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Evaluation of prescribing trends and cost analysis of peptic ulcer disease regimen in tertiary care setting

Sehrish Lakhani, Rabia Bushra, Shazia Alam and Yousra Shafiq*
Department of Pharmaceutics, Faculty of Pharmacy, Ziauddin University, Clifton, Karachi, Pakistan

Abstract: PUDs are extensively prevalent in individuals having *H. Pylori* infections and in chronic NSAIDs' users. Various therapies have been explored for the management of PUDs in different regions of world. An observational study was designed between July to December 2015, to evaluate the current prescribing trends in tertiary care settings of Karachi, Pakistan. Both *H. Pylori* positive and negative patients having gastric or duodenal ulcers from Gastroenterology department were investigated. The effectiveness of various regimens used to manage PUDs was assessed and compared with the standard guidelines for PUDs treatment. PUDs are more common in older aged male individuals. The most effective treatment of PUDs was found to be the triple therapy comprising of proton pump inhibitor (PPIs) with combinations of two antibiotics (amoxicillin and clarithromycin). Moreover, omeprazole/esomeprazole was prescribed commonly for prolong duration as a single medication. However; according to the standard guidelines for PUD management, this mono-therapy is not recommended and workable. The cost of various regimens (given for a week) was also estimated. The mono-therapy was found to be cheaper than any other regimen but as it is prescribed for longer time period, increases the ultimate cost of treatment. No significant difference was found in the cost of dual (PPIs with one antibiotic) and triple regimen. Moreover, Quadruple therapy (with bismuth subcitrate) was not seen in any subject although the effectiveness of this regimen has been well established globally. Besides the fact that current practices are successful in managing the PUDs but regimens need to be revised and inclusion of bismuth subcitrate is highly recommended.

Keywords: Peptic ulcer, duodenal ulcer, PUD, *H. Pylori*, Cost Analysis.
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***Author for Correspondence:** rabia_pharmacist@hotmail.com

INTRODUCTION

Peptic ulcer disease (PUD) is one of the growing dilemmas seen in population of all age groups world[1]. Gastric ulcer (GU) and duodenal ulcer (DU) are embraced in PUD usually associated with gastroduodenal bleeding, damages and blockage leading to high mortality rate[2]. The foremost factors of PUD are excessive consumption of NSAIDs and *H. pylori* infections. The common clinical symptoms of PUD include loss of appetite, mild nausea, ache or upper abdomen discomforts[3].

It has been estimated that *H. pylori* infections are more prevalent in developing countries like Eastern Europe, Asia, Africa and South America. According to a survey conducted in U.S, about 500,000 patients of PUDs are being admitted every year utilizing an approximate expenditure of $10 billion dollars[3]. Additionally the reported occurrence of PUD in Taiwan and Iran was 9.4% and 8.20% respectively[4,5]. It has been noticed that PUD is more common in individuals belonging to rural area (91%) than urban regions (60%)[6]. Duodenal ulcers are more prevalent than gastric ulcers and the estimated incidence of these ulcers were 5:1 and 32:1 in Pakistan and India respectively[7]. A study was conducted in Pakistan to outline the factors of PUD and it was found that 53% of DUs were due to *H. pylori*, 10% were NSAID-related and 29% were non-*H. pylori* and non NSAID-dependent[8].

Different regimens are available for treatment of PUDs worldwide. Eradication therapy is considered to be enough effective in negative users of NSAIDs[9]. Triple therapies comprising of omeprazole+amoxicillin/metronidazole+clarithromycin or omeprazole+metronidazole+clarithromycin recommended for one week have been effectively used universally to cure PUDs[10,11]. Additionally bismuth sub-citrate is included in quadruple therapy for *H.Pylori* eradication[12].

Fortunately, a declining trend for *H. pylori*-based ulcers has been seen recently across various regions of world. Denmark showed a decrease in incidence of physician-diagnosed PUD from 0.18% in 1993 to 0.15% in 2002, Belgium reported a reduction from 0.40% to 0.19% 2003 and Spain stated a fall from 0.22% to 0.14% in 2000[2].

The aim of the present study is to assess the incidence, effectiveness and the treatment cost of PUDs prescribed to the residents of metropolitan city Karachi, Pakistan.

MATERIALS AND METHODS

An observational prospective study was conducted from July to December 2014 in various tertiary care hospitals of Karachi, Pakistan. Patients from Gastroenterology department diagnosed with peptic ulcer disease (hospitalized and non-hospitalized) were included in the study. Eighty nine subjects were recruited between the ages of 20 to 70 years. Patients' profile (including demographic information and provided treatment) was examined in detail and clinical investigation through endoscopy and other tests were done. Pakistan is a middle-income country, the medical cost matters to

the patients and their families hence direct cost of all prescribed drugs (one week) were also estimated. The effectiveness of various regimens of PUDs was also evaluated.

RESULTS

Total 92 human subjects having PUD complaints were recruited in the study but three of them were excluded due to incomplete information. The prevalence of PUDs was found to be greater in *H. pylori* positive patients than non-*H. pylori* ones. It was also seen that these complaints were more common in males than females (Figure 1).

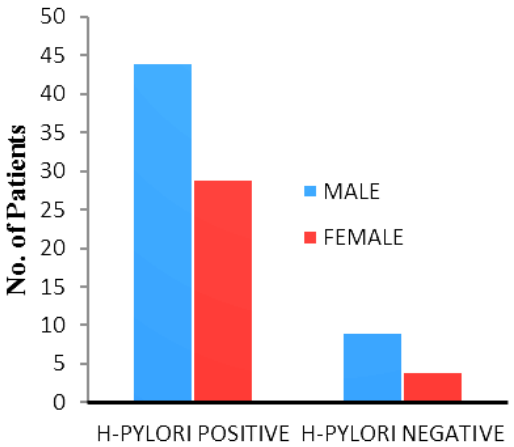

Figure 1: Distribution of male and female patients.

The investigation findings revealed that patients with the age of above 50 years were more prone to the underlying complaint (Figure 2). Positive *H. pylori* was more commonly associated with DU (62%) than in GU (38%) (Figure 3).

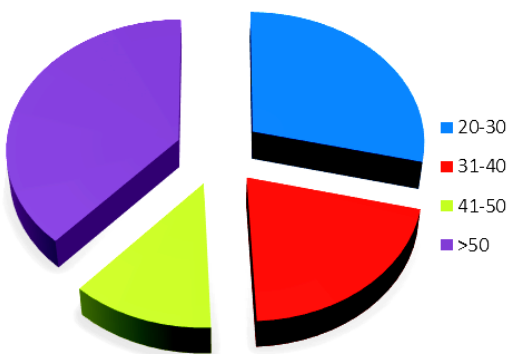

Figure 2: Prevalence of *H. pylori* in different age groups

Various treatment regimens were used for management of PUDs. However; it was observed that the prescribing practice for majority of *H. pylori* positive patients was not according to the universal standard recommendations. Cost of therapy was considered to be one of the major factors that influencing the practice. Cost of various prescribed drugs (one week) was estimated and given in table 1. The most common drug in all regimens was Proton Pump Inhibitor (PPI) (Esomeprazole). The use of bismuth citrate as quadruple therapy was not seen in any case which could be effective as well.

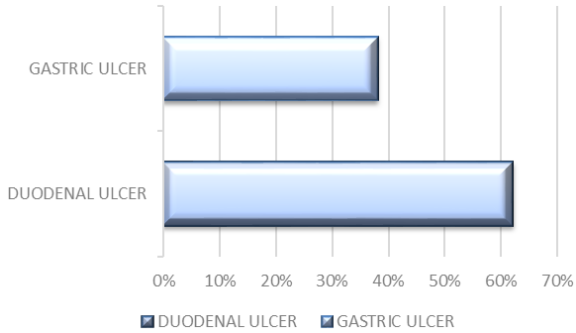

Figure 3: Incidence of GU and DU in study population.

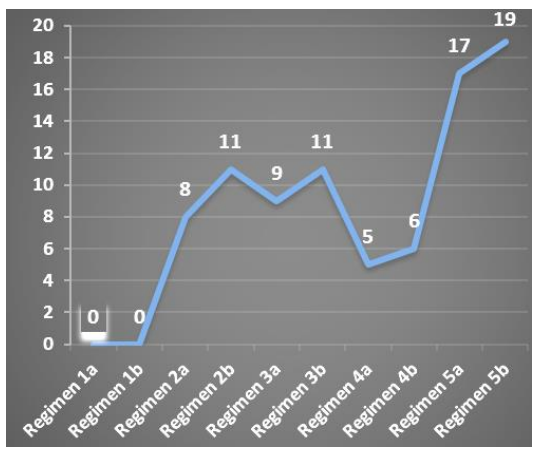

Figure 4: Prescribing trends of PUD regimens.

DISCUSSION

H. pylori infection is considered to be a prime cause of gastric and duodenal ulcers with its attributes persuading the communal health concerns of low socioeconomic countries[13, 14]. The incidences of gastric and duodenal ulcers associated with *H. pylori* infection augment with age and are more common in males than females[15]. The eradication patterns of *H. pylori* have been very well demonstrated in various studies[16]. The present study was designed to assess the compliance of standard treatment guidelines of PUD and to explore the factors that obscure the success of the current practice in Pakistan. Drug cost, antibiotic resistance and accessibility of the drug(s) are the major factors that complicate the treatment[13,17]. These escalating issues necessitate the suitable selection of *H. pylori* PUD regimen for effective outcomes [13, 14].

Table 1: Cost of different PUD regimens.

S.NO	Regimen	Drugs	Dosage	Drug cost per dose PKR ($)	Drug cost per day PKR ($)	Drug cost per treatment* PKR ($)
1a	Quadruple therapy	Colloidal Bismuth subcitrate (Cebe-S)	240mg q.i.d	Rs. 9/= (0.09 $)	Rs. 36/= (0.34 $)	Rs. 252/= (2.39 $)
	(Bismuth + PPI + 2 antibiotics)	Omeprazole (Risek)	20mg b.i.d	Rs. 14/= (0.13$)	Rs. 28/= (0.27 $)	Rs. 196/= (1.86 $)
		Metronidazole (Flagyl)	400mg q.i.d	Rs. 2/= (0.02 $)	Rs. 8/= (0.08 $)	Rs. 56/= (0.53 $)
		Tetracyclines HCl (Tetracycline)	250mg q.i.d	Rs. 0.6/= (0.01 $)	Rs. 2.4/= (0.02 $)	Rs. 16.8/= (0.16 $)
				Rs. 25.6/= (0.24 $)	Rs. 74.4/= (0.71 $)	Rs. 520.8/= (4.94 $)
1b		Colloidal Bismuth subcitrate (Cebe-S)	240mg q.i.d	Rs. 9/= (0.09 $)	Rs. 36/= (0.34 $)	Rs. 252/= (2.39 $)
		Esomeprazole (Esso)	20mg b.i.d	Rs. 11.5/= (0.10$)	Rs. 23/= (0.21 $)	Rs. 161/= (1.52 $)
		Metronidazole (Flagyl)	400mg q.i.d	Rs. 2/= (0.02 $)	Rs. 8/= (0.08 $)	Rs. 56/= (0.53 $)
		Tetracyclines HCl (Tetracycline)	250mg q.i.d	Rs. 0.6/= (0.01 $)	Rs. 2.4/= (0.02 $)	Rs. 16.8/= (0.16 $)
				Rs. 23.1/= (0.22 $)	Rs. 69.4/= (0.65 $)	Rs. 485.8/= (4.60 $)
2a	Standard Triple therapy	Omeprazole	20mg b.i.d	Rs. 14/= (0.13$)	Rs. 28/= (0.27 $)	Rs. 196/= (1.86 $)
	(PPI + 2 antibiotics)	Amoxicillin (Amoxil)	500mg b.i.d	Rs. 7.5/= (0.07 $)	Rs. 15/= (0.14 $)	Rs. 105/= (0.99 $)
		Clarithromycin (Klaricid)	500mg b.i.d	Rs. 65/= (0.62 $)	Rs. 130/= (1.23 $)	Rs. 910/= (8.64 $)
				Rs. 86.5/= (0.82 $)	Rs. 173/= (1.64 $)	Rs. 1211/= (11.50 $)
2b		Esomeprazole	20mg b.i.d	Rs. 11.5/= (0.10$)	Rs. 23/= (0.21 $)	Rs. 161/= (1.52 $)
		Amoxicillin	500mg b.i.d	Rs. 7.5/= (0.07 $)	Rs. 15/= (0.14 $)	Rs. 105/= (0.99 $)
		Clarithromycin	500mg b.i.d	Rs. 65/= (0.62 $)	Rs. 130/= (1.23 $)	Rs. 910/= (8.64 $)
				Rs. 84/= (0.79 $)	Rs. 168/= (1.59 $)	Rs. 1176/= (11.15 $)
3a	Triple therapy	Omeprazole	20mg b.i.d	Rs. 14/= (0.13 $)	Rs. 28/= (0.27 $)	Rs. 196/= (1.86 $)
	(PPI + 2 antibiotics)	Metronidazole	400mg b.i.d	Rs. 2/= (0.02 $)	Rs. 4/= (0.04 $)	Rs. 28/= (0.27 $)
		Clarithromycin	250mg b.i.d	Rs. 36/= (0.34 $)	Rs. 72/= (0.68 $)	Rs. 504/= (4.78 $)
				Rs. 52/= (0.49 $)	Rs. 104/= (0.99 $)	Rs. 728/= (6.90 $)
3b		Esomeprazole	20mg b.i.d	Rs. 11.5/= (0.10$)	Rs. 23/= (0.21 $)	Rs. 161/= (1.52 $)
		Metronidazole	400mg b.i.d	Rs. 2/= (0.02 $)	Rs. 4/= (0.04 $)	Rs. 28/= (0.27 $)

		Clarithromycin	250mg b.i.d	Rs. 36/= (0.34 $)	Rs. 72/= (0.68 $)	Rs. 504/= (4.78 $)
				Rs. 49.5/= (0.46 $)	Rs. 99/= (0.93 $)	Rs. 693/= (6.57 $)
4a	PPI + antibiotic (Clarithromycin)	Omeprazole	20mg b.i.d	Rs. 14/= (0.13 $)	Rs. 28/= (0.27 $)	Rs. 196/= (1.86 $)
		Clarithromycin	500mg b.i.d	Rs. 65/= (0.62 $)	Rs. 130/= (1.23 $)	Rs. 910/= (8.64 $)
				Rs. 79/= (0.75 $)	Rs. 158 /= (1.50 $)	Rs. 1106/= (10.48 $)
4b		Esomeprazole	20mg b.i.d	Rs. 11.5/= (0.10$)	Rs. 23/= (0.21 $)	Rs. 161/= (1.52 $)
		Clarithromycin	500mg b.i.d	Rs. 65/= (0.62 $)	Rs. 130/= (1.23 $)	Rs. 910/= (8.64 $)
				Rs. 76.5/= (0.72 $)	Rs. 153 /= (1.44 $)	Rs. 1071/= (10.16 $)
5a	PPI	Omeprazole	20mg b.i.d	Rs. 14/= (0.13 $)	Rs. 28/= (0.27 $)	Rs. 196/= (1.86 $)
5b		Esomeprazole	20mg b.i.d	Rs. 11.5/= (0.10$)	Rs. 23/= (0.21 $)	Rs. 161/= (1.52 $)

1 PKR = 0.0094829 US Dollar, *one week treatment period

In the last 2 decades, a variety of combinations including different antibiotics and anti-secretory agents were investigated for different treatment periods varying from 7-14 days. The current global consensus suggested standard triple therapy to be considered as the first choice for the annihilation of *H. pylori* infection[2, 18].

In present study the current prescribing regimens that have been observed for *H. pylori* eradication were; **triple therapy,** a combination of PPI (Omeprazole/Esomeprazole) with combination of two Antibiotics (Amoxicillin/Metronidazole+ Clarithromycin), **dual therapy**, a combination of PPI (Omeprazole/Esomeprazole) with Antibiotic (Clarithromycin), **single therapy**, either Omeprazole or Esomeprazole (alone). The most commonly prescribed regimen in both *H. pylori* positive and *H. pylori* negative was single agent (i.e. PPI). The rationale of prescribing only PPIs was to make treatment cost effective however, in contrast to other regimens, PPIs were prescribed for prolong duration and thus no-longer remained cost effective. Additionally it was also not complies with recommendations as a sole prescription for *H. pylori* eradication regimen.

The study depicted no significant saving in cost of regimen 2 (a and b) and regimen 4 (a and b) for the period of 7-days treatment, but the effectiveness of regimen 2 was considerably higher than regimen 4. Whilst, combination of dual therapy was often found to administered for 10-14 days or more for successful recovery and thus consumes more expenditures. In contrast, triple therapy of both type (regimen 2 and regimen 3) have significant cost differences; as Regimen 3 (a and b) was cheaper than regimen 2 (a and b). Regimen 3 including metronidazole and clarithromycin are well known for their resistance. But in practice, regimen 3 was found to be in the same proportion as that of regimen 2.

In accordance with the previous studies in Pakistan, the rate of failure of triple therapy was about 32% despite of using it for 2 weeks treatment, but still practice was not suffice to prescribe as an alternative regimen that is use of Quadruple therapy[13]. Quadruple regimen consists of colloidal bismuth subcitrate, with two antibiotics (Tetracycline and Metronidazole), PPI (Omeprazole or Esomeprazole). In current study, it was evaluated that the cost of quadruple therapy was least in contrast to other regimens and could be effectively incorporated in patients who failed to eradicate *H. pylori* by triple therapy[19].

Misunderstanding for the cost and lesser commercial accessibility of bismuth sub-citrate might be the factors for limiting the prescribing practice of quadruple therapy in local community. It was also noticed that there were non-compliance of patients for polypharmacy (regimen of four drugs). Additionally physicians were often more comfortable with conventional medicines because of their good experience and to fulfill the patient's demand.

It is recommended that practitioners should need to modify their prescribing practice according to the current guidelines for the effective and better management of *H. pylori* infections.

CONCLUSION

It is concluded that the most effective PUD regimen was the standard triple therapy comprising of PPI + 2 antibiotics amongst other regimen. Quadruple therapy is considered to be the most successful therapy globally for *H. pylori* eradication, is still not prescribe in local population of Karachi. However incorporation of bismuth subcitrate is suggested owing to its comparable efficacy and cost effectiveness. Additionally, dual therapy was found to be effective if given for 10-14days. *H. pylori* suppression by PPI is not encouraging as it increases the direct cost and also the management guidelines of PUDs do not support the utilization of PPI as a sole medication agent.

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