Influence of Peritoneal Lavage on Objective Prognostic Signs in Acute Pancreatitis

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In 39 patients with severe attacks of acute pancreatitis, a longitudinal study was done with respect to the influence of peritoneal lavage on objective prognostic signs (WBC, blood-glucose, serum-calcium, hematocrit, serum-creatinine, arterial pO_2, base deficit); amylase activities in peritoneal fluid, serum, and urine; serum-hemoglobin, serum-Na, serum-K, and plasma-insulin. In addition to standard care in the ICU, half of the patients (N = 19) were randomly treated with peritoneal lavage. Peritoneal lavage did not influence overall mortality (13%), incidence of major complications (36%), or hospital stay (23 ± 7 days). None of the prognostic signs was significantly influenced by lavage. Amylase concentration in peritoneal fluid was significantly reduced in the lavaged group after 6 hours compared to 24 hours in controls. Serum and urinary amylase decreased 12 hours earlier in the lavaged group, indicating an efficiency of the lavage procedure *per se*. Still, this study did not reveal any beneficial clinical effects of peritoneal lavage in acute pancreatitis.

ACUTE PANCREATITIS is probably initiated by intrapancreatic activation of trypsinogen followed by activation of other proenzymes pathophysiologically related to different clinical manifestations of the disease.[1,2] In severe forms there is transudation into the peritoneal cavity of fluid containing large amounts of biologically active agents that are resorbed into the circulation mainly *via* the transperitoneal route. Therefore, the concept of peritoneal lavage—to prevent local and remote effects of noxious intraperitoneal agents—is highly attractive. The encouraging results from initial experimental[3,4] and uncontrolled clinical studies[5] were, however, not confirmed in a recent prospective, randomized trial from Great Britain.[6] These contradictory results may be explained by different study populations and the use of varying systems or lack of systems for grading the severity of the disease; another possible explanation is differences in the lavage technique and in the efficiency by which the peritoneal cavity is cleared.

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The primary aim of this study was not to evaluate the effects of peritoneal lavage on mortality or rate of major complications. Because of the relatively low incidence of severe acute pancreatitis and the difficulties in clinically grading the severity of the disease, such studies must be carried out on a multicenter basis in order to achieve a study population great enough for valid conclusions. The effects of peritoneal lavage on parameters other than mortality and major complications could, however, be expected to yield information on the therapeutic value of this procedure. Therefore, the aim of this prospective, randomized series from a single hospital was to study longitudinally the influence of peritoneal lavage on some selected objective prognostic factors. Additionally, the efficiency of lavage in reducing amylase levels in peritoneal fluid, blood, and urine was evaluated.

Methods

Design of the Study (Fig. 1)

During a period of 3 years, all 245 patients admitted to the Department of Surgery, University Hospital, Lund, Sweden, with clinical and laboratory signs of acute pancreatitis were candidates for the study. After a careful examination by one of the coordinators (AE or II), only those considered to suffer a moderate or severe attack were included. They were moved to the surgical intensive care unit (ICU), and a peritoneal dialysis catheter was inserted percutaneously (*vide infra*). If amylase activity was demonstrated in the peritoneal cavity, the patient was

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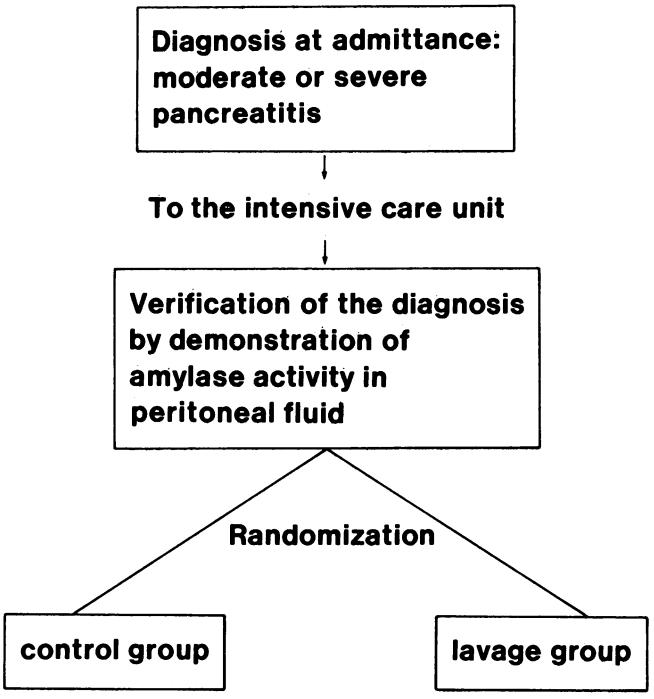

FIG. 1. Design of the study.

included in the study. After informed consent was given, the patient was randomized to the lavage or control group using the sealed envelope technique. The study was approved by the Local Ethical Committee.

Patients

Forty-three patients (18% of all patients with a diagnosis of pancreatitis admitted during the study period) met the criteria for inclusion in the study. Three control patients with mild pancreatitis as assessed after 48 hours were excluded. One patient had a misdiagnosis. He had previously undergone a Billroth II resection and a cholecystectomy and was now admitted in poor condition after a period of alcohol abuse. Three days after the diagnosis of pancreatitis and randomization into the lavage group were made, his condition deteriorated and the diagnosis was questioned because of fecal odor from the lavage fluid. A laparotomy was performed and unmasked a gangrenous small intestine. Twelve hours later the patient died. Autopsy verified a thrombosis in the superior mesenteric artery and a normal pancreas. The remaining 39 patients, with a median age of 58 years (range of 25–89 years) were equally assigned to the lavage and control groups (Table 1). There was a marked preponderance of men (30 men and 9 women), but no differences were found between the groups with respect to sex or age distribution.

In 22 patients (56%) alcohol was the dominating etiologic factor, and in ten (26%) gallstones were present. No clear-cut etiology could be demonstrated in six cases. Eleven patients (28%) had been hospitalized previously with the diagnosis of acute pancreatitis.

The retrospective analysis with the use of a modified Ranson system of the severity of attacks (Table 2) revealed that the majority of the patients had a severe attack. Furthermore, there were no differences between the lavage and control groups in this respect (Table 3). No patient had more than 2 days from onset of symptoms until treatment (± lavage) in the ICU started.

TABLE 1. *Patient Characteristics*

	Peritoneal lavage (N = 19)	Controls (N = 20)
Age (years)	58 ± 3.8*	59 ± 3.1
Male	15	15
Female	4	5
Ethyl	9	13
Gallstones	6	4
Other etiology	4	3
Diabetes	1	1
Previous acute pancreatitis	7	4

* Mean ± SEM.

TABLE 2. *Ranson Criteria Used**

At admission or diagnosis
- Age over 55 years
- WBC over 16×10^9/L
- Blood glucose over 10 mmol/L
- Serum GOT (ASAT) over 1.5 μkat/L

During the initial 48 hours
- Hematocrit fall greater than 10 percentage points
- Serum creatinine rise more than 10 percentage points
- Serum calcium level below 2 mmol/L
- Arterial pO_2 below 8 kPa (60 mmHg)
- Base deficit greater than 4 mmol/L
- Estimated fluid sequestration more than 6 L

* Units according to the SI system.

Statistical Analysis

Student's t-test for unpaired observations was used for the statistical analysis.

Management

All patients received standard intensive treatment, which included a central venous catheter, an indwelling

TABLE 3. *Patients Grouped According to Number of Ranson Criteria Used (Max 10)*

Peritoneal Lavage		Controls	
≤2	≥3	≤2	≥3
4	15	5	15

TABLE 4. *Outcome in 39 Patients with Acute Pancreatitis*

	Peritoneal Lavage	Controls
Death	4 (21%)	1 (5%)
Number of patients with major complications	8 (42%)	6 (30%)
Surgical drainage	1	4
Artificial ventilation needed (number of patients)	5	3
Gastric retention* (ml/48 hours)	1328 ± 263	1471 ± 252
Hospital stay (days)*	23.3 ± 6.6	23.3 ± 6.7

* $\bar{X}$ ± SEM.

urinary catheter, and a nasogastric tube. Intravenous crystalloid solutions and plasma were given according to the needs of the individual patient. Eight patients with hypoxemia (P_aO_2 below 8 kPa) in spite of oxygen therapy were treated by controlled ventilation. Antibiotics were used in cases with signs of infectious complications. Blood samples were drawn every 12 hours during the first week for determination of hemoglobin, hematocrit, white-cell count, serum amylase activity, serum creatinine, serum glucose, plasma insulin activity, and electrolytes, including serum calcium. Acid-base balance blood gases and serum albumin were monitored routinely. Urinary aliquots were taken concomitant with the blood samples for amylase determination. Samples were taken from the peritoneal fluid at 0, 6, 12, 18, and 24 hours and then every 12 hours for determination of amylase activity. In the controls, simple siphonage was significant to obtain the sample. The spontaneous flow of peritoneal fluid from the lavage group was collected shortly before start of the next infusion. Samples for bacterial and viral cultures were regularly taken from peritoneal fluid during the first 4 days.

An attempt to evaluate the intensity of pain was done every 12 hours by the nurse responsible for the patient. Pain was registered as absent (0), moderate (1), or severe (2). Analgetics were given accordingly. None of the patients in this series had an epidural catheter for analgesia.

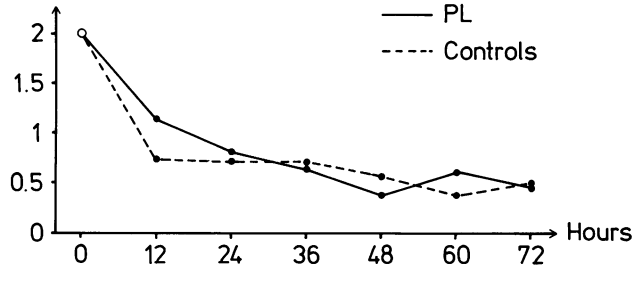

FIG. 2. Mean pain score in patients treated with (PL) or without (controls) peritoneal lavage for acute pancreatitis. Intensity of pain is graded as severe (2), moderate (1), or absent (0).

A standard peritoneal dialysis catheter was introduced in the midline below the umbilicus in local anesthesia. A small skin incision was made, and no attempts were made to visualize the peritoneum. After aspiration of ascites, samples for amylase determination were immediately collected. Free peritoneal fluid was found in the majority of patients. Irrespective of the presence of spontaneous fluid, all patients received an additional 0.5 L isotonic saline infusion into the peritoneum, and samples were again collected for determination of amylase activity. These latter determinations—and not those of the spontaneous flow—were used as reference values.

In ten randomly chosen patients from the control group, the dialysis catheter was left in place for collection of any free ascitic fluid (maximum 10 ml at every occasion), as indicated above. For peritoneal lavage, an isotonic, electrolytic solution (Peritolys®) with the addition of heparin 250 IU/L and ampicillin 125 mg/L was used. The lavage was carried out with the exchange of one liter per hour for approximately 4 days.

Clinical Course (Table 4)

The overall mortality was 13% (5/39). One 74-year-old patient in the control group died from circulatory failure after 3 days. There were four deaths in the lavage group; three in young alcoholic men and one in an elderly man with gallstones. The latter patient died after 5 days as a result of myocardial infarction. In the other three patients, who died after 2–4 weeks, respiratory failure was a contributary cause of death.

Major complications such as intra-abdominal abscesses, septicemia, severe renal and pulmonary insufficiency, and formation of pseudocysts occurred in 36% of the patients, eight in the lavage group and six in the control group. Surgical drainage procedures were needed in five patients. There were no differences between the groups in the amount of gastric retention during the first 48 hours.

Duration of hospital stay was similar in the two groups. As shown in Fig. 2, the intensity of pain did not differ between lavaged and nonlavaged patients. In this small group of patients, there were no obvious differences after a minimum observation time of 6 months concerning general condition, recurrent attacks of the disease, development of diabetes, abscesses, or pseudocysts.

Amylase Levels in Peritoneal Fluid, Serum, and Urine

The ability of lavage treatment to influence the level of amylase activity in peritoneal fluid is shown in Fig. 3. Significant decrease in amylase activity was observed already after 6 hours in the lavage group but not until 24 hours in the control group. Interestingly, serum and urinary amylase decreased 12 hours earlier in the lavage than in the control group (Fig. 3). Furthermore, lowered levels

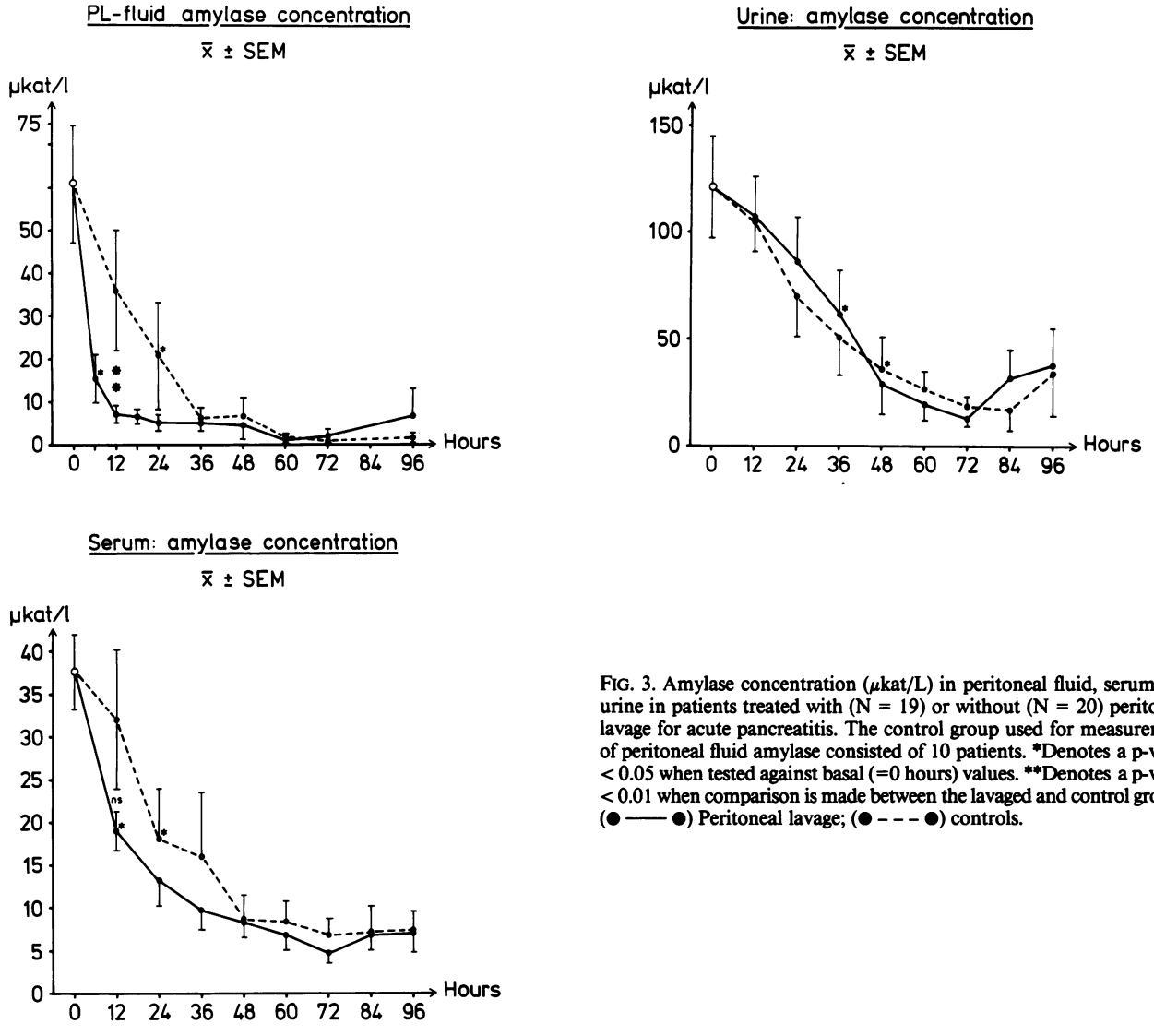

FIG. 3. Amylase concentration (μkat/L) in peritoneal fluid, serum and urine in patients treated with (N = 19) or without (N = 20) peritoneal lavage for acute pancreatitis. The control group used for measurement of peritoneal fluid amylase consisted of 10 patients. *Denotes a p-value < 0.05 when tested against basal (=0 hours) values. **Denotes a p-value < 0.01 when comparison is made between the lavaged and control groups. (● —— ●) Peritoneal lavage; (● - - - ●) controls.

of amylase were noted earlier in the peritoneal fluid than in serum or urine. These data seem to support the opinion that peritoneal lavage may accelerate the elimination of amylase.

Longitudinal Study of Prognostic Signs

During the first week, repeated determinations of white blood cell count, hematocrit, serum creatinine, and serum calcium did not demonstrate any differences between the lavage and control groups (Fig. 4). Patients in the lavage group had higher levels of blood glucose after 24 and 48 hours only (Fig. 4). Probably because of the wide range of the individual insulin values, no statistical difference was achieved although the mean values were constantly higher in the lavage group during the study period (the first week). Levels of serum hemoglobin, sodium, and potassium were not significantly different in the two groups (Table 5). Also, the serum ASAT and ALAT were similar in the two groups during the study period (LDH was not routinely measured) as were P_aO_2, base deficit, and estimated fluid sequestration. As the disease progressed, a decreasing serum hemoglobin concentration (Table 5) was observed in all patients, irrespective of lavage treatment. This corresponds to a similar decrease in hematocrit values, whereas the white blood cell counts were unaffected (Fig. 4). It is noteworthy that serum potassium was higher in the lavage group during the second half of the first week (Table 5). In no patient was any positive bacterial or viral culture found in samples from peritoneal fluid.

Discussion

In this single-center study, the value of peritoneal lavage in acute pancreatitis was studied from certain points of view. Because of the relatively low number of patients

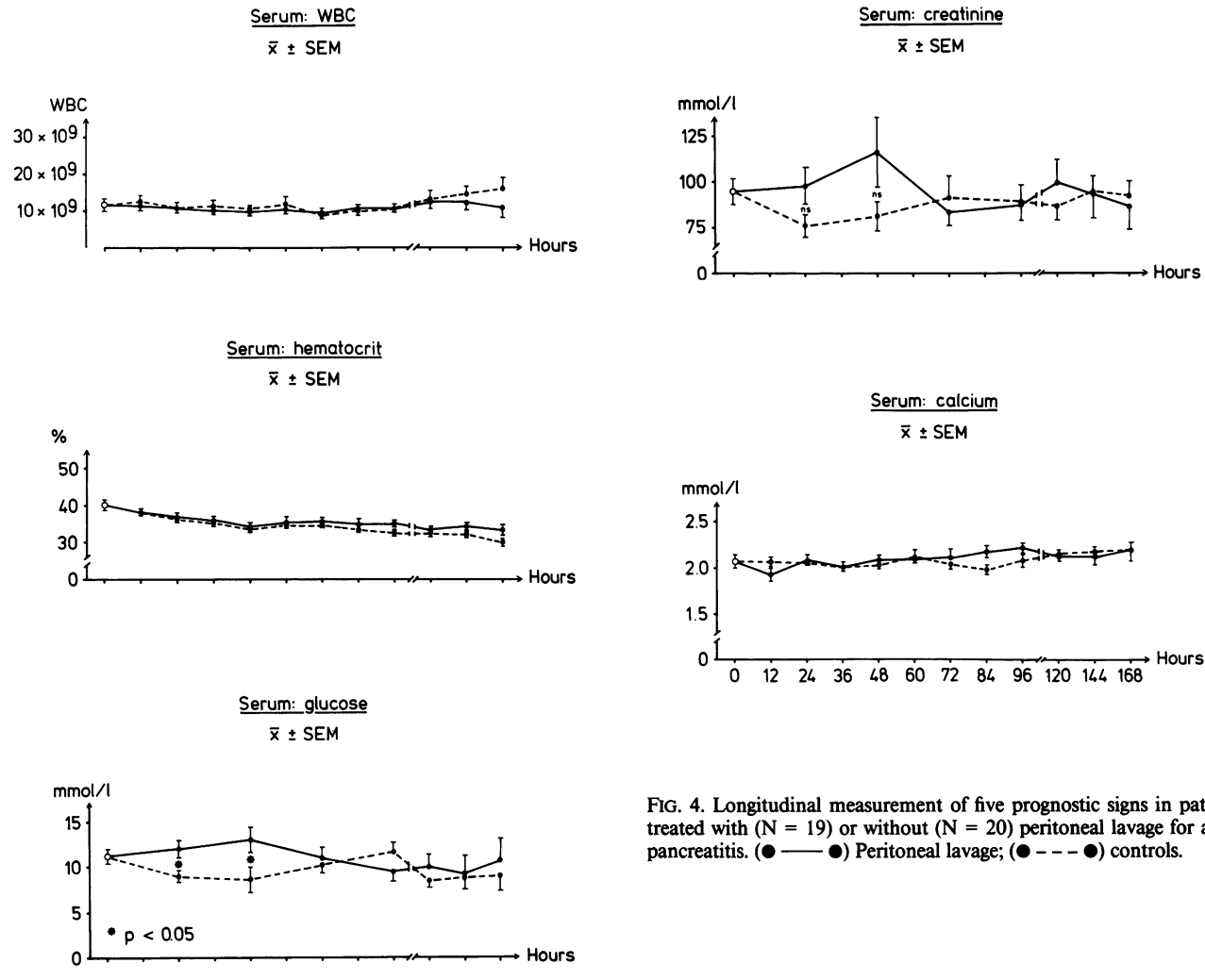

FIG. 4. Longitudinal measurement of five prognostic signs in patients treated with (N = 19) or without (N = 20) peritoneal lavage for acute pancreatitis. (● —— ●) Peritoneal lavage; (● - - - ●) controls.

expected to be included during a realistic time period, the attention was not focused on the mortality or complication rate. Instead, a careful longitudinal study was done on some accepted objective prognostic signs.[7-9] Also, systematic measurements of amylase levels in peritoneal fluid, serum, and urine were made during the first 4 days of the treatment period (± lavage). For such detailed studies, a single-center study is clearly advantageous since multicenter studies involve a great number of doctors and various biochemical assay routines in different hospitals.

In spite of the limited number of patients in this study, it supports and emphasizes the findings of the recent and bigger study by Mayer et al.,[6] who also were unable to substantiate any beneficial effects on mortality and morbidity in acute pancreatitis. The overall mortality rate in their study was 27.5% as compared to 13% in the present study, whereas the number of patients developing major complications in the two studies was the same (36%). The third prospective, randomized study hitherto published is the one by Stone and Fabian.[10] Unfortunately, the patients were allowed to change groups after randomization, and, furthermore, the lavage treatment was continued for only 24 hours. Therefore, their results—a reduction in mortality in the lavage group—must be judged with a great deal of skepticism.

On admission, all patients had a diagnostic lavage with half a liter of saline. It is, however, highly unlikely that this procedure had any therapeutic effects in our patients, especially since the saline infusate was not drawn off the peritoneal cavity. Therefore, the amount of biologically active agents initially eliminated only corresponded to the 10 ml of fluid drawn for examinations.

There were no complications clearly related to the lavage treatment. Since respiratory difficulties—at least theoretically—may be caused by the lavage treatment, however, it is noteworthy that in three of the four deaths in the lavage group respiratory failure was a prominent clinical feature. Contrary to Mayer et al.,[6] we did not recognize any technical or infectious complications of the lavage treatment. A transitory increase in blood glucose was found in the lavage group, which is easily understood. We have, however, no explanation of the high levels of

TABLE 5. *Longitudinal Values of Three Laboratory Tests during the First 7 Days*

Laboratory Test	Group	Day 0	Day 2	Day 4	Day 7
Serum-Hb (g/L)	L	141 ± 6	122 ± 5*	125 ± 6	112 ± 7*
	C	143 ± 5	121 ± 4†	110 ± 5‡	102 ± 5‡
Serum-Na (mmol/L)	L	137 ± 2	136 ± 1	138 ± 1	136 ± 2
	C	137 ± 1	135 ± 1	136 ± 1	135 ± 1
Serum-K (mmol/L)	L	3.92 ± 0.10	4.01 ± 0.14	4.50 ± 0.23*	4.46 ± 0.26*
	C	3.97 ± 0.15	3.80 ± 0.21	3.75 ± 0.22	3.78 ± 0.18

Data from days 0, 2, 4, and 7 are given ($\bar{X}$ ± SEM).
Probability levels of random difference as compared to day 0: * $p < 0.05$, † $p < 0.01$ and ‡ $p < 0.001$.
L = lavage group; C = controls.

serum potassium found in the lavage group at the end of the first week, since they were not related to the corresponding creatinine or insulin levels.

This study did not disclose any beneficial effects of lavage on the prognostic signs studied. Since the two groups were comparable and the study was carried out in a standardized way by a small number of doctors (two) and nurses (six), the findings support our present belief that peritoneal lavage as an isolated invasive treatment is insignificant in the cure of patients with moderate or severe acute pancreatitis. This opinion is further strengthened by our finding of a more rapid reduction of amylase levels in blood and urine in lavaged patients. Thus, even if we managed to approach the methodological goal of the treatment, there was no clinical success. We therefore feel that the whole concept of peritoneal lavage *per se* as a treatment for acute pancreatities should be questioned.

Our finding that peritoneal lavage affects blood and urine levels of amylase is in conformity with previous experimental studies[4] and supports the idea that the peritoneal fluid in acute pancreatitis is an integrated component in the pathophysiology of the disease. In the study by Mayer et al.,[6] lavage did not influence the blood amylase levels. Again, this discrepancy might reflect the difficulties in detecting minor changes due to the heterogeneity of multicenter studies.

In summary, the present study did not reveal any beneficial effects of peritoneal lavage in acute pancreatitis, and the findings even question the whole concept of lavage as a principal treatment of the disease.

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