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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical analysis of peritonitis in peritoneal dialysis patients

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SUMMARY

Introduction/Objective Peritoneal dialysis is a method of treating patients in the terminal phase of renal failure (end-stage renal disease). Peritonitis represents most severe and most common complication of peritoneal dialysis. The most common peritonitis causes are Gram negative microorganisms: *Staphylococcus-coagulase-negative, Staphylococcus aureus, Streptococcus sp, Neisseria sp.* Gram negative microorganisms are: *Pseudomonas sp, Enterococcus, Klebsiella sp, Proteus sp, Acinetobacter sp.*
The aim of the study was to examine the incidence of peritonitis and to determine the differences between patients with and without peritonitis and catheter infection. Other goals of the work were: the most frequent causes of peritonitis, the outcome of treatment, the influence of the length of treatment on the development of peritonitis, the influence of the peritoneal dialysis adequacy on the development of peritonitis, the influence of anemia, nutritional status, iron status, secondary hyperparathyroidism (Ca, P, $CaxPO_4$, parathormone), protein status – albumin and the effect of acid uricum on the development of peritonitis.

Methods Retrospectively, 84 patients were analyzed of peritoneal dialysis (2012–2016) at the Kragujevac Center for Nephrology and Dialysis of Clinical Center. The diagnosis of peritonitis was based on clinical picture, biochemical analyses, leukocyte in sediment of dialysis, findings of peritoneal-culture, signs of inflammation (C-reactive protein, leukocytes). The analysis included: the most common causes, the outcome of treatment, the influence of the length of treatment, the influence of the peritoneal dialysis adequacy, the influence of anemia, the influence of iron status, the influence of secondary hyperparathyroidism, the influence of protein status - albumin, and the effect of acid uricum on the development of peritonitis.

Results In total, 22 patients had one, six patients had two, six patients had three, six patients more than three episodes of peritonitis. The difference in mean values of the number of erythrocytes, hemoglobin, hematocrit, iron, albumin, diastolic pressure, systolic pressure between patients with peritonitis, and those without it, were statistically significant ($p < 0.05$). The difference in mean values of calcium (Ca), phosphor (P), $CaxPO_4$, uricum value, parathormone, peritoneal dialysis adequacy, systolic pressure was not statistically significant ($p > 0.05$). The incidence of peritonitis and death were not associated ($p = 1.000$).

Conclusion Peritonitis is severe complication of peritoneal dialysis. Anemia and nutritional status are risk factors that affect the development of peritonitis in patients on peritoneal dialysis.

Keywords: patients; peritoneal dialysis; infections; peritonitis; biochemical analysis

INTRODUCTION

Peritoneal dialysis is one of the methods for treating patients in the terminal phase of renal failure (end-stage renal disease) in addition to hemodialysis and kidney transplantation [1]. Peritonitis is the most severe and most common complication of peritoneal dialysis, while severe, prolonged peritonitis can functionally alter peritoneum, which permanently disables the use of peritoneal dialysis [2]. Acute peritoneal dialysis is associated with high incidence of peritonitis (0.5–4%), and in late 1970s, the incidence of peritonitis in patients with chronic peritoneal dialysis was six episodes per year [1, 2]. Sterile peritonitis is non-infectious peritonitis due to the leakage of sterile body fluids into peritoneum (blood, gastric acid, bile, urine, pancreatic secretion) [2]. The symptomatology of peritonitis is linked to the causal trigger, as an entity of inflammation and/or diseases [2]. The knowledge of pathogenesis of infections associated with peritoneal dialysis, possible sources and reservoirs of potential causes are the basis for defining effective protocols, i.e., guidelines for the prevention and control of infections associated with peritoneal dialysis [3, 4]. Infection of catheter exit site and "tunnel" infection are the basic types of the infections [5]. In spite of technological innovations (automatic peritoneal dialysis) in the field of cysts and solutions for peritoneal dialysis, better patient education, introduction of preventive measures, peritonitis remains the leading complication of

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peritoneal dialysis [6]. It is manifested by: diffuse sensitivity of abdominal wall (70%), blurring of dialysis fluid with leukocytes > 100/mm^3 (granulocytes > 50%) and isolation of the dialysis fluid causative agent. For initial diagnosis of peritonitis, two of the three listed criteria must be satisfied by guidelines [6]. The most common causes of peritonitis in patients on peritoneal dialysis are Gram positive microorganisms (50%): *Staphylococcus coagulasa negative*, *Staphylococcus aureus*, *Streptococcus sp*., *Neisseria sp*. Gram negative microorganisms are present (15%): *Pseudomonas sp*., *Enterococcus*, *Klebsiella sp*., *Proteus sp*., *Acinetobacter sp*. *Polymicrobial infections*. Gram positive and/or Gram negative microorganisms are represented by 1–4%, while fungal infections are less frequent < 2% [7, 8, 9]. The microbiological diagnosis of peritonitis implies: the dialysate culture should be taken before susceptible peritonitis, and the first blurred bag is the best sample (50 ml of dialysis); delaying a few hours from the sampling time to the time of planting; staining of Gram negative sediment from the dialysis bag proves the presence of microorganisms in 20–30% of cases; microbiological cultivation of a dialysis sample for determining the cause, and antibiotic therapy [10]. Laboratory signs of peritonitis in patients on peritoneal dialysis are: > 100 Le/mm^3 and neutrophil dominance (> 50%); lymphocyte domination in fungal peritonitis; tunnel infection (10%) and less than < 100 Le/mm^3); leukocytosis 10000–15000 Le. [11]. "Tunnel" infection of the exit site may be affected by erythema, edema and skin sensitivity above the pathway of catheter. Many authors have evaluated the role of various catheter implantation techniques and catheter types in lowering the risk of peritonitis in patients [12, 13]. Indications for catheter removal are: refractory peritonitis; relapse peritonitis; peritonitis associated with infection of catheter exit site, i.e., "tunnel" infection; fungal peritonitis; repeated peritonitis caused by: mycobacteria or multiple enteric microorganisms [14]. After the adequate diagnoses of peritonitis (recommended criteria for diagnoses), it is decided to treat it with appropriate antibiotics: first empirical therapy, and later it is adjusted to antibiogram [15]. The duration of therapy, if the effluent is rapidly clear, is about two weeks. In cases where the response to therapy is not adequate, the removal of the peritoneal catheter is advised five days since the treatment beginning [15]. The aim was to analyze the incidence of peritonitis and to determine the differences between patients with and without peritonitis and catheter infection.

METHODS

Patients

Retrospectively, 84 patients (55 women median age: 59.9, 34–86 years, and 29 men median age: 63.06, 36–79 years) were treated with continuous ambulatory peritoneal dialysis 2012–2016 at the Center for Nephrology and Dialysis at the Clinical Center of Kragujevac in Kragujevac, Serbia. The study was performed in accordance with the Declaration of Helsinki, with the approval of local ethics committee on human research (Clinical Center of Kragujevac, Serbia) and informed consent was obtained from each study participant. The diagnosis of peritonitis was made in accordance with the recommended guidelines from the above references. All patients started treatment with empirical therapy according to the guidelines for the treatment of peritonitis in patients on peritoneal dialysis, or if it was relapsed to earlier sensitivity, and upon the arrival of the dialysate culture, the antibiotic was changed to the antibiogram. Peritonitis was treated for two to three weeks depending on the cause and rate of withdrawal symptoms (one peritonitis was treated for more than three weeks with the protection of a fungi, two episodes caused by the *Candida* were recorded).

Clinical parameters

The diagnosis of peritonitis was based on the clinical picture e.g., turbid dialysis fluid, abdominal pain, sensitivity of the abdomen to palpation, high body temperature, vomiting, fever and diarrhea.

Laboratory parameters

The number of leukocytes in sediment of dialysate, the findings of peritoneal dialysis culture and the signs of inflammation such as C-reactive protein, the number of leukocytes, etc. Our analysis included: the most common causes, the outcome of treatment, the influence of the length of the treatment, the influence of peritoneal dialysis adequacy, the influence of anemia, the influence of iron status, the influence of secondary hyperparathyroidism, the influence of protein status (albumin) and the effect of acid uricum on the development of peritonitis. Preliminary results were known after two to three days, definitive after five days of sewing. C-reactive protein was determined by an immune-nephelometric assay (Dade-Behring, BN II, Marburg, Germany). Hematological parameters (anemia, nutritional status) were determined using LH750 hematologic analyzer (Beckman Coulter Inc., Brea, CA, USA).

Adequacy of peritoneal dialysis

Adequate chronic peritoneal dialysis implies a prescribed dialysis procedure to ensure a good quality of life of the patient, the absence of physical problems and morbidity and mortality, which are similar to those of the healthy population. The most commonly used parameter for the minimum acceptable weekly values of Kt/V that indicates creatinine clearance according to the American National Kidney Foundation Dialysis Outcome Quality Initiatives recommendations in patients on continuous ambulatory peritoneal dialysis are 1.7 L, or 60 L/1.73 m^2. For patients on continuous cycling peritoneal dialysis and nightly intermittent peritoneal dialysis, given their intermittent character, the mentioned values are even higher, and are 2.0 L or 2.2 L, and for creatinine clearance 63 or 66 L/1.73 m^2 [20, 21].

The statistical methods included: the mean values of numerical variables between two populations using Student's

t-test and Mann–Whitney test; the categorical variables using χ^2 test for contingency tables and Fisher test, too. This article presents the measures of descriptive statistics: arithmetic mean, standard deviation, frequency and percentages.

RESULTS

In the observation period, peritonitis was diagnosed in 40 (47.6%) patients, while 18 (21.4%) patients did not have peritonitis and 26 (31%) had "sterile" peritonitis in rest (55 women and 29 men; middle-aged of 61.48 ± 2.81 years). Gender, age and occurrence of peritonitis were not statistically related (p = 0.624; p = 0.631). Also, the duration of peritoneal dialysis was not correlated with the occurrence of peritonitis (Table 1).

The most common causes of peritonitis in our patients were: *Staohylococus aureus* (18), *Staohylococus coagulase negative* (10), *E.Colli* (six), *Pseudomonas aeruginosa* (three), *Enterococcus sp.* (three), while other causative agents were rarely represented (Table 2).

Table 1. Demographic characteristics of patients with and without peritonitis

Parameters	With peritonitis	Without peritonitis	p
Gender Male (n) Female (n)	 19 21	 10 7	**0.565**
Age mean ± st.dev.	61.6 ± 12.9	62.2 ± 14.2	**0.998**
Duration of peritoneal dialysis (n of months)	38.3 ±27.4	37.7 ±32.1	**0.976**
Primary disease Diabetes mellitus (n) Hypertension (n) Other disease (n)	 13 18 9	 9 6 2	> **0.05**

Table 2. Distribution of microorganisms isolated from the peritoneum of patients on peritoneal dialysis

Causative agents of infection	n	%
Staphylococcus aureus	18	45
Coagulasa negativni staphylococcus	10	25
E. coli	6	15
Pseudomonas sp.	3	7.5
Enterococcus	3	7.5
Total	40	100

Nine infections of the outlet were identified during the analyzed period, four of them were associated with peritonitis. The most common causes of infection were *Staohylococcus aureus* (four patients), *Staohylococcus coagulase negative* (two patients), *Pseudomonas aeruginosa* (one patient), *Enterobacter* (one patient), *Achromobacter xylosooxidans* (one patient) (Table 3).

Number of peritonitis: 22 patients had one, six patients with two, six patients with three and six patients with more than three episodes of peritonitis, Figure 1.

The difference in mean values of the number of erythrocytes, hemoglobin, hematocrit, iron, albumin, diastolic pressure, systolic pressure between patients with

Table 3. Causes of infections catheter exit site of peritoneal catheter in patients

Causative agents of catheter exit site infection	Number of catheter outlet infections	Percentage
Staphylococcus aureus	4	44.5
Staphylococcus spp.	2	22.2
Pseudomonas	1	11.1
Enterococcus	1	11.1
Achromobacter xylosoxidans	1	11.1
Total	9	100

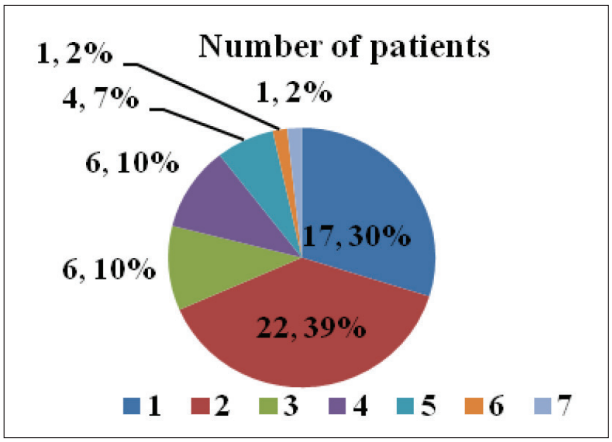

Figure 1. Number of patients with number of episodes of peritonitis

peritonitis, and those without it, statistically were significant and showed in Table 4 (p < 0.05). The difference in mean values of calcium (Ca), phosphor (P), $CaxPO_4$, uricum value, parathormone, peritoneal dialysis adequacy, systolic pressure was not statistically significant (p > 0.05).

Table 4. Variables that affect the occurrence of peritonitis

Variables	With peritonitis	Without peritonitis	p
Erythrocyte	3.09 ± 0.68	3.67 ± 0.97	0.013**
Hemoglobin	97.45 ± 11.7	106.47 ± 15.977	0.021**
Hematocrit	0.28 ± 0.40	0.34 ± 0.07	0.005***
Iron	10.04 ± 4.13	12.51 ± 4.04	0.004***
Albumin	25.13 ± 5.12	30.59 ± 5.33	0.001***
Diastolic pressure	73.12 ± 11.59	78.59 ± 6.86	0.036**
Systolic pressure	124.95 ± 28.64	140.59 ± 18.78	0.044**

The incidence of peritonitis and death were not associated (Table 5, p = 1.000). However, mortality by binary logistic regression was shown to be statistically significantly influenced by the following factors: treatment length, heart rate, erythrocyte, hemoglobin and urea values (Table 5, p < 0.05). Multivariate binary logistic regression showed a simultaneous effect of multiple variables on mortality (erythrocyte count (p = 0.016), iron (p = 0.018) and urea (p = 0.004)). The risk ratio for erythrocyte count is 0.127 (0.024–0.681). The risk ratio for iron is 0.618 (0.416–0.920). The risk ratio for urea is 1.253 (1.053–1.282). With the simultaneous influence of heart rate, erythrocyte count, iron and urea at death, the influence of heart rate is not statistically significant.

Also, mortality by cross tabulation was shown to be statistically significantly influenced by primary disease

Table 5. Variables that affect mortality

Variable	Fatal outcome 0 Mean (SD)	Fatal outcome 1 Mean (SD)	Statistics	
			Z statistics	Sig. p
Treatment length	43.86 (29.8)	14.86 (10.65)	-2.497	0.013**
Pulse	85.25 (20.21)	73.38 (9.12)	-2.441	0.015**
Erythrocyte	3.41 (0.86)	2.77 (0.29)	-3.995	0.000***
Hemoglobin	102.02 (1379)	93.77 (11.28)	-2.143	0.032**
Urea	15.96 (6.72)	24.27 (7.98)	-2.986	0.003**
Albumin	11.48 (4.19)	8.37 (3.51)	-1.875	0.061
Iron	27.59 (5.7)	23.83 (4.97)	-1.821	0.069
Peritonitis Yes No	n of patients with fatal outcome 11 4	n of patients without fatal outcome 29 13		1.000[a]

[a] χ^2 Test

Table 6. Primary disease that affects mortality

Primary disease	Fatal outcome number of patients	Survival number of patients	p
Diabetes mellitus	10	12	0.05*
Hypertension	5	19	0.075
Other disease	0	53	> 0.05

e.g., patients that had diabetes mellitus had statistically significantly increased mortality (Table 6).

DISCUSSION

During analyzed period, 84 patients were treated with peritoneal dialysis, 40 of them had 80 episodes of peritonitis, which is more than the recommended and by the newest guidelines. The most common causes of peritonitis in our patients were: *Staphylococcus aureus*, *Staphylococcus coagulasa negative* and *Escherichia coli*. The incidence of peritonitis decreases was in one for eight and 24 months of the treatment. The significance of peritonitis prevention, quality patient training for independent examination of treatment technique, technological innovations in field of cysts and solutions further reduce the incidence of peritonitis. The incidence of peritonitis in patients in Canada was one episode at 26 patient-months (1996–2005) [16].

In France, one episode was in 29 patient-months (2000–2007) [17]. In the United Kingdom, one episode was in 14 patient-months (2002–2003) [18]. In Latin America, the incidence of peritonitis was one episode in 26 patient-months [19]. "Sterile" peritonitis or culture-negative peritonitis (25.8%) was more commonly reported in our patients, than in patients of other authors – Szeto et al. [20] (17.9%). The other peritonitises were rarely represented as *Streptococcus*-peritonitis (10.3%), *Pseudomonas*-peritonitis (6.9%), *Enterococcus*-peritonitis (4%), *E. coli*-peritonitis (3.4%) [21]. In our patients, the peritonitis caused by *Pseudomonas* were less common than reported by Szeto [20, 21], who found 13.2% peritonitis caused by this causative factor. Szeto et al. [20, 21] found 9.5% of peritonitis associated with infection of the exit site, in the peritonitis caused by *Staphylococcus coagulase negative*, 24.5% in *Staphylococcus aureus*-induced peritonitis [21] and 45.2% in *Pseudomonas*-induced peritonitis [22]. The most common causes of infection of peritoneal catheter exit site were *Staphylococcus aureus* in four patients, and *Staphylococcus coagulase negative* in two patients [22]. In our patients, there were fewer outbreaks of infection during the analyzed period, compared to the other authors, and in particular associated with severe peritonitis. In Australia, Govindarajulu S et al. [23] found 14% of peritonitis caused by *Staphylococcus aureus*. In our patients, the frequency of peritonitis caused by *Staphylococcus aureus* was 9.9%, because it is cause of severe peritonitis with worse prognosis. In Australian patients [23], *Pseudomonas* infections were less common (2.1%), with *E. coli* (6.3%) and *Klebsiella* (4%) more often than in our patients. Fungal infections were not frequent in our center: only two patients had this infection (1.1%), while experts in Australia accounted for 3.1% of fungal peritonitis [23]. A particular problem in all patients on dialysis is anemia [24]. Previous studies showed that patients on peritoneal dialysis had anemia, but less pronounced anemia syndrome than patients undergoing repeated hemodialysis. This beneficial effect of peritoneal dialysis can be explained by higher erythropoietin concentrations, reduced concentration of erythropoiesis-inhibitors and higher quality of nutrition (respectively nutritional status). It is now believed that significant difference in severity of anemia among patients on treatment with peritoneal dialysis and hemodialysis was associated with better clearance of middle molecules, which are essential inhibition factors of the same [24, 25]. During the five-year analyzed period by examining impact of anemia on development of peritonitis, we found that anemia was significant risk factor for the development of peritonitis. The other factors that increase risk of peritonitis include: age, diabetes mellitus, obesity, cardiovascular disease, depression, catheter linkage and/or catheter infections [26]. Prevention of peritonitis associated with peritoneal dialysis represents the high treatment priority [27]. Clinical practice patterns are very different today. Intravenous vancomycin may reduce the risk of early peritonitis and peri-operative treatments. Antifungal prophylaxis with oral nystatin or oral fluconazole may also reduce risk of fungal peritonitis. Another antimicrobial therapy has not shown the adequate efficacy [27]. In Japan, developing effective outpatient protocols for peritonitis treatment and ready and prompt access to home-administered intra-peritoneal antibiotics may reduce the costs associated with peritonitis treatment and peritoneal dialysis therapy. [28]. The authors suggest that biological status of iron in patients on peritoneal dialysis may be a risk factor for the development of infectious peritonitis (improving growth of bacteria through transferring-iron) [29]. Also, in accordance with our results about peritonitis influence on mortality, Tekkarismaz et al. [30] have shown that peritonitis did not reduce patient survival.

CONCLUSION

In the five-year analyze period, 84 patients were treated with peritoneal dialysis and 40 patients had 80 episodes of peritonitis. Anemia, nutritional status, biological status of iron and protein status (albumin) were risk factors which influenced on the development of peritonitis in our patients with peritoneal dialysis. Secondary hyperparathyroidism (Ca, P, CaxPO_4, parathormone), increased acid uricum and the length of peritoneal dialysis treatment or the adequacy of dialysis had no statistically significant effect on the development of peritonitis in our patients who were treated with peritoneal dialysis.

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Conflict of interest: None declared.

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Клиничка анализа перитонитиса код болесника на перитонеумској дијализи

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САЖЕТАК

Увод/Циљ Перитонеумска дијализа је начин лечења болесника у терминалној фази бубрежне слабости (крајњи стадијум бубрежне болести). Перитонитис представља најтежу, најчешћу компликацију перитонеумске дијализе. Најчешћи изазивачи перитонитиса су грам-позитивни микроорганизми: *Staphylococcus-coagulasa-negativ., Staphylococcus aureus, Streptococcus sp., Neisseria sp.* Грам-негативни микроорганизми су: *Pseudomonas sp., Enterococcus, Klebsiella sp., Proteus sp., Acinetobacter sp.*

Циљ студије је био да се испита учесталост перитонитиса и утврде разлике између болесника са перитонитисом и без њега и инфекције због катетера. Остали циљеви рада били су одредити најчешће узроке перитонитиса, исход лечења, утицај дужине лечења на развој перитонитиса, утицај адекватности перитонеумске дијализе на развој перитонитиса, утицај анемије, нутритивни статус, статус гвожђа, секундарни хиперпаратиреоидизам (*Ca*, *P*, *CaxPO*$_4$, паратхормон), статус протеина – албумин и утицај мокраћне киселине на развој перитонитиса.

Методе Ретроспективно је анализирано 84 болесника на перитонеумској дијализи од 2012. до 2016. године у Центру за нефрологију и дијализу Клиничког центра Крагујевац. Дијагноза перитонитиса постављена је на основу клиничке слике, леукоцита у седименту дијализата, налаза културе перитонеумског дијализата, присутних знакова инфламације (це-реактивни протеин, леукоцити). Анализа је обухватала најчешће узрочнике, исход лечења, утицај дужине лечења, утицај адекватности перитонеумске дијализе, утицај анемије, утицај статуса гвожђа, утицај секундарног хиперпаратиреоидизма, утицај протеинског статуса – албумина и утицај мокраћне киселине на развој перитонитиса.

Резултати Двадесет два болесника су имала једну епизоду перитонитиса, шест болесника две, шест болесника три и шест болесника више од три епизоде перитонитиса. Разлика у средњим вредностима броја еритроцита, хемоглобина, хематокрита, гвожђа, албумина, дијастолног притиска, систолног притиска између болесника са перитонитисом и оних без њега биле су статистички значајне ($p < 0,05$).

Разлика у средњим вредностима калцијума (*Ca*), фосфора (*P*), *CaxPO4*, вредности мокраћне киселине, паратхормона, адекватности перитонеалне дијализе, систолног притиска нису биле статистички значајне ($p > 0,05$). Инциденца перитонитиса и смртни исход нису повезани ($p = 1,000$).

Закључак Перитонитис представља најтежу компликацију перитонеумске дијализе. Анемија и нутритивни статус су фактори ризика који утичу на развој перитонитиса код болесника на перитонеумској дијализи.

Кључне речи: болесници; перитонеална дијализа; инфекције; перитонитис; биохемијске анализе