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Abstract: **Aim:** To investigate the effects of oral L-glutamine, insulin and laxative on the severity of acute pancreatitis.

Materials and Methods: Forty adult male Sprague-Dawley rats were divided into 4 groups. Experimental pancreatitis was induced by ligating the main biliopancreatic duct. All groups were given standard rat pellets and tap water. In addition Group II was given 15 mg/kg/day of L-glutamine via a catheter enterally, Group III was given a 3 ml/day fleet enema via a catheter enterally, and Group IV was given 3 IU/kg/day of NPH insulin via a catheter enterally. The rats were sacrificed 96 hours after the induction of pancreatitis. Blood samples for biochemical analyses, and tissue samples from the lung and pancreas for histopathological evaluation were taken.

Findings: Significant increases in amylase levels were observed after the procedure. Five parameters in the L-glutamine group (BUN, glucose, leukocyte, pO_2 and SGOT), 5 parameters in the laxative group (Amylase, BUN, glucose, LDH and SGOT), and 2 parameters in the insulin group (BUN and SGOT) were better than those in the control group. While necrosis was observed in 3 rats in the control group, 3 in the insulin group and in 1 in the laxative group in the histopathological evaluation of pancreas tissue, no rats in the L-glutamine group exhibited necrosis. More severe pancreatitis was observed in the control and insulin groups ($p<0.05$).

Conclusion: L-glutamine, administered in enteral solutions in subjects with acute pancreatitis, will not increase the severity of pancreatitis, but will aid in meeting the energy demand of the subject. Laxative may also be employed in the removal of fecal mass during the early period of the disease.

Key Words: Acute Pancreatitis, L-glutamine, Laxative, Insulin, Pancreatic Necrosis, Prognosis

Introduction

Acute pancreatitis is a serious clinical condition triggered by several factors, among which alcohol and bile stones are the most important, and it has a varying course (1-3). No specific methods or drugs have yet been defined for the treatment of acute pancreatitis. The aims of the conventional methods may be summarized as relieving the pain and preventing development of complications, and, if they develop, treating them. Among these options, ceasing enteral nutrition and nasogastric tube decompression play an important role (3).

Until recently, it was believed that enteral feeding would increase the severity of acute pancreatitis by stimulating excretion of gastrointestinal fluids and pancreas enzymes (3,4). However, some authors led by Imrie argue that enteral nutrition in mild and moderate acute pancreatitis cases will not increase the severity of the disease, but rather may have positive effects (5-8).

The occurrence of septic complications during the course of the disease affects the prognosis adversely. It has been demonstrated that the source of pancreatic sepsis is intestinal bacteria, and that these bacteria reach the pancreas via blood circulation and/or directly (9-11). Bacterial translocation becomes easier in an ischemic and stasis environment. The strength of mucosal barriers in the intestine and the removal of stasis prevent bacterial translocations (12,13).

In this experimentally induced acute pancreatitis model, we investigated the effects of on the prognostic parameters in the blood and on tissue damage of the following: L-glutamine, which is known to have trophic effects on intestinal mucosa; insulin, which is used orally in the treatment of several autoimmune diseases; and laxative, which has been proven to reduce intestinal flora.

Materials and Methods

This study was performed in Selcuk University Experimental Medical Research Center, upon permission of Selcuk University Ethics Committee and upon approval of the Executive Board of the Research Center. The Turkish Law of Animal Rights was taken into account in this study.

Forty adult male Sprague-Dawley rats were included in the study. Their weights were 230-270 g (mean: 248 ± 14 g). The rats were divided equally into 4 groups. All the rats were fed with standard rat pellets and tap water until the eve of the experiment, and then they were fasted. They were anesthetized with 5 mg/kg Ketamine HCl. Hair on the abdominal wall was shaved off, and Betadine solution was applied, after which the abdomen was entered by a midline incision under sterile conditions. The main biliopancreatic duct was isolated and ligated with 3/0 silk from the point just before the duodenum. Abdominal layers were closed by a continuous suture using 3/0 silk. After being placed into their cages, the rats were kept under controlled humidity and temperature conditions.

The groups and their respective nutrition were as follows:

Group I: Control group; standard rat pellets and tap water were given

Group II: L-glutamine group; standard rat pellets and tap water + 15 mg/kg/day L-glutamine (L-glutamine, GNC) via a catheter enterally.

Group III: Laxative group; standard rat pellets and tap water + fleet enema (Sodium Phosphate, Fleet Enema; C.B. Fleet Company, USA) via a catheter enterally.

Group IV: Insulin group; standard rat pellets and tap water + 3 IU/kg/day insulin (Humuline N; Lilly) via a catheter enterally.

The rats were re-anesthetized with 5 mg/kg Ketamine HCl at the postoperative 96th hour. A 7 cc blood sample was taken by cardiac puncture. Of this, 1 cc was put into a heparinized injector for the study of blood gases, another 1 cc was placed into a tube containing EDTA for hematological examinations, and 5 cc was preserved for biochemical analyses. Tissue samples taken from the pancreas and the lung were preserved in formaline solution. Paraffin blocks were prepared from the tissue samples, and sectioned for microscopic assessment. These sections were stained with Hematoxylin-Eosine. Then they were examined under a light microscope, in which the presence of interstitial edema, infiltration of inflammatory cells, hemorrhagic areas and necrosis was investigated. For each finding a score of 1 point was given, and the severity of the pancreatitis was determined by adding the obtained points. The overall scores were between 0 and 4 (0: no pancreatitis, 1: mild pancreatitis, 2-3: moderate pancreatitis, and 4: severe pancreatitis).

Statistical analyses were performed according to the Kruskal-Wallis test and the Mann-Whitney U test. The significant values were checked by Tukey HSD test. Values of $p<0.05$ were considered significant.

Findings

All the rats survived the experimental period. The results of the biochemical, hematological and gasometric determinations are summarized in Table 1.

Amylase levels were found to be higher than normal. This implies that the model we applied produces successful pancreatitis. Amylase levels in the laxative group after the experiment found to be significantly lower than those in the control group ($p=0.02$). There were no significant differences among the other groups ($p>0.05$). Leukocyte counts and levels of BE, Ca^{2+} and hematocrit were similar in all the groups ($p>0.05$). Levels of BUN and SGOT were found to be significantly higher in the control group than in the other groups ($p<0.05$). However, there was no difference among the other groups ($p>0.05$). Glucose levels were significantly lower in the glutamine and laxative groups than in the control group ($p<0.05$), similar between the control and insulin groups ($p>0.05$), and significantly lower in the laxative group than in all the other groups ($p<0.05$). pO_2 levels were significantly higher in the glutamine group than in all the other groups ($p<0.05$). LDH levels were found to be lower in the laxative group than in the control group ($p<0.05$).

Five parameters in the L-glutamine group (BUN, glucose, leukocyte, pO_2 and SGOT), 5 parameters in the laxative group (amylase, BUN, glucose, LDH and SGOT), and 2 parameters in the insulin group (BUN and SGOT) were better than those in the control group. In the glutamine group, 2 parameters (SGOT and pO_2) were better than in the insulin group, 1 parameter (pO_2) was

better than in the laxative group, and 1 parameter (glucose) was worse than in the laxative group.

Severity of pancreatitis in the groups is given in Table 2 according to the histopathological evaluation of the pancreas (Figure 1,2). In the control group, 1 rat had mild pancreatitis, 6 rats had moderate pancreatitis and 3 rats had severe pancreatitis. These figures were 5 mild, 5 moderate and 0 severe in the glutamine group; 3 mild, 6 moderate and 1 severe in the laxative group; and 2 mild, 5 moderate and 3 severe in the insulin group. The severity of the pancreatitis in the glutamine and laxative groups was lower than in the control and insulin groups ($p<0.05$). The insulin group and the control group were found to be similar ($p>0.05$), as were the glutamine group and the laxative group.

Significant increases were observed in the infiltration of inflammatory cells and edema in lung tissue in the control group and insulin group (Figure 3).

Discussion

The basal energy consumption of patients increases in acute pancreatitis depending on the severity of the disease. In the event of this energy requirement not being met from exogenous sources, the patient uses endogenous energy reserves, as a result of which the body's structural elements are rapidly used up and the patient loses weight. During this period, widespread inflammation and necrosis develops in the pancreas and in peripancreatic and retroperitoneal regions. In patients under these conditions, organic functions deteriorate progressively and the mortality rate increases (13-16).

It is emphasized that supportive nutritional treatment in the early period of the disease should be started in patients with heavy pancreatitis in order to end the catabolic phase, to prevent deterioration of organic functions and to alleviate disfunctions of affected organs(15,17,18). Several clinical studies have shown that total parenteral nutrition (TPN) prevents nitrogen losses in acute pancreatitis (17,19). Currently, TPN is still accepted as a standard treatment method in patients who require nutritional treatment (7,17,19-21). However, due to its high cost and significant complications, it is proposed that enteral nutrition may be an alternative to TPN (6-8,20). Kalferentzos et al. (7), in their clinical study, fed a group of patients with acute pancreatitis via

Table 1. Biochemical, Hematological and Gasometric Parameters.

Parameters	Group I	Group II	Group III	Group IV
Amylase (IU/dl)	180±32	158±33	125±24	148±33
SGOT (IU/dl)	736±120	343±230	526±77	538±166
LDH (IU/dl)	1669±411	1271±419	1084±202	1329±432
Glucose (mg/dl)	172±8.7	151.4±22.5	115.1±12.5	165.5±23
BUN (mg/dl)	73±9	55±14	57±12	56±7
Ca^{2+} (mEq/L)	7.4±0.9	8±1	7.9±0.7	7.9±0.3
Htc. (%)	27.3±2.8	29.6±2.5	28.6±2.4	29.4±2
Leukocyte (mm^3)	14±1.5	12.5±1.7	12.5±2.1	12.5±1.7
BE mmHg	-1.46±1.36	-1.5±1.4	-1.1±1.2	-1.1±1.6
pO_2 mmHg	64±6.2	72.2±5.5	64.9±4.7	64.9±6.1

Table 2. Severity of pancreatitis in the groups.

Score (s)	Group I (n)	Group II (n)	Group III (n)	Group IV (n)
0	-	-	-	-
1	1	5	3	2
2	2	4	4	2
3	4	1	2	3
4	3	0	1	3
Total[1]	29	16	21	27

[1] Total score was obtained by multiplying the number of the subjects (n) in a group by the score (s) corresponding to it (Total = s x n).

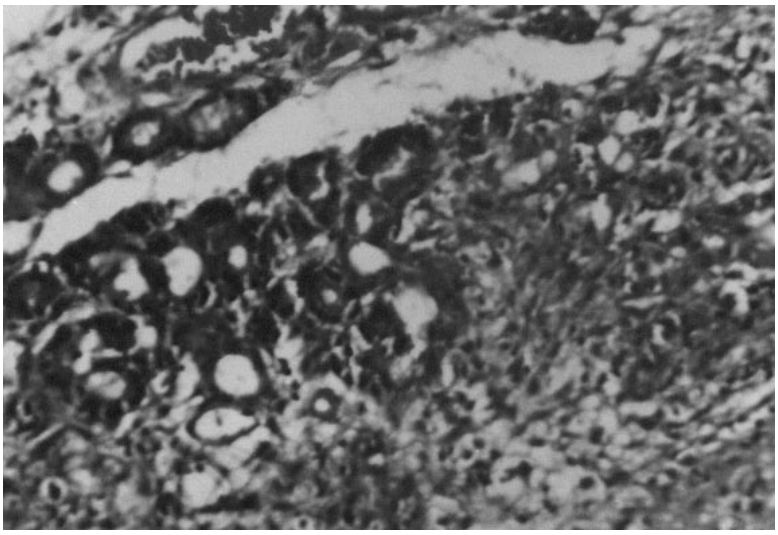

Figure 1. Microscopic view of a rat's pancreas in the control group. Necrosis can be seen (Hematoxylin-Eosin, x200).

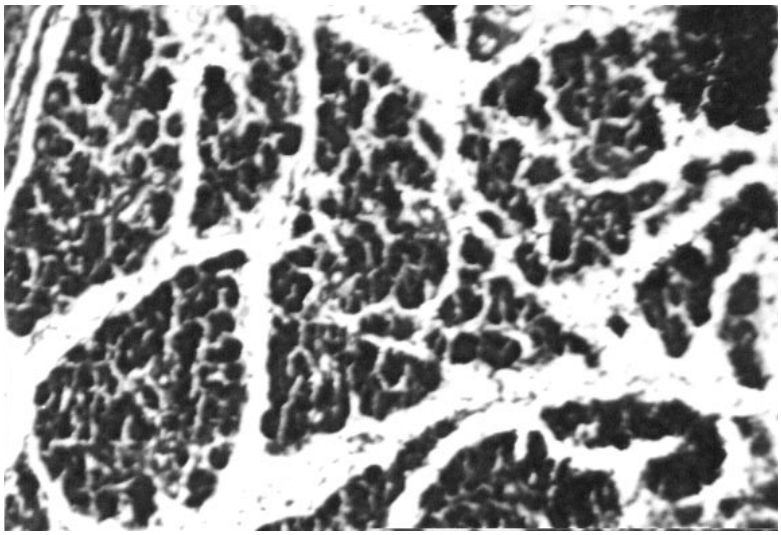

Figure 2. Microscopic view of a rat's pancreas in the L-glutamine group. Normal pancreatic tissue can be seen. (Hematoxylin-Eosin, x200)

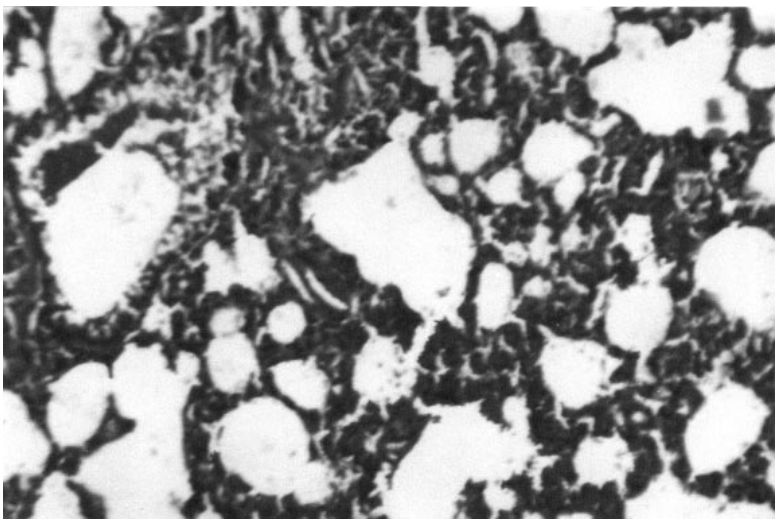

Figure 3. Lung section of a rat in the insulin group. Edema and infiltration of inflammatory cells can be seen (Hematoxylin-Eosin, x200).

a nasoduodenal tube while they applied TPN to another group of patients. They found that the rates of septic and total complications were significantly lower in the group fed enterally.

Ceasing oral feeding is an important part of the conventional treatment of patients with acute pancreatitis, because it is believed that oral feeding leads to the pancreatic enzymatic activation and increases the severity of the disease by stimulating gastrointestinal secretions and hormone release (1-3,22,23). Sahin et al. (6), in their experimental study, reported that, in rats fed enterally, some biochemical parameters were affected adversely but pancreatic tissue was in better condition in the histopathological examination.

We observed that biochemical and histopathological parameters in the L-glutamine and laxative groups were better than those in the control and insulin groups. It was shown in various studies that L-glutamine was the most important energy source for enterocytes, and that it increased protein amounts in the plasma and protein synthesis in muscular tissue (24-27). Kartal et al. (28) reported that L-glutamine prevented atrophy of the villi in defunctioned intestinal loops. Similarly, it was shown in several studies that L-glutamine increased adaptation in intestines that had been damaged by several causes, preserved the integrity and functionality of the intestines, improved intestinal immunity and prevented bacterial translocation (25,29-32). It has been reported that L-glutamine has direct trophic effects on the intestinal mucosa (33), it prevents adherence of bacteria over intestinal walls by increasing secretory IgA secretion (34), it changes the intestinal flora (35), it prevents damage of free oxygen radicals to the mucosa (36) and it induces anabolism by increasing cell hydration in the tissue (37). In our study also, the prognostic parameters in the L-glutamine group were found to be better than those in the control and insulin groups, and no necrosis was observed in any of the subjects in the L-glutamine group.

It has been reported that intestinal flora is the source of septic complications, and it has been suggested that elimination of intestinal stasis and reduction of the bacterial count will reduce septic complications in acute pancreatitis (9,10,13). The development of septic complications intensifies acute pancreatitis and deteriorates the prognosis (9,12). Sahin et al. (13) showed that laxatives reduced the colonic bacterial population and prevented bacterial translocation in acute pancreatitis. Similar results were obtained in several other studies (10,11,38). We also found in our study that prognostic parameters in the laxative group were better than in the control and insulin groups. Histopathological findings were also better in line with prognostic parameters, and pancreatic necrosis was observed in only one subject.

It has been reported that insulin may be employed by nasal, mucosal and oral ways in the treatment of several auto-immune diseases and type 1 diabetes (39-43). Several studies report that insulin used orally regulates T cell proliferation and cytokin secretion, and that it protects beta cells in the pancreas (42-45). Insulin-like growth factors (IGF-I and II) secreted from the salivary glands enhance adaptation in the damaged intestines and improve intestinal functions (46,47). Based on these findings, we investigated how oral insulin influenced the severity of acute pancreatitis. However, all the parameters in the subjects in the insulin group were unfavorable, as in the control group, and not a single positive effect was observed in this group. We think that the peptide structure of insulin, which may be digested in the stomach, may be responsible for this result. Favorable results may be obtained if insulin is allowed to reach the duodenum and the small intestine by being protected against gastric acid.

In conclusion, enteral nutrition with L-glutamine dose not worsen the severity of acute pancreatitis as generally believed; on the contrary, it enables the disease to be managed in a less severe course. Laxatives also reduce the severity of acute pancreatitis, though not to the same degree. Oral insulin had no effect on the course of acute pancreatitis in our experimental model. Based on these findings, oral administration of L-glutamine containing solutions will both meet the energy demand of the patient and diminish septic complications in acute pancreatitis.

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