Smoking is a risk factor for endogenous peritonitis in patients undergoing peritoneal dialysis

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Short title: **Smoking is a risk factor for peritonitis**

Abstract

Background: Peritonitis is one of the most common complications in patients who are undergoing peritoneal dialysis (PD). However, it is difficult to predict or prevent the onset of endogenous peritonitis. In this study, we investigated the risk of developing endogenous peritonitis in patients receiving PD.

Methods: We included all of the patients who underwent PD at our hospital from April 2015 to March 2020. There were 22 cases of peritonitis, including 18 cases of endogenous peritonitis without evidence of exit-site infection or technical failure. We considered older age, female sex, obesity, diabetes mellitus, diverticulosis, and constipation as important risk factors for endogenous peritonitis. We included these as confounding factors with a current or previous history of smoking in univariate logistic regression models.

Results: In this study, previous or current history of smoking ($p = 0.0065$) was the most significant risk factor for endogenous peritonitis in univariate logistic regression model. In addition, smoking was also the most significant independent risk factor for endogenous peritonitis ($p = 0.0034$) in our multivariate logistic regression models. It was not primary objective that diabetes mellitus was also significant in univariate and multivariate logistic regression analysis.

Conclusions: Smoking is the significant independent risk factor for endogenous peritonitis in patients undergoing PD. The discontinuation of smoking may lower the risk of endogenous peritonitis in this patient group.

Keywords: endogenous peritonitis, smoking, diabetes mellitus, peritoneal dialysis

Introduction

Peritonitis is one of the most common complications in patients receiving peritoneal dialysis (PD). PD-related peritonitis is associated with total mortality and transfer from PD to hemodialysis¹⁻⁴. Moreover, peritonitis is associated with a higher risk of cardiovascular and infection-related mortality in patients undergoing PD². Therefore, the prediction and prevention of peritonitis are important in these patients. The International Society for Peritoneal Dialysis published the “ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment” for patients undergoing PD. Many risk factors for PD-related peritonitis were highlighted in the guidelines and in other reports^{1, 3-8}. Specifically, exit-site infection (ESI) is a risk factor for peritonitis and reducing the occurrence of ESI is important for preventing PD-related peritonitis^{3, 9}. However, endogenous peritonitis may present in patients receiving PD without evidence of ESI or technical failure¹⁰. Consequently, the prevention and prediction of endogenous peritonitis is important. Research has shown that smoking is a risk factor for PD-related peritonitis^{1, 3-8}. However, it is unclear if smoking is a risk factor for endogenous peritonitis. In our hospital, we investigated all cases of endogenous peritonitis in current and former smokers undergoing PD and evaluated the risk of them developing endogenous peritonitis.

Methods

We investigated all patients who underwent PD at our hospital from April 2015 to March 2020. We treated 22 patients with peritonitis, including 18 cases of endogenous peritonitis without evidence of ESI or technical failure. Some factors, such as those shown in Table 1, have been previously reported as risk factors for peritonitis^{1, 3-8, 11-16}.

We considered older age, female sex, obesity, diabetes mellitus, diverticulosis, and constipation as important risk factors for endogenous peritonitis in patients undergoing PD. We added these six factors as confounding factors with a current or previous history of smoking in univariate logistic regression models.

Statistical analyses

Statistical analyses were performed using Prism® software version 8 (GraphPad Software, La Jolla, CA, USA). Multiple linear and logistic regression analyses were performed using JMP® software version 12 (SAS Institute, Cary, NC, USA).

Laboratory values are presented as mean $\pm$ standard deviation and p values < 0.05 were considered statistically significant.

Results

This study included 17 men and 5 women, with a mean age of 64.6 ± 12.3 years. The most frequent primary condition, seen in 17 patients, was type 2 diabetes mellitus (77.3%). Table 2 shows the baseline characteristics of all patients.

Risk factors for endogenous peritonitis

We used univariate logistic regression models for smoking, older age, female sex, obesity, diabetes mellitus, diverticulosis, and constipation. We defined older age as those patients over 65 years old and obesity as a body mass index > 25 . We defined patients who received laxatives at onset of PD as having constipation.

In this study, previous or current history of smoking ($p = 0.0065$) was the most significant risk factor for endogenous peritonitis in the univariate logistic regression models. It was not the primary aim that diabetes mellitus ($p = 0.0106$) was also a statistically significant risk factor for endogenous peritonitis in the univariate logistic regression models.

For the multivariate logistic regression models for risk of endogenous peritonitis, we selected smoking and diabetes mellitus as the significant factors in the multivariate logistic regression models. Smoking was the most significant independent risk factor for endogenous peritonitis ($p = 0.0034$) in our multivariate logistic regression model. It was not the primary objective that diabetes mellitus ($p = 0.0055$) was also a significant independent risk factor for endogenous peritonitis in this study.

The results are presented in Table 3.

Discussion

PD-related peritonitis and risk factors

Peritonitis is one of the most common complications in patients undergoing PD and leads to discontinuation of PD and potential fatality¹⁻⁴. Peritonitis is associated with morbidity and mortality caused by cardiovascular events and infections independently². Therefore, the correct management of peritonitis in patients receiving PD is crucial. Our hospital manages patients undergoing PD according to the International Society for Peritoneal Dialysis' 2016 guidelines, which describe the risk factors for developing PD-related peritonitis³. Although many risk factors for PD-related peritonitis have been

reported, currently, only topical exit-site antimicrobial prophylaxis and nasal eradication of *Staphylococcus aureus* have provided sufficient evidence in terms of the reduction in rates of peritonitis in such patients⁴. Moreover, the risk factors for developing endogenous peritonitis in this patient group remain unclear. It is important to predict and prevent endogenous peritonitis as it may present without evidence of ESI or technical failure.

PD-related peritonitis and smoking

Smoking is a modifiable cardiovascular risk factor and is significantly associated with mortality in patients receiving PD^{17-19,20}. In contrast, smoking is not associated with cardiovascular events in patients receiving PD or hemodialysis, despite a reduction in all-cause mortality¹⁸. The guidelines published by the International Society for Peritoneal Dialysis described smoking as a risk factor for peritonitis, and additional studies have confirmed this^{1, 3-8}. However, to our knowledge, no report has clearly described the mechanisms that explain the association of smoking and PD-related peritonitis. In one study, the major cause of peritonitis in current and former smokers was gram-positive cocci⁸. The authors state that this might be due to the management of hygiene and/or care with sterile, no-touch disconnection techniques for the patients.

One study has reported that silent diverticulosis detected using computed tomography is not a risk factor for enteric diverticulosis-related peritonitis²¹. However, another study has shown that diverticulosis may be a risk factor for peritonitis¹². Whether diverticulosis increases the risk of peritonitis in patients receiving PD remains controversial, however, smoking is a significant risk factor for colonic diverticulosis²².

In addition, smoking is associated with complicated diverticulitis and a worse prognosis, and smoking cessation decreases the rate of diverticulitis recurrence^{23, 24}. Moreover, smoking is an independent prognostic factor for colon cancer²⁵, is associated with a failure of gas exchange in the lungs, and is linked to systemic and intestinal ischemia²⁶. In addition, smoking causes angiogenesis and failure in the gastrointestinal tract epithelial barrier²⁶. Smoking affects both the innate and adaptive immunity, worsening the pathogenic immune response or defensive immunity²⁷. Some studies have shown that smoking affects the intestinal microbiome and may lead to the development of intestinal and systemic diseases, such as inflammatory bowel disease²⁸. Moreover, smoking affects the skin and delays cutaneous wound healing caused by dysfunction of the innate immune response in the skin²⁹.

In our hospital, there were 18 cases of endogenous peritonitis without evidence of ESI or technical failure. Smoking was a significant risk factor for endogenous peritonitis in both the univariate and multivariate logistic regression models in this study. As previously stated, the harmful effects of smoking are associated with compromised peritoneal health that may increase the risk of endogenous peritonitis. Moreover, we should be mindful of the harmful effect of smoking on the skin around the exit site. Smoking may also cause ESI and ESI-related peritonitis in patients undergoing PD, although this association was unclear in our study. Further research in this patient group is warranted to confirm this finding.

PD-related peritonitis and diabetes mellitus

Previous guidelines and studies have shown that diabetes mellitus is a risk factor for

peritonitis in patients undergoing PD^{1, 3-6, 11, 30}. It was not primary objective that diabetes mellitus was the second most significant risk factor for endogenous peritonitis after smoking and constipation in our univariate and multivariate logistic regression models. Patients with diabetes mellitus who receive PD are at risk of developing peritonitis, potentially owing to dysfunction of the immune system and technical problems caused by visual impairment³¹. Diabetes mellitus is associated with carcinogenesis³² and, moreover, patients may have cutaneous microbiome dysbiosis that could be a risk factor for cutaneous infection³³. Although the mechanism of association of diabetes mellitus and endogenous peritonitis is unclear, diabetes mellitus was a significant risk factor for endogenous peritonitis in this study. It is possible that diabetes mellitus is associated not only with peritonitis caused by ESI and technical failure, but also with endogenous peritonitis. Further research is necessary to confirm these findings.

In this study, smoking was the most significant independent risk factor for endogenous peritonitis in the univariate and multivariate logistic regression models. It was not primary objective that diabetes mellitus was also a significant independent risk factor for endogenous peritonitis. Current smoking in patients undergoing PD is the treatable and modifiable factor, and the management of the factor may prevent the development of endogenous peritonitis. The prediction and prevention of endogenous peritonitis needs to be considered in addition to ESI in smokers undergoing PD.

Limitations

This study has certain limitations. Firstly, the study was conducted at a single center and

the number of participants was insufficient to allow robust statistical analysis. Secondly, the diagnosis of endogenous peritonitis was made clinically in certain patients, without investigatory confirmation. These limitations may have introduced various biases in our results.

Conclusions

In conclusion, smoking is the significant independent risk factor for endogenous peritonitis in patients receiving PD. The management of the discontinuation of smoking may lower the risk of such patients developing endogenous peritonitis.

Data availability

All data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Statement of ethics

The study protocol was approved by the Ethical Committee of Nippon Medical School Hospital (B-2020-122) and designed in accordance with the Declaration of Helsinki. The study was registered to the University Hospital Medical Information Network (UMIN No.000041046).

Consent

All participants signed written informed consent forms, which included information about the research. Confidentiality of information and patient anonymity were adhered

to in this study.

Conflicts of interest

The authors have no conflicts of interest to declare.

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None

Authors' contributions

KT drafted the first manuscript. KT, YSu, SA, AH, TK, and YSa managed the patients.

YSa coordinated the data analysis and helped with writing the manuscript. All authors participated in discussions and read and approved the final manuscript.

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Legends

Table 1: Risk factors for PD-related peritonitis

PD, peritoneal dialysis.

Table 2: Patients' baseline characteristics and parameters

BMI, body mass index; RASi, renin angiotensin system inhibitor; Vit D, vitamin D; PD, peritoneal dialysis; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; Alb, serum albumin; CRP, C-reactive protein.

Table 3: Logistic regression analysis for endogenous peritonitis

Risk factors for peritoneal dialysis-related peritonitis

Characteristics of patients

- Older age
- Female sex
- Lower socioeconomic status
- Smoking
- Obesity
- Pets
- Living further from PD unit

Comorbidities

- Diabetes mellitus
- Depression

Clinical status

- Hypoalbuminemia
- Hypokalemia
- Absence of vitamin D supplementation

Others

- Nasal Staphylococcus aureus carrier status
- Previous exit-site infection
- Invasive medical interventions (e.g. colonoscopy)
- Patient training

Patients' baseline characteristics and parameters

	total, n	22
Female, n (%)		5 (22.7)
Age (years)		66.6 ± 12.3
BMI (kg/m ²)		23.7 ± 4.0
Smoking , n (%)		13 (59.1)
Diatbetes, n (%)		17 (77.3)
RASi, n (%)		12 (54.5)
Diuretic-use (%)		11 (50.0)
Vit D supplementation at onset of PD, n (%)		7 (31.8)
Malignant tumor, n (%)		9 (40.9)
CVA, n (%)		4 (18.2)
Hepatitis, n (%)		4 (18.2)
History of abdominal operation, n (%)		9 (40.9)
Diverticulosis, n (%)		11 (50.0)
Pancreatic cyst, n (%)		6 (27.3)
Gallstone, n (%)		8 (36.4)
Laxative at onset of PD, n (%)		4 (18.2)
Laxative at onset of petironitis, n (%)		12 (54.5)
Phosphate binder at onset of PD, n (%)		5 (22.7)
Phosphate binder at onset of petironitis, n (%)		13 (59.1)
eGFR at start of PD (mL/ min/1.73m ²)		7.57 ± 5.48
Serum K (mEq/L)		4.64 ± 0.61
Serum Alb (g/dL)		3.18 ± 0.70
CRP (mg/dL)		0.47 ± 1.22
D/P ratio		0.71 ± 0.15
D/D0 ratio		0.37 ± 0.10

Logistic regression analysis for endogenous peritonitis

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	<i>p</i> value	Odds ratio (95%CI)	<i>p</i> value
Older age	0.5238095(0.0232836 - 5.0904939)	0.5931		
Female	0.2(0.0168925 - 2.1865373)	0.1777		
Obesity	1.4999998(0.1514566 - 33.961144)	0.7419		
Diabetes	23.999996(2.0503527 - 658.36579)	0.0106	75847820(1.83e+126 - 4.88e+140)	0.0055
Smoking	92131825(2.7235235 - ND)	0.0065	1.135e+14(5.9276547 - ND)	0.0034
Diverticulosis	3.75(0.3924605 - 84.23298)	0.2599		
Constipation	0.6(0.0508106 - 14.409328)	0.7051		