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AN OBSERVATIONAL STUDY ON EFFICACY AND SIDE EFFECTS OF PPI, DOXYCYCLINE, BISMUTH SUBSALICYLATE AND NITROIMIDAZOLE IN BISMUTH QUADRUPLE THERAPY OF H.PYLORI GASTRITIS PATIENTS - A PILOT STUDY

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ABSTRACT

Background:- Helicobacter pylori (H.pylori) is a type of bacteria that causes infection in the stomach. It is the main cause of peptic ulcers, and it can also cause gastritis and stomach cancer. Tests and procedures for diagnosis of H.pylori include blood test, especially Rapid Urease Test(RUT positive).Bismuth quadruple therapy (BQT), consisting of a proton pump inhibitor(PPI), Bismuth and two antibiotics (Doxycycline and Nitroimidazole) has been recommended in most current H.pylori treatment guidelines as a first line regimen. **Method:-**This is a Prospective Observational Study carried out in 20 patients**.**In this study, we assess the symptomatic improvement caused by Bismuth regimen therapy in H.pylori gastritis patients. The H.pylori patients were given Bismuth subsalicylate, PPI, Doxycycline and Nitroimidazole. The primary endpoint of this study was to evaluate the efficacy and side effects of Bismuth quadruple therapy. The efficacy will be assessed using GSRS(Gastrointestinal symptoms rating scale) and side effects by questionnaire. **Result:-** A total of 20 patients with H.Pylori gastritis fulfilling the study criteria were selected. Bismuth quadruple therapy was given for all patients and their symptomatic improvement and side effects were assessed. Almost all the patients found to relieve symptoms. Most subjects experienced some minor side effects during the course of therapy. There was no mortality or major morbidity recorded in the study. It was observed that bismuth quadruple therapy have maximal beneficial effect for H.Pylori gastritis patients. **Conclusion:-** From this study, it was concluded that Bismuth Quadruple therapy consisting of PPI, Doxycycline, Bismuth subsalicylate and Nitroimidazole has more efficacy with minimal side effects seems to be better treatment option.

INTRODUCTION

Definition

H pylori associated gastritis is a primary infection of the stomach which is caused by Helicobacter bacteria. The most frequent Helicobacter species found in patients with gastritis is Helicobacter pylori (H pylori). H pylori also cause chronic gastritis.H pylori is common and is mainly associated with gastrointestinal disease such as peptic ulcer and gastric cancer.[4]

Epidemiology

H. pylori gastritis is acquired in childhood and adolescence (age less than 20) in more than 50% of cases; the risk and rate of acquisition is highest in early childhood, after which the rate exponentially decreases; new infections occur in adulthood but are rare (annual incidence 0.4%, on average, in Finland).[1]

Etiology

H pylori is a common stomach pathogen that causes gastritis, peptic ulcer disease, gastric adenocarcinoma, and low-grade gastric lymphoma. Helicobacter pylori infection may be asymptomatic or result in varying degrees of dyspepsia. The main diagnostic tests are urea breath test, stool antigen test, and testing of endoscopic biopsy samples.

Factors

Helicobacter pylori infection are related to living conditions such as: Living in crowded conditions. Have greater risk of H. pylori infection if live in a home with other peoples.

Clinical Manifestation

No specific clinical signs have been seen in patients with H pylori infection. Patients have dyspepsia or abdominal

discomfort, gastritis or with epigastric pain. patients also have hungry in the morning and have halitosis.[14]

Complications

Ulcers: Helicobacter pylori can damage the protective lining of the stomach and small intestine.

Inflammation of the stomach lining: H. pylori infection can disturbance in the stomach and may cause inflammation.

Stomach cancer; H pylori also cause stomach cancer.[15]

Pathogenesis

To avoid the acidic environment of the stomach, Helicobacter pylori uses its flagella to burrow into the mucus lining of the stomach. Helicobacter pylori have the ablity to sense the pH gradient in the mucus and then move towards the less acidic region. This also maintains the bacteria from being move away into the lumen with the bacteria's mucus environment, which is constantly moving from its site of creation at the epithelium to its dissolution at the lumen surface.[16]

Helicobacter pylori mainly found in the mucus, on the inner surface of the epithelium, and inside the epithelial cells.[20] It adheres to the epithelial cell surfaces by producing adhesins, which binds to lipids and carbohydrates in the epithelial cell membrane. One such adhesin, BabA, binds to the Lewis b antigen on the surface of gastric epithelial cells. BabA's acid responsiveness enables adherence allowing an effective escape from unfavorable environment. Another such adhesin, SabA, binds to increased levels of sialyl-Lewis x antigen present in the gastritis.In addition to using chemotaxis to avoid areas of low pH, Helicobacter pylori neutralizes the acid in its environment by producing large amounts of urease, which breaks down the urea present in the gastritis to carbon dioxide and ammonia. These react with the strong acids to produce a neutralized area around Helicobacter pylori.[17] Urease expression is not only required for establishing initial colonization but also for avoid the chronic infection.[18-19]

Investigations

H. pylori is not a disease, but a condition associated with a number of disorders of the upper GI tract. Testing for Helicobacter pylori is not routinely recommended. Testing is recommended if the patients have peptic ulcer disease or low-grade gastric MALT lymphoma (MALToma), after endoscopic resection of early gastric cancer, for first-degree relatives with gastric cancer, and in dyspepsia. Several methods of testing include invasive and noninvasive testing methods.

Noninvasive tests for H. pylori infection may include blood antibody tests, stool antigen tests, or the carbon urea breath test (in which the patient drinks 14C – or 13C-labelled urea, which the bacterium metabolizes, producing labelled carbon dioxide that can be detected in the breath).[8-9] It is not known which non-invasive test is more accurate for diagnosis, and the clinical significance of the levels obtained is not clear.

An endoscopic biopsy is an invasive test for H. pylori infection. Low-level infections can be missed by biopsy and multiple samples are recommended. The most accurate method for detecting H. pylori infection is endoscopy biopsy, combined with a rapid urease test or microbial culture.

Transmission

Helicobacter pylori is contagious and the exact route of transmission is not known. Person-to-person transmission is by either oral to oral or fecal to oral route is. The main transmission route is mainly the vomitus.[10-11] The bacteria have been isolated from feces, saliva, and dental plaque of the infected people. Helicobacter pylori is easily transmitted by gastric mucus than saliva.Helicobacter pylori DNA is also detected in human feces.[12-13] Transmission occurs mainly within the families in developed nations and also be acquired from the community in developing countries. Helicobacter pylori may also transmitted orally by means of fecal matter through the ingestion of waste water.

TREATMENT

Gastritis

Superficial gastritis acute or chronic is the most common manifestation of Helicobacter pylori infection. The signs and symptoms of this gastritis have been found to remit spontaneously in many patients without resorting to Helicobacter pylori eradication protocols. The Helicobacter pylori bacterial infection persists after remission. Several antibiotic plus proton pump inhibitor drug regimens are used to eradicate the bacteria and thereby successfully treat the disorder with triple-drug therapy consisting of clarithromycin, amoxicillin, and a proton-pump inhibitor given for 14–21 days is considered as first line treatment. Clarithromycin containing triple therapy is recommended as first line therapy for the treatment of helicobacter pylori infection.[5-6] High dose proton pump inhibitors also exerts antimicrobial activity against helicobacter pylori.[7]

Once Helicobacter pylori is detected in a person with a peptic ulcer, the normal procedure is to eradicate. The standard first-line therapy is a seven days(1 week) "triple therapy" consists of proton-pump inhibitors such as omeprazole and the antibiotics such as clarithromycin and amoxicillin. Variations of the triple therapy have been developed over the years, such as using a different proton pump inhibitor, as with pantoprazole or rabeprazole, and replacing amoxicillin with metronidazole for patients who are allergic to penicillin. In case of clarithromycin resistance, other options are recommended. Such a therapy has revolutionized the treatment of peptic ulcers and has make a cure to the disease. Previously, the only option was s using antacids, H2-antagonists or proton pump inhibitors alone.[2-3]

METERIALS AND METHODS

Data source: All the relevant information regarding the study was collected by case records and direct interview with patient and care givers. Data from case records and care givers are collected by using suitably designed proforma.

Study population: Patients were taken from gastroenterology department of cosmopolitan hospital. Informed consent was obtained. The study was conducted for the period of 6 months.

Assessment of efficacy: The efficacy will be assessed using GSRS(Gastrointestinal symptoms rating scale). GSRS is a disease specified instrument of 15 items combined in to 5 symptoms clusters depicting Reflux, Abdominal pain, Indigestion, Diarrhoea and Constipation.

Assessment of side effects: Details were collected from case records and direct interview by patients and caregivers by using suitable questioners.

Statistical analysis: Data analysis is performed using SPSS.

OBSERVATION ANS RESULTS

The proposed study entitled, "Efficacy and Side Effects of PPI, Doxycycline, Bismuth Subsalicylate and Nitroimidazole in Bismuth Quadruple Therapy of H.Pylori Gastritis Patients" was a prospective observational study carried out in a multispeciality tertiary care hospital. In our study we analyzed the data collected from 20 patients diagnosed with H.Pylori Gastritis. Bismuth quadruple therapy was given for all patients and their symptomatic improvement and side effects were assessed. Almost all the patients found to relieve symptoms. Most subjects experienced some minor side effects during the course of therapy. There was no mortality or major morbidity recorded in the study. It was observed that bismuth quadruple therapy have maximal beneficial effect for H.Pylori gastritis patients.

DEMOGRAPHIC DETAILS OF THE PATIENTS:-

In this section, the data related to demographic details of patients were collected and recorded.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON AGE

The percentage distribution of patients based on age is shown in the following table

Table 1: Percentage distribution of patients based on age.

Age	Frequency	Percent
≤ 40	4	20
41 – 50	6	30
51 - 60	7	35
61 - 70	1	5
>70	2	10
Total	20	100

Average age 49.9± 15.8 years, Age ranges from 22 to 88 years

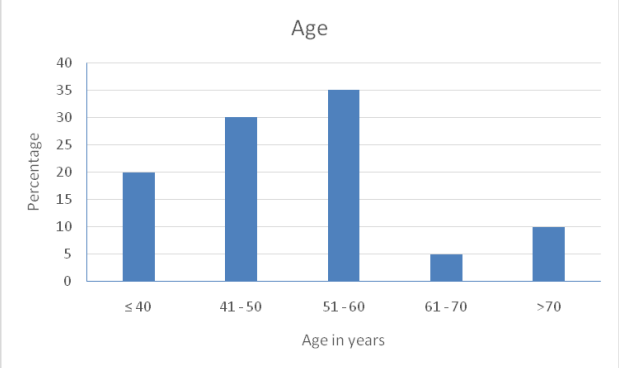

Figure 1: Diagrammatic representation of patients based on age.

From the Table 1, It was observed that out of the total patients with H.Pylori gastritis, 20% of patients were ≤40years, 30% of patient between the age of 41-50years, 35% of patient between 51-60 years, 5% of patient between the age of 61-70years, 10% of patient were >70years. Thus from the above table we concluded that, higher chance of occurrence of H Pylori gastritis was found to be between 51-60 years.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON GENDER

The percentage distribution of patients based on gender is shown in the following table

Table 2: Percentage distribution of patients based on gender.

Gender	Frequency	Percent
Male	12	60
Female	8	40
Total	20	100

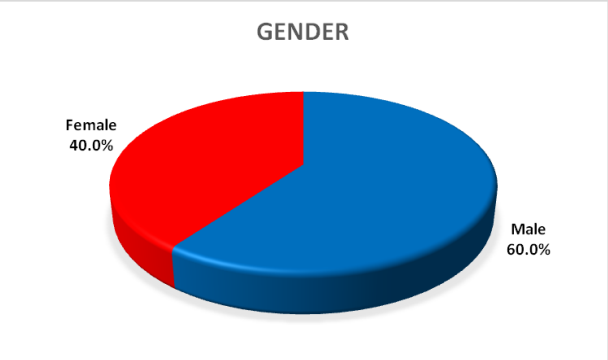

Figure 2: Diagrammatic representation of patients based on gender.

From Table 2, It was observed that out of total patients with H.Pylori gastritis, 40% were females and 60% were males. Thus from the above table we concluded that there is a higher chance of occurence of H.Pylori gastritis in males compared to that of females.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON PRESENTING SYMPTOMS

The percentage distribution of patients based on presenting symptom is shown in the following table

Table 3: Percent of distribution of patients based on presenting symptoms.

Presenting symptoms	Frequency	Percent
Abd pain	17	85
Regurgitation	3	15
Loss of appetite	4	20
Flautulence	10	50
Abd rumbling	6	30
Nausea	4	20
Burnig sensation	1	5
Bloating	11	55
Vomiting	3	15
Pain during swallowing	1	5

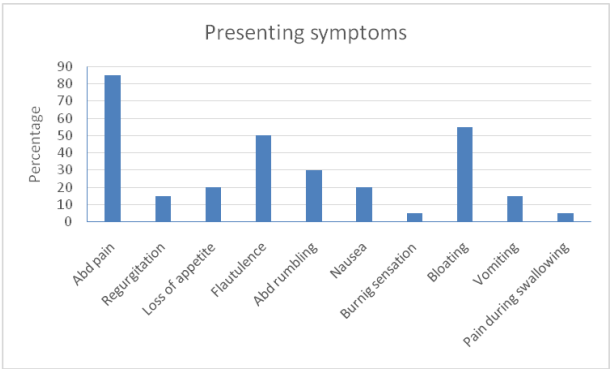

Figure 3: Diagrammatic representation of patients based on presenting symptoms.

From Table 3, It was observed that out of the total patients with H.Pylori gastritis, 85% of patients have abdominal pain, 15% of patients have regurgitation, 20% of patients have loss of appetite, 50% of patients have flatulence, 30% of patients have abdominal rumbling, 20% of patients have nausea, 5% of patients have burning sensation, 55% of patients have bloating, 15% of patients have vomiting, 5% of patients have pain during swallowing. From the above table we conclude that abdominal pain is the most common presenting symptoms that occur as higher chance than other symptoms.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON DRUG ALLERGY

The percent of distribution of patients based on drug allergy is shown in the following table

Table 4: Percent of distribution of patients based on drug allergy.

Drug allergy	Frequency	Percent
Amoxilin	0	0
Clarithromycin	1	5

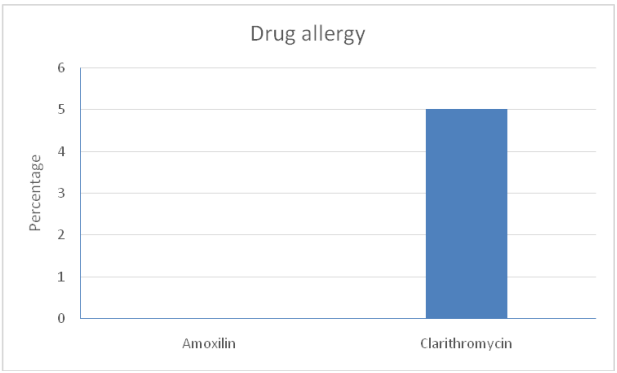

Figure 4: Diagrammatic representation of distribution based on drug allergy.

From the Table 4, it was observed that out of the total patients with H.Pylori gastritis,5% of patients have drug allergy to Clarithromycin and 0% of patient have drug allergy to Azithromycin. From the above table we conclude that drug allergy to Clarithromycin occur in higher chance.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON SOCIAL HISTORY

The percent of distribution of patients based on social history is shown in the following table

Table 5: Percent of distribution of patients based on social history.

Social history	Frequency	Percent
Coffee	15	75
Alcohol	9	45
Smoking	4	20
Oily or fried food	19	95
Soft drink	6	30

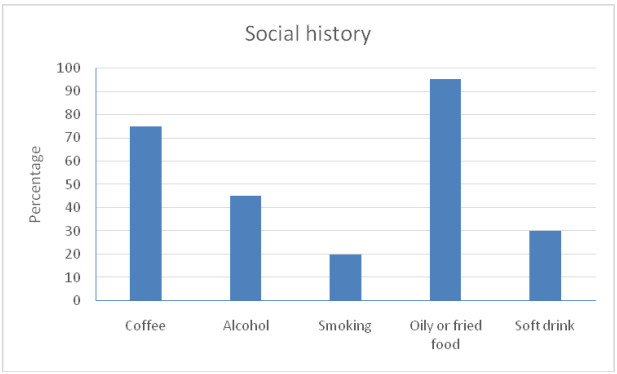

Figure 5: Diagrammatic representation of distribution based on social history.

From the Table 5, it was observed that out of the total patients with H.Pylori gastritis, 75% of patients have coffee intake, 45% of patients have alcohol intake, 20% of patients have smoking habit, 95% of patients consume oily or fried foods and 30% of patients use soft drinks. From the above table we conclude that there is a higher chance of occurence of H.Pylori gastritis in those consuming oily and fried foods.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON PERSONAL HISTORY

The percent of distribution of patients based on personal history is shown in the following table

Table 6: Percent of distribution of patients based on personal history.

Personal history	Frequency	Percent
Smoking	4	20
Alocohol	9	45

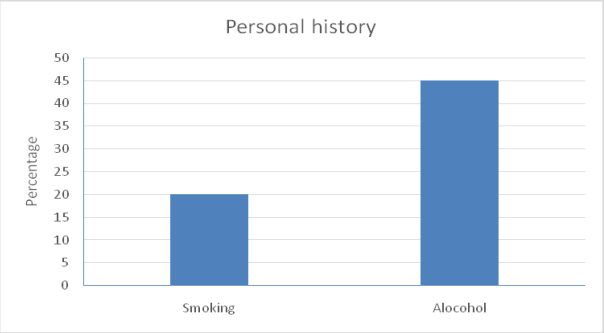

Figure 6: Diagrammatic representation of distribution based on personal history.

From the Table 6, it was observed that out of the total patients with H.Pylori gastritis, 20% of patients have smoking habit, 45% of patients have alcohol intake. From the above table we conclude that there is a higher chance of occurence of H.Pylori gastritis in those having habit of alcohol intake.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON DIAGNOSIS

The percent of distribution of patients based on diagnosis is shown in the following table

Table 7: Percent of distribution of patients based on diagnosis.

RUT	Frequency	Percent
Yes	20	100

From the Table 7,it was observed that out of the total patients with H.Pylori gastritis,100% were diagnosed with RUT positive and 0% with RUT negative.From the above table we conclude that there is a higher chance of occurence of H.Pylori gastritis in those patients with RUT positive.

SYMPTOM ASSESSING USING GSRS SCALE

In this section, the data related to Assessment of symptoms of patients with H.Pylori gastritis is collected. The datas related to quality of life assessment were collected and recorded. The collected data is shown in the following table.

Table 7: Assessment of patient by using GSRS scale.

	N	Mean	sd	Min	Max	Median	Q1	Q3
GSRS score	20	9.0	3.37	4	13	9	5.25	12.75
Side effects score	20	3.25	1.68	1	6	3	2	5

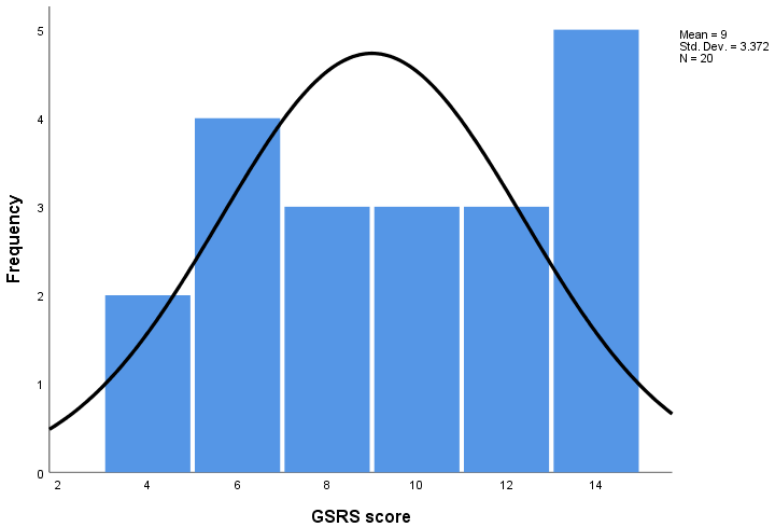

Figure 7: Diagrammatic box plot diagram of assessment of patients based on GSRS score Lower and upper end of the whisker represents minimum and maximum score. Lower border of the box represents 25th percentile and upper border of the box represents 75th percentile. Middle horizontal line represents Median score.

Box plot diagram describing GSRS score

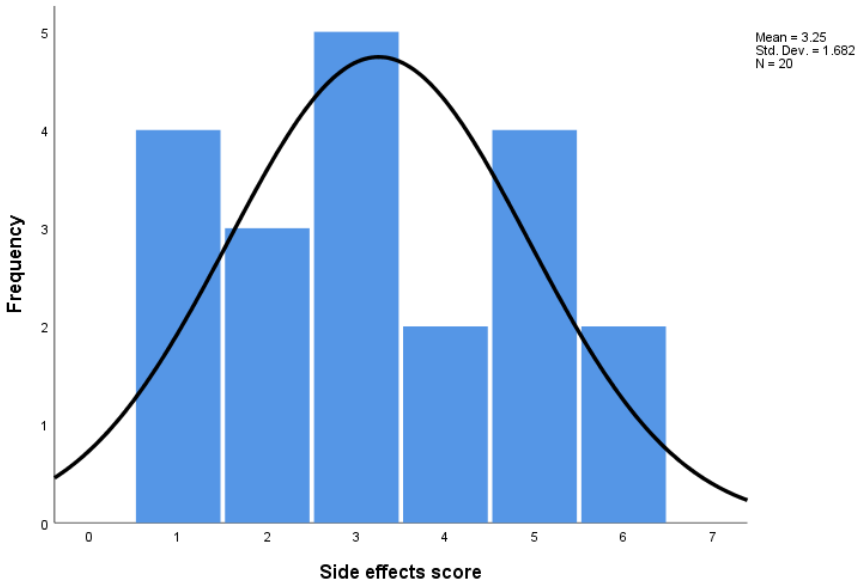

Figure 8: Diagrammatic representation of box plot of assessment of patients based on side effect score. Lower and upper end of the whisker represents minimum and maximum score. Lower border of the box represents 25th percentile and upper border of the box represents 75th percentile. Middle horizontal line represents Median score.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON SYMPTOMS

The percent of distribution of patients based on symptoms is shown in the following table

Table 9: Percent of distribution of patients based on symptom.

Symptoms	Frequency	Percent
Mild	11	55
Moderate	9	45
Total	20	100

Figure 9: Diagrammatic representation of distribution based on symptoms.

From the Table 9, it was observed that out of the total patients with H.Pylori gastritis, 55% patients have mild symptoms, 45% patients have moderate symptoms. From the table it was concluded that patient with H.Pylori gastritis have higher chance of occurrence of mild symptoms.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON SIDE EFFECTS

The percent of distribution of patients based on side effects is shown in the following table

Table 11: Percent of distribution of patients based on side effects.

Side effects	Frequency	Percent
Any one	9	45
More than one	11	55
Total	20	100

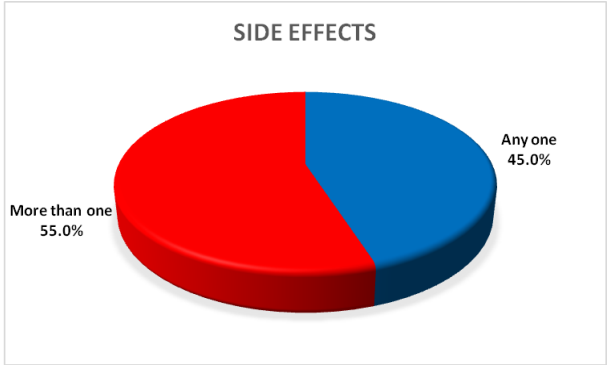

Figure 10: Diagrammatic representation of distribution based on side effects.

From the Table 10, it was observed that out of the total patients with H.Pylori gastritis,45% patients have only one symptom and 55% have more than one symptoms.From the table it was concluded that patient with H.Pylori gastritis have higher chance of occurrence of more than one symptom.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON GSRS (SYMPTOMS)
The percent of distribution of patients based on GSRS(symptoms) is shown in the following table

Table 11: Percent of distribution of patients based on GSRS (symptoms).

GSRS (symptoms)	Frequency	Percent
Pain in upper abdomen	17	85
Heartburn	12	60
Acid reflux	6	30
Hunger pains	3	15
Nausea	10	50
Rumbling	4	20
Bloating	16	80
Burping	4	20
Gas/Flatus	14	70
Constipation	3	15
Diarrhoea	7	35
Loose stool	4	20
Hard stool	2	10
Urgency-bowel movement	3	15
Incomplete bowel emptying feel	1	5

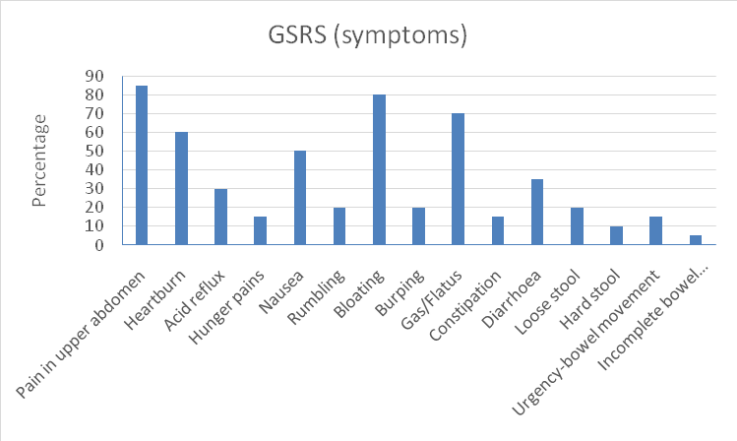

Figure 11: Diagrammatic representation of distribution based on GSRS (symptoms).

From the Table 11, it was observed that out of the total patients with H.Pylori gastritis, 85% patients have pain in upper abdomen, 60% patients have heart burn, 30% have acid reflux, 15% have hunger pains, 50% have nausea, 20% have rumbling, 80% have bloating, 20% have burping, 70% have gas/flatulence, 15% have constipation, 35% have diarrhoea, 20% have loose stool, 10% have hard stool, 15% have urgency-bowel movement and 5% have incomplete bowel emptying feel. From the table it was concluded that patient with H.Pylori gastritis have higher chance of occurrence of pain in upper abdomen as GSRS symptom.

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON DIFFERENT SIDE EFFECTS
The percent of distribution of patients based on different side effects is shown in the following table

Table 12: Percent of distribution of patients based on different side effects.

Side effects	Frequency	Percent
Loss of appetite	3	15
Nausea	3	15
Vomiting	3	15
Taste disturbance	4	20
Dizziness	0	0
Abdominal pain	4	20
Diarrhoea	0	0
Headache	1	5
Rash	2	10
Others	0	0

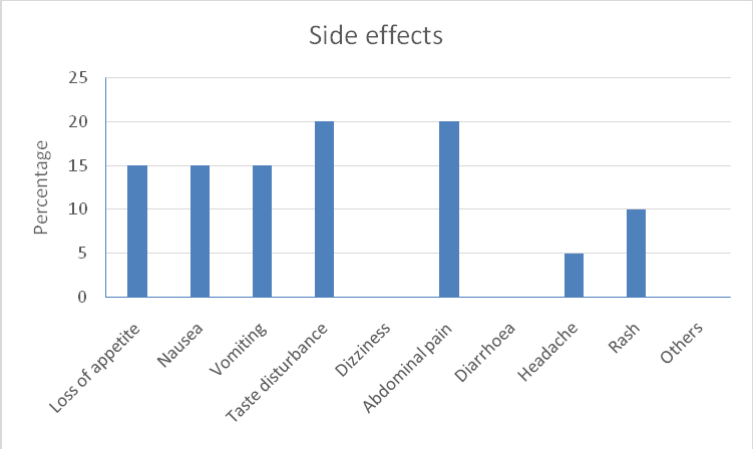

Figure 12: Diagrammatic representation of distribution based on different side effects.

From the Table 12, it was observed that out of the total patients with H.Pylori gastritis, 15% patients have loss of appetite, 15% have nausea, 15% have vomiting, 20% have taste disturbances, 0% have dizziness, 20% have abdominal pain, 0% have diarrhoea, 5% have headache and 10% have rashes. From the table it was concluded that patient with H.Pylori gastritis have higher chance of occurrence of both taste disturbance and abdominal pain as side effect.

DISCUSSION

H pylori gastritis also known as helicobacter pylori is a common type of bacteria that grows in the digestive tract and has a tendency to attack the stomach lining. H. pylori infections are usually less harmful, but they're responsible for the many ulcers in the stomach and small intestine. Infections with this strain of bacteria don't cause symptoms, they can lead to diseases in some people, including peptic ulcers, and an inflammatory condition inside your stomach known as gastritis. Symptoms may include abdominal pain, especially when your stomach is empty a few hours after meals or at night. The pain is usually described as a gnawing pain, and it may come and go.Eating or taking antacid drugs may relieve this pain, excessive burping, feeling bloated, nausea, heartburn, fever, lack of appetite, or anorexia, unexplained weight loss. Tests and procedures for diagnosis of H.pylori include: blood test, especially Rapid Urease Test(RUT positive).

Treatment includes first line standard triple therapy: PPI, amoxicillin 1 g, and clarithromycin 500 mg twice daily metronidazole 500 mg twice daily, sequential therapy: PPI and amoxicillin 1 g twice daily, followed by PPI, clarithromycin 500 mg, and tinidazole 500 mg (Tindamax) or metronidazole 500 mg BD. Second line therapy include concomitant therapy: PPI, amoxicillin 1 g, clarithromycin 500 mg, and tinidazole 500 mg or metronidazole 500 mg BD, Bismuth-quadruple therapy: Bismuth subcitrate 300 mg subsalicylate 525 mg or, metronidazole 250 mg, and tetracycline 500 mg, four times daily; and PPI BD, Levofloxacin-triple therapy: PPI and amoxicillin 1 g twice daily, and levofloxacin 500 mg once daily.

The study aims to assess the efficacy and side effects of PPI, Doxycycline, Bismuth subsalicylate and Nitroimidazole in Bismuth regimen therapy in H.pylori positive patients. The efficacy can be assessed using GSRS(Gastrointestinal Symptom Rating Scale) and side effects can be assessed using side effects questionnaire.

Bismuth quadruple therapy consisting of PPI, doxycycline, bismuth subsalicylate and nitroimidazole Bismuth exerts direct bactericidal effect on H.pylori by different ways: forms complexes in the bacterial wall and periplasmic space, inhibits different kind of enzymes, ATP synthesis and attachment of the bacteria to the gastric mucosa. Bismuth is very known cytoprotective agent, its salts have gastric mucosa protecting action against pepsin damage. This action is initiated by increasing prostaglandin E2 secretion. It act along with antibiotics to produce a synergistic effect and reduces the bacterial load. Bismuth helps in preventing antibiotic resistance or already existing resistance can be overcome. Doxycycline inhibits bacterial protein synthesis by attaching to the 30S ribosomal subunit. It has bacteriostatic activity against a range of Gram-positive and Gram-negative bacteria. Nitroimidazole targets organisms preferentially and reduces the 5-nitro group on the molecule, creating active metabolites that disrupt the helical structure of DNA. This prevents nucleic acid synthesis and eventually leads to cell death Proton pump inhibitor acts by irreversibly inhibiting the stomach's H^+/K^+ ATPase proton pump and there by reducing the gastric acid production.

In this study 20 patients who have undergone endoscopy and have a RUT positive results were taken. These patients were interviewed and GSRS and side effect scale were fill in.

Our study demonstrated that Bismuth quadruple therapy consisting of PPI, bismuth subsalicylate, doxycyline and nitroimidazole is a better treatment regimen with more

efficacy and minimal side effects. The observations of our study was similar to the results of a study conducted by Bilal Ergul et al, in their study on "The efficacy of two-week quadruple therapy with Bismuth, Lansoprazole, Amoxicillin, Clarithromycin on Helicobacter pylori eradication: A prospective study".

We also assessed the gender, which has more number of H.Pylori cases. The result was similar to that of the study conducted by Mohammed Minakari et.al, which concluded that the cases was found to be more in males. In our study we concluded that there is a higher chance of occurence of H.Pylori gastritis in males compared to that of females.

Our study demonstrated that the most occurring side effect was taste disturbance (20%) and abdominal pain(20%). This observation of our study was similar to that of a study conducted by Jonathan YL Lai et al, in their study "Helicobacter treatment with quadruple therapy in primary health care patients with a history of ulcer disease."Their study shows that the most frequent side effect was taste disturbance(41%).

In our study it was observed that out of the total patients with H.Pylori gastritis,5% of patients have antibiotic resistance to Clarithromycin, this oobservation was similar to a study conducted in the journal of clinical Gastroenterolgy and Hepatology, in that study they found out some patients in United States with H.Pylori infection were resistant to antibiotics.

In our study it was found that Bismuth Quadruple therapy has more efficacy with minimal side effects in RUT(Rapid Urease Test) positive patients with H pylori by using the GSRS ans Side effect scale.

CONCLUSION

From this study, it was concluded that Bismuth Quadruple therapy consisting of PPI, Doxycycline, Bismuth subsalicylate and Nitroimidazole has more efficacy with minimal side effects seems to be better treatment option.

We can also convey that among 20 patients surveyed the higher chance of occurrence of H Pylori gastritis was found in between age group 51-60 years and in males compared to females. The most common presenting symptom of H Pylori gastritis was found to be abdominal pain and diarrhoea. Patients having oily or fried food and drinking alcohol was mostly affected by H Pylori gastitis. 85% patients have shown pain in upper abdomen as most common GSRS symptom. Even though the therapy have minimal side effects taste disturbances and abdominal pain was noted as a common effect.

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