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Review Article

Proton pump inhibitor therapy and its association with spontaneous bacterial peritonitis incidence and mortality: A meta-analysis

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ABSTRACT

Background: Previous meta-analyses reported proton pump inhibitor (PPI) therapy is associated with increased incidence of spontaneous bacterial peritonitis (SBP) in cirrhotic patients. However, this conclusion was based on case–control studies. Moreover, the association between PPI use and mortality of SBP has not yet been confirmed.

Aims: To evaluate the association between PPI use and SBP incidence and mortality using case–control and cohort studies.

Methods: We searched Medline, Embase and Web of Knowledge for relevant articles published up to January 2015. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model.

Results: A total of 10 case–control and six cohort studies involving 8145 patients were analyzed. The overall analysis indicated that PPI use was associated with SBP (OR = 2.11, 95% CI: 1.46–3.06). The association was limited in case–control studies (OR = 2.97, 95% CI: 2.06–4.26) but not in cohort studies (OR = 1.18, 95% CI: 0.99–1.14). PPI therapy was not associated with mortality during hospitalization or within 30 days after SBP (OR = 1.54, 95% CI: 0.92–2.59).

Conclusions: We could not establish causality that PPI use increases the incidence or mortality of SBP.

1. Introduction

Spontaneous bacterial peritonitis (SBP) is one of the most serious complications in cirrhotic patients and is associated with increased morbidity and mortality [1]. In patients with liver cirrhosis, small intestinal bacterial overgrowth (SIBO) is apparent and can facilitate bacterial translocation from the intestine to the ascitic fluid [2–5]. Colonized bacteria in the ascitic fluid in these patients can proliferate since there is impaired immune function/barrier in cirrhosis [6].

Proton pump inhibitors (PPIs) are effective acid suppressants that are widely used in patients with cirrhosis for a broad range of indications, such as gastroesophageal reflux disease (GERD) and peptic ulcer [7]. However, the overuse of PPIs has become a problem in cirrhotic populations. For example, there is not clear evidence supporting the use of PPIs after variceal ligation, still it is common practice [8,9]. Such inappropriate use of PPIs is likely to translate into possible significant long-term adverse effects. Recent studies indicate that PPIs potentially predispose individuals to SIBO by altering the intraluminal environment and bacterial flora [10]. Therefore, PPI therapy has been suggested to contribute to an increased risk of SBP [11,12].

Although two meta-analyses on this topic have previously been published [13,14], here we perform an additional meta-analysis for the following reasons: (i) the majority (3034 of 3815) of patients in the closest meta-analysis were only reported in abstract form and were considered as low quality studies [13]; (ii) recently (2013–2015), new high-quality studies with relatively large sample sizes have been performed [15,16]; (iii) the majority (seven out of eight) of studies included in the closest meta-analysis used a case–control design [13], but since then, more than five cohort studies have been published with conflicting results [15–19]; and (iv) it still remains unclear whether PPIs are associated with mortality of SBP. This meta-analysis is designed to evaluate PPI use and its association with incidence and mortality of SBP in cirrhotic patients.

2. Methods

2.1. Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) in conducting this

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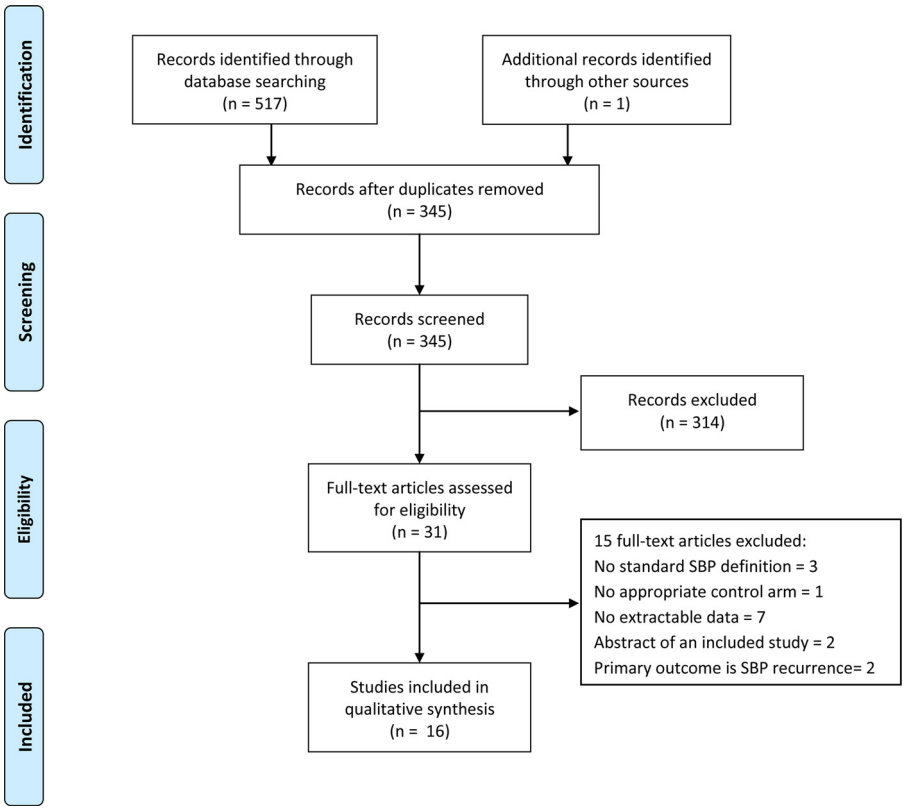

Fig. 1. Flow diagram of studies included in the meta-analysis. SBP, spontaneous bacterial peritonitis.

meta-analysis [20]. A systematic literature search was conducted through three electronic databases (Medline, EMBASE and Web of Knowledge) up until January 2015 with the following keyword combinations: "(proton pump or esomeprazole or lansoprazole or omeprazole or pantoprazole or rabeprazole) and (spontaneous bacterial peritonitis or 'peritonitis and cirrhosis')". The reference lists of relevant articles were also reviewed for additional studies. No language or other restrictions were set in the literature search.

2.2. Inclusion and exclusion criteria

Two reviewers independently screened the titles and abstracts of the studies from the electronic databases to identify all potential eligible studies. Any disagreement about a particular study was resolved in consensus with a third investigator. The following criteria were used for the selection of relevant articles: (i) studies reported the association between PPI therapy and SBP incidence (defined as ≥250 polymorphonuclear leukocytes/μL in the ascitic fluid); (ii) studies were of case–control or cohort design; (iii) study population comprised adult patients (≥18 years); and (iv) the value of relative risk (RR), odds ratio (OR) with 95% confidence intervals (CIs), or the raw data to calculate them, were reported. Exclusion criteria were as follows: (i) no control group of patients; (ii) studies included patients who experienced gastrointestinal bleeding or who were on antibiotic prophylaxis during the last 2 weeks prior to SBP, along with transplanted patients; and (iii) papers were letters, commentaries, editorials, reviews and duplicate publications.

2.3. Data extraction and outcome assessment

Two reviewers extracted data independently from all eligible papers. The data extracted included authors, publication year, country, study design, sample size, patient demographics and clinical characteristics, SBP diagnostic criteria, dosage and duration of PPI use, duration of follow up, single or multi-center design and adjusted confounding variables. Authors were contacted if the relevant information was not available for a particular study. Our primary analysis focused on assessing the risk of SBP among cirrhotic patients who used PPIs. The secondary outcome was the association between PPI use and mortality after SBP.

2.4. Quality assessment

Two reviewers independently graded the methodological quality of each included study using the Newcastle-Ottawa Scale (NOS) [21]. Any disagreement about a particular study was resolved in consensus with a third investigator. The study quality assigned to each study was based on three parts: (i) the selection of the study groups (0–4 points); (ii) the comparability of the study groups (0–2 points); and (iii) the ascertainment of either the exposure or outcome of interest (0–3 points) for case–control or cohort studies, respectively. NOS scores ≥7 were considered as high quality.

2.5. Statistical analysis

Meta-analyses were performed to calculate pooled ORs with 95% CIs. We assumed similarity between the OR and other relative measures, such as RR, because SBP events and deaths were rare [22]. When both the crude and the adjusted OR/RR values were offered, only the adjusted value was adopted for the meta-analysis. If only the raw data was reported, we would calculate the unadjusted OR. Taking a conservative approach, we used a random effects model, which produces wider CIs than a fixed effect model.

We evaluated statistical heterogeneity using the Cochran chi-square (χ^2) and the I^2 statistic [23]. An I^2 value of >50% is suggestive of significant heterogeneity [24]. To detect the source of heterogeneity, we performed subgroup analysis based on study design (case–control or cohort; retrospective or prospective), single or