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Inflammatory Peritoneal Reaction after Perforated Appendicitis: Continuous Peritoneal Lavage versus non Lavage

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Abstract
Introduction: Bacterial peritonitis is a severe medical condition associated with a natural mortality rate of 80-100%. Progress in surgical techniques, new developments in intensive care medicine and antibiotic therapy reduced this rate significantly. Aim of this study was to evaluate sepsis parameter in perforated appendicitis and different postoperative management.
Methods: In 50 consecutive patients with diffuse bacterial peritonitis and perforated appendicitis, laparotomy was performed. Subsequently, 25 patients were treated with adjuvant, continuous peritoneal lavage (CPL) using standard peritoneal dialysis (CAPD)-solution The remaining 25 patients were peritoneally drained without postoperative irrigation (Non-CPL). In all patients endotoxin, tumor necrosis factor-α (TNF-α), interleukin (IL-6), C-reactive protein (CRP) and myeloid-related protein (MRP-8, MRP-14 and Heterocomplex) were determined.
Results: No difference in clinical outcome between CPL and Non-CPL could be established. An uncomplicated clinical outcome was associated with lower levels of inflammation markers. Furthermore, clinical data revealed that mortality depended on co-morbidity, and patient's age.
Summary: In perforated appendicitis a faster decrease of mediator release could not be achieved with either method. In addition, no difference could be established for the clinical parameters like hospitalization, duration of intensive care and morbidity.

Introduction

Bacterial peritonitis is a severe illness that is associated with an exceptional high mortality rate of 80-100% when untreated [1, 3, 8, 10, 11, 14, 19, 22, 23]. Progress in surgical techniques, improvements in intensive care medicine and introduction of antibiotics reduced this rate significantly [16, 19, 24, 27]. Most frequent reasons for developing bacterial peritonitis are perforations of the gastrointestinal tract with contamination of the peritoneal cavity. The peritoneal membrane serves as a barrier between the peritoneal cavity and the circulation. Irritation of the peritoneum due to chemical and bacterial products results in transudation and exudation to the peritoneal cavity. The physiological daily volume of intraperitoneal fluid is less than 100 ml. However, in the course of peritonitis, it frequently sums up to several liters a day. This fluid shift plays a major role in the frequent development of life-threatening hypotension and shock observed in such cases [28].

Established treatment of diffuse peritonitis includes sanitation of the infectious focus with intra-operative irrigation of the peritoneal cavity and limited debridement. Despite these treatment modalities, diffuse bacterial peritonitis is still reported with a mortality rate of up to 30% [25, 29]. Causes for the poor clinical outcome of patients with diffuse peritonitis are ineffective control of the focus and the systemic sepsis syndrome finally leading to multi organ failure and death [13, 16, 18, 21, 26, 27, 31]. Established therapeutic concepts for local control of peritonitis are open package [10, 13, 25], irrigation of the abdominal cavity in intervals [2, 4, 15, 18, 29, 31], placement of abdominal drains [13, 30] and continuous peritoneal lavage (CPL) [12, 20, 21]. The rationale to use CPL is to remove fibrin clots, blood, bacteria and endotoxin from the peritoneal cavity. These surgical approaches come along with intensive care and broad-spectrum antibiotic therapy to treat systemic effects. In this pilot trial, we evaluated the therapeutic effect of an adjuvant therapy with CPL subsequent to surgical debridement, lavage and drainage in patients with the diagnosis of bacterial peritonitis, with respect to outcome and a comprehensive panel of inflammatory markers. Standard dialysis solution, as it is utilized for peritoneal dialysis, served as flush solution in this study.

Material and Methods

Patients and Study Design

The study was approved by the local ethics committee. We investigated the clinical course of 50 consecutive patients with peritonitis due to perforated appendicitis. Inclusion criteria were patients with perforated appendicitis and peritonitis. Exclusion criteria were immunosuppressive therapy, AIDS (acquired immunodeficiency syndrome) or ARCS (AIDS related complex syn-

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drome).All patients were treated by laparotomy, which included sanitation of the infectious focus, intraoperative irrigation of the peritoneal cavity and sufficient debridement. 25 patients were treated by CPL whereas in another 25 patients, a drainage catheter was placed but CPL was not performed (Non-CPL). Demographic and clinical data of all patients are summarized in Table 1.

Continuous Peritoneal Lavage (CPL)

Subsequent to appendectomy, debridement of fibrin clots and intraoperative lavage (10 min x 2000-5000 ml) was performed and drainage tubes were placed to the peritoneal cavity. Two irrigation tubes (Salem) to flush the peritoneal cavity were placed next to the coecum and a large silicon drainage tube was positioned to the Douglas pouch. After closing the abdomen with sutures, CPL was initiated and continued until bacterial cultures of the effluat were sterile. Irrigation tubes were then used as drains without suction. As flush solution we used a standard CAPD dwell (CAPD/DPCA 2, Fresenius Medical Care, Bad Homburg, Germany) comprised of 1.5% glucose, 134 mmol/l sodium, 1.75 mmol/l calcium, 0.5 mmol/l magnesium, 103.5 mmol/l chloride, and 35 mmol/l lactate. In patients suffering from candida sepsis, the same formulation without glucose was used (SH05, Fresenius). In general, the amount of lavage started on a rate of 24 liters per 24 hours on the first postoperative day and was reduced on the following days. The reduction of the lavage depended on the clinical status of the patient and the appearance of the lavage fluid. If the symptoms of peritonitis like fever and elevated inflammatory parameters disappeared, the continuous irrigation was gradually reduced. All patients were treated in the same intensive care unit and received broad spectrum antibiotics with adjustment, according to the microbiological resistograms. No antibiotics were added to the irrigation fluids.

Analysis of Inflammatory Markers

To monitor the inflammatory course endotoxin, IL-6, TNF-α, MRP and CRP plasma levels as well as the amount, quality and subpopulation of granulocytes of the peritoneal exudate were determined daily thru the 10th postoperative day. Blood was drawn under sterile conditions from central venous catheters in pyrogen free diagnostic tubes. The heparinized blood (10 IE/ml) was centrifuged at 2000 × g for 15 min. to obtain platelet free plasma. Plasma samples were divided in aliquots and stored at –70 ºC for up to 3 months until assayed.

The determination of endotoxin and endotoxin neutralizing capacity (ENC) was performed using a chromogenic modification of the Limulus amebocyte-lysate-(LAL)-test [7]. The LAL-test is a two-step endpoint colorimetric assay that was performed in microtiter plates (Greiner Co., Nürtingen, Germany). The following solutions were prepared:

Solution A: Endotoxin lysate (Pyroquant Co., Walldorf, Germany) solved in pyrogen-free

Table 1. Demographic and clinical data of the study group. Mean values, standard deviation and percentage in brackets.

Operation Type	Drainage	CPL	Non Survivor	Survivor	Persisting Peritonitis
N	25	25	2	48	4
Gender (male /female)	12/13	14/11	1/1	24/24	1/3
Age (years)	31 ± 21.7	34.2 ± 28.2	64.5 ± 6.4	31.3 ± 24.6	36.8 ± 32.4
BROCA -Index	17.9 ± 21.8	7.53 ± 17.4	18 ± 25.5	12.2 ± 20.1	13.6 ± 19.5
Apache II-Score	5.1 ± 5.4	6.6 ± 5.1	13.5 ± 3.5	5.5 ± 5,1	9.5 ± 5.8
Abscess	5 (20%)	9 (36%)	1 (50%)	13 (27.1%)	2 (50%)
Estimated duration of preoperative peritonitis *f*	36 ± 24	36 ± 16	60 ± 16	24.0 ± 8.0	48 ± 24
CHF	2 (8%)	1 (4%)	2 (100%)	1 (2.1%)	1 (25%)
Diabetes mellitus	2 (8%)	4 (16%)	1 (50%)	5 (10.4%)	1 (25%)
COPD	4 (16%)	2 (8%)	2 (100%)	4 (8.3%)	2 (50%)
Chronic renal failure	1 (4%)	2 (8%)	1 (50%)	2 (4.2%)	2 (50%)
Re-operation	0	2 (8%)	1 (50%)	0	2 (50%)
Mortality	0	2 (8%)	2 (100%)	0	2 (50%)
Hospitalization *	7 ± 7	13 ± 8.7	13 ± 0	10.2 ± 8.3	18.5 ± 13.1
Lavage duration *		4.3 ± 5.9	3.5 ± 0.7	2.6 ± 4.8	10.5 ± 14.3
Removal drainage *	1.5 ± 2.7	6.6 ± 6	7 ± 0	4.0 ± 5.4	12.8 ± 13.6
Postop. intubation *	0.5 ± 2.2	1 ± 1	10.5 ± 0.7	0.1 ± 0.2	5.3 ± 6.1
Bowel movement *	2.4 ± 1.1	2.5 ± 0.9	5.0 ± 1.4	2.4 ± 0.8	3.8 ± 1.7

COPD: chronic obstructive pulmonary disease, CHF: chronic heart failure, * values given in days, *f* values given in hours

water according to the manufacturer's recommendations
Solution B: Pefachrome (Dietzenbach, Germany), a chromogenic substrate at a concentration of 10 μmol in 6.6 ml of pyrogen-free water
Solution C: 0.2 M NaCl, 0.05 M TRIS/HCl (pH 9.0)
Solution D: 20% acetic acid

In brief, plasma samples were diluted 1:10 with pyrogen free water and heat inactivated for 10 min. at 75 °C. 50 μl of the pretreated samples were added to 50 μl of solution A and incubated for 30 min. at 37 °C. Thereafter, 100 μl of solution B diluted with solution C (1:2) were added and further incubated for 3 min at 37 °C. The reaction was then stopped by adding 200 μl of solution D. The changes in the extinction coefficient were measured spectrophotometrically at a wavelength of 405 nm (SLT Co., Salzburg, Austria). The relative units per ml (EU/ml) of endotoxin activity present in the unknown samples were determined by comparison with the standard curve generated by dilution of EC5-standard (Pyroquant Co., Walldorf, Germany). The lower and upper detection limits were 0.015 EU/ml and 1.5 EU/ml, respectively. The intra- and inter-assay variation coefficients of 30 determinations were below 8% as routinely determined by concomitant testing of samples containing high and low concentrations of endotoxin.

Endotoxin neutralizing capacity (ENC) was quantified after loading plasma with exogenous endotoxin and determining the endotoxin recovery. In short, 20 μl (20 EU) of standard endotoxin NP2 (derived from Salmonella abortus equi; Pyroquant Co., Stadt, Land), were added to 180 μl of plasma and incubated for 60 min at 24 °C. The endotoxin recovery was determined after dilution with isotonic NaCl, 1:10, by the LAL test as previously described but without further inactivation. The incubation time between lysate and sample was reduced to 20 min. and standard curves were established in isotonic NaCl instead of plasma. Inter- and intra-assay variation coefficients were below 6.5% as checked for high and low endotoxin determinations in 30 different samples. Due to the method to measure ENC, it is important to note that high levels of recovered endotoxin in the limulus test indicate a decrease of ENC.

C-reactive protein (CRP) was measured by a Behring nephelometer II (Behring Co., Marburg, Germany). In brief, polystyrene particles coated with antibodies against CRP were mixed with plasma samples. Agglutination of the mixture was measured by intensity changes of the scattered light in the nephelometer. The CRP concentration in unknown samples was calculated in comparison with standard curves generated by dilution of a known concentration. Plasma levels of interleukin-6 (IL-6) were measured by semiautomatic chemiluminescence-based ELISA (IMMULITE, DPC Bierman, Bad Nauheim, Germany) according to the manufacturer's recommendation. TNF-α, Myeloid-related protein (MRP-8, MRP-14), and the heterocomplex of both single proteins were measured by specific ELISA (Biotest, Bad Nauheim, Germany). Also, we measured the granulocytes in the peritoneal fluid.

Statistical Analysis

Mean values, ranges and standard deviation are given. The Mann-Whitney U-test was utilized to determine differences among groups at various time points. Statistical analysis was performed by comparing the area under the curve (AUC) using the Mann-Whitney U-test. $p<0.05$ was accepted as statistically significant. All statistics were carried out using the statistical SPSS for Windows 12 software (SPSS Inc., USA).

Results

When comparing the "Area under the curve" of the inflammatory mediators in CPL with the mediators of the Non-CPL group from patients with an equivalent Apache-II-score, a significant difference could not be established for one of these parameters. Also no difference could be established for the clinical outcome (hospitalization, duration of intensive care and morbidity, $p> 0.05$).

Overall mortality in this trial was 4 % (Table 1). 2 patients who died suffered from preoperative multiorgan failure due to existing comorbidity. The re-operation rate was 0% for the Non-CPL-group and 8% for CPL. Median duration time of postoperative CPL was 4 days. In all patients, the volume of CPL lavage ranged between 8 and 24 liters per day in diffuse 4-quadrant peritonitis. Failure of the irrigation system due to catheter occlusion occurred in 9% of all patients.

Analysis of clinical data gave an indication that postoperative complications and mortality could correlate with co-morbidity and patient's age. Two patients, both over 60 years old, died in the postoperative period. Furthermore, they suffered from congestive heart failure as well as respiratory insufficiency corresponding to an Apache-II Score > 11 (Table 1).

Mediators of inflammatory response evaluated in this trial (endotoxin-, TNF-α-, IL-6-, CRP-, MRP-plasma levels and granulocytes of the peritoneal fluid) where correlated with the clinical outcome. In CPL patients with an uneventful postoperative course the number of granulocytes in peritoneal effluate decreased during treatment (Fig. 1A). In contrast, granulocyte count increased in patients with persisting peritonitis (n = 4).

We further investigated whether other postoperative complications may have influenced the granulocyte count and found that patients with postoperative pneumonia had a prolonged higher granulocyte count compared to those with an uncomplicated course (data not shown).

As expected, CRP levels differed in patients with an uncomplicated course compared to those with persisting peritonitis. Comparing the course of CRP and granulocytes, the latter showed a faster response after surgery and development of other complications. Therefore, the granulocyte count in peritoneal fluid may be used as an indicator of peritoneal inflammation and a signal-parameter to reduce the amount of postoperative lavage.

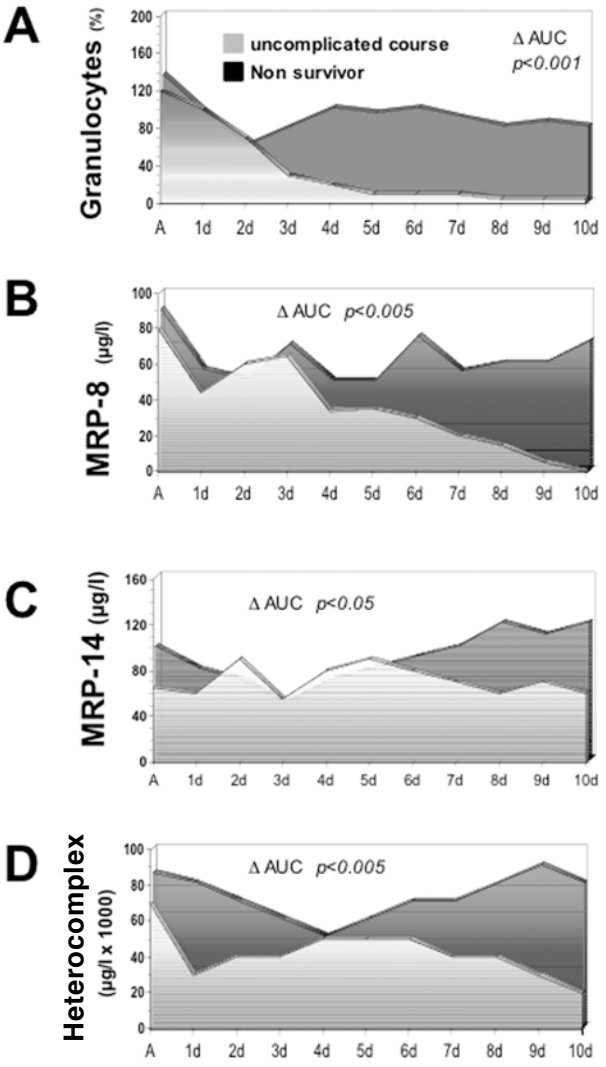

Fig. 1. Time course of granulocytes in peritoneal exudate and plasma concentration of various acute phase proteins during CPL in uncomplicated postoperative courses (n = 21) or with persisting peritonitis (n = 4)
The ordinate gives the median levels of granulocyte counts in peritoneal exudate (plate A), MRP-8 (plate B), MRP-14 (plate C), and heterocomplex, a stochiometric complex of MRP-8 and MRP-14 (plate D). The abscissa shows the points of exudate and blood sampling. A = on admission, 1d - 10d = corresponding postoperative days. Statistical analysis was performed by comparing the area under the curve (AUC) using the Mann-Whitney U-test.

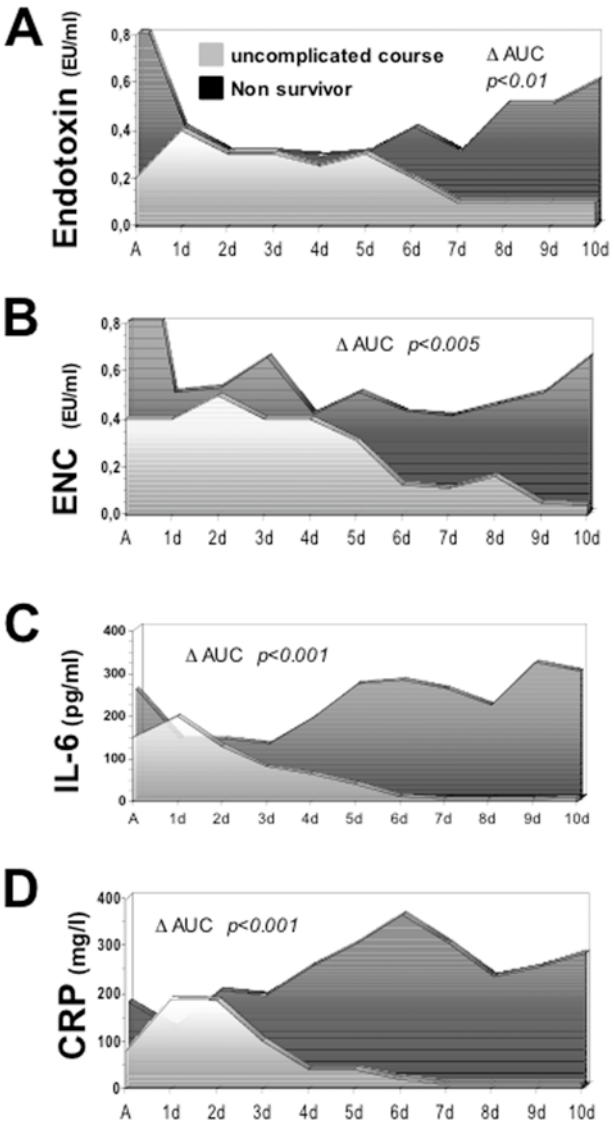

Fig. 2. Release of pro-inflammatory mediators in plasma during CPL in uncomplicated postoperative courses (n = 21) or with persisting peritonitis (n = 4)
The ordinate gives the median levels of endotoxin (plate A), endotoxin neutralizing capacity = ENC (plate B), interleukin–6 = IL-6 (plate C), and C-reactive protein = CRP (plate D). The abscissa shows the points of blood sampling. A = admission, 1d-10 d = corresponding postoperative days. Statistical analysis was performed by comparing the area under the curve (AUC) using the Mann-Whitney U-test.

To evaluate a possible predictive value regarding the clinical outcome of other inflammation markers, levels of endotoxin, IL-6, TNF-α, MRP-8, MRP-14 and the heterocomplex of MRP-8/-14 in 100 patients with diffuse peritonitis were determined.

The inflammatory markers in patients with preoperative diffuse peritonitis with an uncomplicated course (n = 46) compared to those with persisting peritonitis (n = 4) in CPL are shown in Figures 1 and 2. It appeared that patients with persisting peritonitis showed higher levels of MRP-8, MRP-14 and the heterocomplex (Fig. 1) as well as endotoxin, endotoxin neutralizing capacity (ENC), IL-6, and CRP (Fig. 2) when compared to patients with an uneventful postoperative course. No differences among groups were detectable for TNF-α. As expected, the duration of the peritonitis had a negative impact on the amount of the released mediators. Intraoperative evaluation of the state of peritonitis (removal of fibrin clots as a marker of the duration of peritonitis) and correlation of the latter with the amount of mediator release suggested, that mediator plasma levels may be impacted by the duration of the inflammation process. ENC appeared to be a more sensitive predictor than endotoxin. The best predictive value was reached for the MRP-8/-14

heterocomplex. Endotoxin, IL-6 and CRP showed higher levels in patients who died in the postoperative course. The TNF-α plasma levels did not change during our observation time (data not shown).

Discussion

Endotoxin is known to be a trigger of the acute phase response and is often related to infectious complications [5, 7, 9, 17]. In patients undergoing cardiac surgery we demonstrated that subjects developing infections in the postoperative course revealed significantly higher endotoxin levels than patients with an uneventful postoperative course [6]. It is widely accepted that therapeutical approaches in sepsis should aim to remove endotoxin, bacteria, blood clots, and fibrin deposits [17]. In peritonitis CPL is one therapeutical concept in postoperative treatment to continuously remove those components from the peritoneal cavity. However, our data revealed both, no significant impact for CPL neither on the clinical outcome nor on the course of inflammatory markers.

Since fibrin deposition, blood clots, and dead tissue crucially contribute to abscess formation and generation of peritonitis in the postoperative course, sanitation of the infected focus, intraoperative lavage, and debridement are standard surgical procedures [15]. However, for longer-lasting courses of this medical condition, further therapeutic approaches are necessary. One modality is CPL besides others as open package or repeated abdominal irrigation in the operating room within standardized intervals. Another advantage of this therapeutic modality is that changes in both the appearance and the composition of the drained fluid help to make early decisions for a re-laparotomy. Based on our own experience, CPL represents an uncomplicated and appropriate treatment modality [8]. Our own further observation communicated here, confirmed this with catheter occlusion as the only major complication. However, a faster decrease of inflammatory markers could not be achieved with this method.

As expected, young people with diffuse peritonitis were capable of coping with this illness better than older subjects with chronic medical problems who frequently developed multiple organ dysfunction resulting in poor clinical outcome. Comorbidity therefore seems to be a major confounding variable for any of the surgical approaches mentioned.

In summary, this pilot study revealed that granulocyte count and a broad spectrum of pro-inflammatory markers (e.g. endotoxin, IL-6, CRP, MRP-8/14) are suitable for the monitoring of peritonitis. However, for the practical use in the clinical setting our findings clearly favor the granulocyte count. It can be determined within minutes, its analysis is cheap and available in most hospitals.

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