Rifaximin for the prevention of spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis: a systematic review and meta-analysis

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Prophylactic antibiotics have been recommended in patients with a previous history of spontaneous bacterial peritonitis (SBP). Recently, there has been interest in the use of rifaximin for the prevention of SBP and hepatorenal syndrome (HRS). We conducted a meta-analysis to evaluate this association of rifaximin. We searched several databases from inception through 24 January 2017, to identify comparative studies evaluating the effect of rifaximin on the occurrence of SBP and HRS. We performed predetermined subgroup analyses based on the type of control group, design of the study, and type of prophylaxis. Pooled odds ratios (ORs) were calculated using a random effects model. We included 13 studies with 1703 patients in the meta-analysis of SBP prevention. Pooled OR [95% confidence interval (CI)] was 0.40 (95% CI: 0.22–0.73) ($I^2 = 58\%$). On sensitivity analysis, adjusted OR was 0.29 (95% CI: 0.20–0.44) ($I^2 = 0\%$). The results of the subgroup analysis based on type of control was as follows: in the quinolone group, pooled OR was 0.42 (95% CI: 0.14–1.25) ($I^2 = 55\%$), and in the no antibiotic group, pooled OR was 0.40 (95% CI: 0.18–0.86) ($I^2 = 64\%$). However, with sensitivity analysis, benefit of rifaximin was demonstrable; pooled ORs were 0.32 (95% CI: 0.17–0.63) ($I^2 = 0\%$) and 0.28 (95% CI: 0.17–0.45) ($I^2 = 0\%$) for the comparison with quinolones and no antibiotics, respectively. Pooled OR based on randomized controlled trials was 0.41 (95% CI: 0.22–0.75) ($I^2 = 13\%$). For the prevention of HRS, the pooled OR was 0.25 (95% CI: 0.13–0.50) ($I^2 = 0\%$). Rifaximin has a protective effect against the development of SBP in cirrhosis. However, the quality of the evidence as per the GRADE framework was very low. Rifaximin appeared effective for the prevention of HRS. Eur J Gastroenterol Hepatol 00:000–000

Introduction

Patients with cirrhosis and portal hypertension are at risk of ascites, hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), variceal bleeding, and hepatorenal syndrome (HRS) [1–4]. These complications constitute the major causes of death and are the most pressing indications for liver transplantation in such patients. SBP is associated with an annual recurrence rate of 70% and a 30% risk of death [5,6]. HRS can occur in about 18% of patients with decompensated cirrhosis over 1 year [7] and has a 76% mortality rate [8]. Small-intestinal bacterial overgrowth has been reported in patients with cirrhosis – one of the major pathogenic mechanisms postulated for the development of SBP is the translocation of gut bacteria into the systemic circulation [9]. This, coupled with compromised function of the Kupffer cells of the hepatic ;reticuloendothelial system, results in secondary seeding and proliferation in ascitic fluid [9,10].

Antibiotic prophylaxis with quinolones or trimethoprim –sulfamethoxazole is increasingly used to decrease the incidence and recurrence of SBP. Such prophylaxis may result in selective decontamination of the gut and positive changes in systemic hemodynamics, which in turn decrease the chance of developing SBP [11]. The same concept has been extended to decreased incidence of HRS and increased survival in patients with cirrhosis and ascites [11,12]. However, these drugs are associated with systemic toxicity and their use carries some propensity for the development of resistant gut flora. Indeed, Fernandez *et al.* [13] reported an increased identification of Gram-positive organisms as a cause of SBP in patients who were on norfloxacin or trimethoprim–sulfamethoxazole prophylaxis.

Recently, there has been considerable interest in the use of rifaximin for the prevention of SBP and HRS. Rifaximin is a poorly absorbable antibiotic with activity against both Gram-positive and Gram-negative bacteria [14]. Because of this selective decontamination of intestinal flora and improvement in hemodynamics, rifaximin has been evaluated for prophylaxis against SBP and HRS. We conducted this systematic review and meta-analysis to evaluate the role of rifaximin for primary and secondary prophylaxis against SBP and as a protective agent against HRS.

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Methods

Data sources and search strategy

We conducted this systematic review and meta-analysis in accordance with the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis [15]. The search strategies were developed in Ovid MEDLINE and the same keywords and subject headings were applied to Embase, Scopus, Web of Science, and Cochrane databases in various combinations from inception through 24 January 2017. The search terms included 'Rifaximin' OR 'Redactiv' OR 'Xifaxan' OR 'L-105' OR '88747-56-2' OR '*Zaxine*' OR '*Xifaxanta*' OR 'Tixteller' OR 'Targaxan' OR '*Spiraxin*' OR '*Rifatime*' OR 'Rifadom' OR 'Normix' OR '*Lormyx*' OR '*Ifaxim*' OR '*Flonorm*' OR '*Faxinorm*' OR '*Coloximina*' OR '*Colidimin*' OR 'Refero' OR 'Zaxine' AND 'hepatorenal syndrome'/exp OR 'Hepatorenal-syndrome' OR 'hepatorenal-disease' OR 'hepatorenal-failure' OR 'hepatorenal-insufficiency' AND 'Spontaneous-bacterial-peritonitis' OR '(bacterial-infection* OR Bacterial-translocation)' AND 'Peritonitis' (Fig. 1). This search was performed by a medical librarian (W.M.L.) with more than 20 years of experience.

Inclusion and exclusion criteria and retrieval of primary studies

Two authors (F.K. and M.A.K) searched for original studies based on *a priori* inclusion criteria that included observational studies or randomized controlled trials (RCTs) comparing rifaximin with quinolones or with no antibiotics for the prevention of SBP and HRS. These studies could be community-based or hospital-based and included patients above 18 years of age with cirrhosis due to any cause. Studies were excluded if they did not report data on occurrence of SBP or HRS, if they measured only portal venous pressure gradient, included patients less than 18 years, included animal data, or if there were no comparator arms. There was no restriction based on language. We also included peer-reviewed published abstracts. Articles were selected for full-text review on the basis of their title and abstract. We hand-searched bibliographies of retrieved articles to further enhance the yield of our search strategy. All articles were downloaded into Endnote 7.0, a bibliographic database manager; any duplicate citation was identified and removed.

Data extraction and quality assessment

Two reviewers (F.K. and M.A.K.) assessed the eligibility of selected studies and extracted data using data extraction forms. Any disagreement between the reviewers was discussed with a third reviewer (S.K.S.) and agreement was reached by consensus. Extracted data included study design, year and country of publication, patient demographics, type of control group (quinolone or no antibiotics), type of prophylaxis (primary or secondary), number of patients who developed SBP or HRS, model for end-stage liver disease scores, Child–Pugh–Turcotte scores and mortality in each group, and follow-up duration. We used the Newcastle–Ottawa scale for quality assessment of observational studies and the Cochrane tool for assessing risk of bias for RCTs. Two reviewers (M.A.K. and G.C.) performed quality assessment with any disagreement to be discussed with a third reviewer (A.A.). We used the GRADE framework to interpret our findings.

Data synthesis and statistical analysis

Our outcomes of interest were the associations between rifaximin and prevention of SBP and HRS. Pooled data were analyzed using a random effect model and odds ratios (ORs) with 95% confidence interval (CI) derived. Heterogeneity was assessed using the Cochran Q-test and I^2-statistic. A P value less than 0.1 for Cochran Q-test indicated the presence of heterogeneity. Significant heterogeneity was defined as an I^2 value more than 50%. To further examine heterogeneity, predetermined subgroup analyses were conducted based on the type of control group (quinolones or no antibiotics), type of studies (RCTs or observational studies), and type of prophylaxis (primary or secondary). Publication bias was assessed where appropriate using funnel plots and Egger's test. The statistical analysis was performed using Review Manager (RevMan, version 5.3 for Windows; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark, 2014).

Results

Search strategy yield and quality assessment

The search strategy identified 295 articles, of which 84 were removed as duplicates (Fig. 1). Of the remaining 211 articles, 163 were removed after title and abstract review. Forty eight full-text articles were reviewed, of which 13 studies [16–28] with 1703 patients were included in the meta-analysis. Four studies were RCTs [16–19] and nine were observational studies [20–28]. Among the Nine observational studies, four were retrospective [20,24–26] and five were prospective [21–23,27,28]. A total of 686 patients were treated with rifaximin, whereas the remaining 1082 patients acted as controls. In one study [25,] 65 patients who were previously on lactulose only were given rifaximin during the study period. Among the controls, 239 patients received quinolones, whereas 843 did not receive any antibiotics. Eight studies [16,17,19,20,23,24,27,28] reported data on mortality. There were 107 deaths in the rifaximin group and 331 in the control group. Tables 1 and 2 highlight the characteristics of included studies.

One RCT [19] had low risk of selection, performance, detection, attrition, and reporting biases; two other RCTs [16,17] had high risk of performance and detection bias and low risk of selection, attrition, and reporting biases. The remaining RCT [18] had high risk of selection, performance, and detection biases and unclear risk of attrition and reporting bias. Seven observational studies [20,21, 23–27] were moderate quality on Newcastle–Ottawa scale assessment and two [22,28] were low quality.

Meta-analysis

Rifaximin and association with spontaneous bacterial peritonitis

Thirteen studies with 1703 patients were included in the analysis. Lutz *et al.* [21] included three groups (i.e. rifaximin, quinolones, and no antibiotics); therefore, we included comparative data from all three groups. Pooled OR (with 95% CI) was 0.40 (0.22–0.73), Cochran Q-test