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COMPARATIVE STUDY BETWEEN TWO TRIPLE THERAPY REGIMENS ON ERADICATION OF *HELICOBACTER PYLORI (HP)*

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ABSTRACT
Helicobacter pylori (HP) are a bacterium that infects the mucus lining of the human stomach. HP has emerged as one of the most common bacterial pathogens worldwide [1]. It is estimated that about half the world's population is infected with HP [2]. Curing the infection has the best outcome and is clearly the most cost effective management strategy for HP infected patients with ulcer disease [3]. The goal of the therapy is to eradicate the infection. A comparison of two 'triple therapy' regimen to patient with Rapid Urease Test (RUT) and histologically proven HP infection and to evaluation of cost factor of two regimens is studies Regimen-I Omeprazole 20mg bid-Clarithromycin 500mg bid –Amoxicilin 1g bid; Regimen-II Omeprazole 20mg bid-Clarithromycin 500mg bid – Tinidazole-500mg bid. It was hypothesized that Omeprazole – Clarithromycin – Amoxycillin regimen is superior to Omeprazole – Clarithromycin – Tinidazole regimen for eradication of HP. The study was conducted from in Kathmandu University Teaching Hospital, (KUTH- DH), Dhulikhel, Nepal.Eradication rate of regimen-I and II was found 93.8% and 91.4% respectively, However there was no significant difference between regimen-I and II both are effective in eradication of HP. While analyzing cost difference between two regimens, it was found that regimen-II was cheaper (Rs.361.20 per course) than regimen-I and eradication rate was also satisfactory.

Key Words: *Helicobacter pylori*, Method, Triple Therapy Regimen, Endoscopic findings, Cost difference

INTRODUCTION
Helicobacter pylori (HP) are a bacterium that infects the mucus lining of the human stomach. Many peptic ulcers and some types of gastritis are caused by HP infection, although most humans who are infected may never develop symptoms. It is the only known organism that can thrive in that highly acidic environment. It can screw itself into the stomach lining to colonize it [4]. It is causally linked with peptic ulcer, gastric cancer, and gastric mucosa–associated lymphoid tissue (MALT) lymphoma. Microorganisms living in association with the gastric mucosa have been observed for decades [5-6]. These organisms could not be cultured. In 1983 an organism that come to be known as *Compylobacter Pyloridis* was first isolated by Warren and Marshall [6] in Australia. HP has emerged as one of the most common bacterial pathogens worldwide [7]. HP infecting about half the world's population [2]. HP was defined in 1994 as a 'definite biological carcinogen' by WHO/IARC [8]. In most instances infection occurs in childhood, and remains intact unless effective treatment occurs. Re-infection is rare in the western world [9]. Infection is symptomatic in the vast majority of cases, but all infected individuals have some evidence of chronic active gastritis [10]. In first world countries, it infects 25%-40% of the population, with the infection generally becoming less common as standards of living rise [11]. However in developing countries, HP infects most of the population, so that most people in Eastern Europe, Asia, Africa and South America are carriers. It has been identified in up to 80% of gastric and up to 95% of duodenal

ulcers [11]. The rest of the ulcers are caused by drugs such as Aspirin or Non-steroidal anti-inflammatory drugs (NSAID) [12].

MATERIALS AND METHOD

Upper gastrointestinal endoscopy using standard forceps was performed on all the patients after an overnight fasting under local anaesthetic agent (4% Xylocan throat spray). Two biopsy specimens were taken from the antrum and corpus area of stomach. Four pieces of antral biopsy were placed into the buffer urea solution and another two pieces of corpus and antrum biopsy specimens were fixed in 10% formalin and then processed, embedded in paraffin, cut in sequential 4 μm sections and routine stained with H & E Stain. RUT positive was recorded if there was a color change from yellow to pink within 24 hours. When HP was present in slides stained with H&E, the patient was categorized as HP positive if HP absent in slides stained with H&E the patient was categorized as HP negative.

80 patients who were positive for HP (by RUT and histological confirmed) wear randomly divided into two treatments regimen:

Regimen-I: OCA (N = 40): Omeprazole – 20mg bid for 30 days, Clarithromycin - 500 mg bid, Amoxycillin 1000 mg bid for 2 weeks.

Regimen-II: OCT (N = 40): Omeprazole 20-mg bid. for 30 days, Clarithromycin 500 mg bid and Tinidazole 500mg bid for 2 weeks.

A RUT and Endoscopy and Histology was performed at 0 and 6 weeks to check for HP eradication.

Following was the inclusion and exclusion criteria adopted by the study
Inclusion criteria:

- Inpatient as well as outpatient
- Patients having evidence of *H. pylori* infection by RUT and at Biopsy, Histopathology
- Two triple therapy regimen that is prescribing in Kathmandu University Teaching Hospital, Dhulikhel
    i. Omeprazole – Clarithromycin – Amoxycillin
    ii. Omeprazole – Clarithromycin – Tinidazole

Exclusion criteria:

- Age < 16 and > 80 years
- Pregnant or lactating women
- Co-existing gastric carcinoma or pyloric stenosis
- Chronic alcohol or drug abuse (because of probable non-compliance)
- Cirrhosis
- Continued use of NSAIDs and treatment with omeprazole, Tinidazole, Bismuth compounds or antibiotics within 30 days prior to the enrolment endoscopy.
- Unconscious patients.
- Patients who did not return to follow-up.

RESULTS AND DISCUSSION

Demographic Characteristics of Study.

Distribution of patients: Table -1 shows that a total number of 80 patients were enrolled on the basis of inclusion and exclusion criteria. Both outpatients and in-patients were included in this study. Out of total population, 56% (N=45) were males and 44% (N=35) females. Among inpatients 5% (N=4) were males and 5% (N=4) were females. In out patients 51.25% (N=41) were males and 38.75% (N=31) were females.

Distribution of patients according to age group: Table: 2 shows that number of HP infections was found positive patients of the age group between 16-25, 26-35, 36-45, 46-55, 66-75 and above 76 years was16, 29, 19, 12, 3 and 1 respectively. The highest number of HP infection was found in persons aged of 26-35 years.

Clinical findings: Chief complaints: Table 3 showed that out of 80 HP patients, 71.25% of them have reported epigastric pain as a chief complain followed by reflux or bloating 15%, Nausea / vomiting 10% and Indigestion problem 3.75%.

Diagnosis: The table 4 shows findings of endoscopic and laboratory examination of the HP positive patients (N=80), Gastritis was diagnosed in 75% of patients followed by Oesophagitis in 10%, Duodenal ulcer in 7.5%, Gastric ulcer in 3.75% and Duodenits in 3.75%, Higher percentage of patients with HP positive Gastritis (75%), was found in the study.

The table 5 shows that Regimen group-I was assigned with Omiprazol 20 mg bid for 30 days + Clarithromycin 500 mg bid for 14 days and Amoxycillin 1gm bid for 14 days (OCA). Regimen group-II was assigned with Omiprazol 20 mg bid for 30 days + Clarithromycin 500 mg bid for 14 days + Tinidazole 500 mg bid for 14 days (OCT)

Figure 2 and 3 shows that out of 40 patients in regimen-I, 80% (N=32) of them have come for follow up whereas 82.5% (N=35) of patients in regimen-II have come for follow up. It was found that 20% (N=8) in regimen-I and 12.5% (N=5) patient in regimen-II did not return to follow-up. In regimen-I, HP was eradicated in 93.8% and regimen-II, HP eradication was 91.4%.

Adverse effects of therapy: Table 6 shows the number of patients experiencing adverse effects of therapy. In regimen-I 3 % patients have reported anorexia, likewise 6 %, 3 % and 18.6 % have reported nausea, vomiting and diarrhea respectively as adverse side effect
In regimen-II 2.9 % have reported anorexia; likewise 8.6 % and 14 % have reported nausea and metallic test respectively as adverse side effect.

Table 7 shows that the daily medication cost for regimen-I is Rs.140.80 and regimen-II is Rs.115.00 and total cost for regimen-I is Rs.2131.20 and for regimen-II for Rs.1770.00. The regimen -II was cheaper (Rs25.80 per day) and (Rs361.20 per course) than regimen –I., this is also shown in figure 4.

This study shows that in total population 56% were males and 44% were females. 10% of total population was inpatients and 90% were outpatients. Because the trend in HP cases, admission is not required.

Literature shows that HP infection rates are similar in male and females [13-14]. Gender inequalities in HP infection are likely to involve many diverse issues, including cultural values and customs, access to education, access to health services. A study conducted in Tanahun district in 453 households showed that women tend to record more illness, but use health post and hospitals less than men and traditional healers more [15]. The highest number of HP infection was found at the age of 26-35 years. The similar age group with highest prevalence was found in the study conducted by Kate V et al [16]. Gill HH et al. [17].

The prevalence of infection may be due to contamination of food and unhygienic drinks. During examination of 80 HP patients, 71.25% of them have reported epigastric pain as a chief complaint followed by reflux or bloating 15%, Nausea/vomiting 10% and Indigestion problem 3.75% These were major symptoms of HP infection. This evidence is also as supported by Alan Fraser et al. [18].

Higher percentage of patients with HP positive Gastritis (75%)was found in the study. Hoda M. Malaty et al [19] has reported 58.7% Gastritis, 18% Oesophagitis, 8% Duodenitis, 7% Gastric ulcer and 17% Duodenal ulcer was associated with HP infections which were more or less similar to the proportions found from this study.

Curing the infection has the best outcome and is clearly the most cost effective management strategy for HP infected patients with ulcer disease [3]. Regimen group-I was assigned with Omiprazol 20 mg bid for 30 days + Clarithromycin 500 mg bid + Amoxycillin 1gm bid for two weeks (OCA). Regimen group-II was assigned with Omiprazol 20 mg bid for 30 days + Clarithromycin 500 mg bid + Tinidazole 500 mg bid (OCT) for two weeks. The two regimen group division was done on the basis of frequently prescribed medication in the research setting which was supported by Alberta clinical practice guideline, [20] and also the study in United States and Europe have shown that effectiveness of 14-day therapy being superior to both 10-day and 7-day regimens [21].

In regimen-I, 80% (N=32) of them have come for follow up whereas 82.5% (N=35) of patients in regimen-II have come for follow up. 20% (N=8) in regimen-I and 12.5% (N=5) patient in regimen-II did not return to follow-up; may be due to invasive diagnostic technique which is painful or may also be due improvement of their symptoms after taking medication. Similar outcome of noncompliance was found in the study conducted by Dritana Marko et al [22]. This is shown in figure 2and 3

The eradication rate of regimen-I is slightly greater (93.8 %) than that of regimen-II (91.4 %). Result was found $0.72 > 0.05$. Also there was no significant difference between regimen-I and in regimen-II suggesting both regimens equally effective for eradication of HP. A similar study with regimen-I conducted by Habu Y et al. has eradication rate reported was 91.5% [23].

During follow-up period 3 % patients have reported anorexia, likewise 6 %, 3 % and 18.6 % have reported nausea, vomiting and diarrhea respectively who followed regimen-I. In regimen-II 2.9 % of patients reported anorexia, likewise 8.6 % and 14 % have reported nausea and metallic test respectively. Similar type of adverse effect of drug was found in the study conducted by P. Balamourougane et al [24]. One patient of regimen-I has reported vomiting and discontinuance his therapy. In other patients no serious adverse effects were found. Patients did not take extra medicament to correct adverse effect. During the cost difference study between two regimen it was found that regimen -II was cheaper (Rs25.80

per day) and (Rs361.20 per course) than regimen –I. But regimen-II is more economic than regimen-I and eradication rate is also satisfactory.

CONCLUSION

- Two weeks triple therapy regimens, regimen-I (Omeprazole + Clarithromycin + Amoxycillin) and regimen-II (Omeprazole + Clarithromycin + Tinidazole) were found equally effective for the eradication of HP. $P > 0.05$ i.e. $0.72 > 0.05$.
- Disease eradication rate of regimen-I was 93.8 %.
- Disease eradication rate of regimen-II was 91.4 %.
- There was no significant difference in the efficacy of regimen-I and regimen-II to eradicate HP. (93.8 % Vs 91.4 %)
- Regimen-II was cheaper than regimen-I (Rs.1770.00 Versus Rs.2131.20 per course)
- Dropout of the cases in the study were 20 % (N=8) in regimen-I and 14.3 % (N=5) in regimen-II which could be either due to avoiding repeat endoscopies or improvement of symptoms after medication.
- In regimen-I (N=10) 31.3 % patient have reported adverse effect and in regimen-II (N=10) 28.6 % patient have reported adverse effect.

Recommendation:

- Both the regimen, regimen-I (Omeprazole + Clarithromycin + Amoxycillin) and regimen-II (Omeprazole + Clarithromycin + Tinidazole) can be recommended for eradication of HP. Regimen-II is cheaper than regimen-I.
- Regimen-II is also recommended for those HP infected patients who are sensitive for penicillin group.
- However study to conduct in large number of population and at multiple centers is recommended.
- Prolonged follow-up study may be helpful to detect relapse or re-infection of HP.

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Table -1 Distribution of out patients and inpatients by sex (N=80)

Character	Male (%)	Female (%)	Total (%)

Inpatients	5.00	5.00	10
Out patients	51.25	38.75	90
Total	56.25	43.75	100

Table: 2 Distribution of patients according to age group (N=80)

Age Group	N	Patients %	Average
16-25	16	20.00	
26-35	29	36.25	Male 33.89 ± 9.93
36-45	19	23.75	
46-55	12	15.00	Female 34.83 ± 10.95
56-65	0	0.00	
66-75	3	3.75	
Above 76	1	1.25	

Table 3 Distribution of chief complaints associated with HP. (N=80)

Chief complaints	(N)	Study Population %
Epigastric pain	57	71.25
Reflux or bloating	12	15.00
Nausea /vomiting	08	10.00
Indigestion problem	03	3.75

Table 4 Endoscopic findings with HP cases (N=80)

Findings	N	Study population %
Antral Erythema / Gastritis	60	75.00
Oesophagitis	8	10.00
Duodenal ulcer	6	7.50
Gastric ulcer	3	3.75
Duodenitis	3	3.75

Table 5 Distribution of regimen-I and regimen-II and follow-up status

REGIMEN	MEDICATION	STRENGTH (mg)	FREQUENCY /DAY	DURATION
I	OMEPRAZOLE	20	bid	30 days
	CLARITHROMYCIN	500	bid	14 days
	AMOXYCILLIN	1000	bid	14 days
II	OMEPRAZOLE	20	bid	30 days
	CLARITHROMYCIN	500	bid	14 days
	TINIDAZOLE	500	bid	14 days

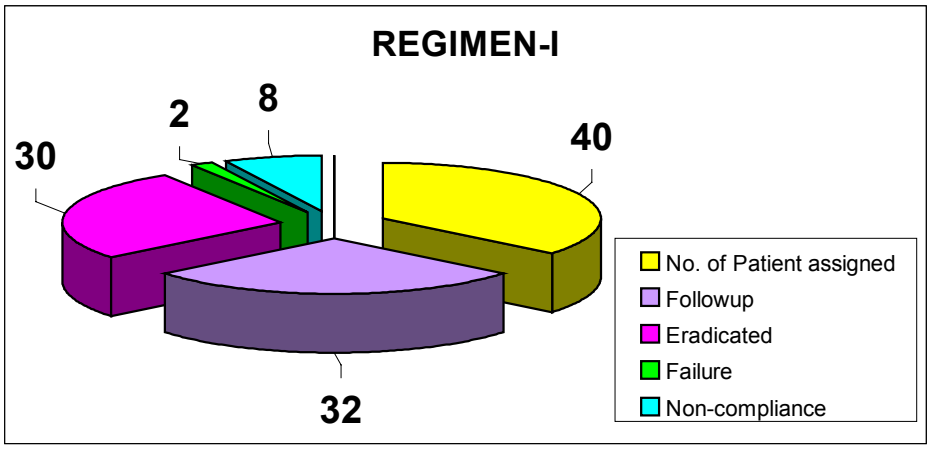

Figure 2 Distribution of regimen-I and follow-up status

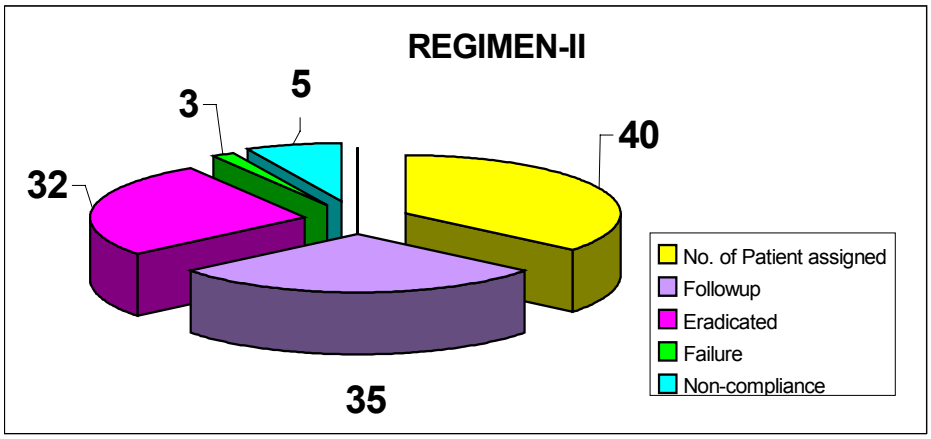

Figure 3 Distribution of regimen-II and follow-up status

Table 6 Adverse effect of therapy reported by patients

Adverse effects	N	Regimen -I %	N	Regimen-II %
Anorexia	1	3 %	2	(5.7
Nausea	2	6 %	3	8.6
Vomiting	1	3 %		-
Diarrhea	6	18.6 %		-
Metallic taste		-	5	14

Table 7 Cost Differences between two different regimens

TRIPLE THERAPY REGIMEN (REGIMEN-I)

Medication (Generic / Brand)	Daily Dose	Daily Cost	Total Cost NRs.
Omeprazole (ZOL-20)	20mg bid	10.00	300.00
Amoxycillin (REYMOXIS-500)	1g bid	34.80	487.20
Clarithromycin (KLARION-500)	500mg bid	96.00	1344.00
Total NRs.		140.80	2131.20

TRIPLE THERAPY REGIMEN (REGIMEN-II)

Medication (Generic / Brand)	Daily Dose	Daily Cost	Total Cost NRs.
Omeprazole (OMI-20)	20mg bid	10.00	300.00
Tinidazole (TRICOZOLE-500)	500mg bid	9.00	126.00
Clarithromycin (KLARION-500)	500mg bid	96.00	1344.00
Total NRs.		115.00	1770.00

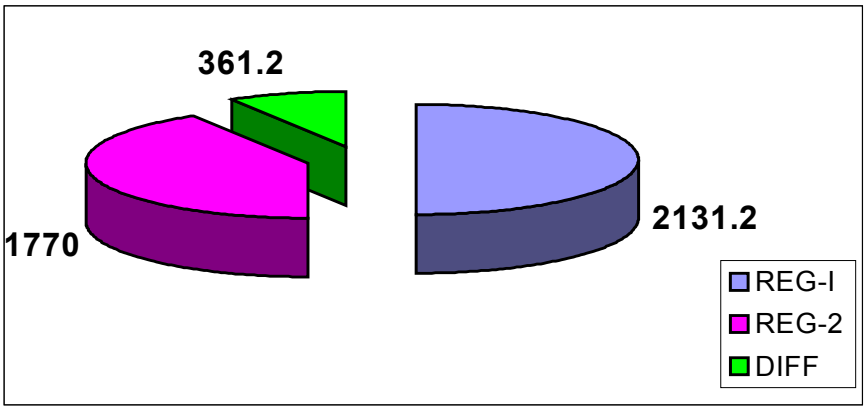

Figure 4: Cost Differences between two different regimens