

Sep 4, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO: 12612.doc).

Title: Probiotics in *Helicobacter pylori* eradication therapy: a systematic review and meta-analysis

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

R: Thanks for these beneficial comments. We have already made format change in the revised manuscript according to editor's suggestion.

2 Revision has been made according to the suggestions of the reviewer

(1) In this meta-analysis the the articles chosen are sufficient by number and the distribution is worldwide. Addition of probiotics may be an option for low eradication regions. Effect of these live but nonpathogenic bacteria on eradication therapy of H.pylori may be by reducing antibiotic related side effects and/or possible antibacterial properties. The studies relating cost-effectiveness of this supplementation should be assessed before clinical usage. Also some other measures increasing the compliance of the patient should be taken into account, as appropriate region based regimens, informing the patient briefly.

R: Thanks for these good comments. We understand the importance of cost-effectiveness for patients with H.pylori infection. In the planning stages we intended to assess the cost-effectiveness of probiotics, however, data on cost-effectiveness were rarely available in these trials. For compliance of the patient included, we intended studies other measures in the future. Finally, we intended conducted stratified analysis based on regimens, however, in several subsets, only one trial included, hence, we conducted a subgroup analysis based on therapy regimens (first line; second line; or not specified) to gave a relative result of probiotics supplementation in specific subpopulations.

(2) The main strong point of this study is that meta-analysis is based on large number of trials. This reviewer would like to point out two concerns in this article. Comment) 1. Eradication rate should be presented as intention-to-treat (ITT) and per protocol analysis respectively. 2. Line 21 and 22 Relative risk of eradication rate is not correct. Please revise.

R: We have adopted this beneficial suggestion and added several sentences in the revised manuscript and listed as follows: "We noted that the use of probiotics plus standard therapy was associated with an increased eradication rate by per-protocol set (PPS) analysis (RR: 1.11; 95% confidence interval [CI]: 1.08-1.15; P < 0.001) or intention-to-treat

analysis (ITT) (RR: 1.13; 95% CI: 1.10–1.16; $P < 0.001$). (*unstructured abstract*); “We noted that the use of probiotics plus standard therapy was associated with an increased eradication rate by per-protocol set (PPS) analysis (RR: 1.11; 95% confidence interval [CI]: 1.08–1.15; $P < 0.001$) or intention-to-treat analysis (ITT) (RR: 1.13; 95% CI: 1.10–1.16; $P < 0.001$).” (*Abstract*); “Both eradication rates by per-protocol set (PPS) analyses and intention-to-treat set (ITT) analyses were collected.” (*Data Collection and Quality Assessment*); “Subgroup analyses were conducted for eradication rates by ITT analyses on the basis of the participant’s age (0-17 years as children; ≥ 18 years as adults; NM: the study was not mentioned or it contained both children and adults), single or multiple probiotic strains, high dose or low dose of probiotics (divided by the average intake dosage per day of all included studies), duration of probiotics use longer than 15 days or not, duration of standard therapy longer than 7 days or not, duration between the end of the therapy and assessment longer than 4 weeks or not, probiotic strains and types of the standard therapy (first-line or second-line)” (*Statistical Analysis*); and “The pooled eradication rates for the probiotics group and the control group by PPS analysis were 86.23% and 76.60%, respectively. Overall, probiotics plus standard therapy significantly increased the eradication rates (RR, 1.11; 95%CI: 1.08-1.15; $P < 0.001$; Figure 1). Similarly, in ITT analysis, the pooled eradication rates for the probiotics group and the control group were 82.31% and 72.08%, respectively. Probiotics plus standard therapy significantly increased the eradication rates (RR, 1.13; 95%; CI: 1.10–1.16; $P < 0.001$; Figure 2). Although significant heterogeneity across the trials by PPS analysis, a sensitivity analysis was conducted and the results suggested that the data were not affected by the sequential exclusion of any particular trial from the pooled analysis.” (RESULTS)

(3) Zhang et al. performed meta-analysis and demonstrated that the use of prophylactic probiotics in *Helicobacter pylori* eradication treatments. This is important in this field. Minor comments 1. In abstract section, lines 3-6, Certain studies have reported.....the efficacy, safety and patient compliance of the use of probiotics in combination with a standard therapy when compared with standard therapy alone for the eradication of *Helicobacter pylori*. 2. In Introduction section, lines 52-53, “....The therapy used for the eradication.....who are at high risk.” Authors should mention there are opposite opinions about this. Authors should refer the following references: (1) Kodaman N, Pazos A, Schneider BG, Piazzuelo MB, Mera R, et al.: Human and *Helicobacter pylori* coevolution shapes the risk of gastric disease. *Proc Natl Acad Sci U S A*. 2014, 111: 1455-60; (2) Kanda T, Yokosuka O. Paradoxical role of *Helicobacter pylori* in Gastric cancer. *Editorial. Biohelikon: Cancer and Clinical Research* 2:a12, 2014.

R: Thank you for pointing out this, we have already cited these two paper and added one sentence: “The success rate of standard therapy ranges 60%–90% using first-line treatment, and around 70% with second-line treatment^[14-16]. Furthermore, the disruption of coevolved human and *H. pylori* genomes might play an important role for the high incidence of gastric disease^[17,18]. Hence, the development of improved strategies is still under investigation to increase the efficiency of eradication or to increase patient compliance, which may contribute to a greater clinical value because of the prevalence of *H. pylori* infection in large populations^[19]. Probiotics have a positive effect on *H. pylori* eradication since these compounds also induce anti-inflammatory and anti-oxidative mechanisms that regulate intestinal microbiota” in the revised manuscript.

3 References and typesetting were corrected

R: We appreciated this good suggestion and followed it.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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