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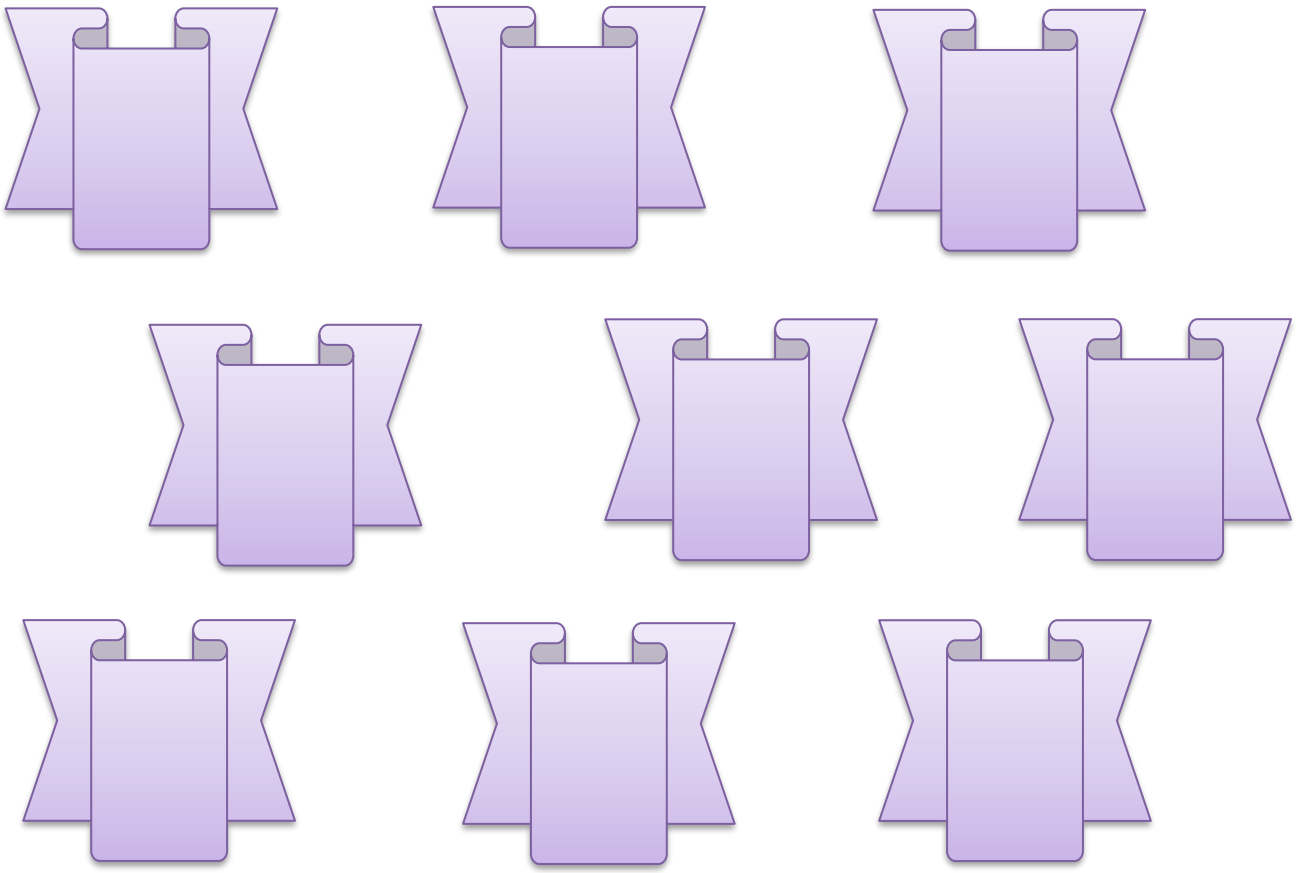

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Original Article

Efficacy of Adding Lactoferrin with Triple Therapy for Helicobacter Pylori Eradication in Egyptian Patients

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ABSTRACT

Background: Bovine lactoferrin [BLF] is a glycoprotein with antiviral, antibacterial, and antifungal activities. It is present in mucosal secretions such as saliva, tears, and seminal fluid. Due to its antibacterial properties, BLF may enhance the eradication rate of H. pylori when used in combination with traditional triple therapy.

Aim of the work: To evaluate the impact of bovine lactoferrin when added to triple therapy for H. pylori eradication in Egyptian individuals.

Patients and Methods: This randomized controlled comparative research was conducted at the Outpatient Clinic of the Hepatology and Gastroenterology Department in Nasser Institute Hospital. The study involved 200 individuals with a positive H. pylori antigen in stool, divided into four groups; Group A: Fifty individuals received clarithromycin-based triple therapy [Clarithromycin 500 mg – amoxicillin 1 gm – p.p.i 20 mg] twice daily for two weeks, Group B: Fifty individuals received levofloxacin-based triple therapy [Levofloxacin 500 mg once daily – amoxicillin 1 gm twice daily – p.p.i 20 mg twice daily] for two weeks, Group C: Fifty individuals received clarithromycin-based triple therapy with lactoferrin 100 mg twice daily for two weeks, and Group D: Fifty individuals received levofloxacin-based triple therapy with lactoferrin 100 mg twice daily for two weeks. H. pylori stool antigen tests were performed before and after treatment in all groups to assess treatment response.

Results: Adding 200 mg of BLF potentiates the effect of clarithromycin-based triple therapy and levofloxacin-based triple therapy on H. pylori eradication rate, increasing the treatment response from 70% to 90% and from 76% to 96% respectively.

Conclusion: Bovine lactoferrin has the potential to play a role when added to triple therapy in the eradication of Helicobacter pylori.

Keywords: Lactoferrin; Clarithromycin; Helicobacter Pylori.

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INTRODUCTION

Helicobacter pylori [H. pylori] infection should be treated as soon as possible after diagnosis, as it contributes to the development of peptic ulcer disease and chronic gastritis, and is also involved in the pathogenesis of gastric lymphoma and stomach cancer [1].

Amoxicillin, clarithromycin, tinidazole, metronidazole, fluoroquinolones, rifabutin, tetracycline, and ampicillin are employed as cures for H. pylori infection [2].

Bacterial infections are notoriously difficult to treat. Antibiotic resistance may be a major reason why H. pylori treatments do not always work. The bacteria can show varying degrees of resistance to the medications listed above [3].

This worrying trend lends weight to the call for cutting-edge methods, such as using an adjuvant to boost the efficacy of medications typically employed in this therapy [4].

A new consensus suggests discontinuing a proton pump inhibitor/clarithromycin-containing triple therapy in areas with a clarithromycin resistance rate of 15% without first conducting susceptibility testing [5].

The selection of therapy regimens must be modified in light of the local resistance pattern if this is known, as resistance rates vary across geographic regions [6].

In regions where the prevalence of clarithromycin resistance is high, triple treatments with bismuth are advised as first-line treatment because of the possibility that the bismuth will help counteract the development of clarithromycin-resistant bacteria [7].

However, bismuth salts are not widely available, thus it is helpful to look for an acceptable alternative that could boost the effectiveness of the regimen used. A growing body of evidence suggests that fermented milk and related whey proteins such as bovine lactoferrin may be useful as supplemental therapy in situations when antibiotic resistance is high or treatment has failed [8].

Bovine lactoferrin is a glycoprotein that has antiviral, antibacterial, and antifungal activities. It is also widely present in mucosal secretions like tears, seminal fluid, and saliva. Bovine lactoferrin's antimicrobial activity is attributed, in part, to its ability to sequester iron, a nutrient required for microbial growth, and in part to a direct effect on the outer membrane of Gram-negative bacteria, which disrupts the movement of the bacteria's flagella. Bovine lactoferrin has been found to have antibacterial action against H. pylori in both in vitro and in vivo studies [9].

It has been shown in clinical trials that bovine lactoferrin, when administered alone to H. pylori-positive patients, can decrease urea production, indicating a capability to suppress but not eradicate H. pylori colonization [10].

Our research set out to determine how well bovine lactoferrin worked in conjunction with triple therapy to eradicate H. pylori in Egyptian individuals.

PATIENTS AND METHODS

This randomized controlled study was done at the Outpatient clinic of the Hepatology and Gastroenterology department in Nasser Institute Hospital.

This research was conducted on 200 patients with positive H. pylori antigen in stool. They were divided into four groups as follow: Group A included 50 individuals who received a Clarithromycin-based regimen [Clarithromycin 500 mg – amoxicillin 1 gm – p.p.i 20 mg] twice daily for two weeks, Group B included 50 individuals who received levofloxacin-based regimen. [Levofloxacin 500 mg once daily– amoxicillin 1 gm twice daily – p.p.i 20 mg twice daily] for two weeks. Group C, included 50 individuals who have received Clarithromycin-based triple therapy with lactoferrin 100 mg twice daily for two weeks besides, Group D included 50 individuals who have received levofloxacin-based triple therapy with lactoferrin 100 mg twice daily for two weeks.

Informed consent was obtained from every patient and ethical approval was obtained from the same institution. We included the patients according to the following criteria:

The inclusion criteria: Individuals with signs related to the upper gastrointestinal tract [GIT] with a positive test for H. pylori infection.

The Exclusion criteria: Individuals with stomach surgery, such as a sleeve gastrectomy or partial gastrectomy, Antibiotic sensitivities,

advanced stages of liver [Child-Pugh class B or C] or renal illness [glomerular filtration rate< 60 mL/min/1.73 m2] disease, any type of cancer, active GIT bleeding, Women who are expecting or nursing, patient's equivocal antigen readings, as well as those who flat-out refused to take part in the research, were excluded.

Data collection

All patients were subjected to complete history taking, physical examinations, routine laboratory investigational Studies [CBC, ALT, AST, creatinine ESR, CRP], radiology [Abdominal U/S], ELISA for h. pylori antigen in stool was used as an initial diagnostic test in addition to confirming eradication after 4 weeks from completion of treatment].

Statistical analysis

The Statistical Program for Social Science [SPSS] version 15.0 was used to analyze the data. The mean and SD were used to express quantitative data, while the frequency and percentage were used to express qualitative data. The following tests were carried out: To compare two means, an independent-samples t-test [T] of significance was used. When comparing non-parametric data, the Chi-square test [X2] was used.

RESULTS

Our research was conducted on 200 patients having H. pylori infection: As regards age, the mean age was 29.88±11.47 years. As regards the sex, there were 86 males [43%] & 114 females [57%] in total the individuals. There was no significant variance among all groups as regards age or sex [table 1].

Dyspepsia is the most evident symptom present in 94[47%] patients with no statically significant difference between studied groups, followed by heartburn in 27 [13.5%] patients, then epigastric pain in 25 [12.5%] patients. Other manifestations include GERD in 22 [11%] patients, Nausea and vomiting in 24 [12%] patients, Dysphagia in 21 [10%] patients, Weight loss in 31 [15.5%] patients, Manifestation of Anemia in 3[1.5%] patients, GIT bleeding in 21 [10.5%] patients [Table 2].

Our results showed that adding 200 mg BLF daily to clarithromycin-based triple treatment increased the eradication rate from 70% to 90%. Also, when 200 mg BLF was added to levofloxacin- treatment-based increased the eradication rate from 76% to 96%. There was no statistically significant difference between patients who received a Clarithromycin-based regimen and patients who received a levofloxacin-based regimen.

There was no statistically significant difference between patients who received Clarithromycin-based triple therapy with lactoferrin and patients who received a levofloxacin regimen with lactoferrin. There were statistically significant differences regarding the presence and absence of H. pylori Ag in stool after treatment between patients treated without lactoferrin group[A&B] and patients treated with lactoferrin group [C&D] [P value less than 0.05], Absence of H. pylori Ag in stool after treatment was more obvious with lactoferrin [93%] than without lactoferrin [73%] [Table 3].

Side effects of treatment between patients treated without lactoferrin [group A&B] and Patients treated with lactoferrin [group C&D], were described in Table 4, with no significant difference between the 2 groups.

Table [1]: Description of age and sex of all studied individuals

	Group A [N = 50]	Group B [N = 50]	Group C [N = 50]	Group D [N = 50]	Total	P value
Age	28.36 ± 12.04	33.06 ± 12.51	27.65 ± 9.92	30.48 ± 11.44	29.88±11.4	0.1538
Sex						
Female	32 [64%]	26 [52%]	28 [56%]	28 [56%]	114 [57%]	0.81
Male	18 [36%]	24 [48%]	22 [44%]	22 [44%]	86 [43%]	0.81

Table [2]: Comparison between studied groups as regarded History and Clinical manifestation

	Group A [N = 50]	Group B [N = 50]	Group C [N = 50]	Group D [N = 50]	Total	P value
Dyspepsia	25 [50%]	21 [42%]	26 [52%]	22 [44%]	94 [47%]	0.85
Epigastric pain	7 [14%]	5 [10%]	7 [14%]	6 [12%]	25 [12.5%]	0.97
Heartburn	7 [14%]	4 [8%]	6 [12%]	10 [20%]	27 [13.5%]	0.523
Nausea and vomiting	6 [12%]	2 [4%]	6 [12%]	10 [20%]	24 [12%]	0.19
GERD	6 [2%]	4 [8%]	5 [10%]	7 [14%]	22 [11%]	0.906
Dysphagia	3 [6%]	5 [10%]	7 [14%]	6 [12%]	21 [10%]	0.76
Weight loss	8 [16%]	9 [18%]	6 [12%]	8 [16%]	31 [15.5%]	0.94
Manifestation of anemia	0 [0%]	1 [2%]	0 [0%]	2 [4%]	3 [1.5%]	0.44
History of git bleeding	3 [6%]	5 [10%]	7 [14%]	6 [12%]	21[10.5%]	0.714

Table [3]: Comparison between all groups as regards the response to H. pylori treatment

	Group A [n=50]	Group B [n=50]	Group C [n=50]	Group D [n=50]	P value
H. pylori Ag in stool 4 weeks after completion of treatment					
Positive	15 [30%]	12 [24%]	5 [10%]	2 [4%]	**0.0001**
Group A vs. Group B					0.499
Group A vs. Group C					**0.012**
Group B vs. Group D					**0.003**
Group C vs. Group D					0.239
Group A & B vs. Group C & D					**0.0001**

Table [4]: Side effect of treatment between patients treated without lactoferrin [group A & B] and Patients treated with lactoferrin [group C & D]

Side effects of drugs among studied groups	Patients treated with lactoferrin [group C&D] [n = 100]	Patients treated without lactoferrin [group A&B] [n = 100]	P value
Diarrhea	12 [12%]	8 [8%]	0.34
Nausea	6 [6%]	7 [7%]	0.79
Vomiting	1 [1%]	2 [2%]	0.57
No side effect	80 [80%]	83 [83%]	0.69

DISCUSSION

Eradicating H. pylori is crucial not only for peptic ulcer treatment but also for reducing its recurrence, minimizing the rate of gastric carcinoma recurrence after early gastric cancer resection, and promoting the regression of MALT lymphoma [11]. However, the rapid development of the COVID-19 pandemic has led to significantly increased resistance rates of H. pylori to both clarithromycin and levofloxacin, owing to wide-spread antibiotic usage during the pandemic. Clarithromycin eradication rates have dropped to 64.66%, while levofloxacin eradication rates stand at 74.36% [12]. Consequently, various strategies have been developed to address treatment resistance. Several studies have explored the role of BLF as an adjunctive therapy for H. pylori eradication, although findings have been inconsistent [13].

The primary objective of this study was to assess the impact of bovine lactoferrin when incorporated into triple therapy for H. pylori eradication among Egyptian patients. A total of 200 patients participated in our study, exhibiting various manifestations. The most prevalent symptom was dyspepsia, observed in 94 patients [47%]. Other reported symptoms included epigastric pain in 25 patients [12.5%], heartburn in 27 patients [13.5%], nausea and vomiting in 24 patients [12%], GERD in 22 patients [11%], dysphagia in 21 patients [10%], weight loss in 31 patients [15.5%], anemia in 3 patients [1.5%], and GIT bleeding in 21 patients [10.5%]. Consistent with the findings of **Hablass *et al.*** [14], our research indicated that dyspepsia was the most common GIT symptom, accounting for 38.9% of cases. Additionally, in 11.2% of instances, patients had a prior history of GIT bleeding [melena and/or hematemesis].

In our research, we discovered that the addition of 200 mg of BLF daily to clarithromycin-based triple therapy [group A] and levofloxacin-based therapy [group B] increased the eradication rate from 70% and 76% to 90% and 96%, respectively.

We observed a significant difference in the presence or absence of Helicobacter pylori Ag in stool after treatment. Furthermore, when comparing patients who did not receive lactoferrin [group A & B] with patients treated with lactoferrin in combination with clarithromycin or levofloxacin [group C & D], the eradication rate was 73% and 93%, respectively, with significant variations. These findings align with the research conducted by **Fawzy *et al.*** [15], who found that the addition of lactoferrin increased the eradication rate of H. pylori infection from 68% to 92%.

The present research is in agreement with that of **Zou *et al.*** [16], who reported that when BLF was used in conjunction with triple therapy, it reduced adverse effects and increased cure rates. Combining BLF with other antibacterial drugs such as esomeprazole, amoxicillin, and clarithromycin may have a synergistic effect, attacking H. pylori from multiple angles simultaneously. This approach could lead to more thorough and rapid eradication of the illness.

Additionally, consistent with our findings, **Di Mario *et al.*** [17] found that a 7-day triple therapy including 200 mg of BLF twice a day resulted in a 92% eradication rate, compared to the standard 7- or 10-day triple therapy rate of 72%.

In our research, we found no significant variance in side effects when lactoferrin was added at a dosage of 200 mg. Our findings are consistent with those of **Di Mario *et al.*** [18], who observed no significant changes in side effects when lactoferrin was incorporated into standard triple therapy throughout the treatment period.

Conclusion: We evaluated the effectiveness of adding bovine lactoferrin to triple therapy for eradicating H. pylori. Based on our findings, adding bovine lactoferrin to the triple therapy regimen proves to be an effective strategy for H. pylori eradication. We observed significant differences in eradication rates among the groups when 200 mg of lactoferrin was added, without any increase in drug-related side effects.

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