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EARLY CATHETER REMOVAL IMPROVES PATIENT SURVIVAL IN PERITONEAL DIALYSIS PATIENTS WITH FUNGAL PERITONITIS: RESULTS OF NINETY-FOUR EPISODES OF FUNGAL PERITONITIS AT A SINGLE CENTER

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♦ ***Background:*** **Fungal peritonitis (FP) is an uncommon but serious complication of peritoneal dialysis (PD) and is associated with high morbidity and mortality. Although previous studies have demonstrated that abdominal pain and catheter *in situ* are associated with mortality in FP patients, the effect of early catheter removal on mortality remains largely unexplored. In this study, therefore, we not only determine the risk factors for mortality but also investigate the effect of immediate catheter removal on mortality in PD patients with FP.**

♦ ***Patients and Methods:*** **This retrospective study was conducted on 94 episodes of FP in 1926 patients that underwent PD at Yonsei University Health System from January 1992 to December 2008. Data including demographic characteristics, laboratory and clinical findings, management, and outcome were collected from medical records.**

♦ ***Results:*** **Among a total of 2361 episodes of peritonitis, there were 94 episodes of FP in 92 patients, which accounted for 4.0% of all peritonitis episodes and occurred in 4.8% of patients. Mean age of patients was 52.1 years and mean duration of PD before contracting FP was 46.1 months. The presenting symptoms included turbid dialysate (93.6%), abdominal pain (84.0%), and fever (66.0%). Intestinal obstruction was complicated in 39 episodes (41.5%). 75% of FP was caused by *Candida* species, among which *Candida albicans* was the most common pathogen, accounting for 41.5% of all episodes of FP. The PD catheter was removed within 24 hours in 39 patients (41.5%), whereas catheter removal was performed between 2 and 9 days after the diagnosis of FP in 42 patients (44.7%). 27 patients (28.7%) died as a result of FP, 59 patients (62.8%) required a change to hemodialysis, and PD was resumed in 8 episodes (8.5%). In addition, the mortality rate was significantly higher in patients with delayed catheter removal (13/41, 31.7%) compared to patients with catheter removal within 24 hours (5/39, 12.8%) ($p<0.01$). Multivariate logistic regression analysis revealed that delayed catheter removal, the presence of intestinal obstruction, and higher white blood cell counts in the blood and in the PD effluent were independently associated with mortality in FP patients.**

♦ ***Conclusion:*** **These results suggest that immediate catheter removal (*i.e.*, within 24 hours after the diagnosis of FP) is mandatory in PD patients with FP.**

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KEY WORDS: Early catheter removal; fungal peritonitis; mortality.

Peritonitis is one of the most frequent and serious complications of peritoneal dialysis (PD) and 1% – 15% of all peritonitis cases are caused by fungal infections (1–12). Although fungal peritonitis (FP) in PD patients is relatively uncommon, it is associated with significantly high morbidity and mortality. Mortality rates for FP have been reported as high as 60.5%, and several studies have demonstrated that abdominal pain and catheter *in situ* are associated with mortality in these patients (10–13). However, the majority of previous studies included only a small number of patients and did not evaluate the timing of catheter removal. Recently, peritonitis treatment recommendations from the International Society for Peritoneal Dialysis (ISPD) suggested that catheters should be removed from FP patients immediately after fungi are identified by either microscopy or culture (14). However, the effect of early catheter removal on mortality has not been fully explored. In this study, therefore, we not only determine the risk factors for mortality but also investigate the effect of immediate catheter removal on mortality in PD patients with FP.

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PATIENTS AND METHODS

This retrospective study was conducted by reviewing the medical records of 94 FP cases among 1926 PD patients that were followed up at Yonsei University Health System from January 1992 to December 2008. The diagnosis of FP was made based on the presence of at least two of the following criteria: presence of clinical symptoms (abdominal pain, fever, cloudy dialysate), presence of more than 100 leukocytes/mm^3 dialysate with at least 50% polymorphonuclear neutrophils, and documentation of fungi in dialysate by either smear or culture (14).

The data recorded included age at the time of FP, gender, duration of PD, cause of end-stage renal disease, residual renal function, comorbidities, presenting symptoms and signs, species of fungus causing peritonitis, presence of coexisting bacterial peritonitis, antibiotic use within the 3 months prior to FP, history of treatment with steroids, catheter removal and the time of removal, and patient outcome. The following laboratory data were obtained at the onset of peritonitis: peripheral white blood cell (WBC) count, hemoglobin, blood urea nitrogen, serum creatinine, albumin, and total cholesterol concentrations, erythrocyte sedimentation rate, C-reactive protein levels, and PD effluent leukocyte count.

Cardiovascular disease was defined as a history of coronary, cerebrovascular, or peripheral artery disease. Coronary disease was defined as history of angioplasty, coronary artery bypass graft, myocardial infarction, or angina. Cerebrovascular disease was defined as a previous transient ischemic attack, stroke, or carotid endarterectomy. Peripheral vascular disease was defined as history of claudication, ischemic limb loss and/or ulceration, or a peripheral revascularization procedure. Fungal peritonitis complicating bacterial peritonitis was defined as FP developing during treatment of bacterial peritonitis (10). Exit-site infection was defined by the presence of purulent drainage with or without erythema of the skin at the catheter–epidermal interface (14). Intestinal obstruction was diagnosed based on radiographic findings, such as diffusely dilated and distended air-filled bowel loop, air/fluid levels, or absence or paucity of colonic gas, in patients with nausea, vomiting, or abdominal distention requiring antiemetic agents or decompression by a nasogastric tube. No residual renal function was defined as daily urine output less than 100 mL at time of presentation. Death related to FP was defined as death of a patient with active peritonitis or sepsis secondary to peritonitis or within 4 weeks of diagnosis of FP (14–16). In contrast, death after 4 weeks of diagnosis of FP in a patient without active peritonitis, even during the hospitalization period, was classified as death unrelated to FP.

STATISTICAL ANALYSIS

All values are expressed as mean ± standard deviation (SD) for parametric data, median values with interquartile range for nonparametric data, or percentages. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Data were analyzed using Student's t-test, chi-square, or Fisher's exact test for comparisons. Independent risk factors for FP-related mortality were determined by logistic regression analysis including all covariates with a p value less than 0.10 on univariate analysis. Interactions between the significant covariates were also examined for all analyses. A p value less than 0.05 was considered statistically significant.

RESULTS

DEMOGRAPHIC, CLINICAL, AND LABORATORY DATA

A total of 2267 episodes of bacterial peritonitis and 94 episodes of FP (in 92 patients) were recorded in 1926 patients treated with PD between January 1992 and December 2008. Fungal peritonitis therefore accounted for 4.0% of all peritonitis episodes and occurred in 4.8% of the patients. The overall rates of bacterial peritonitis and FP were 0.38 and 0.02 episodes per patient-year respectively.

Demographic characteristics, clinical findings, and laboratory data are shown in Table 1. Mean age of the patients at the time of FP was 52.1 (range 18 – 77) years, 52.1% were females, and patients were on PD for a mean of 46.1 (range 0.5 – 194.4) months. Thirty-two episodes (34.0%) of FP developed during treatment of bacterial peritonitis and concomitant exit-site infection was observed in 41 episodes (43.6%). Presenting symptoms included turbid dialysate (93.6%), abdominal pain (84.0%), and fever (66.0%). Intestinal obstruction was complicated in 39 episodes (41.5%).

CAUSATIVE ORGANISMS OF FP

The causative organisms of the 94 episodes of FP are listed in Table 2. *Candida* species were the most common pathogens, accounting for 74.5% of all episodes of FP, among which 55.7% were *Candida albicans* and 44.3% were *Candida* species other than *Candida albicans*.

TABLE 1
Demographic Characteristics, Clinical Findings, and Laboratory Data of Ninety-Four Episodes of Fungal Peritonitis (FP)

Age	52.1±12.9 years
Gender (male:female)	45:49
Duration on PD	46.1±39.2 months
Underlying renal disease	
Diabetes mellitus	29 (30.9)
Hypertension	23 (24.5)
Chronic glomerulonephritis	21 (22.3)
Polycystic kidney disease	2 (2.1)
Others	12 (12.8)
Unknown	7 (7.4)
Comorbid conditions	
Diabetes mellitus	38 (40.4)
Cardiovascular disease	40 (42.6)
Prior antibiotic use within 3 months	63 (67.0)
Current use of steroids	6 (6.4)
FP complicating bacterial peritonitis	32 (34.0)
Concomitant exit-site infection	41 (43.6)
No residual renal function at presentation	60 (63.8)
Symptoms and signs	
Turbid dialysate	88 (93.6)
Abdominal pain	79 (84.0)
Fever	62 (66.0)
Complication by intestinal obstruction	39 (41.5)
Laboratory findings	
Hemoglobin	8.7±1.7 g/dL
Peripheral WBC count	11073±5492/mm^3
Serum albumin	2.5±0.6 g/dL
Serum C-reactive protein	12.9±11.2 mg/dL
PD effluent WBC count	1405±1438/mm^3

PD = peritoneal dialysis; WBC = white blood cell.
Data are expressed as mean ± standard deviation or number of episodes (percent).

TABLE 2
Causative Organisms of Ninety-Four Episodes of Fungal Peritonitis

Causative organism	Episodes [*n* (%)]
Candida species	70 (74.5)
Candida albicans	39 (41.5)
Non-*albicans Candida* species	31 (33.0)
Candida parapsilosis	12 (12.8)
Candida tropicalis	5 (5.3)
Candida krusei	1 (1.1)
Others	13 (13.8)
Non-*Candida* species	18 (19.1)
Aspergillus species	7 (7.4)
Penicillium species	3 (3.2)
Trichosporon beigelii	2 (2.1)
Torulopsis glabrata	2 (2.1)
Cryptococcus neoformans	2 (2.1)
Chromomyces species	1 (1.1)
Zygomycetes species	1 (1.1)
Unspecified species	6 (6.4)
Yeast	5 (5.3)
Mold	1 (1.1)

TREATMENT

As soon as FP was diagnosed — 15 episodes (16.0%) by Gram stain and 75 (79.8%) by culture — antifungal therapy was initiated and was maintained for 2 – 6 weeks. In 4 episodes (4.3%), antifungal drugs were not given because the patients died before a diagnosis of FP could be reached. The regimen used and the route of administration were not uniform among patients with FP. Intravenous amphotericin B (0.5 – 1 mg/kg per day, cumulative dose 0.5 – 2 g) with or without intraperitoneal amphotericin B was used in 78 episodes (83.0%), while intravenous or oral fluconazole (200 mg per day) was used in 12 episodes (12.8%).

Removal of the PD catheter was performed in 88 episodes (93.6%) after a median duration of 2 (range 1 – 9) days after the diagnosis of FP; 39 catheters (41.5%) were removed within 24 hours of the diagnosis of FP (after a median duration of 2 days after presentation with FP), whereas 42 catheters (44.7%) were removed at retard after a median duration of 3 (range 2 – 9) days after the diagnosis of FP. Before the identification of fungi, 7 catheters (7.4%) were removed due to recurrent peritonitis or clinical deterioration. The PD catheter was not removed in 6 cases (6.4%); 4 patients (4.3%) died before the diagnosis of FP and 2 patients (2.1%) refused catheter removal and died after all.

OUTCOME

Table 3 shows the clinical outcomes of patients with FP. Twenty-seven cases of FP (28.7%) resulted in death, among which 23 deaths were related to the FP and the remaining 4 patients died of unrelated causes, including acute myocardial infarction, congestive heart failure, and bacterial pneumonia. The median duration between the diagnosis of FP and death was 21 (range 3 – 83) days; 16 (range 3 – 28) days for FP-related deaths and 63 (range 48 – 83) days for FP-unrelated deaths. Fifty-nine episodes (62.8%) required a change to hemodialysis due to patient preference, intra-abdominal adhesions, or encapsulating peritoneal sclerosis, which developed in 4 patients (4.3%). PD was resumed in only 8 episodes (8.5%) after a median duration of 42 (range 14 – 112) days after catheter removal.

TABLE 3
Clinical Outcomes of Ninety-Four Episodes of Fungal Peritonitis

Outcome	Episodes [*n* (%)]
Death	
Related to peritonitis	23 (24.5)
Sepsis	16 (17.0)
Aspiration pneumonia	3 (3.2)
Upper gastrointestinal bleeding	2 (2.1)
Others	2 (2.1)
Unrelated to peritonitis	4 (4.3)
Changed to hemodialysis	59 (62.8)
Resumed peritoneal dialysis	8 (8.5)

The outcome of FP caused by *Candida albicans* was significantly worse compared to non-*albicans Candida;* 14 of 39 episodes of FP (35.9%) caused by *Candida albicans* resulted in FP-related mortality, whereas only 4 of 31 episodes of FP (12.9%) caused by non-*albicans Candida* resulted in death ($p < 0.05$).

FACTORS PREDICTING MORTALITY

To determine the independent predictors for FP-related mortality, 4 patients that died of FP-unrelated causes and 7 episodes in which the PD catheter was removed before the diagnosis of FP were excluded from the analysis. Therefore, 83 episodes of FP were analyzed, among which there were 62 survivors and 21 nonsurvivors. Cardiovascular disease, no residual renal function, delayed catheter removal (after 24 hours from the diagnosis of FP; 31.7% vs 12.8%), *Candida albicans* infection, fever at presentation, and complication of intestinal obstruction were more prevalent in the nonsurvivor group than in the survivor group (Table 4). In addition, age and WBC counts in the blood and PD effluent were significantly higher in the nonsurvivor group than in the survivor group (Table 4).

Multivariate logistic regression analysis was performed with variables that had been revealed as significant covariates with a *p* value less than 0.10 on univariate analysis. The presence of abdominal pain was also included for multivariate analysis because it has been reported as a significant independent risk factor for FP-related death in many previous studies (10,11). Since 3 patients that died of FP-related causes and with catheter *in situ* were not eligible for multivariate analysis due to 100% mortality, only 80 episodes were included in the analysis. As shown in Table 5, delayed catheter removal, the presence of intestinal obstruction, and higher WBC counts in the blood and in the PD effluent were independently associated with mortality in patients with FP. In contrast, age, the presence of cardiovascular disease, no residual renal function, *Candida albicans* infection, and abdominal pain or fever at presentation were not independent predictors for FP-related mortality. On the other hand, no significant interactions between these variables were observed.

DISCUSSION

Fungal peritonitis is a relatively uncommon but serious complication in PD patients. The results of this study show that the presence of intestinal obstruction and high WBC counts in the blood and in the PD effluent are closely associated with mortality in PD patients with FP. In addition, we demonstrated that early PD catheter removal improves survival in these patients, providing concrete support to the ISPD guidelines of 2005 for early catheter removal for FP.

The incidence of FP in our institute was 4.0% of 2361 peritonitis episodes over a 17-year period, with a FP-related mortality rate of 24.5%, which is not obviously different from the results of previous studies (1–13). Since FP-related mortality is significantly higher than bacterial peritonitis-related mortality, several investigators have tried to identify the risk factors in predicting mortality in patients with FP. To date, abdominal pain with or without fever, complication by intestinal obstruction, and low serum albumin levels have been revealed as predictors for mortality in FP (10–13). In the present study, we also found that intestinal obstruction was independently associated with mortality in FP patients, which is in accordance with the results of previous studies. In contrast, this study did not find the presence of abdominal pain to be a risk factor for mortality. This disparity is likely attributable to the fact that most of our patients had abdominal pain at presentation.

All previous studies have consistently demonstrated that PD catheter *in situ* is an independent factor predicting mortality in FP. Wang *et al.* (10) reported that overall mortality rates were significantly higher in their catheter non-removal group (91%) compared to their removal group (31%), and catheter remaining *in situ* was confirmed by logistic regression analysis to be a significant risk factor associated with mortality. In addition, a study by Prasad *et al.* (11) showed that there was a significant difference, as determined by univariate analysis, in mortality between patients with and patients without catheter *in situ* (100.0% vs 40.9%, $p = 0.01$). Based on these two studies, the ISPD treatment guideline for FP has been changed from optional PD catheter removal to immediate removal after the identification of fungi (14,17).

TABLE 4
Comparisons Between Survivors and Nonsurvivors of Fungal Peritonitis (FP)

	Survivors (*n*=62)	Nonsurvivors (*n*=21)	*p* Value
Age (years)	50.3±12.1	57.1±12.9	<0.05
Gender (male:female)	29:33	10:11	NS
Duration on PD (months)	48.2±37.2	47.8±46.4	NS
Comorbid conditions			
Diabetes mellitus	24 (38.7)	10 (47.6)	NS
Cardiovascular disease	21 (33.9)	14 (66.7)	<0.01
Prior antibiotic use within 3 months	39 (62.9)	16 (76.2)	NS
Current use of steroids	2 (3.2)	3 (14.3)	NS
FP complicating bacterial peritonitis	23 (37.1)	8 (38.1)	NS
Concomitant exit-site infection	29 (46.8)	8 (38.1)	NS
No residual renal function at presentation	35 (56.5)	18 (85.7)	<0.05
PD catheter			<0.01
Removal within 24 hours	34 (54.8)	5 (23.8)	
Removal after 24 hours	28 (45.2)	13 (61.9)	
In situ	0 (0.0)	3 (14.3)	
Causative organism			<0.05
Candida albicans	23 (37.1)	14 (66.7)	
Non-*albicans Candida*	25 (40.3)	2 (9.5)	
Other species	14 (22.6)	5 (23.8)	
Symptoms and signs			
Turbid dialysate	53 (85.5)	19 (90.5)	NS
Abdominal pain	53 (85.5)	19 (90.5)	NS
Fever	35 (56.5)	18 (85.7)	<0.05
Complication by intestinal obstruction	20 (32.3)	14 (66.7)	<0.01
Laboratory findings			
Hemoglobin (g/dL)	8.7±1.8	8.6±1.3	NS
Peripheral WBC count (/mm^3)	10 236±4361	13 854±7461	<0.05
Serum albumin (g/dL)	2.5±0.6	2.5±0.5	NS
Serum C-reactive protein (mg/dL)	13.2±10.5	16.7±13.2	NS
PD effluent WBC count (/mm^3)	1190±1187	2275±1931	<0.05

PD = peritoneal dialysis; WBC = white blood cell; NS = not significant.
Data are expressed as mean±standard deviation or number of episodes (percent).

TABLE 5
Multivariate Logistic Regression Model for Mortality

Variable	OR (95% CI)	*p* Value
Age (per 1 year increase)	1.04 (0.97–1.12)	NS
Cardiovascular disease	1.65 (0.28–9.66)	NS
No residual renal function at presentation	4.11 (0.51–32.96)	NS
Catheter removal after 24 hours	13.73 (2.09–90.36)	<0.01
Candida albicans infection	0.31 (0.05–2.04)	NS
Abdominal pain	2.33 (0.15–37.35)	NS
Fever	6.42 (0.71–57.82)	NS
Complication by intestinal obstruction	10.90 (1.41–84.24)	<0.05
Peripheral WBC count (per 1000/mm^3 increase)	1.23 (1.04–1.46)	<0.05
PD effluent WBC count (per 1000/mm^3 increase)	2.08 (1.12–3.86)	<0.05

WBC = white blood cell; PD = peritoneal dialysis; OR = odds ratio; CI = confidence interval; NS = not significant.

Even though some investigators have reported successful treatment of FP without catheter removal, the cure rates in most large studies were low (18–20). The reason for this high treatment failure has been supposed that fungi colonize and produce a biofilm on the inner surface of the retained catheter, not only serving as a nidus for continuous fungal shedding but also rendering antifungal therapy less effective (21–23). Therefore, most clinicians agree that catheter removal is an integral part of the treatment of FP (5–13). However, concrete evidence for the best time for catheter removal in FP has not been established. Only two studies evaluated the impact of timing of catheter removal on patient outcomes in FP. One study demonstrated that mortality was 0% if the catheter was removed within 24 hours, compared to 31% if catheter removal was delayed until after 24 hours (10). Another recent study revealed there was a significant difference in mortality between FP patients in whom the catheter was removed within 24 hours of diagnosis versus after 24 hours (13). Even though there was a difference in mortality in the former study it did not reach statistical significance, while the predictive value of early catheter removal on mortality in the latter study was not confirmed by multivariate logistic regression analysis, probably due to a relatively small number of patients. In the present study, we show that delayed catheter removal more than 24 hours after the identification of fungi is an independent risk factor predicting mortality in FP patients. Taken together, it is suggested that immediate catheter removal is mandatory in PD patients with FP.

Another independent predictor of mortality identified in this study is high WBC count in the blood and the PD effluent. A few studies have assessed the value of WBC counts in PD effluent to predict outcomes in PD patients with peritonitis but the results are not consistent (24,25). We suppose that the timing of PD effluent collection may contribute to these conflicting results. In general, the WBC count in the second dialysate is higher compared to the initial turbid dialysate in PD peritonitis patients; it is also known that the WBC count in the PD effluent depends on the length of the dwell (26,27). Therefore, even though the results of our study suggest that the severity of the inflammatory process has an effect on the outcome of FP, further prospective study with a clear validation of the initial WBC count in the dialysate is necessary.

The number of FP episodes in the present study is higher than those of previous studies performed at a single center in Hong Kong (10) and in the USA (6) that included 70 and 55 cases respectively. Even though a very recent study by Miles *et al.* (9) was conducted on 162 episodes of FP in PD patients, the data were collected from 66 centers in Australia. Therefore, we consider that the present study is the largest single-center study on FP in PD patients. On the other hand, the mortality rate in our study was 28.7%, which is comparable with that in the study by Goldie *et al.* (6), the largest single-center study in the USA. When compared to the data from Hong Kong (10) and the ANZDATA Registry (9), however, the incidence of death from FP in the present study was lower relative to the Hong Kong study (44.3%) but higher relative to the ANZDATA study (9.0%). We surmise that the higher mortality rates in the Hong Kong study are partly attributable to the longer median duration between the diagnosis of FP and catheter removal (7 days vs 2 days) and the lower proportion of patients transferred to permanent hemodialysis (14.5% vs 62.8%). In contrast, the incidence of death in the ANZDATA study was lower compared to our study, despite the longer median duration to catheter removal (5 days). As the authors conceded, the ANZDATA study did not collect such important information as patient compliance, individual unit management protocols, post-infection surveillance programs, and severity of comorbidities, and lacked an external audit of data accuracy, which may contribute to the difference in the rates of patient death between the ANZDATA study and our study.

In conclusion, this study shows that delayed catheter removal (more than 24 hours after the diagnosis of FP), complication by intestinal obstruction, and high WBC counts in the blood and the PD effluent are independent predictors of mortality in PD patients with FP. These findings suggest that the PD catheter should be removed immediately and certainly within 24 hours after the identification of fungi in patients with fungal peritonitis.

DISCLOSURE

All the authors declare no conflicting interests.

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