens range			
Esomeprazole 20 mg for sequential therapy	0.46-2.45	20	9.2-49
Esomeprazole 20 mg for standard triple therapy		28	12.88-68.6
Amoxicillin 500 mg for sequential therapy	0.23-0.56	20	4.6-11.2
Amoxicillin 500 mg for standard triple therapy		56	12.88-31.36
Clarithromycin 500 mg for sequential therapy	1.16-6.44	10	10.16-64.4
Clarithromycin 500 mg for standard triple therapy		28	32.48-180.32
Tinidazole 500 mg for sequential therapy	1.05-3.74	10	11.05-37.4
Total cost for sequential therapy			35.01-162
Total cost for standard triple therapy			58.24-280.28

Table 2: Patients' baseline characteristics

Characteristic	Standard Triple Therapy (n=88)	Sequential Therapy (n=82)	P	Total (n=170)
Age in yrs., Mean±SD	46.19±14.53	48.39±15.30	0.63	47.25±14.90
Number of comorbidities, Mean±SD	0.85±0.93	1.09±1.24	0.15	0.97±1.09
Gender, n (%)				
Male	39 (44.31)	37 (45.12)	0.12	76 (44.71)
Female	49 (55.68)	45 (54.87)		94 (55.29)
Gastric ulcer	3 (3.41)	4 (4.87)	0.27	7 (4.12)
Duodenal ulcer	4 (4.54)	4 (4.87)	0.28	8 (4.71)
Gastritis	65 (73.86)	58 (70.73)	0.12	123 (72.35)
Duodenitis	25 (28.41)	2 (2.44)	<0.01*	27 (15.88)
Indications for EGD, n (%)				
Abdominal pain	39 (44.32)	36 (43.90)	0.12	75 (44.12)
Epigastric pain	46 (52.2)	45 (54.88)	0.11	91 (53.53)
Nausea	8 (9.09)	20 (24.39)	<0.01*	28 (16.47)
Vomiting	8 (9.09)	10 (12.19)	0.16	18 (10.59)
Hematemesis	1 (1.14)	4 (4.87)	0.14	5 (2.94)
Weight loss	2 (2.27)	3 (3.65)	0.30	5 (2.94)

*P<0.05

on an assumption that the prices of procured drugs in public hospitals can be as low as 50% of the cheapest registered generic drugs. Furthermore, the eradication rates (i.e. treatment success rates) were varied from 62.4% to 64.63% for the 10-day SQT group, and from 65.91% to 67.6% for the 14-day STT group. The variation in the eradication rates was based on the lowest and highest observed rates for each treatment regimen in the utilized data.^[16] The minimum sample size was estimated to be 64 patients for each treatment regimen (i.e., total sample size of 128 patients) based on an allocation ratio of 1:1, medium effect size (Cohen's d = 0.5), $\beta = 0.2$, $\alpha = 0.05$, and power of 80% using G*power software version 3.1. All statistical analyses were conducted using SAS[®] version 9.4 (SAS[®] institute, Cary, NC, USA).

RESULTS

The retrieved data included 170 patients with non-missing observations, in which 82 of them were treated with the 10-day SQT, and 88 were treated with the 14-day STT. The mean age of the participants was 47 years, and around 55% of them were females, with no significant difference between the two treatment groups. Over two-thirds of the patients had gastritis (72.35%) with no significant difference between the two treatment groups. However, the percentage of patients on the 14-day STT who had duodenitis was significantly higher than their counterparts on the 10-day SQT (e.g. 28.41% vs. 2.44%, $P < .0001$). Nausea was more common among patients on the 10-day SQT in comparison to their counterparts on the 14-day

STT (i.e. 24.39% vs. 9.09%, $P = 0.004$). The randomized patients were generally healthy with a mean of one comorbidity and no significant difference between the two treatment groups. Patients' characteristics at baseline are presented in Table 2.

The mean total costs and eradication rates for the 10-day SQT and 14-day STT are presented in Table 3. The mean difference in total cost for the 10-day SQT versus the 14-day STT was SAR – 550.75 (95% CI: –563.84–537.69), which means that the SQT was on average SAR 550.75 cheaper. With regard to the *H. pylori* eradication rate, the mean difference in eradication rate for the 10-day SQT was 3.64% lower than the 14-day STT, which means that on average the 14-day STT is 3.64% more successful in eradicating *H. pylori*, as confirmed by the negative UBT, in comparison to the 10-day SQT. However, this difference is not statistically significant as the difference can be between 6.98% in favor of 14-day STT and 5.88% in favor of the 10-day SQT, as the 95% confidence limits suggest (e.g., 95% CI [–6.98-5.88]). Moreover, the probabilistic sensitivity analysis showed that the 10-day SQT was more likely to be less costly and more effective in eradicating the *H. pylori* in comparison to the 14-day STT in 56.25% of the 10,000 replications, and less costly and less effective in 43.75% of the 10,000 replications, than the 14-day STT, as shown in Figure 1.

DISCUSSION

The high prevalence of *H. pylori* infection among the Saudi population necessitates effective therapy that results

Table 3: The mean eradication rates and costs of standard triple and sequential therapies

Variable	10-day SQT	14-day STT	Mean difference (95% CI)
Cost of treatment (SAR), mean±SD	2,078.51±63.59	2,629.26±111.17	–550.75 (–563.84–537.69)
Mean of eradication rate with a range	63.41 (62.4-64.63)	67.05 (65.91-67.6)	–3.64 (–6.98-5.88)

SAR, Saudi Riyals; SQT, Sequential Therapy; STT, Standard Triple Therapy; CI, Confidence Intervals

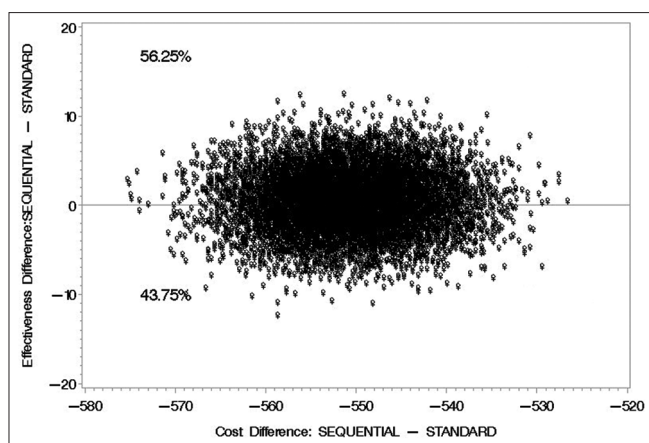


Figure 1: Probabilistic sensitivity analysis of the cost-effectiveness of sequential therapy versus standard triple therapy in the eradication of *Helicobacter pylori*

in complete eradication of the infection.^[4] However, the increasing incidence of antimicrobial resistance has rendered many *H. pylori* treatments less effective in eradicating *H. pylori*.^[11-14] Therefore, the selection of an effective treatment protocol that yields a high eradication rate is recommended.^[6] Although several treatment regimens are used in the management of *H. pylori* infection with variable eradication rates and acquisition costs,^[20-22] none of those regimens have been examined for their cost-effectiveness in eradicating *H. pylori* in Saudi Arabia. Thus, the findings of this study present for the first time the cost-effectiveness of two commonly utilized *H. pylori* treatment regimens in Saudi Arabia.^[15-18] The 10-day SQT was found to be more cost-effective than the 14-day STT with more than 50% level of confidence using probabilistic sensitivity analysis with 10,000 replications, that varied both *H. pylori* eradication rates, drug acquisition costs, and diagnostic procedures. These findings are consistent with previously published studies that showed SQT to be more cost-effective in eradicating *H. pylori*.^[20,21] In a randomized controlled trial that evaluated the *H. pylori* eradication rates of 10-day SQT versus 10-day STT among a small cohort of 73 patients with duodenal ulcer in India, SQT and STT were found to have almost similar rates of eradication and side effects, however, the cost of SQT was lower than STT.^[20] In another randomized open-label trial that included 162 patients with non-ulcer dyspepsia in Italy, the *H. pylori* eradication rates were examined for two 10-day sequential treatment regimens that included a 10-day rabeprazole 20 mg twice daily, a 5-day AMX 1 g twice daily, followed by another 5-day of tinidazole 500 mg and CLR 250 mg or 500 mg each taken twice daily. The difference between the two treatment regimens was only the dosage of CLA (e.g. 250 mg vs. 500 mg). Using PP analysis, there was no difference in the eradication rates between the two

regimens, but the cost for the first regimen that included a CLA dose of 250 mg was lower by 24.6 euros.^[21] However, the previously published research studies used standard and sequential treatment protocols that were not identical with the ones used in the utilized data of a single-center per-protocol non-inferiority clinical trial. Therefore, the results of this study, are to the best of our knowledge, the only ones that reflect the cost-effectiveness of the *H. pylori* treatment regimens that are used in Saudi Arabia.^[16]

According to the findings of this study, the use of a 10-day SQT results in lower cost and higher eradication rate than the 14-day STT, with 56.25% level of confidence, and lower cost and eradication rate with 43.75% level of confidence. This is despite the fact that the mean eradication rates that were considered in the model were all lower than those used for the 14-day STT, which calls into question the value of the 14-day STT in the eradication of *H. pylori*. On average, the use of a 10-day SQT instead of the 14-day STT in the management of *H. pylori* would result in savings of more than SAR 55,000 per 100 patients. Therefore, other treatment regimens for *H. pylori* infection should be considered in case the 10-day SQT has failed, such as the 10-day quadruple therapy.^[23] Finally, although this is the first study to the best of our knowledge that examined the cost-effectiveness of two commonly prescribed treatment regimens for the eradication of *H. pylori*, it has multiple limitations. First, the study was based on data of a single-center, non-inferiority, per protocol analysis clinical trial. Therefore, the generalizability of the study findings is limited. Furthermore, the results may change if higher eradication rates in favor of 14-day STT were assumed in the model. However, our study varied the eradication rate based on the findings of a locally conducted trial and in favor of the 14-day STT. Thus, if the eradication rates of other conducted studies were assumed in this study, the results might be more in favor of the 10-day SQT.

CONCLUSION

The findings of this study suggest that the 10-day SQT is more cost-effective for the eradication of *H. pylori* compared to the 14-day STT. Future studies should examine the cost-effectiveness of the 10-day SQT using data with better external validity and against different treatment regimens for the eradication of *H. pylori* infection.

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Conflicts of interest

There are no conflicts of interest.

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