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양성자펌프억제제와 간경화 합병증의 연관성: 체계적 고찰 및 메타 분석

Correlation between proton pump inhibitors and the complications of liver cirrhosis: A systematic review and meta-analysis

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Correlation between proton pump inhibitors and the complications of liver cirrhosis: A systematic review and meta-analysis

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Abstract

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Background

Proton pump inhibitors (PPIs) are the most commonly used drug for effective gastric acid suppression and play a major role in the treatment of diseases resulting from gastric acid oversecretion. However, stomach acid sterilizes the digestive tract by removing pathogenic microorganisms in addition to playing a role in digestion. Patients with cirrhosis may suffer from immune system dysfunction and studies suggest that gut microbes modified by PPIs may increase portosystemic encephalopathy (PSE) by increasing ammonia levels. Therefore, it is necessary to determine the potential harm caused by the continuous inhibition of gastric acid in patients with cirrhosis and whether it increases their risk of contracting secondary diseases or infections.

Aims

A meta-analysis of previous studies was performed to investigate the association between PPIs and the complications arising from cirrhosis and the risks of PPI use in patients with cirrhosis.

Methods

We used the same methods for our meta-analysis as were used for observational studies following epidemiology guidelines. Data were

extracted from EMBASE, PubMed, Cochrane, and Google Scholar databases. The Newcastle-Ottawa scale was used to assess the quality of the selected studies.

Results

A total of 29 studies (13 case-control and 16 cohort studies) involving 20,484 patients were included in the meta-analysis. The total relative risk (RR) for the 23 studies analyzing spontaneous bacterial peritonitis (SBP) was 1.40; the 95% confidence interval (CI) was 1.22 – 1.61 (I^2 = 56.6%, P < 0.001). The total RR for the 7 studies analyzing PSE was 1.25 (95% CI 0.85 – 1.84, I^2 = 96.1%, P = 0.253). The total RR for the 7 studies analyzing overall infection was 1.37 (95% CI 1.07 – 1.76, I^2 = 79.3%, P = 0.012). The RR for the 2 cohort studies analyzing mortality was 1.39 (95% CI 0.85 – 2.27, I^2 = 0.0%, P = 0.184).

Conclusion

The use of PPIs in patients with cirrhosis increased the risk of SBP, but there was significant heterogeneity among patients in sta. In order to better understand the correlations among cirrhosis complications, a large-scale cohort study with appropriate controls for confounding variables is needed.

Keywords: liver cirrhosis, proton pump inhibitor, PPI, spontaneous bacterial peritonitis, SBP, hepatic encephalopathy, PSE, HE

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Table of Contents

Figure

Table

1 Introduction

Proton pump inhibitors (PPIs) are effective gastric acid suppressors, and play a pivotal role in the treatment of peptic ulcer disease, gastric bleeding, GERD, and *Helicobacter pylori* (*H. pylori*) infection [1, 2]. PPIs are the most commonly prescribed medication for the suppression of gastric acid because of their safety and effectiveness [3, 4]. However, recent studies have shown that PPIs are associated with an increased risk of pneumonia and *Clostridium difficile* (*C. difficile*) infection. PPIs may increase the risk of cirrhosis-related complications including spontaneous bacterial peritonitis (SBP), portosystemic encephalopathy (PSE), and variceal bleeding.

Gastric acid aids in digestion and sterilizes the digestive tract by removing pathogenic microorganisms which enter the tract [5]. The absence of this sterilizing action appears to have a more detrimental effect when the immune system is compromised and normal bacterial defense mechanisms are impaired. In addition to the effect on the immune system, PPIs alter the oral and intestinal microbiota [6].

Patients with cirrhosis show delayed intestinal transit and intestinal dysfunction [7]. In addition, immune dysfunction is remarkable in patients with cirrhosis because of the reduction of hepatic mononuclear cells in the liver and biosynthesis of soluble pathogen-recognition receptors and

complement [8, 9]. Furthermore, bacterial translocation occurs frequently with mucosal barrier dysfunction, which results in infectious disease such as SBP [10].

In cirrhosis patients the half-life of PPIs is increased, leading to increased concentrations and the risk of toxicity. Therefore, the continuous use of PPIs in patients with cirrhosis may increase the risk of infectious diseases such as SBP and *C. difficile* [11, 12]. Studies have suggested that gut microbes modified by PPIs may increase PSE risk by increasing ammonia levels [13, 14].

There have been many studies and meta-analyses investigating the association between PPIs, SBP, PSE, and other infections. However, these studies have limitations including the omission of large numbers of relevant studies and basing conclusions on abstracts without consulting the full-text of the articles. These studies have focused on a single complication in patients with cirrhosis. We conducted a large scale meta-analysis exploring the association between PPIs and multiple cirrhosis-related complications, including mortality.

2 Methods

Our meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

2.1 Study selection

A comprehensive search of published articles was conducted using the MEDLINE/PubMed, EMBASE, and Cochrane databases. A structured search using the keywords “proton pump inhibitor,” “PPI,” “*prazole,” “anti-acid,” “cirrhosis,” “LC,” “hepatic fibrosis,” “portal hypertension,” “complication,” “ascites,” “spontaneous bacterial peritonitis,” “SBP,” “hepatorenal syndrome,” “HRS,” “portosystemic shunt,” “PSE,” “hepatic encephalopathy,” “HE,” “jaundice,” “varix,” “varices,” “variceal bleeding,” “hepatopulmonary syndrome,” “HPS,” “hepatocellular carcinoma,” “HCC” and “mortality” was performed. Criteria for inclusion in the study were: availability of a full-text version of the article, participants had cirrhosis, availability of PPI prescribing data, and outcomes resulting from the complications of cirrhosis were reported. Searches were not restricted based on language. Articles were excluded from the analysis if they did not have a control group, if patients reported prior complications, if antibiotic prophylaxes were used, or if there were previous brain function impairments. When duplicated publications were identified, the most recently published

study was included. We manually reviewed the bibliographies of all studies included in the meta-analysis.

2.2 Data extraction

Data were extracted independently using a predefined information sheet in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [15]. The following characteristics were extracted from the articles: the first author, year of publication, country, institution, study design, complications of cirrhosis, kinds of PPIs, participant's information, and the number of exposed participants among the cases and controls. There were no discrepancies between reviewers.

The Newcastle-Ottawa scale (NOS) was used to assess the quality of the selected studies [16] and quality assessments were performed independently. A paper with a NOS score below 6 was classified as inadequate and a subgroup analysis was conducted.

2.3 Statistical analysis

All statistical analyses were performed using the STATA software (version 15; Stata Corporation, College Station, TX, United States). The relative risk (RR) or odds ratio (OR) and their 95% confidence interval (CI) were considered. ORs were considered similar to RRs due to the low incidence of

cirrhosis-related complications. The random-effects method was used when analyzing results between studies. The heterogeneity among studies was evaluated using Cochran's Q-test and Higgins' I^2 [17, 18]. P-values < 0.1 indicated heterogeneity between studies using the Q-test. Heterogeneity was defined using I^2 as follows: $I^2 < 25\%$, no heterogeneity; $25\% < I^2 < 50\%$, mild heterogeneity; $50\% < I^2 < 75\%$, moderate heterogeneity; and $I^2 > 75\%$, high heterogeneity. Publication bias was assessed by Begg's rank correlation test and Egger's regression test. P-values < 0.05 indicated significant publication bias.

3 Results

Of the 1,455 studies identified using MEDLINE/PubMed, EMBASE, and the Cochrane library 190 were excluded due to duplication and two additional studies were added after manual review. After screening titles and abstracts, 1,060 articles were removed. After full-text reviews, 29 studies were selected for the final analysis. Thirteen articles reported the results of case-control studies [19-31] and 16 the results of cohort study [12, 13, 32-45] Figure 1 summarizes the study selection process and Table 1 shows the characteristics of the studies involved. A total of 20,484 participants across the 29 studies were included in the meta-analysis. All studies focused on the

use of PPIs in patients with cirrhosis. Twenty-two studies evaluated correlations between PPIs and SBP, seven studies evaluated correlations between PPIs and overall infection, and six studies evaluated the use of PPIs and PSE.

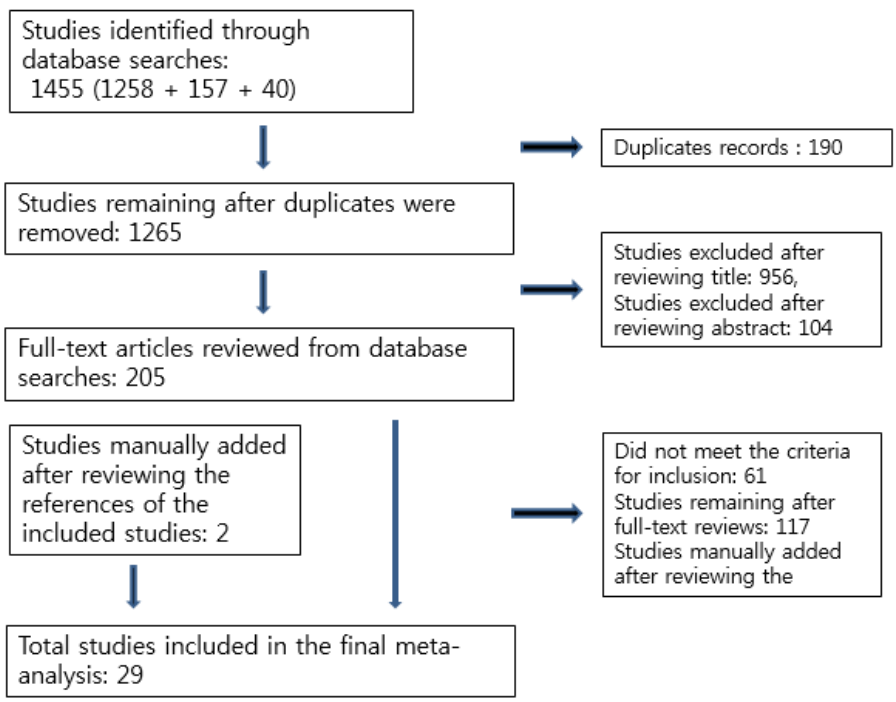

Figure 1. Flow chart of the decision-making process regarding the inclusion or exclusion of records based on pre-determined selection parameters.

3.1 Spontaneous bacterial peritonitis

The RR for the 23 SBP studies was 1.40; the 95% confidence interval (CI) was 1.22 – 1.61 (I^2 = 56.6%, P < 0.001) (Table 2). Analyses of the 12 cohort studies for SBP showed that the use of PPIs was not significantly associated

with increased risk of SBP (RR = 1.14, 95% CI: 0.95 – 2.03, P = 0.152) and that there was moderate heterogeneity between the studies (I^2 = 58%, P = 0.006; figure 2). However, analyses of the 11 case-control studies for SBP showed that the use of PPIs were significantly associated with increased risk of SBP (OR = 2.69, 95% CI: 2.11 – 3.43, P < 0.001) and there was no heterogeneity between the studies (I^2 = 0.0%, P = 0.581; figure 3).

3.2 Portosystemic encephalopathy

The RR for the 7 PSE studies was 1.25 (95% CI 0.85 – 1.84, I^2 = 96.1%, P = 0.253) (Table 2). Analyses of 5 cohort studies for PSE showed that the use of PPIs was not significantly associated with increased risk of PSE (RR = 0.98, 95% CI: 0.64 – 1.51, P = 0.921) and there was high heterogeneity between the studies (I^2 = 97%, P < 0.001; figure 2). However, analyses of the 2 case-control studies for PSE showed that the use of PPIs was significantly associated with increased risk of PSE (OR = 5.18, 95% CI: 2.97 – 9.01, P < 0.001) and there was no heterogeneity between studies (I^2 = 0.0%, P = 0.785; figure 3)

3.3 Overall infection

The RR for the 7 studies evaluating overall infection was 1.37 (95% CI 1.07 – 1.76, I^2 = 79.3%, P = 0.012) (Table 2). Analyses of the 6 cohort studies for

overall infection showed that the use of PPIs was significantly associated with increased risk of overall infection (RR = 1.37, 95% CI: 0.96 – 1.33, P = 0.012) and there was moderate heterogeneity between studies (I^2 = 51.1%, P = 0.069; figure 2). The analysis of a single case-control study for overall infection showed that the use of PPIs was significantly associated with increased risk of overall infection (OR = 3.90, 95% CI: 2.26 – 6.73, P < 0.001). Heterogeneity could not be measured because there was only one case-control study included

3.4 Mortality

Analyses of 2 cohort studies for mortality showed that the use of PPIs was not significantly associated with increased risk of mortality (RR = 1.39, 95% CI: 0.85 – 2.27, P = 0.184) and there was moderate heterogeneity between studies (I^2 = 0%, P = 0.582; figure 2). There was no case-control study included for mortality.

3.5 Heterogeneity analyses and publication bias

With the exception of mortality, heterogeneity among the studies was moderate (I^2 > 0.5, P < 0.001). No significant publication bias was found using Begg's and Egger's methods (Table 2).

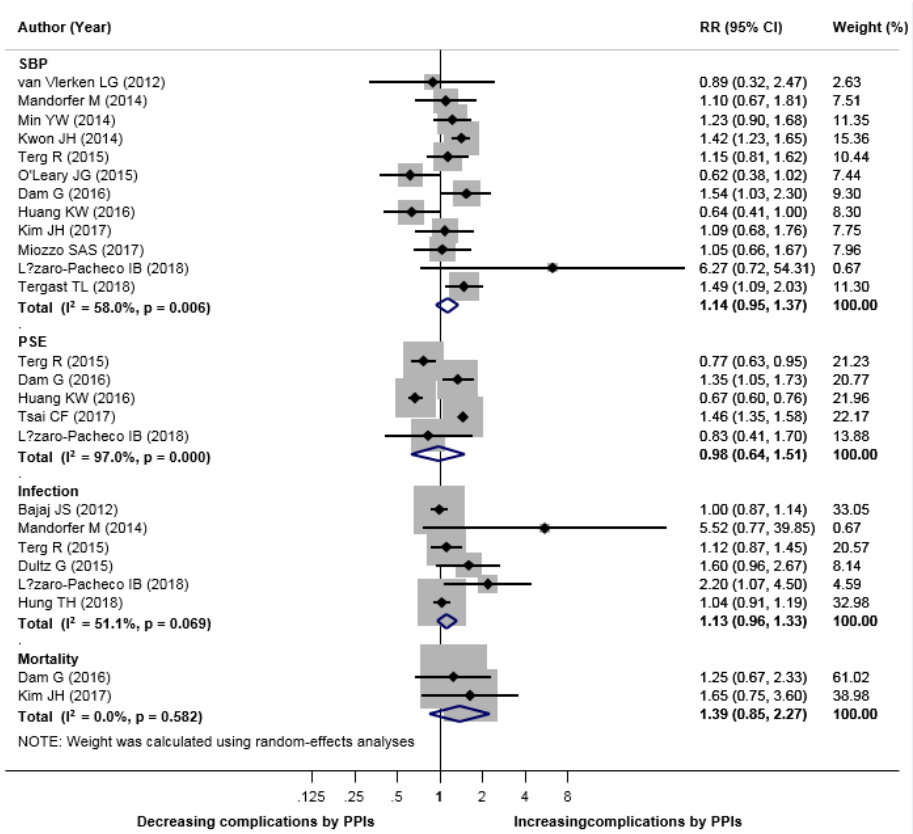

Figure 2. Forest plots for unadjusted relative risk at a 95% confidence interval for complications of cirrhosis in individuals using proton pump inhibitors for 25 cohort studies. RR, relative risk; SBP, spontaneous bacterial peritonitis; PSE, portosystemic encephalopathy; PPI, proton pump inhibitor.

No.	Author	Year	Country	Study design	Center	Events	Kinds of PPI	Male (%)	Mean age	No.		
										PPI (+)	PPI (-)	NOS
1	Campbell MS *et al.*	2008	US	Case-control	Single	SBP	-	67.2	54.6	43	73	8
2	Bajaj JS *et al.*	2009	US	Case-control	Single	SBP	-	56.4	54.5	70	70	7
3	Choi EJ *et al.*	2011	Korea	Case-control	Single	SBP	Esomeprazole, Pantoprazole, Rabeprazole	78.4	55.5	21	155	8
4	Goel GA *et al.*	2012	US	Case-control	-	SBP	-	63.9	57.6	91	39	7
5	de Vos M *et al.*	2013	Belgium	Case-control	-	SBP	-	68.6	58.4	38	64	7
6	Matsumoto S *et al.*	2014	Japan	Case-control	Single	SBP	Lansoprazole, Omeprazole, Rabeprazole	61.8	63.1	55	102	5
7	Ratelle M *et al.*	2014	Canada	Case-control	Single	SBP	-	74.5	60.6	74	77	7
8	Miura K *et al.*	2014	Japan	Case-control	Single	SBP	Lansoprazole, Omeprazole, Rabeprazole	67.7	66.3	43	22	7
9	Merli M *et al.*	2015	Italy	Case-control	Single	SBP	Esomeprazole, Omeprazole, Pantoprazole, Rabeprazole	70.3	61.5	127	40	6
10	Hayat MK *et al.*	2018	US	Case-control	Single	SBP	-	48.0	42.6	100	100	7
11	Lin ZN *et al.*	2014	China	Case-control	Single	PSE	-	78.2	44.0	119	46	5
12	Zhu J *et al.*	2018	Canada	Case-control	Single	PSE	-	36.3	56.1	85	71	7
13	Elzouki AN *et al.*	2018	Qatar	Case-control	Single	Infection	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	78.1	52.8	171	162	8
14	van Vlerken LG *et al.*	2012	Netherland	Cohort	Multi	SBP	Omeprazole, Pantoprazole	67.0	55.0	17	34	6
15	Mandorfer M *et al.*	2014	Austria	Cohort	Single	SBP, Infection	-	70.0	57.5	520	87	8
16	Nin YW *et al.*	2014	Korea	Cohort	Single	SBP	Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole	68.3	57.9	402	402	8
17	Kwon JH *et al.*	2014	Korea	Cohort	Multi	SBP	Pantoprazole	75.4	62.4	129	1011	9
18	Terg R *et al.*	2015	Argentina	Cohort	Multi	SBP, PSE, Infection	-	69.0	57.0	165	219	7
19	O'Leary JG *et al.*	2015	US	Cohort	Multi	SBP	-	54.4	56.3	116	72	8
20	Dam G *et al.*	2016	Denmark	Cohort	Multi	SBP, PSE, Death	-	68.7	57.4	340	525	8
21	Huang KW *et al.*	2016	Taiwan	Cohort	Multi	SBP, PSE	-	76.2	54.1	1870	1190	9
22	Kim JH *et al.*	2017	Korea	Cohort	Single	SBP, Death	Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole	77.9	57.7	58	149	8
23	Mozzo SAS *et al.*	2017	Brazil	Cohort	Single	SBP	Omeprazole	63.0	53.6	151	107	9
24	Lázaro-Pacheco IB *et al.*	2018	Mexico	Cohort	Multi	SBP, PSE, Infection	-	42.5	62.1	44	69	9
25	Tergast TL *et al.*	2018	Germany	Cohort	Single	SBP	Pantoprazole	62.0	56.1	506	107	8
26	Tsai CF *et al.*	2017	Taiwan	Cohort	Multi	PSE	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	74.2	53.1	693	1639	9
27	Bajaj JS *et al.*	2012	US	Cohort	Single	Infection	-	98.6	-	1256	1256	8
28	Dultz G *et al.*	2015	Germany	Cohort	-	Infection	Esomeprazole, Omeprazole, Pantoprazole	66.9	57.0	213	59	9
29	Hung TH *et al.*	2018	Taiwan	Cohort	Multi	Infection	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	67.5	62.6	1004	4016	9

* No, number; PPI, proton pump inhibitor; NOS, Newcastle-Ottawa scale; SBP, spontaneous bacterial peritonitis; PSE, portosystemic encephalopathy

Table 1. Main characteristics of all studies in the meta-analysis

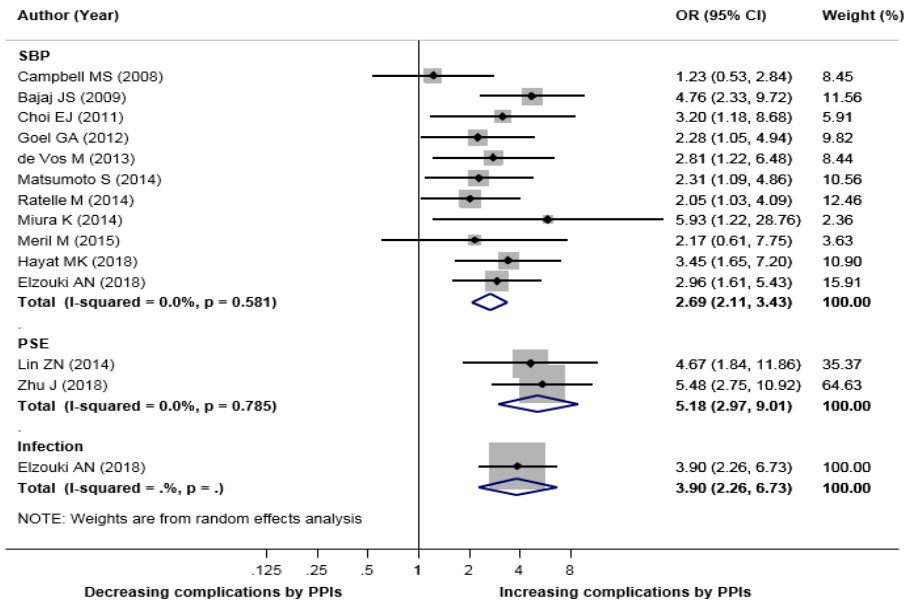

Figure 3. Forest plots for unadjusted overall infection at a 95% confidence interval for complications of cirrhosis in individuals using proton pump inhibitors for 14 case-control studies.

		Studies	Heterogeneity			Effect size				Publication bias	
Complications of LC	Study design	No.	I^2 (%)	P_H	M	RR	OR	(95% CI)	P_{ES}	P_{Begg}	P_{Egg}
SBP	Cohort study	12	58.0	0.006	R	1.14	–	(0.95-1.37)	0.152	0.217	0.203
	Case-control study	11	0.0	0.581	R	–	2.69	(2.11-3.43)	<0.001	0.815	0.810
	Total	23	56.6	<0.001	R	1.40	–	(1.22-1.61)	<0.001	0.303	0.685
			65.9	<0.001	R	–	1.69	(1.34-2.14)	<0.001	0.096	0.149
PSE	Cohort study	5	97.0	<0.001	R	0.98	–	(0.64-1.51)	0.921	1.000	0.539
	Case-control study	2	0.0	0.785	R	–	5.18	(2.97-9.01)	<0.001	0.317	–
	Total	7	96.1	<0.001	R	1.25	–	(0.85-1.84)	0.253	0.652	0.980
			96.2	<0.001	R	–	1.51	(0.79-2.88)	0.210	0.652	0.552
Infection	Cohort study	6	51.1	0.069	R	1.13	–	(0.96-1.33)	0.147	0.015	0.001
	Case-control study	1	–	–	R	–	3.90	(2.26-6.73)	<0.001	–	–
	Total	7	79.3	<0.001	R	1.37	–	(1.07-1.76)	0.012	0.051	0.018
			80.8	<0.001	R	–	1.56	(1.12-2.19)	0.009	0.099	0.022
Mortality	Cohort study	2	0.0	0.582	R	1.39	–	(0.85-2.27)	0.184	0.317	–
	Case-control study	0	–	–	R	–	–	–	–	–	–

* LC, liver cirrhosis; No., number; P_H, p value for heterogeneity; M, model for meta-analysis; R, random-effect model; RR, relative risk ; OR, odds ratio; P_{ES}, p value for effect size; P_{Begg}, p value for Begg's test; P_{Egg}, p value for Egger's test

Table 2. Meta-anaylsis of relationship between PPI use and complications of liver cirrhosis.

4 Discussion

Proton pump inhibitors are often prescribed inappropriately to patients with cirrhosis; recent studies suggest up to 60% of PPIs are prescribed inappropriately [46, 47]. There have been meta-analyses investigating the association between PPIs and cirrhosis-related complications, but there are few meta-analyses exploring cirrhosis-related complications comprehensively. We found PPIs are associated with increased risk of SBP and overall infection. However, there were no significant associations between the use of PPIs and portosystemic encephalopathy or mortality. This is the largest meta-analysis, to the best of our knowledge, on the association between PPI use and complications from cirrhosis. The meta-analysis included 20,484 patients from 29 studies on the association between PPI use and complications of cirrhosis and this is the first meta-analysis assessing the association between PPIs and cirrhosis-related mortality. This study provides valuable insight, especially considering that randomized controlled trials cannot be used to study adverse drug-related events.

Our study demonstrated that PPIs are associated with increased risk of SBP and overall infection. This is consistent with previous meta-analyses [48-51], supporting the correlations. However, the heterogeneity between

our samples was high, so we performed subgroup analyses. The subgroup analyses of SBP, overall infection, and PSE were performed, and the cohort study achieved an RR > 1 (Table 2), suggesting that PPIs affected each complication but not to a significant degree ($p > 0.05$). Heterogeneity was high in SBP, PSE, overall infection (Table 2). However, when a subgroup analysis was performed on the case-control studies, the OR of PPI users was significant ($p < 0.001$) and there was no heterogeneity ($I^2 = 0$). Cohort studies did not produce significant results but showed a tendency, and the case-control studies did show significance which provides support for the tendencies seen in the cohort studies. This may be a result of differences in research methods. Selection bias may have been present in the case-control studies because patients were chosen based on the presence of cirrhosis-related complications before PPI use was determined. In addition, cohort studies rely on follow-up assessments of complications to determine PPI use and it is possible that complications may have occurred if the follow-up period was longer.

Previous meta-analyses demonstrated a significant correlation between PPI and PSE, but PSE and mortality were not significantly related to PPI use [52]. Bian et al. [52] only included three studies: Tasi et al., Dam et al., and Lin et al. [13, 29, 42] in their meta-analysis associating PPIs with PSE. Perhaps some articles may have been omitted because it did not meet

inclusion criteria in the previous meta-analysis or there might have been publication bias.

A limitation to this meta-analysis was many of the source articles did not clearly state information regarding the patients PPI use, including the type of PPI used, and the duration of use. Additionally, there was no information on the follow-up period in many of the studies, which may be one of the variables contributing to differences in outcomes between case-control and cohort studies. *H. pylori* infection status and antibiotic use, which may contribute to increased blood ammonia levels resulting in an increased risk of PSE, was not reported in many of the papers, and this relationship may be a confounding factor.

5 Conclusion

This was the largest meta-analysis of its type among published papers and to the best of our knowledge the largest meta-analysis on this subject. This is a significant study because it explored the relationship between PPIs and SBP and other cirrhosis-related complications. To the best of our knowledge, no other studies have investigated this combination of variables. PPIs are often inappropriately prescribed to patients with cirrhosis. Recent studies suggest

up to 60% of PPIs are inappropriately prescribed [46, 47]. The use of PPIs in patients with cirrhosis increased the risk of SBP and overall infection but there was high heterogeneity among the studies. To clarify the correlation between cirrhosis-related complications a large systematic cohort study is needed, which controls the type of PPI, duration of use, and follow-up interval.

Widespread usage PPIs in cirrhosis patients' must be reconsidered and only used if necessary and preferably for a limited period of time.

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초 록

연구 배경

양성자펌프억제제는 효과적인 위산 억제를 위해 가장 일반적으로 사용되며, 위산의 과다분비로 발생한 질병 치료에서 가장 중요한 역할을 하는 약물이다. 위산은 소화작용뿐만 아니라 소화관으로 들어오는 미생물을 살균하는 역할을 한다. 간경변 환자는 정상 면역 체계가 파괴 된 상태에 있어 위산분비를 억제하는 양성자펌프억제제의 사용이 감염성 질환에 이환되기 쉬울 수 있을 것이며, 또한 양성자펌프억제제의 사용으로 인한 장 미생물의 변화가 혈중 암모니아를 증가시킴으로써 간성뇌증을 유발 시킬 수 있다고 이전의 연구들에서 주장한 바 있다. 이러한 이유로 간경변 환자에서 양성자펌프억제제의 사용이 감염성 질환 및 기타 질병의 위험성에 대한 상관관계를 알아보고자 하였다.

연구 목적

우리는 양성자펌프억제제와 간경변의 합병증에 대한 상관 관계를 조사하기 위해 이전 연구를 통합한 메타 분석을 실시하여 간경변 환자에서 양성자펌프억제제 사용의 위험성에 대해 알아보고자 하였다.

연구 방법

이 연구에서 사용한 메타분석은 역학 지침에서의 관찰연구방법과 동일한 방법을 사용하였다. 2 명의 리뷰어가 MEDLINE/PubMed, EMBASE, and the Cochrane library 에서 논문을 검색하고 추출하였다. 연구의 검색기한은 2018 년 10 월 31 까지 데이터베이스에 등재된 연구까지로 하였다. 리뷰어는 검색된 논문의 초록과 전문을 읽고 포함-제외 기준에 따라 연구에 대한 메타분석에 대한 적합성을 평가하였다. 선택된 연구의 질 평가는 뉴캐슬-오타와 척도를 사용하였다.

결과

13 건의 사례대조군 연구 및 16 건의 코호트 연구, 총 29 건의 연구가 메타 분석에 포함되었으며, 이들 29 개 연구에 포함 된 총 환자 수는 20,484 명이었다. 자발성세균복막염에 관한 총 23 건의 연구에 대한 상대위험도는 1.40 이었고, 95 % 신뢰 구간은 1.22-1.61 (I^2 = 56.6 %, P < 0.001)였다. 간성뇌증에 관한 총 7 건의 연구에 대한 상대위험도는 1.25 (95 % CI 0.85-1.84, I^2 = 96.1 %, P = 0.253)였다. 전체 감염에 관한 총 7 건의 연구에 대한 상대위험도는 1.37 (95 % CI 1.07-1.76, I^2 = 79.3 %, P = 0.012)이었다. 사망에 관한 총 2 건의 코호트연구에 대한 상대위험도는 1.39 (95% CI 0.85-2.27, I2 = 0.0%, P =0.184)이었다.

결론

간경변 환자에서 양성자펌프억제제의 사용은 자발성세균복막염의 위험도를 증가 시킨다는 것을 알 수 있었으나 이질성이 매우 높게 나타나고 있엇다. 이에 간경변증 합병증 사이의 상관 관계를

명확히하기 위해, 통제 변수를 적절하게 조절하는 대규모 코호트 연구가 필요할 것으로 보인다.

주요어 : 간경변, 간경화, 양성자펌프억제제, 프로톤펌프억제제 자발성세균복막염, 간성뇌증, 간성혼수

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