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Meta-Analysis for The Treatment of Helicobacter Pylori

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ABSTRACT

Purpose: To assess whether Helicobacter pylori (H. pylori) eradication therapy benefits patients with functional dyspepsia (FD). **Methods:** Randomized controlled trials (RCTs) examining the efficacy and safety of H. pylori eradication therapy for patients with functional dyspepsia published in English (till November 2016) were recognized by searching PubMed, EMBASE, and The Cochrane Library. Pooled estimates were measured using the fixed or random effect model. Overall effect was expressed as a pooled risk ratio (RR) or a standard mean difference (SMD). All data were analyzed with Review Manager 5.3 and Stata 12.0.

Results: This analysis involved 15 RCTs with a total of 3567 patients with FD. These studies were used to assess the benefits of H. pylori eradication therapy for symptom improvement; the pooled RR was 1.26 (95%CI: 1.10-1.40, P < 0.0001). H. pylori eradication therapy demonstrated symptom improvement during long-term follow-up at ≥ 1 year (RR = 1.27; 95%CI: 1.13-1.41, P < 0.0001) but not during short-term follow-up at < 1 year (RR = 1.26; 95%CI: 0.83-1.92, P = 0.27). Four studies showed no benefit of H. pylori eradication therapy on quality of life with an SMD of -0.01 (95%CI: -0.09 to 0.07, P = 0.74). Four studies demonstrated that H. pylori eradication therapy reduced the development of peptic ulcer disease compared to no eradication therapy (RR = 0.34; 95%CI: 0.17-0.67, P = 0.002). Three studies showed that H. pylori eradication therapy increased the likelihood of treatment-related side effects compared to no eradication therapy (RR = 1.87; 95%CI: 1.08-3.47, P = 0.02). Ten studies demonstrated that patients who received H. pylori eradication therapy were more likely to obtain histologic resolution of chronic gastritis compared to those who did not receive eradication therapy (RR = 7.05; 95%CI: 3.59-13.74, P < 0.00001).

Conclusion: The decision to eradicate H. pylori in patients with functional dyspepsia requires individual assessment.

Keywords: Peptic ulceration, functional dyspepsia, Helicobacter pylori eradication, symptom improvement, quality of life.

INTRODUCTION

Functional dyspepsia (FD) is a mutual gastrointestinal disorder and affects as many as 21%of the population worldwide [1]. Characterized by postprandial fullness, epigastric pain, and early satiation without organic causes, functional dyspepsia undesirably influences the patient's quality of life. Functional dyspepsia is diagnosed by Rome III criteria, which are symptom-based criteria [2].

Even though the pathophysiology is not well established, gastro-duodenal motility dysfunction [3], visceral hypersensitivity [4], and psychological disturbance [5] may play a role in the pathogenesis of functional dyspepsia. Helicobacter pylori (H. pylori) infection is more common in patients with dyspepsia (OR = 2.3; 95%CI: 1.9-2.7) in comparison to healthy controls [6]. Nonetheless, the effects of helicobacter pylori eradication treatment in functional dyspepsia are unpredictable in

earlier published randomized trials and meta-analyses.

Previous meta-analyses largely focused on symptom improvement after H. pylori eradication therapy; their findings (whether or not to eradicate) were not consistent due to variable study designs and follow-up durations [7, 8]. One meta-analysis conducted by Moayyedi et al [9] provided an economic assessment and recommended that H. pylori eradication therapy is the most cost-effective treatment technique.

We carried out this meta-analysis not only to assess benefits of H. pylori eradication therapy for symptom relief, but also to argue the effects on the quality of life, adverse events, and the risk of subsequent peptic ulcer disease.

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We performed a comprehensive meta-analysis in order to evaluate the overall clinical impact of H. pylori eradication therapy in this population.

MATERIALS AND METHODS

A standard protocol, based on current PRISMA guidelines, was implemented for study inclusion, data extraction, and data analysis. PubMed, EMBASE, and The Cochrane Library were searched for published randomized controlled trials (RCTs) in English from 1987 to 2016. Two reviewers reviewed all the titles and abstracts unconventionally. Data was extracted from eligible full-text studies. The data included study population, demographical characteristics, year of publication, country, age, gender, H. pylori eradication regimens, duration of follow-up, H. pylori eradication rate, and study outcomes.

The primary outcome for this study was the pooled risk ratio (RR) of successful treatment (presence of no more than mild pain or discomfort after treatment) with a 95%CI. The secondary outcomes were the pooled RR of improvement of dyspepsia at short-term (< 1 year) and long-term (≥ 1 year) follow-up, standard mean difference (SMD) of improvement in quality of life (SF-36), pooled RR of incidence of peptic ulceration during follow-up, pooled RR of development of treatment-related adverse events, and pooled RR of histologic resolution of chronic gastritis. If the studies were homogeneous (I^2 < 50%), the fixed-effects model was used; otherwise (I^2 > 50%), the random-effects model was chosen. Intervention was considered statistically significant when a P-value was < 0.05.

The study was done according to the ethical board of King Abdulaziz university.

RESULTS

According to the search strategy, 1837 citations were identified from three databases. After removing the duplicates (n = 948), two reviewers screened the titles and abstracts of potentially relevant studies (n = 889) independently. Out of 92 full-text studies that were reviewed, 77 did not meet the inclusion criteria. 15 RCTs with a total of 3567 people which met the inclusion criteria were included in this meta-analysis (Figure 1) [10-24]. The demographic data, eradication regimens, and eradication rates are listed in Table 1.

Table 1: Characteristics of studies included in the meta-analysis

Study	Sample (M/F)	Age mean	Country	Last visit (M)	Helicobacter pylori eradication
Froehlich, 2001	144 (64/80)	44.6	Switzerland	12	75%
Greenberg, 1999	100 (31/69)	46.5	United States	12	70.5%
Gwee, 2009	82 (38/44)	40.4	Singapore	12	68.3%
Koelz, 2003	181 (74/107)	47.5	Switzerland	6	51.7%
Lan, 2011	195 (89/106)	47.4	China	3	85.7%
Malfertheiner, 2003	800 (380/420)	46.2	Germany	12	63.9%
Mazzoleni, 2006	89 (20/69)	41.3	Brazil	12	91.3%
Mazzoleni, 2011	404 (86/318)	46.0	Brazil	12	88.6%
McColl, 1998	318 (155/163)	42.1	United Kingdom	12	88%
Miwa, 2000	85 (40/45)	51.5	Japan	3	85.4%
Naeeni, 2002	157 (47/110)	32.5	Iran	9	52.6%
Talley, 1999	293 (133/160)	46.4	United States	12	80%
Talley, 1999 (ORCHID)	275 (98/177)	50.0	Australia	12	85%
Varasa, 2008	48 (21/27)	37.0	Spain	12	81.4%
Xu, 2013	396 (135/261)	40.0	China	12	76.36%

Eradication therapy groups were treated with antibiotics, proton pump inhibitors, and bismuth, while control groups were treated with placebo, prokinetics, and/or proton pump inhibitors. Primary analysis demonstrated that 740 (38.6%) of 1914 patients in the eradication therapy group and 464 (31%) of 1495 in the control groups had no or mild symptoms during the last follow-up visit (pooled RR = 1.26; 95%CI: 1.10-1.40, P < 0.0001). Although there was no significant heterogeneity (I2 = 42%) among the selected studies.

H. pylori eradication therapy demonstrated symptom improvement at long-term (≥ 1 year) (RR = 1.27; 95%CI: 1.13-1.41, P < 0.0001) but not at short-term (< 1 year) (RR = 1.26; 95%CI:

0.83-1.92, P = 0.27) follow-up. The studies that reported short-term outcomes demonstrated significant heterogeneity (I^2 = 64%).

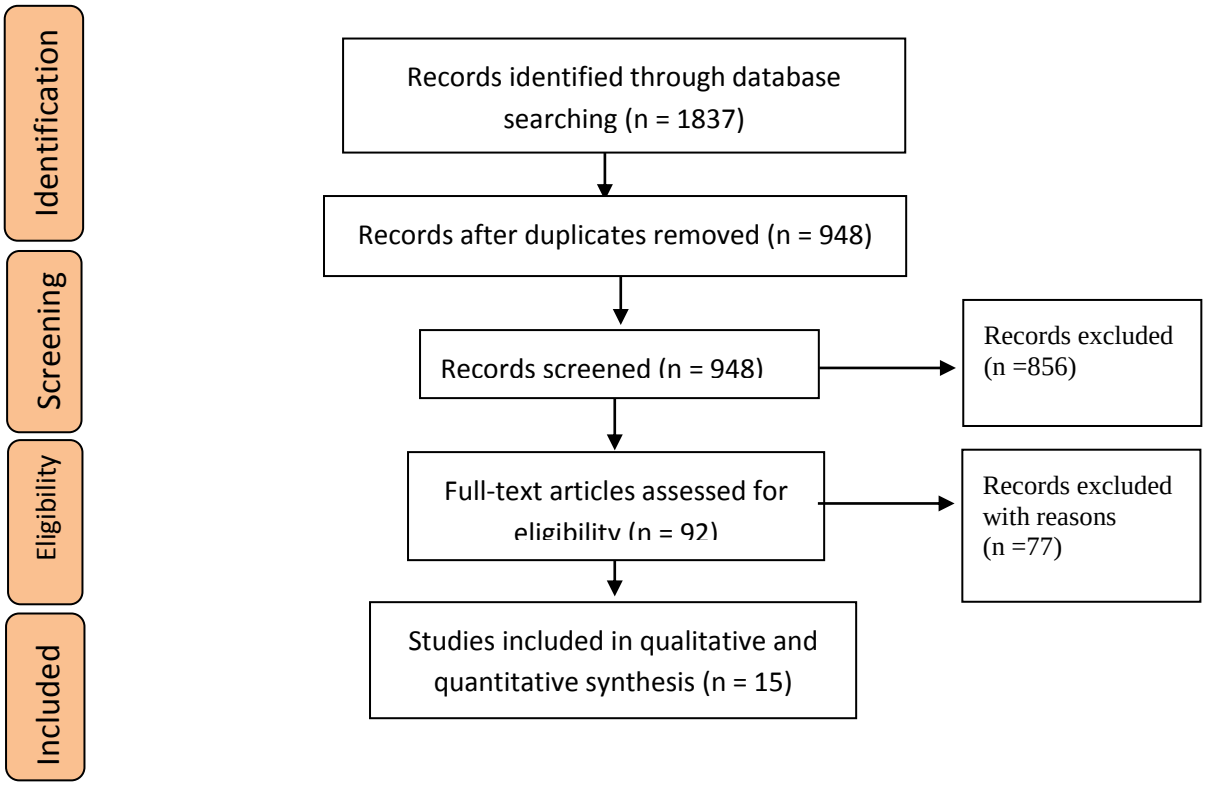

Figure 1: Flow diagram showing the selection criteria of assessed studies[25].

Table 2: Helicobacter pylori eradication therapy *vs* control on symptom relief

	Eradication		Control		Risk ratio
	Events	Total	Events	Total	
Long-term effect					
Froehlich, 2001	15	74	13	70	1.09 [0.56, 2.13]
Gwee, 2009	10	41	3	41	3.33 [0.99, 11.24]
Malfertheiner, 2003	196	534	89	266	1.10 [0.90, 1.34]
Mazzoleni, 2006	16	46	9	43	1.66 [0.82, 3.36]
Mazzoleni, 2011	94	201	72	203	1.32 [1.04, 1.67]
McColl, 1998	33	154	11	154	3.00 [1.57, 5.72]
Talley, 1999	69	150	71	143	0.93 [0.73, 1.18]
Talley, 1999 (ORCHID)	32	133	31	142	1.10 [0.71, 1.70]
Xu, 2013	157	262	68	134	1.18 [0.97, 1.43]
Subtotal (95%CI)		1595		1196	1.27 [1.13, 1.41]
Total events	622		367		
Short-term effect					
Koelz, 2003	55	89	61	92	0.93 [0.75, 1.16]
Lan, 2011	36	98	19	97	1.88 [1.16, 3.03]
Miwa, 2000	15	48	9	37	1.28 [0.63, 2.60]
Naeeni, 2002	12	84	8	73	1.30 [0.56, 3.01]
Subtotal (95%CI)		319		299	1.26 [0.83, 1.92]
Total events	118		97		
Total (95%CI)		1914		1495	1.26 [1.10, 1.40]
Total events	740		464		

Four studies stated data on quality of life both at baseline and at the last visit required for the meta-analysis. A fixed effect model (I^2 = 0%) was performed on all four studies. Generally, H. pylori eradication therapy had no significant benefit on quality of life, with an SMD of -0.01 (95%CI: -0.09 to 0.07, P = 0.74). Four studies reported endoscopic data at the last visit to evaluate for the development of peptic ulcer disease. H. pylori eradication therapy compared to no eradication therapy reduced the development of peptic ulcer disease (RR = 0.34; 95%CI: 0.17-0.67, P = 0.002). There was no significant study heterogeneity (I^2 = 0%). Three studies provided data on development of common side effects associated with the intervention. Patients who received H. pylori eradication therapy were more likely to have side effects compared to controls (RR = 1.87; 95%CI: 1.08-3.47, P = 0.02). The random effect model was used because significant study heterogeneity (I^2 = 89%) was detected. Three studies reported histological outcomes following intervention. Patiiveents who received H. pylori eradication therapy were more likely to obtain histologic resolution of chronic gastritis compared to control (RR = 7.05; 95%CI: 3.59-13.74, P < 0.00001).

DISCUSSION

Our meta-analysis based on well-designed RCTs demonstrated that the effective size of symptom relief from H. pylori eradication therapy in patients with FD was small (RR = 1.26; 95%CI: 1.10-1.40, P < 0.0001) with an undetectable short-term benefit. Eradication therapy was nearly three times more likely to reduce the development of peptic ulcer disease compared with no eradication therapy. Moreover, histologic findings of chronic gastritis were more likely to resolve after H. pylori eradication therapy compared to controls. Though, H. pylori eradication therapy did not develop the quality of life for patients with FD compared to anti-acids, prokinetics, or placebo therapy. Eradication therapy was likewise more likely to be linked with side effects (RR = 1.87; 95%CI: 1.08-3.47, P = 0.02) compared to control. H. pylori infection is more predominant in Asia than in Western countries. Eradication therapy appears to be more effective in Asian populations as shown by the meta-analysis conducted by Jin and Li [26]. Their study showed that H. pylori eradication therapy compared to controls increased the probability of enhancement in dyspeptic symptoms by 3.6-fold. Another meta-analysis performed by Zhao et al [8] found that H. pylori eradication therapy compared to no eradication therapy was beneficial for improvement of dyspepsia in European (OR = 1.49; 95 CI% 1.10-2.02) and American populations (OR = 1.43; 95%CI: 1.12-1.83).

H. pylori is toughly connected with many diseases, containing functional dyspepsia, gastric cancer, gastric or duodenal ulcer, and gastric mucosa-associated lymphoid tissue lymphoma [27]. Though, H. pylori-induced gastritis is the most important risk factor for improvement of peptic ulcer disease. Most patients with H. pylori infection have asymptomatic gastritis, and experience variable clinical symptoms depending on bacteria, host, and environmental factors. Whether H. pylori infection delays gastric emptying is unclear [28], but H. pylori appears to alter gastric acid production by changing gastrin and somatostatin secretion. Abnormal gastric acid secretion causes mainly dysmotility-like, dyspeptic symptoms. Duodenal acid exposure indirectly brings epigastric pain, bloating, and fullness by suppressing antral contractions, which might contribute to overdue gastric emptying [29].

According to the outcomes of this meta-analysis, choice to eradicate H. pylori can be influenced by several key points. First, eradication therapy might be desirable amid patients with risk factors for peptic ulcer disease or gastric cancer. Our study showed long-term benefits for example, reduction in occurrence of future peptic ulcer disease and resolution of gastritis, which are related with gastric cancer [30]. Second, due to deceptive adverse effects allied with eradication therapy, alternative validated therapy for FD for example, prokinetics, acid suppression, or lifestyle changes for mild dyspeptic symptoms ought to similarly be deliberated. A large study of 1425 patients presented that H. pylori infection was a significant hazard factor for dyspepsia. Nevertheless, other factors such as NSAIDs use, unemployment, and heavy smoking validated larger magnitude of association compared to H pylori infection [31]. Moreover, increasing prevalence of antibiotics resistance and H. pylori reinfection cannot be

ignored. Third, it has been well established that the occurrence of psychiatric disorders, for example, anxiety disorder, is more mutual in patients with functional gastrointestinal disorders than in the general population [32]. Psychiatric treatment with antidepressants is supportive in the decrease of dyspeptic symptoms. Anxiety and depression are reflected to be the best predictors of quality of life [33]. Cognitive-behavioral therapy (CBT), anxiolytics, psychotherapy and antidepressants can also relieve dyspeptic symptoms.

CONCLUSION

Helicobacter pylori eradication therapy compared to no eradication therapy has a statistically significant but small magnitude of benefit for symptom relief and can likewise decrease the development of peptic ulcer disease. Though, Helicobacter pylori eradication therapy was allied with higher occurrence of adverse events throughout the treatment and failed to demonstrate any effect in improving the quality of life. Moreover, to helicobacter pylori eradication therapy, alternative therapies such as prokinetics, acid-suppression, psychotherapy, and anxiolytics ought similarly to be considered after an individualized assessment.

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