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Effects of infectious complications on patients' survival in peritoneal dialysis

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Abstract. – AIM: To investigate the impacts of infectious complications on mortality and morbidity; and to identify the other potential factors effective in mortality in peritoneal dialysis (PD) patients.

PATIENTS AND METHODS: We included patients who initiated therapy between 2001-2011. Patients were divided into two groups regarding to presence or absence of infectious complications. Socio-demographic data and clinical courses were compared and the reasons for PD withdrawal were obtained. Survival analysis of all patients was performed and the effects of infectious complications on mortality were investigated.

RESULTS: 301 patients were included in this retrospective study. 214 patients (mean follow-up time 28.7±16.5 months) had infection history, 87 patients (mean follow-up time 48.9±29.6 months) had no infection history. There were no statistically significant difference in comparison of the groups in terms age, gender, education levels, hemodialysis history. In patients with infection history, 465 peritonitis and 213 catheter exit site infection attacks were diagnosed. The most frequently agent was methicillin-sensitive *Staphylococcus aureus* and *Methicillin-resistant Staphylococcus aureus* in both conditions, while 25% of catheter exit site infection and 25% of peritonitis attacks were culture negative.

During follow-up period, 60 patients transferred to hemodialysis, 58 patients died, 18 patients had renal transplantation in patients with infection history. In other group, 27 patients died, 23 patients had renal transplantation and 11 patients transferred to hemodialysis. Mean survival times were 56.3±2.8 months in patients with infection history and 86.8±6.1 months in other group. Mortality rate was found higher in patients with infection history (long-rank: 0.030). PD preference (OR: 5.213, $p < 0.001$), pretreatment low serum albumin (OR: 0.378, $p = 0.001$), low hemoglobin levels (OR: 0.810, $p = 0.029$) were found as predictors of survival in patients with infection history.

CONCLUSIONS: Infectious complications have negative effects on patient survival. Nature of PD preference, initial hypoalbuminemia and anemia were found to increase the mortality rate. The major causes of deaths were peritonitis and/or sepsis in patients with infectious complications, while the major cause of death was cardiac reasons in patients without infectious complications.

Key Words:
Peritonitis, Catheter exit site infection, Mortality, Peritoneal dialysis.

Introduction

Peritoneal dialysis (PD) has become commonly used renal replacement treatment worldwide after being considered as an alternative treatment method to hemodialysis treatment due to its better blood pressure control and electrolyte balance maintenance, and not requiring a hospital/center care, as well as offering a better quality of life and lesser costs[1-3].

Peritonitis and/or catheter exit site/tunel infections are the most significant complications of PD[4]. Peritonitis is not the reason of technical insufficiency only, but also the most important cause of mortality in this patient population. Although it differs from center to center, peritonitis was routinely observed to be 0.5 attacks per patient-year in the previous year[4].

The aim of this study is to determine the infectious complications in peritoneal dialysis patients; to investigate the impacts of these complications on mortality and morbidity; and to identify the other potential factors affective on mortality in our PD unit.

Patients and Methods

This retrospective study was conducted with the medical records of consecutive 322 PD patients who were followed up from January 2001 to December 2010. Totally 21 patients were excluded because of recovering renal function and

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no longer dialysis requirement, being below 18 years old, having missing data (came from another city for the first PD control to us but inaccessible anyway after this time), being followed by other PD units. Remaining 301 patients' data were evaluated.

All patients performed PD with a double-cuffed, straight Tenckhoff catheter. PD catheters were inserted by Seldinger method in our Unit. Surgical technique was used if patients were obese or Seldinger method was unsuccessful. Antibiotic prophylaxis (at least 1 hours prior to the procedure with intravenous cefazolin 1 g vial) was administrated to all patients prior to PD catheterization. After catheter insertion, patients were educated and ,approximately 2-3 weeks later, continuous ambulatory peritoneal dialysis (CAPD) or automatic peritoneal dialysis (APD) was started.

Age, gender, educational levels of all patients, socio-demographic characteristics including presence of anyone to help to administer PD (e.g. by themselves, their children or other persons like health caregivers), nature of decision to PD (patient own preference, or compulsory choice) were investigated in-depth. PD preference means preferring PD treatment by patients' themselves or by mandatorily because of many causes (vascular problems, cardiac problems, attainability of the center, etc.).

Follow-up time of PD therapy, type of PD modality, if present, presence and duration of hemodialysis (HD) history before PD therapy were noted. Etiology of end stage renal disease (ESRD), additional systemic diseases such as hypertension, cardiovascular disease (CVD), cerebrovascular events, malignancy, etc. were recorded.

Systolic and diastolic blood pressure measurements, daily urine volumes, daily mean ultrafiltration amounts, cardiothoracic indices all of patients were recorded at the beginning and during last visit of PD therapy. Serum urea, creatinine, calcium, phosphorus, albumin, intact parathyroid hormone (iPTH), hemoglobin, ferritin values and transferrin saturation were recorded at initiation of PD treatment and during the last visit.

Frequency of peritonitis and catheter exit site/tunnel infection attacks, culture results of all patients were recorded.

Patients were classified as having peritonitis if they fulfilled at least two of the following criteria: (1) presence of clinical symptoms (pain, fever, cloudy dialysate); (2) presence of more than 100 leukocytes/mm^3 dialysate, with at least 50% polymorphonuclear neutrophils; and (3) positive culture or Gram stain. Culture of the dialysate has been performed as recommended by the ISPD[5]. Whole dialysate (50 mL) is concentrated by centrifugation, resuspended in sterile saline, inoculated into blood culture media, and observed for at least 72 hours to document pathogens. Antimicrobial susceptibility is determined by standard disk-diffusion method. In empirical treatment of peritonitis, vancomycin (intravenous or intraperitoneal vial) and ciprofloxacin (intravenous or orally vial) were used in our Unit. Then, the treatment was changed according to the culture results.

Presence of local tenderness, redness, purulent drainage and/or positive culture from catheter exit site was categorised as tunnel infection. In the case of suspicion for catheter exit site/tunnel infection, exit site drainage cultures were obtained together with dialysate fluid cultures. Empirical treatment of catheter exit site infections were done by local mupirocin pomade and, if purulent drainage was present, oral ciprofloxacin. We may postpone therapy until the results of the exit site culture if only pericatheter erythema or local tenderness without purulent drainage was present.

Patients were divided into 2 groups according to presence of peritonitis and/or catheter exit site/tunnel infection. Patients having of peritonitis and/or catheter exit site/tunnel infection at least once consisted one group while patients without peritonitis and/or catheter exit site/tunnel infection consisted other group.

Socio demographic data and clinical courses were compared, and the reasons for PD withdrawal were obtained between groups. Survival analysis of all patients was performed and the effects of infectious complications on mortality were investigated.

Statistical Analysis

Statistical analyses with the Scientific Package for Social Science (version 13.0; SPSS Inc., Chicago, IL, USA) was used for analysis. Mann Withney U test was used for nonparametric variables. Independent-samples t test was used for analyzing clinical and biochemical parameters at initiation and the last visit values. Pearson and spearman correlation tests were performed for correlation analyses. Patient survival rate were calculated by Kaplan-Meier test and outcomes compared by the log rank test. Risk factors and calculated hazard ratio (HR) for patient mortality were also analyzed by backward logistic regression of the Cox

proportional hazards method. Parametric variables were presented as mean ± standard deviations. Differences were considered statistically significant if p value was less than 0.05.

Results

Three hundred and twenty two patient's data were evaluated. Totally 21 patients were excluded from the study because of following reasons: 1 patient's renal functions recovered and required dialysis no longer; 3 patient was below 18 years old; 5 patients had missing data;12 patients were followed by other PD units. As a result, remaining 301 patients' data were evaluated. Mean age at initiation of PD was 45.7±15.9 years. Mean PD duration was 34.6±23 months and 162 of them were female. Incidence of peritonitis was 26.7±22.9 (2-128) patient-months and that of catheter exit site/tunnel infection attacks was 32±25 (4-128) patient-months. Fifty eight patients had mean 31.4±36 months of hemodialysis history before PD. Sixty five patients choose peritoneal dialysis mandatorily due to vascular reasons. Two hundred fifty eight patients performed continuous ambulatory peritoneal dialysis (CAPD). It was determined that 85% (n=256) of the patients made their PD therapy by themselves, remaining 15% of the patients made PD by help of their children or other persons like health caregivers.

Two hundred fourteen patients had infection (peritonitis and/or catheter exit site/tunnel infection) at least once during the follow-up period. Eighty seven patients had no peritonitis and/or catheter exit site/tunnel infection. There was no statistically significant difference between two groups in terms of age, gender and duration of hemodialysis treatment before PD. Follow-up time was significantly longer in patients without infection history ($p < 0.001$). Demographic data of each group are presented in Table I.

Forty seven patients in patients with infection history and 18 patients without infection history started peritoneal dialysis compulsory due to vascular access problems. There was no statistically significant difference between two groups in terms of preference way of PD.

It was found that 81.7% (n=175) and 95.4% (n=85) patients of group 1 and 2 were performing their own PD treatment by themselves, respectively. The number of patients receiving treatment by the help of their partners, children or care givers was higher in Group 1 ($p = 0.003$).

The major educational status of patients in both groups was a primary school (61.6% and 52.8% respectively). There was no significant difference between two groups ($p = 0.96$).

Cause of ESRD in patients with infection history was chronic glomerulonephritis in 28.2%, diabetic nephropathy in 22.4%, hypertensive nephropathy in 6.5%, obstructive nephropathy in 6.5 % while it was chronic glomerulonephritis in 25.3%, diabetic nephropathy in 23%, hypertensive nephropathy in 6.9%, obstructive nephropathy in 12.6 % in patients without history of infection. There was no statistically significant difference in comparison of etiological factors ($p = 0.72$).

Apart from diabetes and hypertension in patients with history of infection, sixteen patients had coronary artery disease, 8 patients had tuberculosis, 3 patients had cerebrovascular event, and 3 patients had malignancy as additional systemic diseases. Four patients had coronary artery disease, 4 patients had tuberculosis, 1 patient had cerebrovascular accident and 1 patient had malignancy as additional systemic disease in patients without infection history. Rate of additional systemic diseases was found to be similar between two groups ($p = 0.55$).

Clinical and laboratory data are given in Table II and III involving values at initiation of PD and last visit. In patients with infection, 465 peritonitis and 213 catheter exit site infection attacks

Table I. Demographic data of the patients in two groups.

	Group 1 (n=214)	Group 2 (n=87)	p
Gender (M/F)	96/118	43/44	0.47
Age (years)	45.9 ± 15.6	45.5 ± 16.4	0.83
Number of patients with hemodialysis history	42	16	0.94
Mean duration of hemodialysis (months)	33.1 ± 39	26.8 ± 27.2	0.55
Mean follow-up period for PD (months)	28.7 ± 16.5	48.9 ± 29.6	< 0.001
Modality of the first line therapy (CAPD/APD)	179/35	79/8	0.16

Table II. Physical examination findings.

	Group 1 (n = 214)	Group 2 (n = 87)	p
Baseline urine output (ml/day)	388 ± 484	361 ± 448	0.65
Last visit urine output (ml/day)	136 ± 286	141 ± 286	0.88
Baseline systolic blood pressure (SBP) (mm/Hg)	117 ± 25	116 ± 30	0.93
Last visit SBP (mm/Hg)	113 ± 26	112 ± 29	0.82
Baseline diastolic blood pressure (DBP) (mm/Hg)	75 ± 15	72 ± 17	0.17
Last visit DBP (mm/Hg)	72 ± 16	72 ± 19	0.98
Baseline cardiothoracic index (CTI) (%)	47 ± 0.6	47 ± 0.6	0.31
Last visit CTI (%)	47 ± 0.6	47 ± 0.6	0.88
Baseline ultrafiltration rate (UF) (ml/day)	1026 ± 473	1041 ± 397	0.79
Last visit UF rate (ml/day)	1093 ± 550	1095 ± 552	0.98
Baseline Kt/V urea	2.04 ± 0.44	2.15 ± 0.60	0.20
Last visit Kt/V urea	2.45 ± 0.61	2.22 ± 0.42	0.19

Table III. Baseline and last visit biochemical data and complete blood counts of the groups.

	Group 1 (n = 214)	Group 2 (n = 87)	p
Baseline Creatinine (mg/dl)	8.7 ± 3.1	9.0 ± 3.0	0.42
Last visit Creatinine (mg/dl)	8.5 ± 2.7	9.7 ± 27	0.001
Baseline Potassium (mEq/dl)	4.0 ± 0.6	4.0 ± 0.8	0.87
Last visit Potassium (mEq/dl)	4.4 ± 0.7	3.9 ± 0.7	0.65
Baseline Calcium (mg/dl)	9.0 ± 0.9	8.8 ± 1.0	0.16
Last visit Calcium (mg/dl)	9.1 ± 0.9	9.4 ± 0.9	0.019
Baseline PTH (pg/dl)	361 ± 474	317 ± 275	0.42
Last visit PTH (pg/dl)	508 ± 619	374 ± 328	0.07
Baseline Albumin (g/dl)	3.3 ± 0.6	3.5 ± 0.6	0.05
Last visit Albumin (g/dl)	3.5 ± 0.6	3.6 ± 0.5	0.16
Baseline Hemoglobin (Hb) (g/dl)	10.7 ± 1.8	11.3 ± 1.8	0.09
Last visit Hb (g/dl)	11.2 ± 2.0	11.3 ± 2.0	0.87
Baseline Ferritin (ng/dl)	433 ± 433	407 ± 353	0.62
Last visit Ferritin (ng/dl)	395 ± 394	357 ± 341	0.46

were diagnosed. Most frequently isolated microorganisms were methicillin sensitive *Staphylococcus aureus* and *Methicillin resistant Staphylococcus aureus* in peritonitis and catheter exit site/tunnel infections episodes. Twenty five percent (n=118) of peritonitis attacks and 25 % (n=32) of catheter exit site infection attacks were found culture negative. Causative microorganisms for peritonitis and catheter exit site/tunnel infection are given in Table IV.

Table IV. Microorganism causing peritonitis and catheter exit site infection.

	Peritonitis (n=465)	Catheter exit site/tunnel infection (n=213)
Methicillin-sensitive Staphylococcus aureus	140	95
Methicillin-resistant Staphylococcus aureus	91	54
Pseudomonas aeruginosa	12	21
Escherichia coli	34	0
Enterobacter species	15	2
Diphtheroid species	10	0
Streptococcus species	20	3
Klebsiella pneumoniae	13	2
Acinetobacter species	8	0
Fungal species	14	0
Culture negative	118	32

Table V. The reasons for transferred to hemodialysis or mortality.

	Group 1 (n = 214)		Group 2 (n = 87)	
	Transferred to HD (n: 60)	Exitus (n: 58)	Transferred to HD (n: 11)	Exitus (n: 27)
Peritonitis and/or sepsis	41	29	0	0
Cardiac reasons	1	16	2	19
Insufficient dialysis	17	2	3	0
Malnutrition	0	5	2	4
Preference of patients	1	0	3	0
Unknown causes	0	6	1	4

During the follow-up period, 136 patients were withdrawn from PD among patients with infection history. Sixty (28%) of them transferred to hemodialysis, 58 (27%) of them had died and 18 (8.5%) patients were transplanted. In this group, 70 patients continued follow-up visits regularly in our Unit, while 8 patients were followed-up in other centers. On the other side, 61 patients were withdrawn from PD among patients without infection history. Twenty seven of them had died, 23 patients were transplanted, 11 of them were transferred to hemodialysis (HD) in this group. Number of patients followed up regularly in our unit was 18 and 8 patients were followed by other centers. Causes for deaths and transfer to hemodialysis in both groups are shown in Table V.

Mean patient survival time was 78.4 ± 4.6 months in Kaplan-Meier analyses. Mean patient survival time were 56.3 ± 2.8 in patients with infection history and 86.8 ± 6.1 months in patients without infection history. Mean survival rate in the patients with infectious complications was found as 88.9% for 1 year, and it was detected as 79.8%, 68.3%, 64.4% and 56.3% for 2, 3, 4 and 5 years, respectively. Mean survival rate of patients without infectious complications was found as 93% for 1 year, while it was 86.5%, 80.6%, 77.4% and 74.6% for 2, 3, 4 and 5 years, respectively (Figure 1). The mortality rate was found higher in patients with infection history when compared with patients without infection history (long-rank = 0.030).

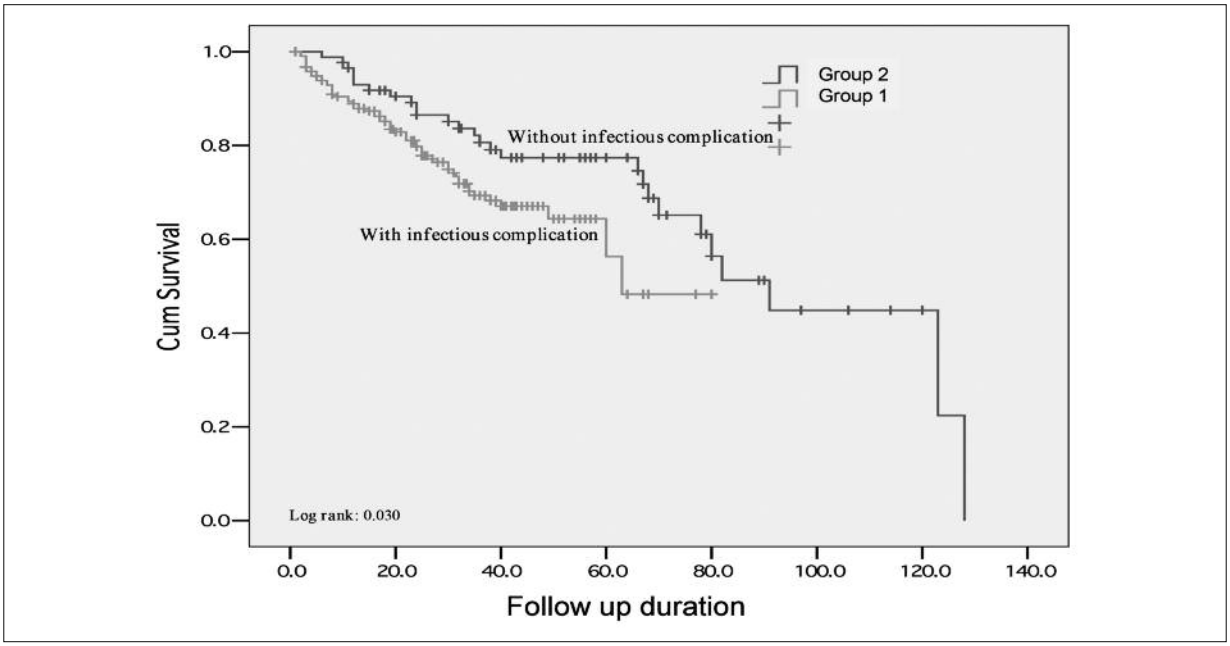

Figure 1. Survival of patients with and without infectious complications.

Age, gender, educational status, preference nature of PD, presence of anyone for administration of PD, presence of HD history, treatment modality at the time of PD initiation, presence and types of additional systemic diseases, baseline urine volume (> 100 ml/day or < 100 ml/day), pretreatment serum albumin, calcium and hemoglobin levels were analyzed using Cox proportional hazard model backward stepwise LR (Likelihood Ratio) to identify independent risk factors of mortality. Compulsory preference of PD (OR: 5.213, 95% CI: 2.564-10.596, $p < 0.001$), initial low serum albumin (OR: 0.378, 95% CI: 0.223- 0.642, $p = 0.001$) and low hemoglobin (OR: 0.810, 95% CI: 0.671-0.979, $p = 0.029$) levels were found to be predictors of poor patient survival.

Discussion

In this study, PD patients with peritonitis and/or catheter exit site infection were found to have a worse survival. Patients without infectious complications had a 5 year survival rate of 74.6%, while it was 56.3% in patients with infectious complications. Compulsory preference of PD, presence of hypoalbuminemia and anemia at the time of PD initiation increased the mortality rate. *Staphylococcus aureus* was found to be the most frequent causes of infections in our unit, accounting for more than half of the episodes. The major causes of deaths were peritonitis and/or sepsis in patients with infectious complications, while the major causes of deaths were detected to be the cardiac reasons in patients without infectious complications.

Different survival rates have been reported from different countries and regions for PD. Recently, better 5 year survival rates were reported in Eastern Asian countries[6,7]. In contrast, 5 year survival rates reported from the Western countries vary between 30% and 50%[8]. In our country, limited number of studies reported survival rates. Study performed in 2001 by Utas et al, reported that the rate of 3 year and 5 year survival were detected to be 84.5% and 68.9%, respectively[9]. Mean 5 year survival rate was detected to be 74.6% and 56.3% in patients without and with infectious complications respectively in our Unit.

Reasons for different survival rates may be multifactorial. Socio-demographic characteristics, comorbid diseases including diabetes, cardiovascular diseases, etc., and factors like malnutrition and decreased residual renal function were determined to affect the mortality rate[10-15].

Although catheter designs and double bag systems improved up to date, better identification of risk factors like nasal carriage, and the usage of prophylactic antibiotics for catheterization procedures, peritonitis has still negative impact on technical failure, hospitalization and patient mortality[5,16-20]. Peritonitis was defined to be the main cause of deaths in 1% to 6% of PD patients[21-23]. Fontan et al[24] reported that 7.2% of their patients died due to peritonitis-related conditions. Another study reported that infection/sepsis was the cause of the peritonitis related deaths; non-peritonitis related deaths were in rates of 68.5% and 15.2%, respectively[25]. In our work, we determined that sepsis-based deaths were related with peritonitis and/or other infectious causes, in which peritonitis was not reported to be the only reason. Peritonitis and/or sepsis were found to be the reasons for 9.6% of overall deaths in our investigation.

In this study, compulsory preference of PD, hypoalbuminemia and anemia at initiation of PD were found to affect the mortality in patients with infectious complications. Peritoneal dialysis requires a significant patient compliance, family support and a clear understanding about the application technique. PD, as the first choice of treatment modality, should be applied under suitable conditions and own wishes was reported to be effective on the survival rates favorably[26]. The main obligatory reason for choosing PD was vascular access failure in HD patients[27]. The other mandatory reasons for choosing PD treatment were patients' access problems to a dialysis center and problems in social insurance benefits. We have determined in our study that patients' choices affect survival. In other words, we determined that those who received PD mandatorily had decreased survival rates due to infectious complications. We consider that most of these patients possibly had medical and/or social problems which prevent them to receive the other treatment modalities.

In many studies, low serum albumin level was reported to be a risk factor for overall mortality[28,29]. Some other works have reported that patients with serum albumin levels less than 3.0 g/dl had increased risk of peritonitis[30-32] and it was emphasized that low socio-economical level was associated with decreased albumin levels. Our patients with peritonitis also had low baseline serum albumin levels. We determined baseline serum albumin level as an independent risk factor of infection-related mortality.

In most of the studies, Gram positive microorganisms were reported to be most frequent causes of peritonitis[33,34]. Lobo et al reported similar rates of Gram positive and Gram negative microorganisms in patients with peritonitis, and the most frequently isolated microorganisms were *Staphylococcus aureus* in 27.8%, *Escherichia coli* in 13.4% and *Klebsiella* species in 9.7% of the episodes[34]. Data from Latin America also demonstrated *Staphylococcus aureus* was the most frequently detected etiological agent[33-35]. Similarly, we detected *Staphylococcus aureus* as the most frequent agent that in peritonitis attacks, accounting for almost half of the episodes.

ISPD guidelines recommend that rate of culture negative peritonitis cases should not exceed 20%. The rate of culture negativity was reported to be between 26% and 33.7% in various reports[34-36]. It was 25% of the episodes in our unit. Although this rate is less than the rates obtained in the other centers, it was still higher than recommended in guidelines. Baretti et al investigated the reason for high rates of culture negativity and they reported that the laboratories did not properly collect and incubate the samples as recommended in guidelines[37]. We think that our high rates of culture negativity could be possibly due to laboratory procedures.

Many studies reported an association between etiological agents and mortality. The mortality was observed to be increased in the presence of enteric[38,39], fungal[40,41] and Gram negative agents[42,43]. Fried et al detected a significant association between peritonitis related mortality and gram negative agents[25]. We could not detect etiological agents as an independent marker of mortality. Half of episodes were due to *Staphylococcus aureus* in our Unit, which was the reason why etiology could not be detected in these cases, however, *Staphylococcus species* were the most benign agents of peritonitis[42-44].

Various studies reported that sociodemographic variables had potential impacts on quality of life, peritonitis and mortality[30,31,33,45-47]. Diabetic nephropathy, advanced age, low income levels and low education levels were reported to be associated with poor prognosis in some studies[28-31,46-49], while no significant association could be detected in some others. Lobo et al observed that advanced age, presence of diabetes and low income levels were not associated with the development of peritonitis[34]. Fontan et al stated that diabetes was not an independent marker of peritonitis-related mortality or all-cause mortality[24]. We determined that age and the presence of diabetes had no effect on mortality in patients with infectious complications. The possible reason of this difference may be due to the younger mean age of our patients and low rate of diabetic nephropathy in our study compared to others.

We did not find a significant difference between groups in terms of education levels. Low income and low education levels are reported to be the risk factors for peritonitis development, and associated with poor prognosis[30,31,45,47]. In contrast, it was detected that education levels had no impact on mortality in out study. Fontan et al[24] reported that the requirement of a partner for dialysis increased the risk of peritonitis, however, had no effect on mortality. We similarly determined that administration of patients' treatments by others (partner, children, nurses) increased the risk of infection, but had no effect on mortality.

Conclusions

Infectious complications have negative effects on patient survival in PD treatment, which is commonly used worldwide. Compulsory preference of PD, the presence of hypoalbuminemia and decreased hemoglobin levels at the time of treatment initiation were found to increase the mortality rate. The major causes of deaths were peritonitis and/or sepsis in patients with infectious complications, while the major cause of death was detected to be the cardiac reasons in patients without infectious complications. *Staphylococcus aureus* was the most frequently detected agent for peritonitis and catheter exit site infection. Pathogenic microorganisms could not be isolated in 25% of the episodes.

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