بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / مني مغربي أحمد

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Study The Effect Of Adding Rebamipide On The Eradication Therapy For Helicobacter Pylori Infection

Thesis

Submitted for Partial Fulfillment of Master Degreein ***Gastro-Enterology and Hepatology***

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2022

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

My deepest gratitude to my supervisor, ***Prof. Dr.*** **Azza Emam Mohamed Yassin**, *Professor of Gastro-enterology and Hepatology, Faculty of Medicine, Ain Shams University, for his valuable guidance and expert supervision, in addition to his great deal of support and encouragement. I really have the honor to complete this work under his supervision.*

I would like to express my great and deep appreciation and thanks to, ***Prof. Dr.*** **Hany Haron Kaisr Saad**, *Assistant Professor of Gastro-enterology and Hepatology, Faculty of Medicine, Ain Shams University, for her meticulous supervision, and her patience in reviewing and correcting this work.*

I must express my deepest thanks to ***Dr.*** **Gina Gamal Naguib**, *Lecturer of Gastro- enterology and Hepatology, Faculty of Medicine, Ain Shams University, for guiding me throughout this work and for granting me much of her time. I greatly appreciate her efforts.*

Special thanks to my ***Parents***, *my* ***Wife*** *and all my* ***Family members*** *for their continuous encouragement, enduring me and standing by me.*

Ahmed Mohammed Ebrahim Abdo

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LIST OF ABBREVIATIONS

Abb.	*Full term*
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
API 2	Cellular inhibitor of apoptosis 2
BID	twice daily
Cag A	Cytotoxin-associated gene A
CLO	Campylobacter-like organism Test
EGF	Epidermal growth factor
EMR	Endoscopic mucosal resection
ESD	Endoscopic sub mucosal dissection
FDA	Food and Drug Administration
FSSG	Frequency scale for the symptoms of GERD
GERD	Gastro esophageal reflux disease
IL-1β	Interleukin-1βeta
IL-8	Interleukin 8
MALT	Mucosa-associated lymphoid tissue.
MUC1	Mucin 1
NF-KP	Nuclear factor kappa- light –chain- enhancer of activated B cells
NSAIDS	Non steroid anti inflammatory drugs
PPI	Proton Pump Inhibitor
QD	Once daily
QID	Four times daily
RAU	Recurrent aphthous Ulcers.
RCT	Randomized controlled clinical trial
SHH	Sonic Hedgehog
SPP	Species
SPSS	Statistical Package for Social Sciences
TH1	T Helper cell 1
TID	Three times daily
TNF	Tumor necrosis factor
UBT	Urea breath test
WHO	World Health Organization

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic, spiral-shaped and flagellated bacterium infecting about half the world's population whose main reservoir is the human stomach. The prevalence of infection varies by geographic area, age, ethnicity and socioeconomic status; in fact, the prevalence is higher in developing countries and in those with poor socio-economic conditions **(Leclerc ,2006 ; Mandeville et al.,2009).** H. pylori infection is a leading etiological factor for various gastroduodenal diseases, including chronic gastritis, peptic ulcers and duodenal ulcers, as well as adenocarcinoma and MALT lymphoma of the stomach (**Suzuki et al.,2016 ; Malfertheiner et al .,2014) .** According to the latest European **(Maastricht V, 2015)** and North American **(Toronto, 2016;American College of Gastroenterology,2017)** recommendations for the diagnosis and treatment of H. pylori infection, eradication therapy should be administered to all infected people .Such sterategy can achieve resolution of inflammatory changes in the gastric mucosa and prevent the development of precancerous conditions [atrophic gastritis, intestinal metaplasia] **(Zhou et al.,2003 ; Lee et al.,2003)** .However in the last decade ,there has been a negative trend in the effectiveness of classic eradication therapy regimens, which has largely been determined by the emergence and spread of antibiotic resistance **(Malfertheiner et al.,2014 ; Safavi et al.,2016)**

In this regard the addition of the gastroprotective drug **Rebamipide** to eradication regimens has shown great potential of increasing efficacy of antibiotics **(Hojo M et al., 2000; Naito Y et al 2014).**The principal mechanisms of action of **Rebamipide** are the induction of prostaglandin synthesis in the gastric mucosa, neutralization of oxidative stress products, and inhibition of neutrophil activation **(Naito Y et al.,2014)** . **Rebamipide** does not have a direct anti-helicobacter action; however, in experimental studies, it was shown that it inhibits the adhesion of H. pylori to epithelial cells of the gastric mucosa**(Hayashi et al.,1998)** and reduces the activation of nuclear factor kappa- light –chain- enhancer of activated B cells (NF-kB) and Interleukin 8 (IL-8) production induced by H.pylori**(Lee .et al.,2011)**

AIM OF THE WORK

Study the effect of adding **Rebamipide** on the eradication therapy for helicobacter pylori infection in Egyptian patients.

H. pylori infection

INTRODUCTION

Helicobacter pylori is a spiral-shaped bacterium that grows in the digestive tract. Helicobacter pylori infection has a very high prevalence, and may be present in more than half of the world's population. It infects the stomach during childhood. In developing countries, children are very commonly infected. Helicobacter pylori may be passed from person to person through direct contact with saliva, vomit, or fecal matter. Risk factors for Helicobacter pylori infection are related to: living in crowded conditions - living in a home with many people, living without a reliable supply of clean water, living with someone who has a Helicobacter pylori infection **(Öztekin et al., 2021).**

The frequency of people infected may somehow be related to race. About 60% of Hispanics, about 54% of African Americans and about 20 to 29% of White Americans have detectable organisms **(Diaconu et al., 2017).**

Helicobacter pylori is adapted to live in the harsh, acidic environment of the stomach. These bacteria can change their environment and reduce their acidity thus allowing them to survive. While infections typically do not have symptoms, they can lead to other diseases, including peptic ulcers (about 10% of the people infected with Helicobacter pylori) and gastritis. The long-term use of non-steroidal anti-inflammatory drugs also increases the risk of peptic ulcers. Helicobacter pylori gastritis causes a mixed acute and chronic inflammatory reaction, stimulating both neutrophils and eosinophils, as well as mast and dendritic cells. While Helicobacter pylori has been traditionally considered a non-invasive pathogen, recent studies have shown that it is a facultative intracellular bacterium of innate immune cells, capable of interfering with the phagosome maturation which could explain the difficulty in eradicating

the bacteria. Helicobacter pylori infection, along with Ebstein-Barr infection, are known risk factors for gastric carcinoma **(Ieni et al., 2016).**

EPIDEMIOLOGY

Prevalence and Geographical Distribution

The prevalence of *H. pylori* shows large geographical variations. In various developing countries, more than 80% of the population is *H. pylori* positive, even at young ages. The prevalence of *H. pylori* in industrialized countries generally remains under 40% and is considerably lower in children and adolescents than in adults and elderly people. Within geographical areas, the prevalence of *H. pylori* inversely correlates with socioeconomic status, in particular in relation to living conditions during childhood. In Western countries, the prevalence of this bacterium is often considerably higher among first- and second-generation immigrants from the developing world **(Ryan et al., 2019).**

While the prevalence of *H. pylori* infection in developing countries remains relatively constant, it is rapidly declining in the industrialized world **(Hooi et al., 2017).**

The latter is thought to be caused by the reduced chances of childhood infection due to improved hygiene and sanitation and the active elimination of carriership via antimicrobial treatment. In developing countries, *H. pylori* infection rates rise rapidly in the first 5 years of life and remain constantly high thereafter, indicating that *H. pylori* is acquired early in childhood. However, in industrialized countries the prevalence of *H. pylori* infection is low early in childhood and slowly rises with increasing age. This increase results only to a small extent from *H. pylori* acquisition at later age **(Ryan et al., 2019).**

In **Egypt**, a high prevalence of H. pylori infections has been reported, ranging from 70 up to 88% in the general population **(Al-Eraky et al., 2018).**

The incidence of new *H. pylori* infections among adults in the Western world is less than 0.5% per year; the higher prevalence of infection among the elderly thus reflects a birth cohort effect with higher infection rates in the past. The active elimination of *H. pylori* from the population and improved hygiene and housing conditions have resulted in a lower infection rate in children, which is reflected in the age distribution of this lifelong-colonizing bacterium . Overall, new infection more commonly occurs in childhood and lasts for life unless specifically treated **(Javadzadeh & Hamedeyaz 2014).**

Transmission and Sources of Infection

The exact mechanisms whereby *H. pylori* is acquired are largely unknown. *H. pylori* has a narrow host range and is found almost exclusively in humans and some nonhuman primates. *H. pylori* has on rare occasions been isolated from pet animals; thus, the presence of pets may be a risk factor for *H. pylori* infection **(Castro-Muñoz et al., 2017).**

As conclusive evidence for zoonotic transmission of *H. pylori* is not yet available , new infections are thought to occur as a consequence of direct human-to-human transmission, via either an oral-oral or fecal-oral route or both. *H. pylori* has been detected in saliva, vomitus, gastric refluxate, and feces, but there is no conclusive evidence for predominant transmission via any of these products. This may be due to the fact that most research on transmission has focused on adults. It appeared that there was no clear increased risk for being a carrier of *H. pylori* among dentists, gastroenterologists, nurses, partners of an *H. pylori*-positive spouse, or visitors to a clinic for sexually transmitted diseases

(Rajindrajith et al., 2009).

As a result of these and other investigations, it is generally believed that acquisition mostly occurs in early childhood, most likely from close family members .Premastication of food by the parent is an uncertain risk factor for transmission of *H. pylori* **(Khalifa et al., 2010).**

Childhood crowding in and outside the family are all positively associated with *H. pylori* prevalence, whereas among adults crowding appears less important, with the exception of certain circumstances, such as among army recruits. Several studies have reported the presence of *H. pylori* DNA in environmental water sources, but this probably reflects contamination with either naked DNA or dead *H. pylori* organisms. To our knowledge there is only a single report of *H. pylori* being successfully cultured from water, but this involved wastewater and as such may well represent fecal contamination of the water source. Spread via fecal contaminants is supported by the occurrence of *H. pylori* infections among institutionalized young people during outbreaks of gastroenteritis **(Kusters et al., 2006).**

Other possible sources include contaminated food, as *H. pylori* may survive briefly on refrigerated food. Coupled with the extreme sensitivity of *H. pylori* to atmospheric oxygen pressure, lack of nutrients, and temperatures outside the 34 to 40°C range, direct person-to-person transmission remains the most likely transmission route **(Albisher et al., 2018).**

CLINICAL ASPECTS OF *H. PYLORI*-ASSOCIATED DISEASES

Colonization with *H. pylori* is not a disease in itself but a condition that affects the relative risk of developing various clinical disorders of the upper gastrointestinal tract and possibly the hepatobiliary tract. Testing for *H. pylori* therefore has no relevance by itself but should be performed

to find the cause of an underlying condition, such as peptic ulcer disease, or for the purpose of disease prevention, such as in subjects with familial gastric cancer. In these cases, a positive test result justifies treatment and a negative test result may indicate the need to search for other etiologic factors or preventive measures. For these reasons, a correct understanding of the clinical course of *H. pylori*-associated disorders and the effect of *H. pylori* eradication is needed **(Obleaga et al., 2016).**

Virulence factors

After entering the host stomach, *H. pylori* utilizes its urease activity to neutralize the hostile acidic condition at the beginning of infection. Flagella-mediated motility is then required for *H. pylori* to move toward host gastric epithelium cells, followed by specific interactions between bacterial adhesins with host cell receptors, which thus leads to successful colonization and persistent infection. Finally, *H. pylori* releases several effector proteins/toxins, including cytotoxin-associated gene A (CagA), and vacuolating cytotoxin A (VacA), causing host tissue damage [Fig. 1]. In addition, the gastric epithelium layer, which forms the major interface between *H. pylori* and the host, secretes chemokines to initiate innate immunity and activate neutrophils, and further lead to the formation of clinical diseases such as gastritis and ulcer. In summary, four steps are critical for *H. pylori* colonization and pathogenesis: **(1)** Survival under acidic stomach conditions; **(2)** movement toward epithelium cells through flagella-mediated motility; **(3)** attaching to host receptors by adhesins; **(4)** causing tissue damage by toxin release. [Fig. 1] **(X. Yang et al., 2014).**