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Local serum application: restoration of sufficient host defense in human peritonitis

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Abstract. Intra-abdominal host defense in human peritonitis is hampered by a severe dysfunction of phagocytosis due to an almost complete breakdown of bacteria opsonization. This defect relates to some opsonin consumption, but mainly to proteolytic and oxidative opsonin destruction. To restore and protect intact opsonins we have developed a clinical approach of intra-operative peritoneal serum application. In a prospective, controlled, and randomized study of 30 patients with generalized peritonitis we have investigated the impact of this adjuvant therapy on biochemical parameters and clinical features. Serum application induced a rise in opsonin concentration and, even more pronounced, opsonin function ($P<0{\cdot}01$) of several hours' duration, leading to a distinct improvement of bacteria elimination. In addition, α_1-proteinase inhibitor (α_1-P)I levels were significantly increased after 1 h ($P<0{\cdot}05$) in the treatment group.

The follow-up by APACHE II scoring indicated an improvement in the therapy group over the whole observation period of 14 days. Lethality in the therapy group was 33% compared to 53% in controls. These results indicate that the intra-operative restoration of physiologic intra-abdominal milieu can improve bacteria opsonization and elimination, thus contributing to a favourable clinical course in abdominal sepsis.

Keywords. Host defense, opsonins, opsonization, peritonitis, proteolysis.

Introduction

In treating abdominal sepsis the surgical eradication of the source of peritonitis is the crucial prerequisite for a favourable outcome [1]. At the end of the surgical procedure, however, large quantities of bacteria remain in the abdominal cavity in spite of thorough mechanical cleansing and lavage [2]. After therapeutic abdominal lavage procedures some part of the rinse solution is inevitably left behind. Such fluid has been proven to further hamper bacterial elimination probably because it dilutes the local defense components [3]. Thus, in the postoperative course the result of the competition between bacterial growth and bacteria elimination by physiological defense systems and therapeutic manoeuvers determines the patient's situation. Persisting abdominal infection in this situation leads to immunosuppression, endotoxinaemia and septic organ failure causing a high mortality [4,5]. Just recently, we could demonstrate pronounced pathological changes of the local intra-abdominal setting in abdominal infection resulting in a severe impairment of the local defense capacity [6]. Large quantities of neutrophils undergo extensive stimulation by complement split products, cytokines and bacteria with a consecutive drastic release of both lysosomal proteinases and oxygen metabolites. In purulent peritonitis exudates proteinase inhibitor consumption became obvious allowing proteolytic as well as oxidative destruction of functional proteins, e.g. proteinase inhibitors, complement components and immunoglobulins. Thus bacteria opsonization by complement and immunoglobulin components, a main prerequisite for sufficient phagocytosis, was almost abolished in such exudates, although the numerous phagocytes were highly prestimulated and intact regarding particle uptake and metabolic activities [6,7,8]. In order to restore a physiologic assembly of the intra-abdominal humoral defense components three main aspects have to be taken into account:

1 Supplementation of intact opsonins (complement components and immunoglobulins).
2 Application of proteinase inhibitors to prevent further proteolytic degradation.
3 Supply of radical scavengers or oxidizable substrates to detoxify oxygen metabolites and thus protect functional proteins.

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Table 1. The Mannheimer Peritonitis Index

Risk factors	Loading (if present)
Age over 50 years	5
Female sex	5
Organ failure	7
Non-related malignancy	4
Pre-operative peritonitis (> 24 h)	4
Primary focus not colon	4
Diffuse generalized peritonitis	6
Exudate	
clear	0
cloudy-purulent	6
fecal	12

To meet all these requirements and coincidentally develop an approach ready for clinical application we chose the local intra-abdominal application of normal serum. Thereby the ideally balanced composition of humoral defense systems, as developed by evolution itself, was implanted in the abdominal environment. The impact of this therapeutic approach for human abdominal sepsis on the efficiacy of local host defense parameters was evaluated.

Patients and methods

Thirty consecutive patients with abdominal sepsis were enrolled into this prospective, controlled, and randomized study. The study protocol had been approved by the local ethical commission. Entrance criteria were: diffuse peritonitis (purulent exudate in more than one quadrant); leukocyte count in exudate $> 3000\ \mu l^{-1}$; surgical eradication of the source of peritonitis possible (e.g. not pancreatitis); no primary peritonitis (infected ascites); age over 18 years. After intra-operative diagnosis of a diffuse peritonitis, patients qualifying for the study on basis of the mentioned criteria were randomized into two groups. Surgical treatment followed standard procedures [9] including identical antibiotic regimens. In patients on risk for persistent peritonitis scheduled relaparotomies were performed every other day until sanitation of the abdominal cavity was obtained. In all cases an intra-operative abdominal lavage was performed with 10 l of Ringer's solution. In the therapy group one unit (about 300 ml) of blood-group compatible normal donor serum (fresh frozen serum supplied by the blood bank) was then applied intra-abdominally to the patient. Testing and safety procedures for serum were the same as for fresh frozen plasma. Serum application was preferred (instead plasma) to avoid fibrin deposition. In control patients no sham therapy was added, because intra-abdominal application of inert fluids is known to deteriorate bacterial elimination [3].

Patient classification

By the time of the first operation scoring of severity was performed with the Mannheimer Peritonitis Index [10,11] (see Table 1) and the APACHE II system [12,13,14]. A follow-up was performed with the APACHE II on days 3, 7, 10 and 14, as suggested by the Surgical Infection Society [15].

Sampling procedures

Abdominal exudate was drawn at the beginning and the end of the peritonitis operation and drainage effluate was pooled at 1, 2 and 8 h postoperatively. These time intervals were chosen according to pilot studies to best follow the opsonin kinetics. Blood samples were drawn simultaneously and processed to serum and EDTA-plasma. Aliquots of the exudates were centrifugated at $2000 \times g$ for 10 min and stored at -70 C.

Microbiology

Exudate samples were incubated in aerobe and unaerobe media (culture bottles Bactec, Becton Dickinson). At the same time culture plates (blood agar and McConkey agar) were inocculated with crude exudate and exudate dilution 1:100. Processing and analysis followed microbiological standard procedures. Results are given as colony forming units (CFU) and relative CFU, that is CFU in percent of initial concentration.

Protein concentration

To allow for precise determination of the low protein concentrations in postoperative exudates a sensitive assay (Protein Micro Determination, Sigma) was employed according to the manufacturer's instruction. The serum standard was 7,1 g 100 ml^{-1}.

Concentration of opsonins IgG and complement C3, and of α_1-proteinase inhibitor (α_1PI)

Immunological quantification of all three proteins was performed by radial immunodiffusion on standardized (NOR) plates (Behringwerke, Marburg, Germany). For exact measurement a reading projector was employed. C3 plates contained C3c antibody thus measuring whole C3 and C3c containing fragments. To prevent complement activation all tests were performed in EDTA-exudates. The plasma standard was 79·9 mg 100 ml^{-1}. IgG plates contained polyclonal antihuman IgG Gamma antibody. The serum standard was 11·3 g l^{-1}. For the α_1PI concentration the serum standard was 229 mg 100 ml^{-1}.

α_1PI activity

Alpha$_1$ PI function was determined as trypsin inhibition employing a specific chromogenic substrate for trypsin ($\alpha_1$antitrypsin test kit, Boehringer Mannheim).

Chemiluminescence assay for opsonic activity

Opsonic activity was determined using a specific modification of a chemiluminescence assay [16].

Table 2. Individual patient classification

No.	Age	Sex	Peritonitis origin	Peritonitis exudate	Operation	Primary surg.succ.	Survival
A serum application (therapy group)							
1	87	f	perf.ulcer	fi	simple suture	y	y
2	76	f	perf.appendix	fi	appendectomy	y	y
3	78	f	sigma ca	fe	Hartmann proc.	n	n
4	88	m	polypectomy	b	simple suture	y	n
5	63	f	gastric lymphoma	fi	gastrectomy	y	n
6	81	f	gastric perf.	p	simple suture	y	y
7	78	m	gastric perf.	fi	B I-resection	y	y
8	78	f	gastric perf.	fi	simple suture	y	y
9	39	f	endometriosis colonperf.	fe	Hartmann proc.	y	y
10	59	m	colonperf.	fe	resection	n	n
11	50	f	perf.ulcer	fi/p	B I-resection	n	n
12	89	m	rectum-ca	p/fe	Hartmann proc.	y	n
13	83	f	sigma ca	p	resection	n	n
14	48	f	Meckel's div.	p	ileum resection	n	n
15	69	f	diverticulitis	fe	Hartmann proc.	y	y
B no serum application (control group)							
1	74	m	post gastrectomy	fi/b	suture, drain.	n	n
2	69	f	colon fistula	fi/p	a.p., excision	n	n
3	84	f	colon necrosis	fi	resection	y	y
4	56	f	intest.leakage	p	suture	n	y
5	93	f	sigmaperf.	fe	resection	y	n
6	61	f	intest.leakage	fi/p	resection	y	y
7	75	f	mesenteric ischaemia	fi/p	resection	y	y
8	71	f	colonperf.	p	Hartmann proc.	y	y
9	69	m	colon ca	p	resection	y	y
10	74	f	Hartmann necrosis	p	resection	y	y
11	66	m	colon ca	fe	resection	n	n
12	75	f	gastric perf.	p	suture	n	n
13	61	f	colonperf.	fe	Hartmann proc.	y	y
14	64	f	diverticulitis	fe	Hartmann proc.	y	y
15	51	m	gastric perf.	p	suture	y	y

fe = fecal; fi = fibrinous; b = bile; p = purulent; primary surg.succ. = successful surgical sanitation on first operation; y = yes; n = no.

Briefly, zymosan A was pre-opsonized by incubation with normal serum, patient's serum or patient's exudate for 15 min at 37 C respectively. The final assay solution contained 0·05 ml diluted EDTA blood from healthy donors (1:15 in phosphate-buffered saline (PBS)), 0·8 ml Veronal buffer and 0·1 ml luminol solution (0·7 mM), resulting in a final blood dilution of 1:300. The reaction was started by adding 0·05 ml of pre-opsonized zymosan (20 mg ml^{-1}). Chemiluminescence was measured with the six channel Biolumat LB9505 (Laboratorium Professor Berthold, Wildbad, Germany) and the results were integrated over 30 min by means of a microcomputer (Apple IIe). Opsonic activity of patient serum or exudate was expressed as the percentage of the value obtained using normal serum (= 100%) [16].

Statistics

Statistical analysis was performed with SPSS software. Figures display mean and (double) SEM. Group comparison for continuous variables employed the Wilcoxon test for related and the Mann Whitney test for unrelated variables. Classified parameters were compared by Chi square tests.

Results

Patient characteristics

Individual patient classification is listed in Table 2 as to cause and characteristics of peritonitis, surgical procedure, success of surgical cure within one operation, and outcome. The two groups were comparable as to age, sex ratio and the underlying cause of peritonitis (see Table 3). The therapy group revealed a trend towards a higher rate of malignoma and postoperative peritonitis. Due to technical reasons operation time varied from 0·5 to 3 h. Generally it was short in simple suture and lavage operations but longer in anatomical resection.

Scoring the severity of peritonitis during the first operation with the Mannheimer Peritonitis Index and APACHE II both systems assigned the therapy group to higher scores, indicating increased risk (see Table 3). The follow-up by APACHE II revealed considerable differences between both groups especially within the

Table 3. Group classification (MPI = Mannheimer Peritonitisindex; median/range)

	Therapy group ($n = 15$)	Controls ($n = 15$)
Male : female	1:2·0	1:2·8
Age (years)	67·5/42	70·1/50
APACHE II	17/18	16/11
MPI	27·1/22	25·4/17
Malignancy (%)	53·3	33·3
Postoperative peritonitis (%)	40·0	33·3

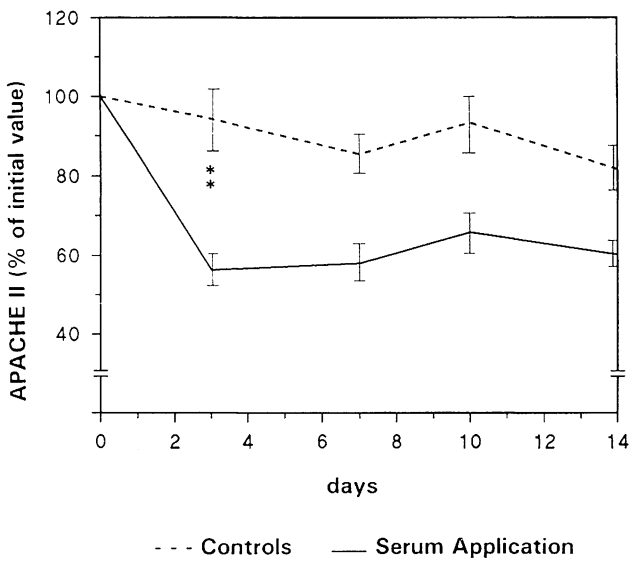

Figure 1. Follow-up of the APACHE II score on postoperative days 3, 7, 10 and 14 (in percent of initial value = 100%; difference significant with $^{**}P < 0{\cdot}01$).

Table 4. Classification of the clinical course (median/range)

	Therapy group ($n = 15$)	Controls ($n = 15$)
Re-operations required/pat.	2·5/13	3·9/11
ICU treatment (days)	20·5/53	24·1/88
Hospital stay (days)	27·3/88	29·3/88
Survival (%)	66·7	46·7

first days. In controls APACHE was fairly constant with (median/range) 16/11 intra-operatively, 15/16 on day 3 and 14/11 on day 14. In the therapy group APACHE (median/range) was 17/18 initially, dropped to 10/20 on day 3 and was 12/15 on day 14. In Fig. 1 the course of APACHE II is delined related to the initial value (= 100%); on day 3 the difference between both groups was significant ($P < 0{\cdot}01$).

Therapy group patients required less reoperations for complete sanitation (mean values 2·0 versus 3·4) (see Table 4). The ICU stay and total hospital stay

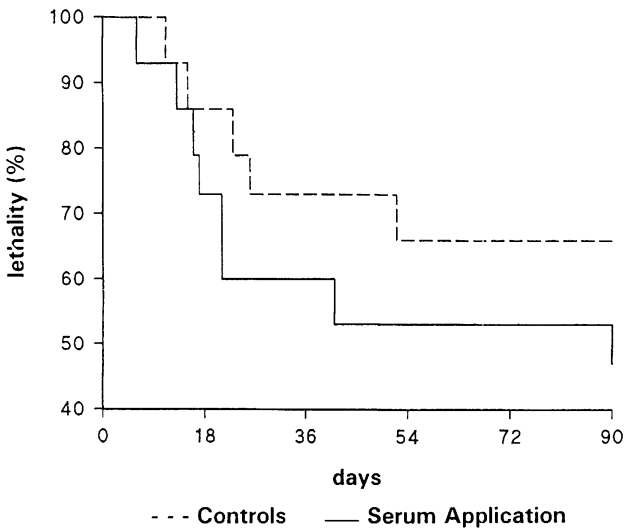

Figure 2. Survival rate according to Kaplan-Meier for peritonitis patients with and without serum application.

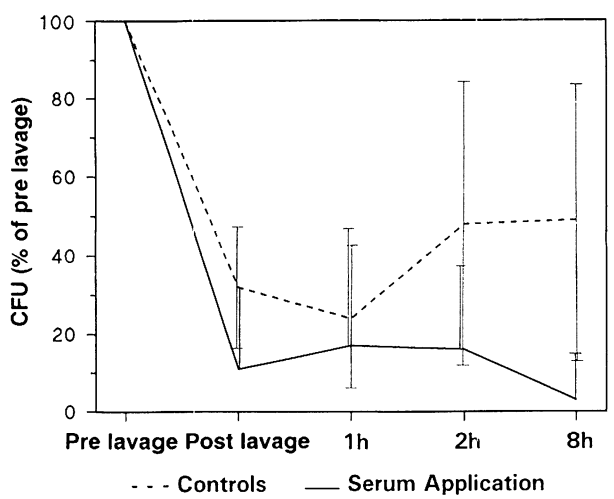

Figure 3. Impact of the serum application on colony forming units (CFU) in peritoneal exudate (% of initial exudate concentration = 100%).

were similar in both groups. All time intervals date from the onset of peritonitis. Lethality in the study group was 33% compared to 53% in controls. Due to the sample size this difference was not significant in a log rank test. The difference in survival became obvious only 2–3 weeks after operation (see Fig. 2).

Microbiological findings

The number of colony forming units (CFU) in the exudates varied considerably. The extensive abdominal lavage led only to a moderate bacteria elimination. This bacteria concentration remained rather constant in controls. Therapy group exudates revealed a slight increase after 1 h, yet, after 8 h a considerably reduced bacteria concentration was found in this group. In Fig. 3

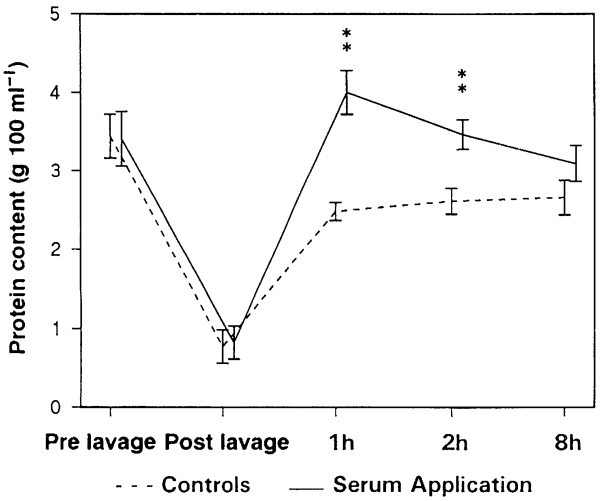

Figure 4. Impact of the serum application on the overall protein content (g dl $^{-1}$) in peritoneal exudate. Significant difference with $^{**}P < 0.01$).

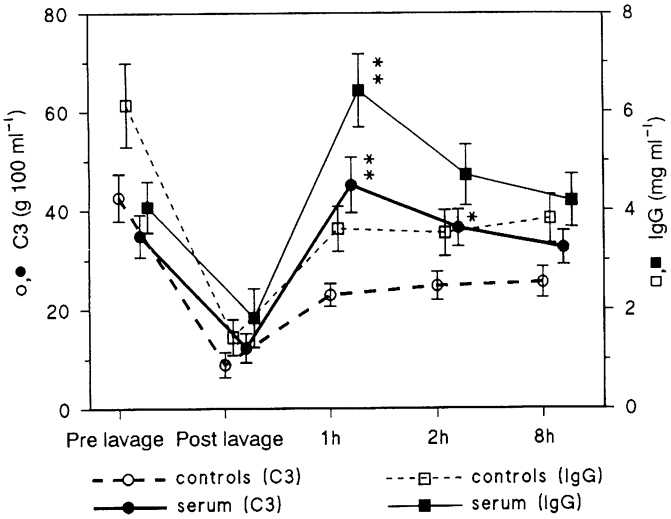

Figure 5. Impact of the serum application on opsonin concentration in peritoneal exudates (C3: —o—, IgG: —■—). Significant difference with $^{**}P < 0.01$; $^{*}P < 0.05$).

CFU concentrations are delined in relation to the initial value (= 100%). After 8 h CFU concentrations were 49% of initial in controls but only 3% of initial in serum treated patients. *E. coli* was predominant, unaerobe bacteria were present in 10% of the patients.

Protein content

The median serum protein content of the control group (median/range) was 4·3/2·2 g dl^{-1} and of the therapy group 4·0/2·4 g dl^{-1}. In the peritonitis exudate of the control group the concentration was 4·1/3·8 g dl^{-1}, in the therapy group 3·4/4·5 g dl^{-1}. In both groups protein content was reduced to a similar extent by the abdominal lavage (see Fig. 4). Serum application resulted in a pronounced increase of protein concentration after 1 and 2 h, respectively. This increase was significantly higher than in the control group ($P < 0.01$). Eight hours post lavage the protein content in both groups was approximately the same.

Complement C3

Entrance median C3 serum concentration (median/range: 52·4/24·9 mg dl^{-1}) and C3-peritonitis exudate concentration of the control group (49·2/74·2 mg dl^{-1}) exceeded insignificantly the corresponding therapy group concentrations (C3 in serum 51·9/27·7 g dl^{-1}; C3 in peritonitis exudate: 33·3/49·5 mg dl^{-1}) (see Fig. 5). Lavage reduced the intraperitoneal C3-concentration both in controls and in the therapy group. The postoperative C3-concentration in drainage effluate in controls raised up to (median/range) 21·8/32·7 mg dl^{-1} after 1 h and remained rather stable in the further course. In contrast, local serum application led to a drastic increase of C3-concentration after 1 h followed by a moderate decrease after 2 h and after 8 h, respectively. The group differences were significant up to 2 h ($P < 0.05$) post-treatment.

Immunoglobulin G

IgG serum concentrations were subnormal in all study patients. In the control group initial IgG serum concentration (median/range: 6·6/3·9 g l^{-1}) as well as IgG peritonitis exudate concentration (5·6/10·7 g l^{-1}) exceeded the corresponding concentrations found in the therapy group (IgG in serum 5·4/4·1 g dl^{-1}; IgG in peritonitis exudate 4·2/10·2 g l^{-1}). The abdominal lavage reduced IgG concentration both in controls and in the therapy group (see Fig. 5). In controls IgG concentration was moderately increased after 1 h and then remained rather constant. Local serum application, however, led to an immediate rise of the IgG concentration up to (median/range) 6·2/7·2 g l^{-1} after 1 h. After 2 h the concentration was reduced to 5·1/8·4 g l^{-1} and after 8 h to 4·2/8·2 g l^{-1}. One hour after treatment a significant ($P < 0.01$) difference between both patient groups became obvious.

Opsonic capacity

The median opsonic capacity in serum was slightly subnormal, both in control (median/range: 75·5/38%) and in therapy patients (76·6/48%). In peritonitis exudates opsonic capacity in controls (6·0/27%) was quite different from the activity in therapy-group exudates (14/50%) (see Fig. 6). The intra-operative lavage drastically reduced these values. In controls a moderate postoperative recovery was observed. In contrast, serum application led to a pronounced increase of intra-abdominal opsonic capacity after 1 h, which persisted over the whole observation period. The differences between both groups were highly significant ($P < 0.01$) throughout this post-treatment period.

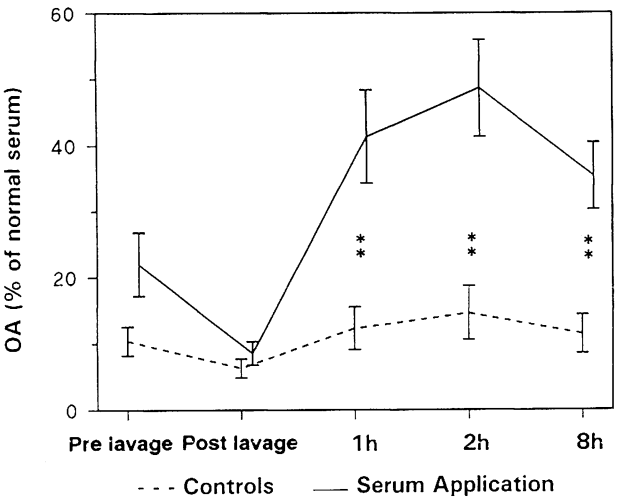

Figure 6. Impact of serum application on the opsonin activity in peritoneal exudates (OA, in percent of normal serum activity). Significant difference with $^{**}P < 0{\cdot}01$).

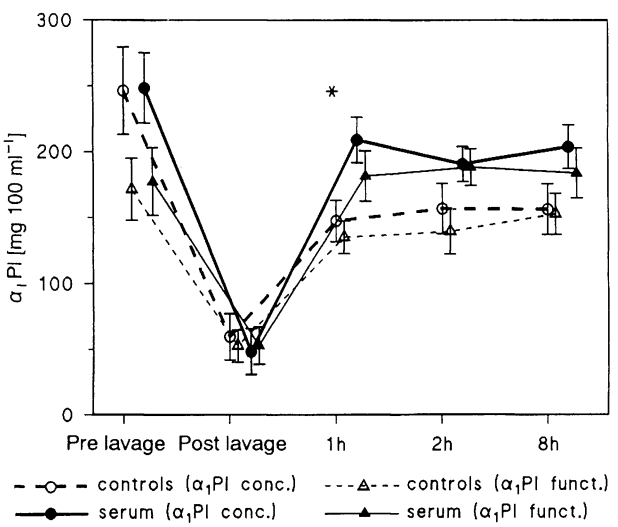

Figure 7. Impact of serum application on the α_1-PI concentration (—o—) and α_1PI function (—■—) in peritoneal exudate. Significant difference with $^{*}P < 0{\cdot}05$).

α_1-Proteinase inhibitor

Median serum concentrations of α_1PI were enhanced to the upper limit of normal in all study patients (controls: (median/range) 243/198 mg dl^{-1}; therapy group: 279/172 mg dl^{-1}). In the exudates both groups revealed a similar peri-operative pattern (260/449 mg dl^{-1} in controls and 283/345 mg dl^{-1} in the therapy group) (see Fig. 7). By the end of the operation the concentration declined. The serum application provoked a distinct rise of the α_1PI concentration whereas in controls only a moderate increase was noticed. In the further course controls and therapy group showed parallel though not identical concentration patterns with significant differences only 1 h after serum application ($P < 0{\cdot}05$). α_1PI function in peritonitis exudates revealed a similar course, but about 30% of the immunologically detected α_1PI was inactive in both patient groups (see Fig. 7).

Discussion

The first hours and days after operative treatment of peritonitis essentially determine the further course of the disease. Increase of oxygenation and haemodynamical stabilization indicate a favourable development, progressing multiorgan dysfunction characterizes a persistance of septic problems. A definite failure to eliminate the bacteria from the abdominal cavity leads to abscess formation or recurrent abdominal sepsis. Even a delay in bacteria reduction is accompanied by prolonged endotoxinaemia, leading to immunosuppression with high risk for the development of septic organ failure [4,5,17]. A specific clinical follow-up of intra-abdominal inflammation and infection in the early peri-postoperative hours of peritonitis has not been presented so far. Thus, our data provide for the first time detailed information about the impact of the operative treatment on microbiological and biochemical parameters involved in this disease and substantiate a novel approach in treating peritonitis patients.

Postoperative course without serum

Our data give striking evidence of the great amount of bacteria remaining in the peritoneal cavity at the end of a presumably effective operation. Similar results from animal studies have been published by Edmiston *et al.* [2] indicating that a major part of bacteria adhere to mesothel and fibrin. Yet, systematical quantitative bacteriological controls of the intra-operative lavage procedure have not been published up to now in the relevant literature [18].

According to our results the lavage procedure lead to a more or less pronounced reduction of all proteins. The rather wide variation is probably due to the interval between lavage and the end of the operation (when the 'post lavage samples' were drawn), rather than to a different efficacy of the lavage itself.

Although in the 'spontaneous' course (without serum application) a fast, moderate influx of serum proteins like IgG and C3 could be observed, the increase of activity of the opsonins IgG and C3 was very limited. The distinct divergence between opsonin concentration and function persisted, indicating rapid inactivation of the circulation-derived proteins in the peritoneal cavity.

Impact of the local serum application on the intra-abdominal infection

The local application of normal serum abruptly, though short-termed, created a 'physiological milieu' in the abdominal cavity, providing the treated patients with a complete and intact humoral and antiproteoly-

tic defense system. But obviously the applied serum underwent substantial diminution by means of resorption and exudation already during the first hours after intraperitoneal administration.

We could demonstrate a trend towards an improvement of bacteria elimination in the therapy group, which became especially obvious after 8 h. At this time a vigorous influx of granulocytes from the circulation occurs [19,20], bringing about abundant phagocytic capacity. Thus the conclusion seems reasonable that the intra-abdominal serum application provoked a regeneration of phagcytosis by a restitution of bacteria opsonization. Interestingly, the substitution of functionally intact proteins was more striking than the mere rise of the protein concentration. Compared to the controls, therapy group opsonins revealed a three-times increased function/concentration ratio, indicating that the high content of antioxidants [21] and proteinase inhibitors [22] in the administered serum protected the opsonins from oxidative and/or proteolytic inactivation. In this respect, the restoration of α_1PI levels in the peritoneal cavity due to local serum instillation may serve also as an indicator for the supplementation of other important proteinase inhibitors (e.g. α_2-macroglobulin).

Impact of the local serum application on the clinical course

Abdominal sepsis can develop from a considerable variety of underlying diseases and thus presents as a inhomogenous and polymorph syndrome. Therefore, the impact of single therapeutic additives on the clinical course is difficult to evaluate [8,15,23]. Besides the normalization of biochemical parameters any new therapeutic approach aims at improvement of the clinical course. Such benefit, however, is hard to define. Most peritonitis and sepsis scores are not constructed for follow-up purposes [24,25]. Just recently, the complexity of peritonitis studies has been discussed in extense [15]. After thorough evaluation, scoring with the APACHE II system on days 0, 3, 7, 10 and 14 has been recommended by this group of specialists, even though some of the APACHE II parameters are subject to easy therapeutic correction and the index has originally been designed for an initial graduation only [12,13,14,26]. In this respect some modifications to improve continuous APACHE II-scoring have been proposed [27].

Compared to controls the APACHE II score in our therapy group revealed a slightly higher initial (preoperative) infection severity but a considerably more favourable further course in these patients. Persistence or increase of septic organ failure in the course of peritonitis therapy is associated with persisting or recurrent abdominal sepsis and it carries a poor prognosis [4,5]. The APACHE II difference between our two study groups as a parameter of sepsis and organ failure was especially pronounced and significant on day 3 after serum application, indicating a positive early impact of this therapy on relevant pathophysiologic features.

Both study groups were well comparable as to age, sex and underlying diseases. The higher initial APACHE II score and higher incidence of underlying malignoma in the study group indicated a higher severity of disease. Yet, these patients required slightly shorter ICU treatment and hospitalization. Lethality in the study group was 20% lower than that of controls. This difference marks a distinct positive trend, yet, due to the sample size, statistical significance is not achieved.

Lethality in abdominal sepsis is mainly caused by septic organ failure. Such organ impairment develops in the early stage or in recurrent sepsis due to inflammatory mediators (e.g. endotoxin, TNF, activated complement components) but can be compensated for a long time by means of modern intensive care treatment (e.g. technical organ substitution by ventilation, haemofiltration etc). This phenomenon is reflected by our results. The positive impact of serum application on the (sepsis and organ failure related) APACHE II score was especially pronounced in the early stage, whereas the difference in lethality became obvious only after 3 weeks.

Unvariably, the urgent and definite surgical cure of the source of peritonitis is of central importance. Our results indicate, however, that an adjuvant therapy, aligned to pathophysiological mechanisms, might essentially contribute to a reduction of the still high lethality of abdominal sepsis. Our new therapeutic approach, that is local serum application, turned out to successfully ameliorate the severe impairment of bacteria opsonization that had previously been demonstrated in detail in peritonitis exudate by our group [6]. Although in the present study a beneficial effect of local serum could be demonstrated for the crucial initial time after operation, a prolonged therapy by repeated application should be of even more beneficial efficiency and thus deserves further investigation.

Acknowledgment

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