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Evaluation of Peritonitis Attacks in Patients Applying Peritoneal Dialysis

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ABSTRACT

Peritoneal dialysis is one of the renal replacement therapies used to treat patients with end-stage renal disease. Peritonitis is a common complication of peritoneal dialysis. Although the incidence of peritonitis has decreased, it is still a problem and the most important determinant of hospitalization, mortality, and morbidity. The aim of this study was to evaluate the incidence of peritonitis in peritoneal dialysis patients, compare culture methods, and determine the causative microorganisms and antibiotic susceptibility.
Patients who were on the peritoneal dialysis treatment program and developed peritonitis were included in the study. Demographic, clinical, and laboratory data of the cases were recorded. The growth rates of pathogens in the peritoneal fluid, causative microorganisms, and antibiotic susceptibility results were evaluated in the peritonitis cases.
During the study, 47 episodes of peritonitis occurred in 28 patients. The mean incidence of peritonitis was 0.57 attacks/patient-year. Growth rates in the blood culture system and solid media were 51% and 46.1%, respectively, and there was no significant difference between them. According to the culture results, 75% were Gram-positive microorganism and the most common pathogens were coagulase-negative staphylococci.
In our study, no significant difference was found between inoculation of peritoneal fluid into blood culture bottles and solid media. The most common pathogens were coagulase-negative staphylococci. As methicillin-resistant staphylococci are common, treatment with vancomycin seems appropriate. It was thought that ceftazidime, which is used for gram-negative bacteria, may not be sufficient due to resistance, and studies with more gram-negative cases are needed to evaluate this.

Keywords: Peritoneal dialysis, peritonitis, microorganisms

Introduction

Continuous ambulatory peritoneal dialysis has a long-time use in acute kidney injury and end-stage renal disease. Despite a decline in its use in recent years, there has been a resurgence of interest and it remains an appropriate treatment model for patients with renal failure, both in the intensive care unit and in the community (1).

Peritonitis is one of the most common complications of peritoneal dialysis (PD) and it is still a problem despite the decrease in its incidence with advances in technology (2). Peritonitis remains the main cause of the transition from PD to hemodialysis, hospitalization, and mortality in patients with PD (3).

Identifying the causative agent of peritonitis, knowing the susceptibility of the microorganism, and initiating appropriate treatment are important in reducing morbidity and mortality.

In this study, peritonitis attacks in patients who underwent peritoneal dialysis in the dialysis unit of our hospital were evaluated prospectively and peritonitis agents and antibiotic susceptibility were investigated. With these results, it was aimed to determine the appropriate treatment method for the agents, culture results, and resistance status.

Materials and Methods

The diagnosis was made by the presence of at least one of the symptoms associated with peritonitis, the presence of ≥100 cells/mm3 in the cell count of the dialysis fluid, and the presence of more than 50% of these cells as polymorphonuclear cells and/or the presence of microorganisms in the Gram stain or culture.

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After the end of treatment, recurrent attacks of peritonitis with the same microorganism within 4 weeks were called relapse, recurrent attacks with different agents within 4 weeks were called recurrence, and the development of peritonitis with the same agent after 4 weeks was called "repeat peritonitis". Cases of peritonitis that did not respond to treatment within five days were considered to be refractory peritonitis.

Age, sex, level of education, who performed the dialysis procedure, number of years of peritoneal dialysis, type of peritoneal dialysis catheter, cause of renal failure, peritonitis and symptoms and their duration, catheter removal, treatment used and response to treatment were recorded for all patients. Blood cultures, routine biochemical tests (serum creatinine, total protein, albumin), haemogram, erythrocyte sedimentation rate, and C-reactive protein (CRP) were assessed. After the diagnosis of peritonitis and collection of the necessary samples for laboratory investigations, patients were started on intraperitoneal treatment with vancomycin 15-30 mg/kg, ceftazidime 500 mg/liter/loading, 125 mg/liter/day maintenance dose every 5 days. This is consistent with the recommendations of the International Society of Peritoneal Dialysis (ISPD) guidelines (Piraino et al, 2005). Patients were monitored for clinical and laboratory response throughout treatment.

Dialysis fluid was collected from the dialysis bag prior to antibiotic treatment at the time of admission in cases with a pre-diagnosis of peritonitis. Part of the collected peritoneal fluid was used for cell counting on the Thoma slide and 5 ml of this was examined by Gram staining after centrifugation. The remaining 10 ml was seeded directly into the automated blood culture system (BacT/ALERT FA, Biomerieux). After growth, the samples were passaged on blood agar, eosin methylene blue (EMB) agar, and Sabouraud dextrose agar plates. Growing on the plaque were identified using an automated/semi-automated identification and antibiogram system (PhoenixTM Biomerieux, MiniAPI Biomerieux), and their antibiograms were performed.

In addition, 40 ml of the collected peritoneal fluid was centrifuged at 3000 rpm for 15 minutes and the sediments were diluted with 0.5 ml physiological saline and inoculated on 5% sheep's blood agar, EMB agar, Sabouraud dextrose agar and the plates incubated at 37 °C for 24-48 hours. Identification and antibiograms were performed when growth was observed.

Statistical Analysis: Descriptive statistics for continuous variables, mean, standard deviation, minimum, and maximum values were expressed as numbers and percentages for categorical variables. In addition, to determine whether there was a difference between the groups in the incidence of some categorical variables, a comparison of proportions was made using the Z-test. The statistical significance level was set at 5% in the calculations and the SPSS statistical package program (version 22) was used.

Results

During the study period, 47 episodes of peritonitis occurred in 28 of 63 patients in the peritoneal dialysis program. The mean frequency of peritonitis was 0.57 attacks/patient-year (1 attack in 20.9 months). During the study period, 6 of the patients (one with peritonitis) had an exit site infection and one patient had a tunnel infection.

Eighteen (64.3%) of the 28 patients followed up for peritonitis were female and 10 (35.7%) were male. The age of the patients with peritonitis ranged from 18 to 85 years (51.3±17.4), and the mean duration of peritoneal dialysis was 46.5±25.4 months (2 months-7 years). When evaluating the causes of end-stage renal disease in patients with peritonitis, hypertension (14.2%) and diabetes (14.2%) were the most common in 4 patients, while the cause of renal failure was unknown in 12 patients (42.9%) (Table 1).

Fifteen (53%) of the patients who developed peritonitis were illiterate. 7.1% were literate and 39.3% had completed primary school. While 11 (39.3%) of the patients were performing dialysis themselves, 17 (60.7%) were performed by their relatives. All patients with peritonitis used classical peritoneal dialysis and all but one used a bent-tip Tenckhoff catheter.

When looking at peritonitis attacks, 10 patients (35.7%) had their first attack of peritonitis. When the attacks experienced during the study were evaluated, 16 patients experienced one attack, 10 patients experienced two attacks, one patient experienced five attacks, and one patient experienced six attacks. When looking at the number of peritonitis attacks that developed during the first year of PD, 22 patients (78.5%) had no peritonitis attacks during the first year, four patients (14.3%) had one attack, one patient (3.6%) had two attacks, and one patient (3.6%) had three attacks.

The most common complaints in the cases were abdominal pain and peritoneal fluid opacity, which together were present in 97.9% of the patients

Table 1. Causes of End-Stage Renal Disease In Peritoneal Dialysis Patients

Etiology	N	%
Diabetes mellitus	4	14.2
Hypertension	4	14.2
Urolithiasis-obstructive nephropathy	3	10.7
Amyloidosis	1	3.6
Polycystic kidney disease	1	3.6
Alport Syndrome	1	3.6
Systemic Lupus Erythematosus	1	3.6
Vesicourethral reflux	1	3.6
Unknown	12	42.9
Total	28	100.0

Table 2: Finding and Symptoms Seen In Peritonitis Attacks In Patients

Finding /Symptom	N= 47	%
Turbidity in dialysis fluid	47	100
Abdominal pain	46	97.9
Nausea	29	61.7
High fever	23	48.9
Anorexia	19	40.4
Chills/coldness	9	19.1
Sweating	5	10.6
Diarrhea	5	10.6

(Table 2). The mean time between the onset of symptoms and hospital admission was 2.0±1.6 days.

The leukocyte count in the dialysis fluid of peritonitis patients ranged from 200 to 23,500 per cubic millimeter (3859.6±4628). Neutrophils were predominant in 44 (93.6%) attacks and lymphocytes in 3 (6.4%) attacks.

Microorganisms were seen in 14 attacks (29.8%) on Gram staining. Of these, 11 (78.6%) were compatible with the agent produced in culture and one was different. In two stains with microorganisms, no growth was detected in culture. In our study, Gram-positive microorganisms were detected in 10 attacks (41.7%), Gram-negative in one (20%) and Candida in one attack (33.3%) by direct Gram staining of attacks with positive cultures.

When the cultures of the cases were evaluated, the causative organism was found in 32 (68.1%) of 47 peritonitis attacks, and no growth was observed in 15 (31.9%) of them. While growth was observed in 24 (75%, 51.1% of all attacks) peritonitis attacks in blood culture, growth was observed in 22 (68.75%, 46.8% of all attacks) in solid media. In fourteen (29.8%) peritonitis attacks, the causative microorganism was grown in both standard solid media and blood culture systems (Table 3). Factors detected in solid media and blood culture were similar. The detection rate of the pathogen with the blood culture system was higher than the growth rate detected by cultivation in solid media, but there was no statistically significant difference (p = 0.577).

Of the organisms cultured, 24 were Gram-positive (75%), 5 were Gram-negative (15.6%) and 3 were *Candida spp.* (9.4%). Of the Gram-positive microorganisms, 12 (37.5%) were coagulase-negative staphylococci (CNS), 6 (18.75%) were *Staphylococcus aureus (S.aureus)* and 4 (12.5%) were *Enterococcus fecalis* (E.fecalis) (Table 4). While 41.7% of CNSs were methicillin-resistant, 83.3% of *S.aureus* isolates were methicillin-susceptible. All Enterococcus species were susceptible to ampicillin and vancomycin. *Escherichia coli* (6.3%) was the most common Gram-negative microorganism.

The white blood cell count of patients who developed peritonitis ranged from 4200-27300/mm3 (11351.1±5548.1), and leukocytosis was observed in 25 (53.2%) of the peritonitis attacks (Table 5). C-reactive protein (CRP) levels

Table 3: Culture Method and Growth Rates

Culture method	Growthing	%
Blood culture system	24	51.1
Solid media	22	46.8
Only blood culture system	10	21.3
Only solid media	8	17.0
Both blood culture and solid media	14	29.8

Table 4: Agent Microorganisms In Culture-Positive Peritonitis Attacks

Agents	N	(%)
Gram-positive	24	75
Coagulase negative staphylococcus	12	37.5
Staphylococcus epidermidis	7	21.9
Staphylococcus haemolyticus	4	12.5
Staphylococcus saprophyticus	1	3.1
Staphylococcus aureus	6	18.7
Streptococcus spp	2	6.3
Enterococcus fecalis	4	12.5
Gram-negative	5	15.6
Escherichia coli	2	6.3
Pseudomonas aeruginosa	1	3.1
Enterobacter cloacae	1	3.1
Acinetobacter haemolyticus	1	3.1
Fungus	3	9.4
Candida albicans	2	6.3
Candida parapsilosis	1	3.1
Total	32	100

Table 5: Laboratory Findings Detected In Peritonitis Attacks

Test	Value ranges	Average values
White blood cell	4200-27300	11351.1 ± 5548.1
C-reactive protein (mg/L)	6-513	156.81 ± 115.8
Sedimentation rate (mm/h)	10-70	49.23 ± 17.72
Serum albumin (g/dl)	1.4-4.0	3.08 ± 0.53

were higher than normal in all (100%) of the peritonitis attacks. The mean erythrocyte sedimentation rate was 49.23±17.72. The serum albumin level was below 3 g/dl in 8 patients (28.6%).

In 30 (63.8%) of the peritonitis attacks, a response was achieved in the first 48 hours in the form of resolution of clinical symptoms and a decrease in cell count. Intra-abdominal abscess development was noted in two (4.3%) cases during follow-up. In one of the cases with abscess, the causative organism was Candida, and in the other, methicillin-sensitive *S.aureus* (MSSA).

Intraperitoneal combination therapy with ceftazidime and vancomycin was started in 45 attacks, except in two of the patients with peritonitis (revised treatments were started in the previous attack due to the thought of relapse in two patients). In 10 (21.3%) attacks, there was an inadequate response to empiric treatment and the treatment was changed. Treatment was changed in three of them because of resistance to the empirically started drugs on the antibiogram and in three because of Candida peritonitis. In the cases with fungal growth, the catheters were removed. In the other 4 patients, changes were

made after 72 hours because there was no adequate clinical response. In two of these four patients, the catheter had to be removed and one of them died 5 days (day 8) after the change in treatment.

In six (12.8%) cases of peritonitis attack, the peritoneal catheter was removed and peritoneal dialysis was stopped. Three of these patients had refractory peritonitis and 3 had fungal peritonitis. While the cause was unclear in one of the refractory peritonitis cases, S. aureus and S. epidermidis grew in one case each. There were six recurrent episodes of peritonitis (two relapses of peritonitis, two recurrent peritonitis, and two repeat peritonitis). Refractory peritonitis was present in all seven attacks (15.9%). Peritonitis attacks led to death in two patients (7.1%), in both cases the pathogen could not be identified.

Discussion

Continuous ambulatory peritoneal dialysis is one of the replacement therapies that can be used as an alternative to hemodialysis and transplantation in patients with end-stage renal disease and is used in approximately 10% of patients. Although the incidence of peritonitis, the most feared and important complication, has been reduced by developments in the treatment and technology of PD, it still remains an important problem (2). Peritonitis is one of the most important determinants of hospitalization and mortality in PD patients, accounting for 1-6% (Fried and Piraino, 2000). Mortality from peritonitis developing in PD is also reported to be 6-8% (3). In our study, mortality was observed in two cases (2/28 patients; 7.1%, 2/47 attacks; 4.3%). When the causes of renal failure and comorbidities in patients undergoing peritoneal dialysis were examined, hypertension (HT) 35.1-56.7% and diabetes mellitus (DM) 6.7-31% were reported to be the most common diseases (6-9). In our study, HT and DM were equal (14.2%) and were the most common causes of renal failure.

The incidence of peritonitis in Turkey in 2007 was reported to be 1/39 months (10). It was reported as 0.38, 0.64, and 1.51 attacks/year in three different national studies (3,6,8). Although the frequency of peritonitis in our study was 0.57 attacks/patient-year (1/20.9 months), which was higher than the 2007 data in the country, it was in a similar range to the studies.

Approximately 60% of peritoneal dialysis patients have at least one episode of peritonitis in the first year (4). In one study, an attack of peritonitis was found in 34.3% of cases in the first year of PD (6). In our study, 21.4% of cases had an attack of peritonitis within the first year. This situation may be related to the close follow-up of patients in the first year and the fact that patients pay more attention to rules and hygiene in the first year.

In patients with peritonitis, peritoneal fluid opacity and abdominal pain are the most common findings suggestive of peritonitis (4). In three national studies, peritoneal fluid turbidity was 94-100% and abdominal pain was 93.5%-100% (6,7,11). In all our cases (100%), peritoneal opacity and abdominal pain were the most common complaints (97.9%).

Although the sensitivity of Gram staining has been reported to be low, ranging from 7-32% in studies, it is recommended as it can be helpful in planning treatment, particularly for fungal peritonitis (6). Studies have shown that gram-positive microorganisms are seen at a higher rate with gram staining (12,13). In the study by Engin et al (11), microorganisms were seen on Gram stain in 51% of cases, and 43% of these were found to be compatible with the pathogen grown in culture. In three different national studies, microorganisms were found in 53.6%, 3.3%, and 19.6% of culture-positive cases by Gram staining (6,7,14). In some foreign studies, the sensitivity of Gram staining was 14 and 32%, respectively (12,15). In our study, similar to the literature data, microorganisms were seen on Gram stain in 14 (29.8%) attacks, and 11 of them (23.4%) were compatible with the pathogen in culture.

To increase the detection rate of agent microorganisms in peritoneal dialysis fluid, various methods are recommended. These include culture of peritoneal fluid after centrifugation, use of various blood culture systems, and culture of excess fluid (16 - Rayner 1993). Direct seeding of dialysis fluid onto agar and enrichment broth cultures have long been used as culture methods. While the culture-negative rate of peritoneal fluid, which has been widely used in recent years, has been reported to be in the range of 17.9-33.4% when transplanted directly into the blood culture bottle, the ISPD recommends that this rate should not exceed 20% (4,13,17-19). In our study, the culture positivity rate was 68.1%; although the isolation of the pathogen was higher with the blood culture system (51%) than with the solid medium (46.8%), no statistically significant difference was found (p=0.577). Among the cases with growth, the growth rate was 75% in blood culture and 68.75% in solid media. We found that the rate of culture negativity was higher (31.9%)

than recommended by the guideline; this may be due to the culture samples of the exchange fluid after the start of antibiotics in a few patients and the waiting period of the peritoneal fluid taken in some of them.

The detection rate of pathogens in PD fluid is low using classical culture methods. This is due to the low concentration of microorganisms in a large volume of fluid (7). Some studies have shown that positive results are obtained earlier and the chance of isolating the pathogen is increased when PD fluid is cultured using automated blood culture bottles (7,18). The blood culture bottle seeding method saves time because it is simple and requires less processing. In a study comparing traditional methods and blood culture systems, 54% of pathogens were detected using the traditional culture method, compared to 89% using the blood culture system (16). In four different studies, while inoculation to the blood culture system was 77%, 71.6%, 78.3%, and 93.3%, respectively, while inoculation to plate medium, growth was detected as 43%, 55.6%, 46.7%, and 63%, respectively (6,7,18,20). In our study, it was found to be 46.8% in the peritoneal fluid inoculation and 51.1% in the blood culture system, but no statistically significant difference was observed (p=0.577). While the plaque cultivation results were similar to the studies, the blood culture system results were lower than the studies and ISPD recommendations, which may be related to the reasons mentioned above.

The most common causes of peritonitis associated with peritoneal dialysis are Gram-positive bacteria originating from the skin flora. With the technological innovations in recent years and the awareness of the importance of exit site care, peritonitis caused by Gram-positive microorganisms has decreased significantly and there has been a relative increase in the rates of Gram-negative microorganisms (11,14,18,21). Kim et al. (21) found that Gram-positive bacteria were the causative agents in 71.2% of 1108 peritonitis attacks, most common CNS (39.9%), less frequently *S.aureus* (21.6%), and streptococci (7.9%) were detected. In the same study, 23.3% of Gram-negative microorganisms (*Escherichia coli* 8.6%, *Pseudomonas aeruginosa* 4.6%) were detected. In the study by Aliskan et al. (18), CNSs were 41.1%, *Streptococcus spp* 20%, *S.aureus* 15.6%, *E.coli* 11.1%, *P.aeruginosa* 4.4%, *Enterococcus spp*. 3.3% and non-albicans *Candida spp.* 3.3% isolated. In many other studies, CNS growth accounts for 24.4%-57.1% of all cultures. In addition, *S.aureus* 6.3%-29.1%, streptococci 2.8-20%, Gram-negative bacteria 8.7-35.9%, and *Enterococcus spp* 2.1-9.8% are reported. Polymicrobial peritonitis, fungi, mycobacteria and anaerobic infections are generally seen in less than 5% (3,4,6,7,11,14,18,21-24). In our study, gram-positive bacteria were found in 75% of cases, of which CNSs (37.5%) was the most common, followed by *S. aureus* (18.8%) and *E. fecalis* (12.5%). Gram-negative bacteria were detected in 15.6% of cases, and *E.coli* (6.3%) was the most frequently isolated. In our study, the distribution of microorganisms causing peritonitis was similar to the results of studies carried out in our country and abroad.

Long-term antibiotic use increases the risk of fungal peritonitis (5). In some studies, fungal growth was found to be between 1.3-4.3% (6,18,22,24). In our study, Candida species were isolated in 3 patients (9.4%), which is higher than in the other studies, and two of these patients had been on broad-spectrum antibiotics for two weeks.

Studies have reported methicillin resistance ranging from 33-73.9% in CNS and 35.1-67.0% in *S.aureus*, with a significant increase in methicillin resistance rates, particularly in coagulase negative patients (21,25,26). National studies have reported methicillin resistance rates of 12.5-66.7% for CNS and 64.0% for *S.aureus* (3,7,18). In our study, methicillin resistance was found in 33.3% of all staphylococci, 41.7% of coagulase negative staphylococci, and only one (16.7%) of *S.aureus*. Since methicillin resistance in CNS was 41.7%, the use of vancomycin in empirical treatment was considered an appropriate choice.

Catheter removal, the need for hospitalization, and mortality rates in peritonitis have been found to be significantly higher in gram-negative infections (23). In our study, gram-negative infections were rare, and because empirical treatment (ceftazidime) was not effective, treatment was changed in 60% of them and catheter removal was required in one case.

It has been stated that blood leukocytosis is not a good indicator of the development of peritonitis in peritoneal dialysis patients (27). While blood leukocytosis ranged from 33.3% to 48.7% in three national studies (6,7,11), leukocytosis was found in 53.2% of attacks in our study.

Serum levels of C-reactive protein (CRP) are elevated in many conditions associated with bacterial infection and inflammation. CRP levels increase significantly in peritonitis, reflecting the severity of the inflammation (6,18). In cases where CRP elevation persists, resistant microorganisms

and recurrent episodes of peritonitis have been observed. It has been suggested that CRP levels are important in monitoring treatment response and that high levels may be associated with catheter-related infection and mortality (28). In three national studies, serum CRP elevation was found to be 85-96.7% (6,7,11). In our study, CRP was found to be high in all attacks (100%), and in one of the cases with death, CRP was found to be the highest at 513 mg/L. CRP monitoring was considered to be an indicator of treatment response and mortality.

The most common reason for catheter removal and transition to hemodialysis in peritoneal dialysis patients is the development of infectious complications. In the study by Pollack et al (29), peritonitis was the most frequent cause of catheter removal with a rate of 31.9%. Most cases of dialysis catheter removal due to infection involve recurrent or treatment-resistant episodes of peritonitis, usually exit site or tunnel infections. One study reported that the peritoneal catheter should be removed or replaced in 35.3% of peritonitis attacks, while another study reported that dialysis was stopped in 42.2% of peritonitis cases due to refractory or recurrent peritonitis (23,30). In our study, the PD catheter was removed in 6 patients (21.4% of patients, 12.8% of exacerbations) due to peritonitis (3 refractory peritonitis, 3 fungal peritonitis).

By preventing peritonitis and reducing its frequency, it will provide a longer and higher quality of life for PD patients. In this regard, it is important to know the causative microorganisms and their antibiotic susceptibility, to initiate appropriate treatment and to take the necessary precautions.

In our study, a total growth rate of 68.1% was found in peritoneal fluid cultures and 51.1% when the fluid was inoculated into a blood culture bottle. In our study of cultures, 75% of peritoneal fluid cultures were gram-positive, of which CNS (37.5%) and 15.6% were gram-negative microorganisms. Methicillin resistance was found in 41.7% of CNS and 33.3% of all staphylococci. As methicillin-resistant staphylococci are common, empirical treatment with vancomycin seems appropriate. In the initial treatment of gram-negative bacteria, the use of ceftazidime is not sufficient due to the 60% ceftazidime resistance, so it may be appropriate to start alternative treatment options, but it was felt that studies with larger numbers of gram-negative cases were needed to evaluate this.

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