The efficacy of triple and quadruple therapy for the treatment of peptic ulcer disease

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Abstract

This study was designed to determine the efficacy of triple and quadruple therapy for the treatment of peptic ulcer disease. Seventy five patients underwent Helicobacter Pylori associated peptic ulcer ,as determined by endoscopy and rapid urease test of biopsy were participated in this study. They were divided to 4 groups. Three of them were treated with triple therapy. The triple therapy in the first group consisted of omprazole 20 mg BID + amoxicillin 500 mg QID + metronidazole 500 mg TID . For the second group , only omprazole was replaced by ranitidine 150 mg BID , while for the third group metronidazole was replaced by clarithromycin 500mg BID . All triple therapies were given for 2 weeks. However , for the fourth group , a quadruple therapy consisted of omprazole 20mg BID + amoxicillin 500mg QID + clarithromycin 500mg BID + metronidazole 500mg TID , was given for one week. The efficacy in the four groups, was 91.3, 88.89, 90, and 100% respectively. All treatmentregimens were well tolerated and no sever side effects necessitated cessation of the treatment.

دراسة كفاءة العلاج الثلاثي والرباعي في مرض القرحه الهضميه

علي اسماعيل عبيد السنافي و حسن خضر رجب

المستخلص

لقد صممت هذه الدراسة لاستقصاء كفاءة التركيبه الدوائية الثلاثية والرباعية في علاج أمرض ألقرحه الهضمية . شـــارك في الدراســة خمس وسبعون مريضا ممن يعانون من مرض ألقرحه الهضمية المقترن بوجود بكتريا الهاليكوبكتر بايلوري حيث تم التشخيص بواسطة الناظور الداخلي وفحص اليوريز السريع للخزع المأخوذة أثناء الناظور .قسم المرضى إلى أربع مجاميع عولج ثلاث منهم بتركيبه علاجيه ثلاثية فيما عولجت ألمجموعه الرابعة بتركيبه علاجيه رباعية. كان العلاج الثلاثي في ألمجموعه الأولى يتكون من الاومبرازول 20 ملغم مرتين يوميا مع الاموكسيسلين 500 ملغم ثلاث مرات يوميا والمترونيدازول 500 ملغم أربع مرات يوميا .وفي ألمجموعه ألثانيه أستبدل الاومبرازول بالرانتدين 150 ملغم مرتين يوميا، وفي ألمجموعه ألثالثه استبدل المترونيدازول بالكلرثرومايسين 500 ملغم مرتين يوميا أعطيت جميع العلاجات الثلاثية لمدة أسبوعين . وفي ألمجموعه الرابعة أعطي المرضى علاجا رباعيا يتكون من الاومبرازول 20 ملغم مرتين يوميا والاموكسيسلين 500 ملغم ثلاث مرات يوميا والكلرثرومايسين 500 ملغم مرتين يوميا والمترونيدازول 500 ملغم أربع مرات يوميا واستمر العلاج لمدة أسبوع واحد. كانت كفاءة العلاجات في المجاميع الأربع 3و91 ، 89و88 ، 90 و 100% على التوالي وكان تحمل المرضى لجميع العلاجات جيدا ولم تسجل أعراض جانبيه خطيرة تقتضي إيقاف العلاج.

Key words: Peptic ulcer, Ranitidine, Omprazole, Amoxicillin, Clarithromycin, etronidazole,Treatment

Introduction

In 1983, Warren and Marshall described the presence of curved bacilli on gastric epithelia taken from patient with active chronic gastritis [1]. Subsequently , it appeared that high proportion (at least 90%) of peptic ulcer disease were associated with the presence of H.pylori infection; the infection rate tend to increase with increasing age [2]. H. pylori is capable to survive in acidic media of stomach since it is able to secrete enzyme that neutralize the acid [3]. Furthermore, the survival of H. pylori in acidic environment is probably due to its ability to establish a positive inside-membrane potential [4], and subsequently to modify its microenvironment through the action of urease and other enzymes [5]. After ingestion of the bacteria, H. pylori can survive under a very hostile environment because of its urease activity creating alkaline cloud around it . The flagella, then helps the bacterium to invade gastric mucosal layer attaching itself directly to the mucus secreting surface. The bacterium does not invade the mucosa itself, but stays attached to the mucosa causing continous irritation which reduce immunoresponse to the cytotoxic product of the bacterium .The mucosa will then be invaded by inflammatory cells and the inflamed mucosa will be a very good environment and nutrient for H. pylori. This helps H. pylori to survive and to produce increased cytotoxic products such as (urea, lipopolysaccharides, platelets aggregation factor, vaculating toxin and immunocytotoxin antigens) with which gastric activating peptides will be produced .The gastrin will increase and the acid production in the parietal cells will be stimulated, with the increase of the acid output and weakness of mucosal barrier, peptic ulcer were developed [6].

It has been suggest that H. pylori is responsible for a variety of gastroduodenal condition including acute gastritis (antral non autoimmune gastritis)
type B, peptic ulcer (65 – 100) % , (65-100) % of gastric ulcers and (80-100) % of duodenal ulcer [11,14,15,16]. Non ulcer dyspepsia in a proportion of individuals complaining of heart burn, flatus, and epigastric pain or discomfort , and gastric carcinoma are also signs and symptoms of the same infection [1].
Treatment of H. pylori did not only improve ulcer healing and make patient free of symptoms, but also reduce the Possibility of recurrence. The therapy include the combination of two or three antibiotics plus acid suppressor or gastric protector. The antibiotic regimens recommended for the patients may differ across the world because of the possibility of H. pylori resistance to the antibiotics [7-31].This study is an attempt to determine the efficacy of triple therapy for two weeks and quadruple therapy for one week for the treatment of H.pylori associated peptic ulcer disease.

Patients and Methods

This study was carried out at Kirkuk General Hospital from July 2003 to January 2004. Eighty six patients who underwent symptoms of peptic ulcer disease were included. A questionnaire was prepared to take the history of the disease and other relevant data of each patient; it includ age, sex, the duration of complain, smoking, alcohol intake, NSAIDs usage, spicy food intake, presence of familial history, signs, symptoms and previous treatment.
From those patients with positive endoscopic examination, only 75 who showed positive rapid urease test of

biopsy were included in this study. They were divided randomly into 4 groups. The first three groups were given triple therapy for two weeks , while the last one was given quadruple therapy for one week as shown in table(1). The efficacy of the treatment was determined by re-endoscopic examination, and in fewer cases who refused the re-endoscopic examination we depend on the clinical improvement in which the signs and the symptoms of patients were completely disappeared ,which was taken as a sign of positive result . All side effects appeared during treatment were recorded.

Table (1)The treatments used in patients with peptic ulcer disease and the duration of each treatment .

Group	Treatment	Duration
1	Omeprazole 20mg BID + Amoxicillin500mg QID +Metronidazole500mg TID	2-Week
2	Ranitidine150mg BID + Amoxicillin500mg QID +Metronidazole500mg TID	2-Week
3	Omeprazole 20mg BID + Amoxicillin500mg QID+Clarithromycin500mg BID	2-Week
4	Omeprazole 20mgBID + Amoxicillin500mg QID + Metronidazole500mg TID + Clarithromycin500mg BID	1-Week

Results:

This study was performed on 75 patients aged 15-70 years (mean=35.75 years) ,41 male (54.6%) and 34 female(45.4%) ,17 patients had gastric ulcer , and 58 patients had duodenal ulcer , 28(37.3%) of them with positive familial history of peptic ulcer disease, 5 (6.6%) were alcohol drinkers ,26 (34.6%)were smokers, and 10 (13.3%) were non steroidal anti-inflammatory drugs users (table 2).

Table (2) Properties of the treated groups.

Type of ulcer	No. of Patients	Smokers	alcohol drinkers	NSAIDs	positive familial history
G.U	17	7=41.5%	2=11.76%	4=23.5%	8=47.2%
D.U	58	19=32.8%	3=5.2%	6=10.4%	20=34.5%
Total	75	26=34.6%	5=6.6%	10=13.3%	28=37.3%

Table (3) The efficacy of each therapy in treatment of peptic ulcer disease.

NO.	Treatment	Duration	Efficacy
1	Omeprazole20mgBID+Amoxicillin500mg QID +Metronidazole500mgTID	1-2week	91.3% (21of 23)
2	Ranitidine150mgBID+Amoxicillin500mg QID+Metronidazole500mgTID	1-2week	88.89% (16 of18)
3	Omeprazole20mgBID+Amoxicillin500mg QID+Clarithromycin500mgBID	1-2week	90% (18 of20)
4	Omeprazole20mgBID+Amoxicillin500mg QID+Metronidazole500mgTID +Clarithromycin500mgBID	1week	100% (14 of14)
	Total efficacy		92% 69 of 75

As shown in table (3) , a combination of omprazole and amoxicilline either with metronidazole (group 1) or with clarithromycin(group 3)gave the same efficacy in treatment of peptic ulcer disease when used for two weeks (91.3 and 90% respectively).When ranitidine in combination with amoxicillin and metronidazole (group 3) was used for the same period , the efficacy reached 88.89%. However, quadruple therapy including omprazole , amoxicillin, metronidazole and clarithromycin(group 4) was 100% efficient for the treatment of peptic ulcer disease when used for one week. Although it appeared that these treatment regimens were more efficient in the treatment of duodenal ulcers compared with gastric ulcers, the differences were statistically insignificant (table 4). The study showed that these treatments regimens failed for 6 cases . All these cases were with risk factors , all cases underwent chronic complain , 5 of them were smokers , 4 of them were alcohol drinkers, 3 of them were geriatric patients , and one of them was non steroidal anti-inflammatory drugs user (table 5). All side effects appeared during the treatment were recorded to determine the safety of the treatment .However, no sever side effect necessitate cessation of the treatment were recorded (table 6).

Table (4)The efficacy of triple and quadruple therapy in healing of peptic ulcer (gastric and duodenal ulcer) .

Ulcer type	No. of Patient	Healed	Unhealed	Efficacy	P value
G.U	17	14	3	82 %	2.78(N.S)
D.U	58	55	3	94.8%	
Total	75	69	6	92 %	

(N .S): not significant P > 0.05

Table(5) The risk factors of uncured patients .

Un response Patients	Risk factors				
	Smoking	Alcohol Drinking	NSAID Usage	chronicity	Elderly
1	+ve	-ve	-ve	+ve	+ve
2	+ve	-ve	-ve	+ve	+ve
3	+ve	+ve	-ve	+ve	-ve
4	+ve	-ve	-ve	+ve	+ve
5	-ve	+ve	+ve	+ve	-ve
6	+ve	+ve	-ve	+ve	-ve

Table (6)The percentage of side effects observed for each group

group	Side effects					
	Nausea	Vomiting	headache	dizziness	Skin rash	metallic taste
1	3=13 %	-	2=8.7%	-	-	-
2	1=5.6%	1=5.6%	5=27.7%	-	1=5.5%	-
3	4=20 %	-	-	-	1= 5%	3=15%
4	3=21 %	1=7%	-	2=14%	-	2=14%
Total	11=14.6%	2=2.7%	7=9.3%	2=2.7%	2=2.7%	5=6.7%

Discussion

Peptic ulcer is a serious illness of 10% prevalence [32] .It was treated previously with many types of medications .These include gastric anti-secretary drugs H_2-blockers (cimetidine, ranitidine, famotidine and nizatidine) ,muscarnic antagonist (pirenzepine and telenzepine) , proton pump inhibitors (omeprazole ,lansoprazole, rabeprazole and pantoprazole) and octreotide . However, the mucosal protective agents like sucralfate , colloidal bismuth citrate, carbenoxolone and prostoglandin analogs[32] were also extensively used. All these medications improve patients complains , but the symptoms usually return back on withdrawing the medications .The recurrence of the ulcer reach more than (70.6%) [21] .In 1983 a curved bacilli was demonstrated in biopsies from the stomach [6]. With the introduction of Helicobacter pylori as a pathogen associated with peptic ulcer disease ,the previous understanding of the pathogenesis of peptic ulcer has been revised [21] . Anti-microbial agents were started to be used to eradicate the H. pylori. Then after, a problem appear against this approach

,represented by development of H.pylori resistance to the antibiotics especially to metronidazole (26.8%), clarithromycin (9.5%) and amoxicillin (0.3%) [33] .This push the researchers to use a combination of more than one antibiotic in order to eradicate the bacterium .Eradication of H. pylori prevents the recurrence in more than 90% of patients[21,34] . The recurrence rate of peptic ulcer after this therapy decreased to less than 10% two years after cessation of treatment [30,50] . There is a general agreement that H. pylori should be eradicated in patients with peptic ulcer , but the optimal therapeutic regimen to be used enhances healing of the ulcer and still remain a matter for many investigators .However, using of more than one antibiotic in eradication of H. pylori decreases the chance for the development of H.pylori resistance[35-36].

The prevalence of H. pylori among patients with peptic ulcer disease in this study was 87.2% , (94.8% in duodenal ulcer and 82% in gastric ulcer).Many previous studies reported the same results. Ormond et al [37] and Rauws et al [38] found that >95% of patients of duodenal ulcer and about (70-80)% of patients of gastric ulcer are H. pylori positive .Jury Metzger et al [7] found 73.3% positive cases of H.pylori in peptic ulcer disease. Marshall et al [39] and Al-Karawi [6] found that the prevalence of H. pylori reached >90% in duodenal ulcer and 65%in gastric ulcer. Gianpiero[21] recorded 61% H. pylori prevalence. Hart et al [1] found that (80-100) % of gastric ulcer and 90% of duodenal ulcer patients were H. pylori positive.

In this study 90.65% efficacy was recorded by combing proton pump inhibitor with two antibiotics for two weeks as in group 1 and 3 (omeprazole 20mg BID, amoxicillin 500mgQID and metronidazole 500mgTID) in the first group, and (omeprazole20mgBID,amoxicillin 500 mg QID and clarithromycin 500 mgBID) in the third group .this combination healed 91.3% and 90% in duodenal ulcer and gastric ulcer respectively. These results in agreement with the other investigators authors who obtain 85 to 100 % of efficacy [7-10,11-14,22-24]. However many other authors[35-36]reported low efficacy rate which could be attributed to the development of H. pylori resistance .
Efficacy of 88.89% was obtain by combing H_2 blocker (ranitidine 150 mg BID)with two antibiotic (amoxicillin 500mg QID and clarithromycin500 mg BID) for two weeks .These results are in agreement with many researchers who obtain 80 to 92 % efficacy for this treatment , when used ranitidine with different types of antibiotics [8,16,20,26,29] . Efficacy of 100% was recorded when the proton pump inhibitor was combined with three antibiotics (omeprazole 20mgBID with three antibiotic, amoxicillin 500mg QID, metronidazole 500mgTID and clarithromycin 500 mg BID) for one week. These results are in agreement with those of many authors [12,20,23,28] who obtain 85-100% efficacy using quadruple therapy. However, other authors[21,40] recorded low healing rate which is clearly attributed to the use of different antibiotics in their quadruple therapy. According to results of this study , It could concluded that triple and quadruple therapy are safe and effective treatment for peptic ulcer disease .Failure of treatment may occur with the presence of risk factors which decrease the efficacy of the treatment .

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