International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 9; Issue 08(C); August 2020; Page No.23019-23027
DOI: http://dx.doi.org/10.24327/ijcar.2020.23027.4552

Research Article

THERAPEUTIC EVALUATION OF UNANI FORMULATION IN PEPTIC ULCER SINGLE BLIND, BEFORE AND AFTER COMPARISON CLINICAL TRIAL

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A R T I C L E I N F O

Article History:
Received 10th May, 2020
Received in revised form 2nd June, 2020
Accepted 26th July, 2020
Published online 28th August, 2020

Key words:

Peptic ulcer; Upper GIT; Endoscopy; VAS; 5PLS

A B S T R A C T

Background and objectives: Peptic ulcer are characterized by the presence of ulcers in any portion of gastrointestinal tract (GIT) exposed to acid in sufficient concentration and duration. Peptic ulcer has been a major threat to the world's population over the past two centuries, with a high morbidity and substantial mortality. Duodenal ulcer is more common than gastric ulcer; about 75% to 80% of the peptic ulcers are found in the duodenum. The predominant age at which duodenal ulcers occur is between 20 and 50 years, whereas gastric ulcers most commonly occur in patients more than 40 years old. Despite extensive scientific advancements, this disease remains an important clinical setback, largely because of H. pylori infection and widespread use of non-steroidal anti-inflammatory drugs (NSAIDs).The present study was designed with the objective to investigate the efficacy and safety of a poly herbal formulation (comprise of *Sibr, Anzaroot, Kundur, Aslussoos* and *Murmakki*) in the management of peptic ulcer.

Methods: This was a single blind, before and after compression interventional trial conducted at National Institute of Unani Medicine Hospital, Bengaluru from February, 2016 to February, 2017. 22 patients were enrolled after screening 117 patients. The test formulation was obtained from classical text of Unani Medicine, Ghinna Munna. 4g of test formulation was given in divided doses orally after meals for 30 days. All the patients were assessed by subjective and objective parameters (UGI Endoscopy, VAS and 5PLS). The SPSS version 16, Wilcoxon rank test, pared proportion test and student's t test were used to analyze the significance of differences before and after treatment.

Result: Statistical analysis showed highly significant improvement in pain in abdomen and overall symptom relief ($p<0.001$). The mean number of ulcers before and after treatment was 3.36 ±2.34 and 0.18±0.66 respectively while the mean size of ulcer before and after treatment were10.32±4.58 and 0.64±2.08 respectively. UGIT Endoscopic investigation revealed strongly significant improvement in healing of ulcer ($p<0.001$).

Conclusion: The study confirmed that the test formulation was significantly effective in relieving symptoms and healing ulcer of upper GIT. No adverse effect was observed during the trial. Hence, it can be concluded that the test formulation is safe and effective. Thus, this trial validates the use of test formulation in the treatment of peptic ulcer.

INTRODUCTION

Peptic ulcer is one of the most common ulcers, refers to ulcer of the gastrointestinal tract. This is an important cause of morbidity and mortality throughout the world affecting the lives of millions of people in their everyday life [1,2]. Peptic ulcer is a defect in the mucosa of the gastrointestinal tract (GIT). In order to be called an ulcer, the defect must involve the full thickness of the mucosa reaching muscularis mucosa.

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Though predominantly occurring in the stomach and duodenum, they are reported to occur elsewhere in the gastrointestinal tract, as well. This is one of the commonest structural disorders of gastrointestinal tract [3].

In Unani classical text gastric ulcer (*Qarhe Medi*) and intestinal ulcer (*QarheMevi*) are narrated separately. *Qarha* is an Arabic word which means "wound". In *Tib*, *Qarha* means breach in continuity of any muscle or organ with suppuration [4]. Further any type of wound in muscle is called "*Jarahat*"[5]. In Unani Medicine an ulcer is defined when there is any type of discontinuity spreading over an organ or especially in a muscular organ associated with pus formation [6].

Epidemiological data for this disease and its complications have shown striking geographical variations in incidence and prevalence [7,8].Approximately 500,000 new cases and 4 million recurrences of peptic ulcer are reported each year, contributing to the approximately 10% of Americans developing peptic ulcer disease during their lifetime [2].The annual incidence of gastric ulcers varies from approximately 1 case per1000 population in Japan to 1.5 cases per 1000 population, in Norway to 2.7 cases per 1000 population in Scotlan. [2,8].

Peptic ulcer is formed due to exposure of stomach and duodenum to pepsin and gastric acid. Imbalance occurs between aggressive factors like acid, pepsin, NSAIDs, *H. pylori* and defensive factors such as gastric mucus, bicarbonate ions, and prostaglandins along with innate resistance of mucosal cells [9].The most common cause of ulcer is *H. pylori*, a bacterium that colonizes the stomach of nearly half the world's population. Infection caused by *H.pylori* is causally linked with many gastrointestinal diseases, including up to 75% of peptic ulcers. Moreover, NSAIDs along with *H. pylori* combine the caustic effects of gastric acid and pepsin, which disrupts the normal defense mechanism of the gastrointestinal mucosa[10,11,12,13].

According to the concept of Unani Medicine, the causes of *qurooh wa busoore medi* (gastric ulcer) are *Khilte haad* (irritant and corrosive humour), *fuzlat* (waste materials which accumulate in the stomach and get infected), *Nazla wi rutoobat* (descendants which get purulent), intake of hot and spicy food, excessive use of alcohol, prolong stress, strain, chronic gastritis and indigestion. It can be also caused by the rupture of an abscess[14,15].

Chief complications of peptic ulcer are upper gastrointestinal bleeding, perforation, gastric outlet obstruction, fluid and electrolyte imbalance, malignancy (with gastric ulcer only), pancreatitis and gastro-colic fistula[2,9].

Most of the anti-secretory drugs such as proton pump inhibitors (Omeprazole, Lansoprazole, etc.) and H_2-receptor blocker (Ranitidine, Famotidine, etc.) are extensively used to control increased acid secretion and acid related disorders caused by stress, NSAID's and *H. pylori*, but there are reports of adverse effects and relapse in the long run. Furthermore, many of these drugs do not fulfill all the therapeutic requirements. Although these drugs have brought about remarkable changes in ulcer therapy but efficacy and safety of these drugs are still controversial. The clinical evaluation of these drugs showed development of tolerance and incidence of relapse and side effects that make their efficacy questionable. This has been the rationale for the development of new and safe antiulcer drugs [11].

The aim of treating peptic ulcers is to relieve pain, heal the ulcer and prevention of ulcer recurrence. Currently there is no cost-effective treatment that meets all these goals. Hence, efforts are on to find a suitable treatment from herbal sources. Recently, many researchers found that the extraction from herbs have properties to treat the peptic ulcer. Some of the plants have been proved as potential anti ulcerogenic properties. Since time immemorial, herbs have been used in traditional medicine to treat a wide range of ailments, including gastrointestinal disorders such as dyspepsia, gastritis and peptic ulcer [16].

Some of the drugs described in Unani Medicine as being effective in gastritis and peptic ulcer have been investigated scientifically in different experimental models and showed promising results [17,18,19,20,21].As far as Unani treatment for ulcer is concerned, it is advised that the drug containing major properties of *Munaqqi* (cleansing), *Mudammil* (healing) and *Mumbite Laham* (tissue growing) should be used. There is a list of single and compound drugs used by eminent physicians such as *Maul asl, Ayarij Faiqara, Qurs Gulnar, Qurs Kahruba, Damul Akhwain, Kundur, Kahruba and Gulesurkh* [6,13].Among the single drugs *Sibr, Anzaroot, Kundur, Mur Makki* and *Aslussoos* are also possessing same properties and have been used as effective therapy for gastrointestinal tract ulcer. Considering the effectiveness of the above drugs, a poly herbal formulation (*Sibr, Anzaroot, Kundur, Aslussoos* and *Mur Makki*) was chosen to conduct this clinical trial [22].

MATERIAL AND METHODS

Before and after analysis interventional study without control was conducted in the department of Moalejat, National Institute of Unani Medicine Hospital, Bangalore and approved by Institutional Ethical Committee of National Institute of Unani Medicine, Bangalore under IEC No: NIUM / IEC / 2014-15 / 007/ Moal / 08, dated 16/04/2015.This study was carried out between, February, 2016 to February, 2017 on 22 patients for a duration of 30 days.

Study participants

The patients were enrolled in the study after fulfilling the following criteria:

Inclusion criteria: 1) patient's age within the range of 20-70 years; 2) Patients of either sex; 3) Haemodynamically stable and diagnosed patients with the complaining of abdominal pain and tenderness, epigastric burning, early satiety, nausea and vomiting as main complaint; 4) Presence of ulcer confirmed by upper GIT Endoscopy.

Exclusion criteria*:*1) Patients below 20 years and above 70 years of age; 2) Pregnant and lactating women; 3) Patients with Haemetemsis and malena; 4) Patients with severe respiratory, cardiovascular and renal diseases; 5) Patients with malignancy; 6) Patients who were not willing to participate in study.

Study interventions

The study medications included powders (*safoof*) of *Sibr (Aloe barbadensis Linn.), Anzaroot (Astragalus sarcolla Dymock.), Kundur (Boswellia serrata Roxb), Aslussoos (Glycyrrhiza glabra Linn) and Murmaki (Commiphoramyrrha Engl)* taken in equal quantity. A good quality of drugs was procured by the Pharmacy of National Institute of Unani Medicine (NIUM).

Identification of these drugs was done by chief pharmacist of NIUM, to ensure their originality and authenticity. The drugs were cleaned from weed and unwanted material and then pounded to form a fine powder and all the five ingredients were mixed together. The Powdered (*sufoof*) test drugs were filled into capsules each weighing 1g and capsules were given to the patient in transparent auto lock cover in sufficient amount to be consumed for 30 days.

Study procedure

Known cases of (*Qarahe Hazmiya)* peptic ulcer or patients with history of burning sensation, pain abdomen, nausea or vomiting were taken up from Moalajat OPD / IPD. The patients were subjected to laboratory investigations (HbSAg, HIV, Rapid Urease Test, Stool test for occult blood) and confirmation of diagnosis made by UGIT Endoscopy. Patients who fulfilled the inclusion criteria were enrolled into the study after obtaining a written voluntary informed consent.

During the selection procedure complete history of the patient including general physical and systemic examination were carried out and recorded on a prescribed proforma which was designed with the prior consultation of the guide. Accordingly, the patients were enquired about their demographic characteristics such as name, age, sex, weight, marital status, address and occupation. Further details were recorded about their chief presenting complaints and duration. While taking history, much emphasis had been paid on past history of any disease, specifically diabetes, hypertension, cardio vascular disease. Dietary habits, smoking, alcohol intake, beetle chewing was also enquired under personal history.

Regarding family history, patients were asked about the presence of any significant history of peptic ulcer in his/her family. In socioeconomic history, patients were queried about their monthly income. By using Kuppuswamy's socioeconomic scale (modified 2014) patients were graded into different socioeconomic strata. After history taking, general physical examination and local examinations were done with special emphasis on the blood pressure, respiratory rate, temperature, built, pulse. The *Mizaj* of the patient was determined on the assessment of *Ajnās-e-Ashra*(10 determinants) mentioned in classical Unani literature.

30 days study was divided into three visits of follow-ups made at an interval of every 10 days. At every visit patients were asked about symptoms of PUD. Concomitant treatment such as antacid and PPI was not allowed.

Improvements in the symptoms were assessed by change in the subjective parameters (major symptoms) using (Visual Analogue Scale (Intensity of abdominal pain), and 5 Point Likert Scale (Severity of symptoms) while UGIT Endoscopy findings were used as objective parameters, (number of ulcer and size of ulcer)). The patients were also asked for any adverse effects noted during the trial period. Pre and post treatment values of subjective and objective parameters were analyzed and subjected to comparison statistically to evaluate the efficacy of the test drug. After completion of the trial on 30th day, the subjects were asked to report on 45th day for follow up to note any recurrence in the symptoms.

Outcomes

The primary outcome measure was assessed by change in UGIT Endoscopy findings (number of ulcer) and secondary outcome measures were assessed by change in Visual Analogue Scale / VAS (Intensity of abdominal pain) and 5 Point Likert Scale (Severity of symptoms) at the end of 30 days from baseline.

Visual Analogue Scale (VAS) score adopted for the assessment intensity of pain (Baseline: 4-8 and Pain relief <4). Five Point Likert Scales (Base line- 3, 4, 5 and Symptom relief -1, 2), this severity scale was used to measure the severity of the symptoms such as epigastric pain, epigastric burning, postprandial fullness /early satiety, nausea and vomiting(1- No complaints, 2- Few complaints,3- Moderate complaints, 4- Many complaints; and 5-serious complaints that significantly affect daily life).

Safety evaluation

- UGIT Endoscopy
- Rapid Urease Test
- Haemogram with ESR
- RBS
- LFT (AST and ALT)
- KFT (Blood Urea and Serum Creatinine)
- Stool test for occult blood

All the efficacy variables were assessed at every visit of follow-up. No any adverse reactions were observed throughout the course of study. Investigations (Haemogram, ESR, RBS, ALT, AST, Blood urea, and Serum creatinine were carried out in each case to exclude the patients with pathological conditions mentioned under exclusion criteria and to assess the safety of test drug.

Statistical analysis

Descriptive and inferential statistical analysis had been carried out in the present study. Results on continuous measurements were presented on Mean ± SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance. Student t test (two tailed, dependent) and Wilcoxon rank test had been used to find the significance of study parameters on continuous scale within group. Paired Proportion test had been used to find the significance of proportion in paired data.

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel had been used to generate graphs, tables etc.

RESULTS

In this study, a total of 117 patients were screened. Out of them 95 patients were excluded because they did not fulfill the inclusion criteria, remaining 22 patients were enrolled. All the

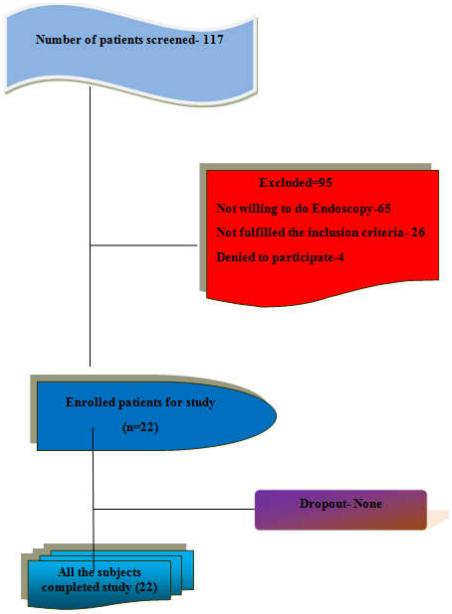

Figure No. 01 The CONSORT flow diagram

The demographic characteristics of participants are shown in Table No.01. Medical history and habits of patients studied are shown in Table No.02

Efficacy outcome

Efficacy assessment was done on the basis of primary and secondary outcome.

Primary outcome

Test drug formulation was effective in reducing number and size of ulcers in UGIT Endoscopy findings ($p<0.001$) shown in Table No 5.

Secondary outcome

The effect of test drug formulation on various subjective parameters such as improvements in the major symptoms and intensity of abdominal pain were assessed at baseline, 10th, 20th and 30th days, and evaluated on the basis 5 Point Likert Scale and VAS score at baseline and after treatment are shown in Table No. 03 and 04 respectively. In intragroup comparison using paired't' test, findings were statistically highly significant ($p< 0.001$), it indicates that symptoms showed significant reduction on5 Point Likert Scale and VAS scores.

Table 1 Demographic and patient characteristics

Age in years	Number	(%)	Occupation	Number	(%)
20-30	7	31.8	Unemployed	8	36.4
31-40	6	27.3	Unskilled worker	8	36.4
41-50	4	18.2	Semi-Skilled Worker	4	18.2
51-60	4	18.2	Semi professional	1	4.5
60-70	1	4.5	Skilled Worker	1	4.5
Total	**22**	**100.0**	**Total**	**22**	**100.0**
Mean ± SD 40.50±13.32					
Gender and religion distribution of patients studied					
Gender	**No**	**(%)**	**Religion**	**Number**	**No (%)**
Female	4	18.2	Hindu	10	45.5
Male	18	81.8	Muslim	12	54.5
Total	**22**	**100.0**	**Total**	**22**	**100.0**
Mizaj and education distribution patients studied					
Mizaj	**No**	**(%)**	**Education**	**Number**	**No (%)**
Damvi	4	18.2	Illiterate	3	13.6
Balghami	4	18.2	Primary	9	40.9
Safravi	13	59.1	SSLC	6	27.3
Saudavi	1	4.5	PUC/diploma	2	9.0
			UG	2	9.1
Total	**22**	**100.0**	**Total**	**22**	**100.0**
Marital status and KSSS distribution of patients studied					
Marital status	**No**	**(%)**	**KSSS**	**Number**	**%**
Married	18	81.8	Lower	2	9.1
			Lower Middle	5	22.7
Unmarried	4	18.2	Upper Lower	14	63.6
			Upper Middle	1	4.5
Total	**22**	**100.0**	**Total**	**22**	**100.0**

Table 2 Past medical history and habits of patients studied

PMH	Number	(%)	PTH	Number	(%)
Not Significant	20	90.9	NON	14	63.6
Hemetemesis	1	4.5	PPI	5	22.7
HTN, DM	1	4.5	NSAID	2	9.1
			Anti-diabetic	1	4.5
Total	**22**	**100.0**	**Total**	**22**	**100.0**
Diet and smoking habit distribution of patients studied					
Diet	**Number**	**(%)**	**Smoking**	**Number**	**%**
Vegetarian	1	4.5	None	19	86.4
Mixed	21	95.5	Yes	3	13.6
Total	**22**	**100.0**	**Total**	**22**	**100.0**
Alcohol and beetle chewing habit distribution of patients studied					
Alcohol	**Number**	**%**	**Beetle chewing**	**Number**	**%**
None	21	95.5	**Beetle chewing**	**Number**	**%**
Yes	1	4.5	No	20	90.9
Total	**22**	**100.0**	Yes	2	9.1
			Total	**22**	**100.0**

Table 3 5PLS**:** An assessment before and after treatment of patients studied

5PLS	Mean ± SD	Difference	P value
Day 0	4.41±0.50	-	-
Day 10	4.09±0.61	0.32	0.005**
Day 20	3.13±0.71	1.27	<0.001**
Day 30	2.23±0.75	2.18	<0.001**

Table 4 VAS**:** An assessment before and after treatment of patients studied

VAS	Mean ± SD	Difference	P value
Day 0	8.18±0.96	-	-
Day 10	7.77±0.75	0.41	0.009**
Day 20	5.14±0.94	2.05	<0.001**
Day 30	3.87±1.48	4.32	<0.001**

Table 5 Comparison of ulcer number and size before and after treatment

Ulcer	N		Baseline		After treatment		P value
	Baseline	After treatment	Mean	SD	Mean	SD	
Number	64	4	3.36	2.34	0.18	0.66	**<0.001**
Size (mm)	227	14	10.32	4.58	0.64	2.08	**<0.001**

Table 6 RUT and SOB distribution of patients studied

Test	Baseline		After treatment	
RUT	**Number**	**%**	**Number**	**%**
Positive	7	31.8	7	31.8
Negative	15	68.2	15	68.2
Total	**22**	**100**	**22**	**100**
SOB	**Number**	**%**	**Number**	**%**
Positive	0	0.0	0	0.0
Negative	0	0.0	0	0.0

Table 7 Safety parameters before and after treatment

Investigations	Before treatment (Mean / SD)	After treatment (mean / SD)	P value
RBS	113.0 ± 36.13	108.77± 23.79	0.961
Blood urea	24.23± 3.62	25.23± 5.08	0.400
Serum creatinine	0.8727± 0.14	0.8445±0.198	0.632
Hb%	13.232± 1.873	13.523± 1.833	0.289
TLC	7081± 1510	7672± 1542	0.181
Neutrophil	61.32± 7.8	63.86± 8.7	0.075
Lymphocyte	30.95± 7.3	28.5± 7.6	0.084
Eosinophil	4.50± 0.80	4.55± 0.91	0.854
Monocyte	4.23± 1.54	4.00± 1.02	0.326
Basophil	0.045± 0.21	0.095± 0.43	0.317
ESR	14.82± 13.36	10.77± 8.92	0.115
ALT	27.27± 6.24	29.00± 9.87	0.086
AST	27.91± 7.34	28.86± 9.00	0.426

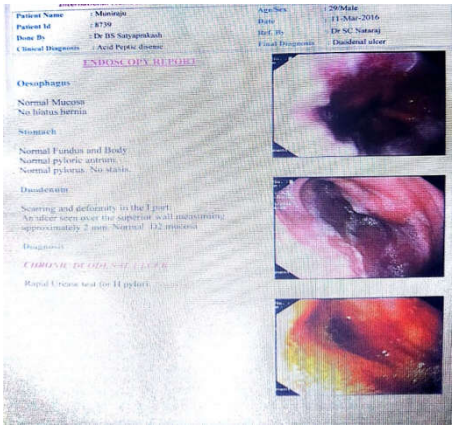

Figure 2

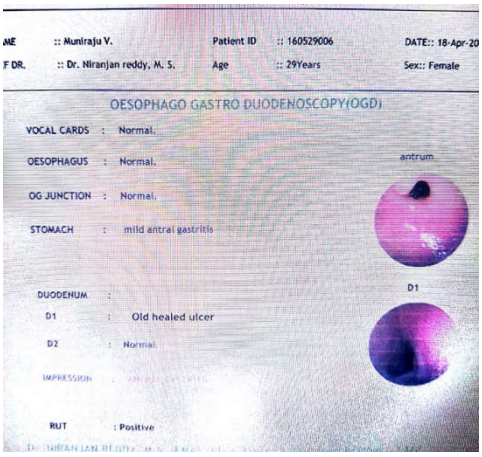

Figure 3

DISCUSSION

This study showed that patients with Upper GIT ulcers who were treated for 30 days with the test Unani formulation which comprised of *Sibr, Anzaroot, Kundur, Mur Makki and Aslussoos* significantly effective in healing the ulcers and these drugs were being claimed to have *munaqqi e fuzlath, mulaaiyin, mushil, jali, mujaffiferutoobath* (desiccant), *musakkinesozishwa Dard me'da, musakkine, muqavveme'da, muhallileriyah, Mulattif* (demulcent), *Qabiz* (astringent), *Habisuddum* (styptic), *Mugharri* (agglutinant), *Mubarrid* (cooling) and *Mudammilequrooh* (Healing of ulcer) properties [23,24].

Age Incidence: Peptic ulcer may be found in any age group, from adolescence to the geriatric age but it is more common in third and fourth decades of life. In the present study youngest patient was 20 years old and the oldest was 70 years, with maximum number of patients (5) being in 20 to 30 years while second majority (6) was in the age group of 31 to 40 years. In contrast to present findings Avijeet *et al* recoded maximum number of patients in 31 to 40 years age category. Mean age of patient in present study was 40 years (Table 1) however Avijeet *et al* revealed mean age as 37 years[3].

Sex incidence: Peptic ulcer tends to affect males more commonly than females. There was marked variation in the sex ratio with geographical locations suggesting that probably habits and environmental factors, in addition to diet, have a role to play in the causation of peptic ulcer. In the present trial 18 of them were male and 4 of them were female (Table 1). Sex ratio male to female was 9:2. Most of the study findings concluded that the male preponderance of this disease [26,27].

Habits: Smoking and alcohol usage were the common habits seen in the patients of PU. In current study 3 of them were smokers, 2 patients were chewing beetle and 1 patient was alcoholic (Table No 02). We were unable to assess what effect, on relapse pattern if any, due to smoking and drinking habits, as recorded at entry to the trial**,** since the study duration was short.

Mizaj: 13 patients were *safravi* in *mizaj*. I patient was *saudavi* and 4 patients each were *damvi* and *balghami* in *mizaj*respectively (Table No. 1). This observation conflicts with the view of *Ibn Sina* and *Razi*who stated that accumulation of *Balgham*was chief cause for *QaraheHazmiya* [4,6].

Stool for occult blood was negative in all the patients at baseline and end of treatment (Table No.06). while mean haemoglobin percentage and ESR were 13.22 g % and 14.8 mm 1st hour at baseline and 13.52g % and 10.77mm 1st hour at the end of treatment respectively (Table No. 07). Hence there were no alarming signs in none of the patients studied. A previous study concluded that perforation, followed by haemorrhage was the most frequent complications among the

Indian population. In contrast present trial the study population was less and conducted on OPD patients mostly, that might be the reason for not finding any patient with serious complication[3,25, 27,28].

RUT was negative in 15 subjects and 7 of them had positive RUT (Table No.06). There was no change in the RUT among the subjects before and after treatment which indicated that there was no effect of test formulation on H pylori eradication.M. Hemalata *et al* conducted a survey in Bangalore in 2013 and they found 37.5%of prevalence of H pylori, in contrast this study revealed 32% patients with RUT positive. The reason for slight difference might be the previous study was done in a larger population comparing to this study sample [29].

In recent years many studies suggested a significant proportion of PU was not related to risk factors. There are variations in the reported rate of non-H pylori related ulcers [30]. Recent findings of Kambiz Yazdanpanah *et al* showed more number (72.7%) of patient with positive RUT,in contrast there was a smaller number of patients with positive RUT in current study population [31].

The overall incidence of gastric and duodenal erosive disease in other areas of the world is 4%-19%. Present study showed 54 % gastric and duodenal erosion. The difference might be due to limited number of patients were screened compared to worldwide prevalence and there was no considerable number of patients using NSAIDs for longer duration [32].

Assessment of efficacy and safety

Assessment of symptom relief after treatment

Pain in upper abdomen and epigastric burning sensation

PU Symptoms were recorded at the baseline and during each follow up visits. Pain in upper abdomen [22(100%) reduced to 6(27.3%)] and epigastric burningsensation [22(100%) reduced to 7(31.8%)] and improvedsignificantly when compared to baseline (P<0.001).

VAS: The mean VAS Score for pain in abdomen at baseline was 8.09±0.811 and 3.86± 1.49 after treatment. The test formula showed highly significant reduction in VAS score for pain (P<0.001). This significant improvement of pain in abdomen and epigastric burning sensation may be due to various therapeutic effects of test drugs mentioned in Unani medicine such as analgesic, detergent, deobsruent and laxative etc. Further the test drugs also have action of eliminating the morbid matter occluded in the stomach particularly *Aslussoos* and *Sibr*[33].

Early satiety: The test drug showed significant improvement in early satiety as compared to baseline 19(86.4%) and end of the study 3(13.6%). Observed P value was P<0.001. This improvement may be due to cleaning and elimination of morbid matter infiltrated in the stomach and healing of ulcer and erosion as well as the tonic action (*muqaviemeda)* of test drug particularly *sibr* and *anzaroot*[6,34,35].

The chief presentation of PU was epigastric pain and epigastric burning among most of the patients. A previous study done by KambizYazdanpanah *et al* revealed maximum number of patients with epigastric pain and epigastric burning sensation 88.6% and 54.5 % respectively. Present study findings coincide with the previous study[31].

According to medical examination and assessment of hospitalized patients, annual global incidence of gastric and duodenal ulcer was 0.1 -0.19% and 0.03 -0.17%, respectively. Our results showed 0 .05% and 0.14% respectively. The reason for this pattern may due to different statistical population [31].

Ulcer healing was assessed by UGIT endoscopy findings before and after treatment. Total number of ulcer and its size were compared at baseline and end of treatment.

Number of ulcers: Mean number of ulcers before and end of treatment were 3.36±2.34 and 0.18±0.66 respectively. It showed highly significant reduction in number of ulcers at the end of trial (P<0.001).

Size of ulcers: Similarly, total size of ulcers was compared at baseline and end of treatment. Mean size of ulcers before and end of treatment were10.32 ±4.58mm and 0.64±2.08mm respectively. It showed highly significant reduction in size of ulcers at the end of trial (P<0.001).In this study, the mean ulcer number and their size had been reduced significantly at the end of treatment.

Test drugs consisted of following collective actions as mentioned in various classical text book of Unani Medicine: *munaqqifuzlatmeda, mullayyinwa mushil bagham ,jali, mujaffif, mudammilequrooh, munabiteleham, musakkiensozishwadard* (burning and pain), *muhallileriyah (Carminative)* and *muqavvimeda.(tonic)*[36,34,35,37,38].The improvement in healing of ulcersmay be due to above mentioned actions of test drugs.

Different previous experimental studies had already documented that *Sibr* had antibacterial [39], anti-ulcer[40],and anti-inflammatory action[41], *kundur* possessed anti-ulcer activity[42],*Aslussoos revealed* wound healing, anti-inflammatory[43], and anti-bacterial Activity [44], while *murmaki* also confirmed the actions of anti-inflammatory[45], antibacterial [46], analgesic effect[47], and *anzaroot* had wound healing activity[48]. Hence these actions of the test drugs had prompted towards the improvement of overall symptoms and significant effectiveness in healing of ulcers. Although the exact mechanism of action of the test formulation was not described directly, it can be assumed that all the above-mentioned experimental studies on individual drug activity provide evidence for how the test formulation brought about significant efficacy in PU.

The results of scientific studies and actions mentioned in classical text of Unani medicine of thetest drugs,it was evident that the test formulation wasinstrumental for the highly significant outcomesof this trial with regard to safety and efficacy.

Albina *et al* reported test drug which consisted of *Aslussoos, Aspaghol, Samgh e arabi, Mastagi* eradicated 98.8% of *H.pylori*. But in conflict with their finding our study did not show any changes in RUT findings at the end of trial although *Aslussoos* was also an ingredient in this test formula. Thisdifference in resultsmay be considered due to rest of the ingredient were not same as the Albin *et al* test drugs [19].

The safety parameter investigations for test formulation were RBS, Hb%, TLC, Neutrophil, Lymphocyte, Eosinophil, Monocyte, ESR, Blood urea, Serum creatinine, ALT, AST and urine analysis. There was no statistically significant difference (P>0.05) between pre and post treatment investigation values for each safety parameters (Table No. 7). This analysis had not revealed any shifts in haemoglobin, in white cell count, or in indicators of liver and renal function, over time. K. D. Bardhan*et al* conducted a study on long term effects of conventional drugs and also conclude the same that there were no significant trends of changes in haematology or serum biochemistry revealed by regular blood sampling[49].

One of the problems reported with any clinical trial was that the patients leave by default and by withdrawal. In contradictory this present trial none of the patient among the 22 studied failed to attend scheduled visits or withdrawn for protocol violation. Further no patient reported or complained of noncompliance or intolerance to test drug as well as not sought or offered alternative treatment. This proved the better patient compliance observed among the patients in this study towards the test formulation.

CONCLUSION

Results of the present study demonstrated that test drug formulation in the present study was safe and effective in the management of PU (*Qarahe Hazmiya)* and conventional medicine or surgical intervention should no longer be the only treatment option to the patients. Further studies were imperative to confirm these results. Moreover, studies on efficacy of different doses and treatment duration of test drug formulation were required to fine-tune these observations.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

Authors acknowledge the scholars whose articles cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed. Our special thanks go to the colleagues and the staff of National Institute of Unani Medicine, Bangalore. We are thankful to all subjects who were volunteered to be participated in this trial. Authors are grateful to the Journal editorial board members and Journal team of reviewers who have helped to bring quality to this manuscript.

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How to cite this article:

MHM Hafeel *et al* (2020) ' Therapeutic Evaluation of Unani Formulation in Peptic Ulcer Single Blind, Before and After Comparison Clinical Trial', *International Journal of Current Advanced Research,* 09(08), pp. 23019-23027.
DOI: http://dx.doi.org/10.24327/ijcar.2020. 23027.4552

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