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Intra-peritoneal chronic loculation in peritoneal dialysis patients – a new medical management approach

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Abstract

Peritoneal dialysis (PD) limitation as renal replacement therapy is mostly due to peritonitis and complications. Formation and persistence of intra-abdominal loculations is often under-diagnosed. Encapsulated peritoneal sclerosis (EPS) is a life-threatening complication, but malnutrition, recurrent peritonitis and early membrane failure are insidious enemies that need to be emphasized. It is important to highlight the persistence of intra-abdominal fluid collection after clinical resolution of peritonitis in PD patients and to indicate a new medical management approach for an early diagnosis. During five years, we selected PD peritonitis cases followed by a six months interval free of infections. Ninety-seven subjects were followed at six months and one year after the first peritonitis. Tomography had been performed to patients presenting a positive inflammatory state without a specific infectious cause. Subjects presenting documented localized fluid collection (31 cases) were divided into: drug-treated group and those undergoing laparoscopy by a new surgery technique (seven patients); a comparison regarding the clinical state and biohumoral parameters was assessed in both groups. The prevalence of intra-abdominal loculation following an apparent resolved peritonitis was high (31.9%). The cases undergoing laparoscopy presented a better evolution – improved clinical status (p=0.001), higher hemoglobin values (p=0.06), significant lower doses of erythropoietin requirement (p=0.03), improved dialysis adequacy (p=0.005) and inflammatory state. In cases with confirmed fluid encapsulated loculation, an active attitude (screening imaging protocol and laparoscopic exploration) appears to be mandatory, decreasing the risk of EPS, a serious complication which pathology and treatment are incompletely understood.

Keywords: peritoneal dialysis, peritonitis, intra-abdominal loculation, new surgery technique, outcome.

Introduction

The limitation of peritoneal dialysis (PD) method as renal replacement therapy (RRT) is a frequent consequence of recurrent peritonitis events and their complications [1–3]. It is known that especially *Pseudomonas* and fungal peritonitis are complicated by the persistence of residual collections, even after the removal of the peritoneal catheter [4–6]. The formation and the persistence of intra-abdominal fluid collections of different sizes and localizations is not a rarely encountered phenomenon and it is caused by a wide range of germs [3, 4]. Our personal observations reinforce these assertions: in many cases, in PD patients who were transferred to hemodialysis (HD) for other reasons than severe peritonitis, intraperitoneal loculations persist for many years, even without clinical manifestations. They are not matching the diagnosis of encapsulated peritoneal sclerosis (EPS), but they can evolve with recurrent infectious complications and malnutrition, with or without peritoneal sclerosis and sub-occlusive bowel phenomena. The early diagnosis and on-time treatment of such intra-abdominal collections can improve the evolution and reduce the risks for end-stage renal disease (ESRD) individuals in need of RRT.

Considering these aspects, the aim of our study is to indicate a new and precise medical management approach for an early diagnosis and prevention of abdominal cocoons development. Additionally, the novelty of the research is highlighted by the proposal of a new surgical technique that decreases the risk of peritoneal fluid leaking and enables immediately postoperative PD start.

Patients and Methods

During a 5-year period, a randomized and prospective trial had been performed including all PD individuals, admitted for various reasons in the Department of Nephrology and Dialysis, and Department of General Surgery, "St. John" Emergency Clinical Hospital, Bucharest, Romania. After obtaining each patient's consent, several study groups had been formed according to our designed trial protocol (*e.g.*, associated pathologies, recommended lab tests and therapy); specific morphopathological, treatment and evolutive features were assessed in all included cases.

The present study is part of this exhaustive trial and it is focused on the problem of intra-abdominal fluid collection persistence after clinical resolution of a peritonitis episode in PD patients. Additionally, it emphasizes the controversial evolution of peritoneal loculations and impact on patients' outcome.

This research included patients admitted in the previously mentioned Departments for an acute peritonitis event secondary to PD method. One hundred and thirty-seven cases of acute peritonitis secondary to PD were documented in 118 patients and we included them in the study after the first episode of peritonitis. The selected patients were followed up to one year from the moment of the first peritonitis event. After the antibiotic treatment initiation according to ISPD (*International Society for Peritoneal Dialysis*) guidelines and infectious phenomena resolution, all included individuals were again evaluated after six months (resistant cases were excluded). Furthermore, we selected only those patients with no further peritonitis episodes and without the need of surgical interventions (*e.g.*, catheter pathology or other abdominal surgery). In addition, we excluded subjects: with PD duration <3 months; with insulin-dependent diabetes mellitus; with diagnosed intestinal inflammatory disorders – uremic hemorrhagic rectocolitis, Crohn's disease, intestinal neoplasia, colonic diverticulosis, hepatic cirrhosis; that did not express their consent or were not compliant during the medical visits.

The included patients (n=97) were assessed according to the designed study protocol after six months from the first peritonitis event: medical history – all subjects were required to answer a questionnaire specific for the monthly evaluation of PD patients (*e.g.*, fatigue, dyspnea, appetite, fever, motility disorders, abdominal pain, quality of life); physical examination – presence of non-cardiac edema, signs of peritoneal irritation, changes of dialysis fluid; lab investigations – complete blood and platelet counts, C-reactive protein (CRP), serum albumin, tests to exclude other intestinal inflammatory causes (*e.g.*, stool bacteriology, Adler test); ESA (erythropoiesis-stimulating agents) doses used according to PD protocol; monthly Kt/V assessment.

Abdominal and pelvis tomography (using contrast substance) was performed in all selected patients that presented positive inflammation tests, gastrointestinal phenomena, normocytic-normochromic anemia, ESA therapy resistance or overdosed (according to *European Best Practice Guidelines and Kidney Disease Outcomes Quality Initiative* recommendations) in the last three months. When intraperitoneal loculation was emphasized, diagnostic and curative laparoscopy was indicated using a new and innovatory method – "fixing and sealing device for Tenckhoff catheter" (patent rights request No. A/00428). Additionally, patients' consent was obtained. After six months from admission, both patients undergoing surgery and those conservatory treated were evaluated according to our study protocol previously mentioned, and a comparison of clinical state and lab findings between the two groups was performed.

Statistical analysis

The statistical analysis included descriptive methods, ANOVA, Student's *t*-test in order to compare results, and linear correlation Pearson *chi*-square for independent parameters.

Results

Between 2009 and 2014, 137 acute peritonitis events secondary to PD were observed in 118 patients. Peritonitis was diagnosed based on three elements: cloudy peritoneal effluent and abdominal pain; leukocyte count over 100/mm^3 in PD fluid; positive bacteriology of PD fluid.

Only the first episode in this interval was recorded for our study and patients who never reported a new episode in a six months period and consented to the research were selected. These criteria applied for a number of 97 patients. Demographic and some baseline medical characteristics of interest were summarized in Table 1.

Table 1 – ***Patients features with no peritonitis event relapsed in six months***

Characteristics	Values
Age (mean value) [years]	51±13.7
Gender (male/female) (mean value)	42/55
PD duration	32.3 (8–87) months
Previous peritonitis episodes/patient (mean value)	1.3±0.9
Incriminated germs:	
▪ *Staphylococcus aureus*	49
▪ *Pseudomonas aeruginosa*	11
▪ *Escherichia coli*	19
▪ *Klebsiella pneumoniae*	13
▪ Fungi	0
▪ Miscellaneous	5
Primary renal disease:	
▪ glomerulonephritis	21
▪ tubulo-interstitial nephritis	29
▪ polycystic kidney disease	9
▪ hypertension	18
▪ miscellaneous	20

Residual intra-peritoneal loculation was suspected in 42 patients, after assessing all clinical and biohumoral parameters. Therefore, abdominal and pelvis tomography with contrast substance was performed. The imaging test highlighted residual intra-abdominal fluid collections (cocoons localized in the parietal peritoneum, marginal to or surrounding the bowel loops) (Figure 1) in 31 patients (Table 2), representing 31.95% from the total of 97 initial cases with cured peritonitis event.

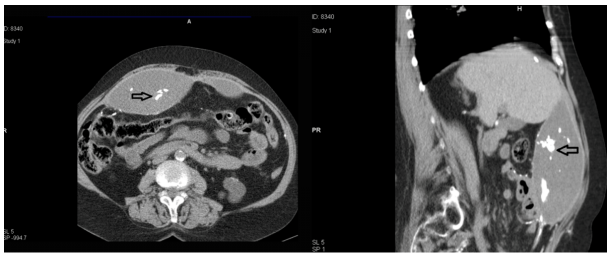

Figure 1 – ***Residual intra-abdominal fluid collections (cocoons localized in the parietal peritoneum, marginal to or surrounding the bowel loops).***

Table 2 – ***Features of patients with documented residual intra-peritoneal loculation***

Characteristics	Values
Symptomatology:	
▪ motility disorders	21
▪ abdominal pain	11
▪ occasional nightly low-grade fever	7
▪ weight loss	19
▪ asymptomatic	4
CRP >6 mg/dL	29
Hb <10 g/dL	21
Serum albumin <3.5 mg/dL	27
Mean Kt/V	1.8±0.4

Characteristics	Values
Previous peritonitis episodes/patient (mean value)	2.8±1.8

CRP: C-reactive protein; Hb: Hemoglobin; Kt/V: Urea dialyzer clearance × dialysis time/urea volume of distribution.

In three patients, EPS was suspected and urgent surgical intervention was indicated with PD catheter removal. Among the 28 individuals with no surgery emergency necessity, seven of them accepted curative laparoscopy using the innovatory device.

Surgical technique of the innovatory device

The patient was placed in supine position. The free-end of Tenckhoff catheter was introduced through the device that was perfectly sealed by the negative pressure (produced by the specific pump) (Figure 2). Pneumoperitoneum was created with an open procedure. A small subumbilical incision was made (2 cm) and subcutaneous layer was transacted. The anterior rectus sheath was opened and a suture was placed to lift the anterior sheath. Posterior sheath and subsequently the peritoneum were digitally opened. If adhesions were present close to the wall incision, they were transacted. A 10 mm trocar or a screw trocar was inserted into the abdomen and CO_2 gas was insufflated to create a pneumoperitoneum of 12–14 mmHg. A Veres needle technique could also be adopted. After the 10 mm trocar was in place, the diagnostic laparoscopy was performed with a 0^0 or 30^0 laparoscope. Other two trocars (5 mm each) were placed under direct vision. Whole peritoneal cavity was explored and adhesions were transacted with electrified scissors, hook electrocautery or blunt dissection. Consequently, peritoneum biopsy and cocoon sampling for histopathology/bacteriology was performed.

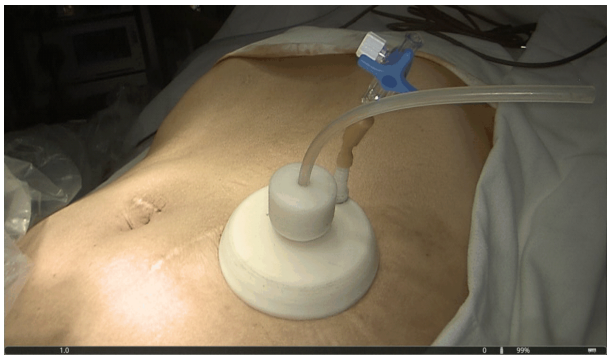

Figure 2 – ***The fixing and sealing device for Tenckhoff catheter (patent rights request no. A/00428).***

In five (71.42%) cases, infected intra-abdominal fluid collections (Figure 3) with different types of germs were identified (Table 3). In two patients, we performed peritoneum biopsy with histopathology exams of the peritoneum and the ascites, showing abundant inflammatory reaction and massive fibrinopurulent exudate. Additionally, the histological changes seen in our patients were almost similar with specific features presented in medical literature [7, 8] – mesothelial denudation, moderate interstitial fibrosis, microvasculopathy of some areas.

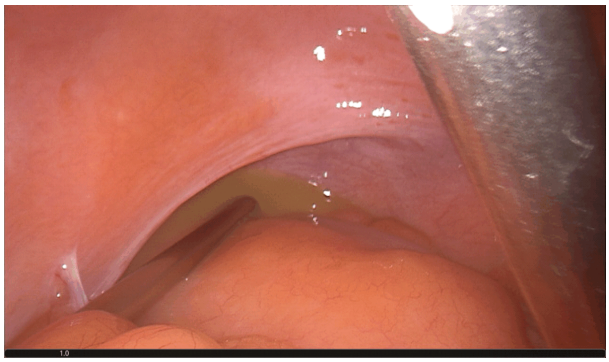

Figure 3 – ***Infected intra-abdominal fluid collection: intraoperative aspect.***

Table 3 – ***Characteristics of identified germs***

Type	No. of positive bacteriology (germs)
Staphylococcus aureus	2
Klebsiella pneumoniae	1
Escherichia coli	1
Pseudomonas aeruginosa	1

The postoperative evolution was favorable in all patients and PD was restarted in 12–24 hours as it follows: an initial 500 mL fluid exchange that was gradually increased – doubled to each new session. In the selected group undergoing therapeutically laparoscopy (n=7), PD continued for the next six months up to the moment of second planned medical visit.

Among the group that refused the surgical intervention, two patients needed PD catheter removal for treatment non-responsive peritonitis, and one was transferred to HD for peritoneal membrane failure (important elevated levels of nitrogenous waste products, inadequate Kt/V, inefficient dialysis). In the end, excluding the previously mentioned three cases, a number of 18 subjects (patients without surgery) were compared with the group undergoing exploratory laparoscopy (Table 4).

Table 4 – ***Comparison between the two groups of patients with documented residual intra-peritoneal loculation***

Patients	No.	Kt/V	Serum albumin [g/dL]	Hb [g/dL]	PCR <6 mg/dL	Symptoms	No. of peritonitis events
Group A	7	1.8±0.3	3.9±0.2	11.1±12	7	1	0
Group B	18	1.2±0.4	3.3±0.4	10.2±0.8	1	14	8

CRP: C-reactive protein; Hb: Hemoglobin; Kt/V: Urea dialyzer clearance × dialysis time/urea volume of distribution.

Patients undergoing surgery presented no postoperatively complications and a good evolution emphasized by significant rise of serum albumin and hemoglobin levels, adequate dialysis, and no signs of inflammation or symptoms at six months evaluation (Figure 4).

Analyzing the main characteristics in both groups, we observed significant statistically differences, especially regarding the clinical evolution (no peritonitis episode in patients undergoing surgery – p=0.32 – and only one symptomatic individual – p=0.6), inflammatory status (p=0.32 for CRP high levels), albumin values (p=0.001), and dialysis adequacy (p=0.005 for Kt/V mean level). Furthermore, hemoglobin mean values were different between the two groups (10.2 g/dL in patients without

surgery and 11.1 g/dL in those undergoing laparoscopy). Additionally, ESA dose requirement was significantly decreased in patients surgically treated comparing to non-operated group (Darbepoetin Alfa mean dose of 20 µg/week *versus* 46.67 µg/week; p=0.03) (Figure 5).

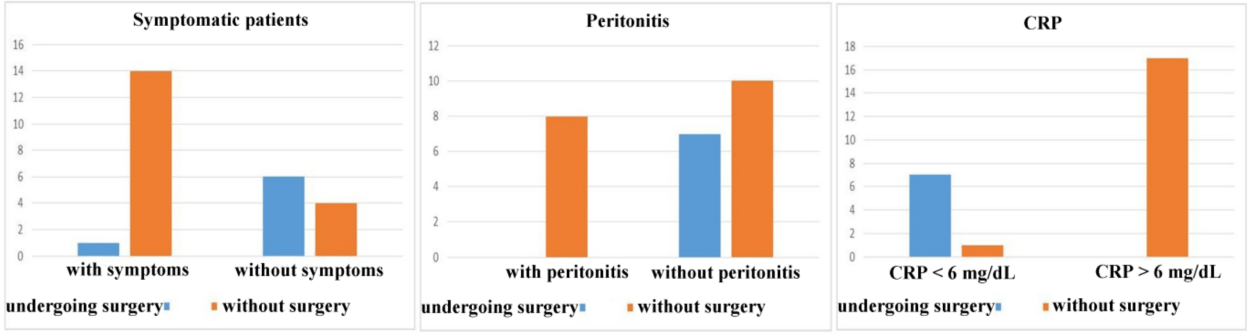

Figure 4 – ***Clinical and inflammatory biomarkers evolution in both groups at six months postoperatively.***

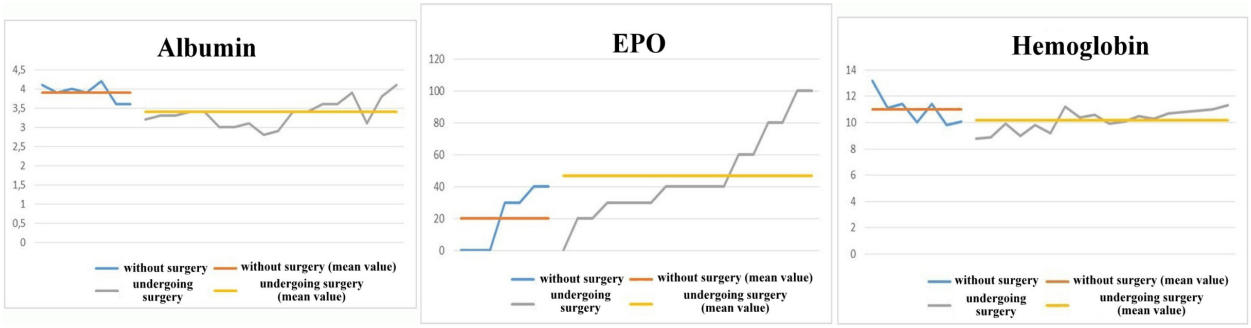

Figure 5 – ***Biohumoral markers evolution in both groups.***

Discussion

The major threat concerning peritoneal dialysis patients, with a very high rate of mortality (24 to 60% within four months of diagnosis) is the development of EPS [9–11]. Its underlined features are: extensive peritoneal sclerosis inducing important intestinal loop entrapment (abdominal cocooning) [9]. The consequences are severe with important impact on the overall prognosis; usually there is noticed a general disturbance of intestinal normal function characterized by: motility disorders, nutrient absorption failure, ileus with obstruction, hemorrhagic ascites, anorexia, weight loss. In addition, the inflammatory status is highlighted by: low-grade fever, hypoalbuminemia, increased values of C-reactive protein (CRP) and other proinflammatory markers [9, 12–14]. The imaging techniques reveal the presence of peritoneal calcifications and abdominal cocoons, emphasized also by histopathological tests [9, 12–14].

Although significant steps have been made in better comprehend the physiopathology and etiology of this disease, there are still many pieces missing from the puzzle: some individuals, presenting predisposing risk factors, never develop EPS, and the mortality rate is still increased, related to therapy and intestinal obstructions complications [9, 15, 16]. Recent data suggested that the highest incidence was observed in Australia and Japan, but with increased prevalence also in Europe, possible due to the awareness of this lethal disorder and early diagnosis detection [9, 15, 16].

The efficiency of the treatment can be achieved only in initial stages and it includes corticotherapy or other immunosuppressive agents, antifibrotic drugs (tamoxifen), surgery (desobstructive interventions of enclosed bowels) [9, 15–18]. Unfortunately, no preventions measurements are available, as the underlined pathological mechanisms are not entirely understood [9]. Therefore, an early diagnosis remains the cornerstone of therapy [9, 15–18].

In a study performed in our clinic in 2010, we reviewed the problems regarding EPS, tested its new treatment modalities and concluded that the prevention and an early diagnosis are best ways to decrease the mortality due to this pathology; the first step is to be more suspicious when PD patients present gastrointestinal symptoms [19]. The present study performed during a five-year period is focused on the same theme and aims to clarify precursor phases of EPS, emphasize the danger represented by peritonitis for peritoneal dialysis patient's evolution, and propose an active attitude in preventing severe infectious complication in these patients.

In our research, the presence of peritoneal collections was diagnosed in a relatively important number of all peritonitis cases (31.95%), and in the majority of cases (73.8%) among patients with suggestive manifestations. In the group of subjects undergoing surgery, we noticed positive bacteriological test in five out of seven cases, representing a significant 71.42% of contaminated fluid of the intra-abdominal cocoons.

To all 31 patients with confirmed intra-peritoneal collections, we suggested the necessity of laparoscopy explaining the risks involved by cocoons persistence and the impact on their prognosis. Therefore, we developed a fixing device of peritoneal catheter directly to abdominal wall that would decrease the risk of peritoneal catheter cuff migration and totally reducing any peritoneal fluid leaking at catheter implant site. At six months evaluation, we noticed that the group undergoing surgery showed an improvement of PD patients' specific biohumoral

values and clinical features (*e.g.*, serum albumin and hemoglobin levels, adequate dialysis, no signs of inflammation or symptoms, no peritonitis events, decrease of ESA dose requirement).

Summarizing, surgically treated patients comparing to non-operated group presented a better long-term prognosis, regardless of laparoscopy procedure associated stress and discomfort.

Conclusions

Intra-abdominal loculations in PD patients are easily overlooked and the risk of EPS development is increased. Even in patients with apparently resolved peritonitis events, a medical passive attitude can predispose to a dangerous subclinical evolution that, in time, can irreversible affect the peritoneum and highly compromise the immune system, inducing ESA resistance, malnutrition and dialysis inefficiency. Therefore, according to our research, we propose an active attitude for PD population, at six months distance after the first acute peritonitis event: routine imaging scan in patients presenting positive clinical and biohumoral criteria; performing exploratory laparoscopy in all cases with documented intra-abdominal fluid collections, using "fixing and sealing device for Tenckhoff catheter" that decreases the risk of EPS onset, peritoneal fluid leaking and enables immediately post-operative PD start.

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