European Journal of Internal Medicine 33 (2016) 112–117

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Early eradication has a lower risk of peptic ulcer bleeding in *Helicobacter pylori*-infected chronic kidney disease patients

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ARTICLE INFO

Article history:
Received 1 May 2016
Received in revised form 29 June 2016
Accepted 29 June 2016
Available online 19 July 2016

Keywords:
End stage renal disease
Peptic ulcer bleeding
Helicobacter pylori
Eradication
Chronic kidney disease

ABSTRACT

Background: End stage renal disease (ESRD) contributes to a higher mortality rate in peptic ulcer bleeding (PUB) patients. A crucial question is whether early *Helicobacter pylori* (*H. pylori*) eradication therapy is necessary for *H. pylori*-infected chronic kidney disease (CKD) patients. To explore whether *H. pylori* eradication therapy has a lower risk of PUB at the pre-ESRD stage than at the ESRD stage.
Methods and patients: Patients meeting 2 criteria were defined as newly diagnosed ESRD cases: (1) patients diagnosed with ESRD and receiving regular dialysis between 2000 and 2009; and (2) patients with no history of dialysis between 1997 and 1999. We divided the study participants into pre-ESRD and ESRD groups on the basis of the time between *H. pylori* eradication and dialysis. The date of the first PUB diagnosis was defined as the primary endpoint. Stratified Cox proportional hazard regression analysis was used to estimate the effect of *H. pylori* eradication at the pre-ESRD and ESRD stage on the occurrence of PUB.
Results: We included 476 patients in the pre-ESRD cohort and 476 patients in the matched ESRD cohort. After adjustment for age, sex, the presence of comorbidities, and medication use, the hazard ratio of PUB was 0.66 times less in the pre-ESRD cohort than in the ESRD cohort. Factors such as Charlson's score more than 3, and nonsteroidal anti-inflammatory drugs were associated with an increased risk of PUB.
Conclusion: Our result supports that early *H. pylori* eradication has a lower risk of PUB in *H. pylori*-infected CKD patients.

1. Introduction

The incidence of upper gastrointestinal bleeding has not been reduced despite a decreasing incidence of peptic ulcers, strategies to eradicate *Helicobacter pylori* (*H. pylori*) infection, and prophylaxis against ulceration from nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, other factors might be involved in the pathogenesis of gastrointestinal bleeding [1]. Current epidemiologic data suggest that patients most affected are older with medical comorbidities [2]. End stage renal disease (ESRD) is associated with a substantial health care burden in hospitalized patients with peptic ulcer bleeding (PUB) and contributes to a higher mortality rate, longer hospital stays, and an increased need for surgery in PUB patients [3]. A population-based study [4] revealed that the incidence of peptic ulcer disease was 10–12 times higher in patients with chronic kidney disease (CKD) than in those without CKD. Previous reports have demonstrated that patients with ESRD who received hemodialysis exhibited a high risk of PUB [5] and recurrent PUB [6].

H. pylori plays a central role in PUB development [7]. Hopkins et al. [8] reported that peptic ulcer disease recurrence can markedly decrease from 70% to 10% or lower following *H. pylori* eradication. However, Kang et al. [9] reported an *H. pylori* infection rate of 29% in ESRD patients who developed peptic ulcer disease, implying the diverse gastric characteristics of ESRD patients. Factors such as reductions in mucosa prostaglandin [10] or in hypergastrinemia [11], drugs such as NSAIDs [12], and local or systemic circulatory failure [13] influence the onset of recurrent peptic ulcer disease in ESRD patients. ESRD patients who suffer from PUB are at risk of excessive rebleeding and mortality with frequent occurrences of delayed rebleeding [14]. The mechanism of excessive bleeding in patients with ESRD is still unclear but may be multifactorial [15]. Sugimoto et al. [13] showed that the prevalence of *H. pylori*

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http://dx.doi.org/10.1016/j.ejim.2016.06.035
0953-6205/

infection decreased in the first 4 years of dialysis. A crucial question is whether early *H. pylori* eradication therapy is necessary for *H. pylori*-infected patients who contracting with CKD. Clarifying the role of *H. pylori* eradication in the pathogenesis of PUB in patients at pre-ESRD and ESRD stages is critical.

We divided the study participants into pre-ESRD and ESRD groups on the basis of the time between *H. pylori* eradication and dialysis. The current study explored whether *H. pylori* eradication therapy has a lower risk of PUB at the pre-ESRD stage than at the ESRD stage.

2. Material, method and patients

2.1. Ethical considerations

The National Health Insurance Research Database (NHIRD) is a secondary database. The identities of patients in the database were scrambled before the data were released for research purposes. Patient records and information were anonymized and deidentified prior to analysis. This study was approved by the National Health Research Institutes and the Institutional Review Board (IRB) of Taipei City Hospital (IRB No.: TCHIRB-1030906-E). The IRB waived the requirement of written consent.

2.2. Data source

In this population-based cohort study, we recruited patients with ESRD who received regular dialysis according to data from Taiwan's NHIRD. This nationwide cohort study was based on patient data obtained from the NHIRD, which is managed by the National Health Research Institute. The NHIRD contains health care data on 99% of the Taiwanese population (approximately 23 million people). The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to define the diseases. The NHIRD contains comprehensive patient information, including demographic data, the dates of clinical visits, diagnostic codes, and prescription details.

2.3. Study population

In Taiwan, patients with ESRD who require dialysis can apply for a catastrophic illness card. Patients in the NHIRD who meet the following 2 criteria were defined as patients with newly diagnosed ESRD: (1) patients diagnosed with ESRD and receiving regular dialysis between 2000 and 2009 (at least 2 years of follow-up during the whole 12-year (2000–2011) observation period) and (2) patients with no history of dialysis between 1997 and 1999.

The *H. pylori* status was determined using a ^{13}C-urea breath test, rapid urease tests, or a histological assessment that employed hematoxylin and eosin staining. The *H. pylori* eradication therapy was a triple or quadruple therapy consisting of proton pump inhibitors, clarithromycin or tetracycline, amoxicillin or metronidazole, and bismuth or no bismuth. First, patients who underwent at least one treatment of *H. pylori* eradication therapy during the 12-year observation period were enrolled. In addition, only patients who had received another *H. pylori* test after the final *H. pylori* eradication without receiving further eradication therapy were enrolled, thus implying successful *H. pylori* eradication.

2.4. Study cohort

The eligible participants were divided into 2 groups on the basis of the time between the *H. pylori* eradication and different stages of CKD (pre-ESRD is within 2 years before receiving dialysis and ESRD is within 2 years after receiving dialysis). Patients younger than 20 years old and diagnosed with inpatient PUB between 1997 and 1999 were excluded from the study. Patients who were diagnosed with gastric cancer during the observation period (1997–2011) and who underwent a gastrectomy before the events were also excluded. We also excluded those who underwent *H. pylori* eradication more than 2 years before or after receiving dialysis. The demographic data of the patients in the pre-ESRD and ESRD cohorts were first compared; subsequently, each patient with pre-ESRD was matched with 1 patient with ESRD on the basis of propensity scores. Fig. 1 provides a flowchart of the patient selection process.

2.5. Assessing confounders and covariates

The propensity score was calculated using logistic regression as described by Rosenbaum and Rubin [16]. The mean and median propensity scores of the 2 cohorts were compared. All diseases included in the Charlson comorbidity index were analyzed [17]. Age, sex, comorbidities, and the Charlson score were included in the propensity score. Conditions that required inpatient care between January 1, 1997 and December 31, 2011 were defined as comorbidities in our study. The following comorbidities were identified in our cohort: coronary artery disease (ICD-9-CM codes: 410–414), congestive heart failure (ICD-9-CM code: 428), cerebral vascular disease (ICD-9-CM codes: 430–438), liver cirrhosis (ICD-9-CM codes: 571.2, 571.5, and 571.6), and chronic obstructive pulmonary disease (ICD-9-CM codes: 490–492, 494, and 496), and diabetes mellitus (ICD-9-CM code: 250). Specific drugs that can alter the risk of PUB, such as aspirin, NSAIDs, cyclooxygenase-2 specific inhibitors, and steroids, were analyzed. Exposure to these drugs was defined as being exposed for more than 10% of the observation period (1997–2011) [18].

2.6. End point

All of the inpatient records for each patient in the propensity-score-matched ESRD and pre-ESRD cohorts were followed up until the occurrence of PUB (the top three diagnoses), death, or the end of 2011. The date of the first PUB diagnosis according to ICD-9-CM codes after January 1, 2000 was identified; an ICD-9-CM code for one of the following diagnoses within the follow-up period was defined as the primary end point: gastric ulcer with hemorrhages (531.0, 531.2, 531.4, or 531.6), duodenal ulcer with hemorrhages (532.0, 532.2, 532.4, or 532.6), or nonspecific peptic ulcer with hemorrhages (533.0, 533.2, 533.4, or 533.6).

3. Statistical analysis

The chi-squared test and Student's t test were used to examine the differences between the pre-ESRD and ESRD cohorts. Stratified Cox proportional hazards regression analyses of age, sex, comorbidities, the Charlson score, and medications were used to estimate the effect of *H. pylori* eradication on the occurrence of PUB. An alpha level of 0.05 was considered statistically significant at pre-ESRD and ESRD stage for all analyses. Cumulative incidence analyses were performed using the Kaplan–Meier method, and the differences between the curves were calculated using the 2-tailed log rank test. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using the pre-ESRD cohort as a reference. Matched regression models with adjusted variables are presented. All statistical analyses were performed using SAS System for Windows Version 9.3 software (SAS Institute, Cary, NC, USA).

4. Results

4.1. Demographic characteristics

We first selected 672 pre-ESRD and 651 ESRD patients from 2000 to 2009. Table 1 lists the demographic data including age, sex, comorbidities, and medications. The original propensity scores of the pre-ESRD patients (mean = 0.45) were significantly lower than those of the ESRD patients (mean = 0.53; $p < 0.001$). The Charlson scores of the pre-ESRD patients (mean = 4.14) were significantly higher than those of the ESRD patients (mean = 3.73; $p < 0.001$). We used propensity scores to match 1 patient in the pre-ESRD cohort with 1 patient in the matched