EFFECTS OF SOMATOSTATIN AND OCTREOTIDE ON BACTERIAL TRANSLOCATION IN ACUTE PANCREATITIS

Nusret AKYÜREK, M.D., Hüseyin BERKEM*, M.D., Ertuğrul KAFALI**, M.D.,
Rukiye BERKEM***, M.D., Halil SARAÇOĞLU*, M.D., Mustafa KEÇELİ*, M.D.

Gazi University, Faculty of Medicine, Department of Surgery, Ankara, Turkey
Ankara Training and Research Hospital, Fourth Surgical Clinic* and Department of Microbiology, Ankara, Turkey**
Selçuk University, Faculty of Medicine, Departments of Emergency Medicine and Department of General Surgery*, Konya, Turkey**
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SUMMARY:

Background: *The majority of deaths in acute pancreatitis result from septic complications. Several medical methods are used in the treatment of acute pancreatitis, including somatostatin or octreotide.* ***Aim:*** *We aimed to investigate the possible effects of somatostatin and octreotide on bacterial translocation in an acute pancreatitis model.* ***Material and Methods:*** *Sixty Wistar-Albino type male rats were randomly assigned to four groups. Group I was the sham operated group. In group II, pancreatobiliary duct ligation(PBDL) was performed. In group III, PBDL was followed by octreotide administration (20 μg/kg). Group IV, received somatostatin (5 μg/kg) following PBDL. The rats were sacrificed 48 hours later, and blood for blood culture (1-3 ml), and tissue samples from the mesenteric lymph nodes (MLN), liver, spleen and pancreas were taken under sterile conditions in order to investigate bacterial translocation (BT).* ***Results:*** *BT was observed in the MLN of only one rat (8%) in Group I. Growth was observed in 7 (58%) of the MLN cultures and in 8 (67%) samples of the liver, spleen or pancreas cultures in Group II. In Group III, 9 (75%) of the MLN and pancreas samples, and 8 (67%) of the liver and spleen samples showed bacterial growth. All the samples of the liver, spleen and pancreas in Group IV showed growth (100%).* ***Conclusion:*** *In planning somatostatin and octreotide administration in the treatment of acute pancreatitis, it should be borne in mind that especially in necrotizing acute pancreatitis, somatostatin might cause increases in bacterial translocation.*

Key Words: *Acute Pancreatitis, Bacterial Translocation, Somatostatin, Octreotide.*

INTRODUCTION

Eighty percent of deaths in patients with acute necrotizing pancreatitis result from septic complications caused by bacterial infections (1, 2). Such complications, varying between 1 to 9 percent, are observed as infected pancreatic necrosis, infected pancreatic pseudocyst, or pancreatic abscess (3). Bacteria causing the infection are often of enteric origin (4). Bacterial translocation (BT) is the term generally used to define the passage via the gastrointestinal route of live bacteria and bacterial products into extra-intestinal areas such as mesenteric lymph nodes (MLN), spleen, kidney, or blood circulation (5, 6). It has been shown that thermal burns (7, 8), hemorrhagic shock (9-11), biliary obstruction (12,13), total parenteral nutrition (14-16), acute pancreatitis (1) or immunosuppressive chemotherapy (17) cause bacterial translocation.

Bacterial translocation results from the excess growth of intestinal bacteria, damages the immune defense of the host, and causes disruption of the intestinal mucous barrier (3, 5, 18-22).

During the last 20 years, somatostatin (SS) or octreotide (OCT) has been used in the treatment of subjects with acute pancreatitis (23, 24). SS and its analogue OCT have inhibitory effects on of the small intestine, stomach and pancreas (25). Several studies have claimed that somatostatin or octreotide increases bacterial translocation (26, 27). Our aim was to investigate the possible effects of SS and OCT on bacterial translocation in an experimental pancreatitis model.

MATERIALS AND METHODS

Study Design

The study was approved by the Local Ethics Committee of the Research Center.

Sixty Wistar type male rats, weighing between 200 and 250 g were used. The rats were kept for a period of 7 days before the experiment in standard rooms where 12 hours light and 12 hours dark conditions were maintained at 20-22°C.

The rats were divided into four equal groups, each consisting of 15 animals.

Group I (sham operated group): Portal elements were dissected by laparotomy but the pancreatic duct was not ligated. Neither SS nor OCT was given to this group.

Group II (control group): The pancreatobiliary duct was ligated and pancreatitis was induced. This group did not receive SS or OCT.

Group III (OCT group): Pancreatobiliary duct ligation was followed by OCT administration.

Group IV (SS group): Pancreatobiliary duct ligation was followed by SS.

Surgical procedures and administration of OCT or SS

The rats were anaesthetized by ketamine HCl (Ketalar®) 10 mg/kg and xylazine (Rompun® Bayer, Leverkusen, Germany) 8 mg/kg, given intramuscularly. Following skin preparation with povidon iodine and under sterile conditions, laparotomy was carried out via a midline incision. The retroduodenal surface was explored, the pancreaticobiliary duct was ligated with 4-0 vicryl close to its entrance to the duodenum, and acute pancreatitis was induced. The abdomen was closed with 2-0 silk thread in two layers. When the abdomen was closed, the first dose of somatostatin (5 μg/kg) was given by intravenous an infusion(Group IV). Later, SS was given as intravenous infusion for 48 hours at a dose of 25 μg /kg/hr. In group III, two daily doses of 20 μg /kg OCT were given subcutaneously following PBDL. The rats in all the groups were sacrificed 48 hours after the last doses, under ketamine anesthesia. Blood samples for biochemical analyses and culture (1-3 ml), MLN for BT study, and tissue samples from the liver, spleen and pancreas were taken under sterile conditions. On histopathologic examination, interstitial edema, infiltration of inflammatory cells, hemorrhagic areas, and necrosis were investigated. For each finding one point was given, and the severity of pancreatitis was determined by adding the obtained points. The overall scores were between 0-4; 0: no pancreatitis, 1: mild pancreatitis, 2-3: moderate pancreatitis, and 4: severe pancreatitis.

Lymph nodes and tissue samples taken from liver, spleen and pancreas were placed in pre-weighted tubes containing 5 ml thioglycolate medium (Merck Diagnostica, Darmstadt, Germany) for quantitative culture. The tissue samples were homogenized , and inoculated in blood agar and Eosine Methylene Blue (EMB) agar medium (Bio-Merieux, Marcy I'Etoile, France) for aerobic culture. The plaques were incubated at 37°C for a 24-48 hour period.

The blood samples were inoculated in aerobic and anaerobic BacTec (Becton-Dickinson Bactec Peds Plus/F) pediatric blood culture bottles containing 40 ml tryptic soy broth. The bottles were incubated in an automated blood culture system at 37°C, and growth was observed for 7 days. The samples with growth were stained with Gram stain, and sub-cultured in blood agar and EMB agar (Bio Mérieux Marcy I'Etoile-France) mediums for isolation of microorganisms.

Grown organisms were identified using the standard microbiologic methods and API identification (API 20 E; Bio Mérieux 69280 Marcy I'Etoile-France) tests.

Statistical Analysis

Chi-square tests under SPSS for the Windows statistical program was used in the comparison of rates in two independent groups (Pearson chi-square). We used the same test for assessing different pancreatitis levels.

RESULTS

All the rats in groups II, III, and IV were found to have developed pancreatitis at the second laparotomy 48 h after PBDL. In these groups, parenchymal inflammation/necrosis, peripancreatic fat necrosis, various degrees of bile reflux, and peritoneal fluid accumulation were observed macroscopically. Three rats in group II, two in group III, and three in group IV died before the harvesting laparotomy, these rats possibly had severe pancreatitis and were excluded from the study.

On histopathologic examination of the pancreas, no pancreatitis was observed in group I. In group II, moderate pancreatitis was observed in 5 rats and severe pancreatitis in 7 rats. In group III, 6 rats showed moderate and 6 rats showed severe pancreatitis. In group IV, 7 cases of moderate and 5 cases of severe pancreatitis were noted. Except for the sham group, the severity of pancreatitis did not differ significantly between the study groups for all comparisons ($p>0.05$).

BT was limited to a single rat (8%) in Group I. Growth was observed in 7 (58%) of MLN cultures and in 8 (67%) samples of liver, spleen and pancreas cultures in Group II. In Group III rats, 9 (75%) of MLN and pancreas samples, and 8 (67%) of liver and spleen samples showed growth. All the culture samples of MLN, liver, spleen and pancreas in Group IV showed growth (100%) (Table 1). When compared with respect to BT in MLNs, a significant increase was observed in Groups II, III and IV as compared to Group I ($p<0.05$) for all comparisons. While no difference was observed in Groups II and III with respect to MLN and distantly located BT ($p>0.05$), both MLN and distantly located BT was found to be more frequent in Group IV, compared with all others ($p<0.05$). Growth was observed in one (8 %) of the blood samples in Groups I, and II. On the other hand, 3 blood samples (25%) in Groups III and IV showed growth. The most frequent occurrence of microorganisms were Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae and Salmonella subgroup, in descending order (Table 2).

DISCUSSION

In acute pancreatitis, bacterial translocation is caused by three main factors (3, 5, 18-22). These include excess growth of intestinal bacteria, disruption of the immune defense of the host and disruption of the intestinal mucosal barrier. In acute pancreatitis, the intestinal barrier becomes disrupted, and this disruption takes place with complex mechanisms (4, 23). The reason why we have chosen this model of acute pancreatitis was to avoid manipulations which could damage carulein which might give rise to intestine motility, and which could also cause trauma, and disrupt intestine and pancreas integrity. In addition, associated paralytic ileus causes excess growth of intestinal bacteria (3). The source of pancreatic infection and sepsis in subjects with acute pancreatitis is enteric bacteria originating from the gastrointestinal system. In several types of acute pancreatitis models, BT was found to occur at the rate of 70-100% (1, 3, 33, 34) in MLNs and 33-75% in distant organs (1, 34). In another study, BT was found to be higher in earlier periods (90% at the 24th hour), and lower in later periods (40% at the 96th hour) of pancreatitis (33). In our experimental work, rats with acute pancreatitis induced by ligation of the pancreatobiliary duct, developed BT at the rate of 58% (7/12) in MLNs, and 67% (8/12) in distant organs. It is known that bacterial translocation takes place first in MLN and then in distant

Table - 1: Bacterial growth observed in the study groups (percentage are shown in parenthesis).

	Sham (n:12)	Control (n:12)	OCT (n:12)	SS (n:12)
Mesentery Lymph Node	1 (8)	7 (58)	9 (75)	12 (100)
Liver	1 (8)	7 (58)	8 (67)	12 (100)
Spleen	1 (8)	7 (58)	8 (67)	12 (100)
Pancreas	1 (8)	8 (58)	9 (75)	12 (100)
Blood	1 (8)	1 (58)	3 (25)	3 (25)

Table - 2: Distribution of microorganisms in the study groups according to locations.

	n:12	MLN	Liver	Spleen	Pancreas	Blood
	Sham					
E.coli	Control	4	4	4	5	1
	OCT	3	4	4	4	1
	SS	7	6	6	6	1
	Sham	1	1	1	1	1
P.mirabilis	Control	2	2	2	2	
	OCT	3	1	2	2	
	SS		1	1	1	2
	Sham					
K.pneumonia	Control					
	OCT					
	SS	2	2	2	2	
	Sham					
Salmonella	Control					
Subgroup I	OCT	1				1
	SS					
	Sham					
E.coli+	Control	1	1	1	1	
P.mirabilis	OCT	2	3	2	2	1
	SS	2	2	2	2	
	Sham					
P.mirabilis+	Control					
K.pneumoniae	OCT					
	SS	1	1	1	1	
	Sham					
E.coli+	Control					
Salmonella	OCT				1	
Subgroup I	SS					

locations. It is also known that the infection in acute pancreatitis is caused mostly by enteric origin bacteria. In our study, we also observed that the bacteria identified were of enteric origin (Table 3).

SS and OCT have been used frequently in the treatment of subjects with acute pancreatitis during the last twenty years (23,24). SS and its long-acting analogue OCT have inhibiting effects on the intestine, stomach, and pancreatic exocrine and endocrine secretions (25). It has been reported that SS and OCT decrease complications and mortality in acute pancreatitis (28-31). Several publications report that SS and OCT cause bacterial translocation (26, 27), but these studies were not performed on pancreatitis models. They were studies reporting the negative contributory effects of SS and OCT on bacterial translocation. Intestinal mucosal barrier is adversely affected as a result of inhibitor effects of these two substances on the secretion and motility in the gastrointestinal system. In addition, excess bacterial growth takes place (26, 27). In our study, it was determined that SS, but not OCT, caused significantly more BT ($p<0.05$).

In conclusion, when planning SS and OCT administration in the treatment of acute pancreatitis, it should be taken into account that, especially in necrotizing type acute pancreatitis, SS might cause in increase in BT.

Correspondence to: Nusret AKYÜREK, M.D.
Kaptanpaşa Sok. No: 27/5
Gaziosmanpaşa
06000 ANKARA - TÜRKİYE
Phone : 312 448 02 12
E-mail: berkemh@yahoo.com

REFERENCES

1. Runkel NSF, Moody FG, Smith GS. The role of the gut in the development of sepsis in acute pancreatitis. J Surg Research 1991; 51: 18-23.

2. Medich DS, Lee TK, Melhem MF. Pathogenesis of pancreatic sepsis. Am J Surg 1993;165: 46-52.
3. Tarpila E, Nystrom PO, Franzen L. Bacterial translocation during acute pancreatitis in rats. Eur J Surg 1993; 159: 109-113.
4. Andersson R, Wang XD. Gut barrier dysfunction in experimental acute pancreatitis. Ann Acad Med Singapore 1999; 28: 141-146.
5. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. Infect Immun1979; 23: 403-411.
6. Berg RD. Bacterial translocation from the gastrointestinal tract. Adv Exp Med Biol 1999; 473: 11-30.
7. Deitch EA, Winterton J, Berg R. Effect of starvation, malnutrition, and trauma on the gastrointestinal tract flora and bacterial translocation. Arch Surg 1987; 122: 1019-1024.
8. Deitch EA, Maejima K, Berg R. Effect of oral antibiotics and bacterial overgrowth on the translocation of the GI tract microflora in burned rats. J Trauma 1985; 25: 385-392.
9. Kale IT, Kuzu MA, MD, Berkem H, Berkem R.The presence of hemorrhagic shock increases the rate of bacterial translocation in blunt abdominal trauma. J Trauma 1998; 44: 171-174.
10. Baker JW, Deitch EA, Li M. Hemorrhagic shock induces bacterial translocation from the gut. J Trauma 1988; 28: 896-906.
11. Sori AJ, Rush BF, Lysz TW. The gut as source of sepsis after hemorrhagic shock. Am J Surg 1988; 155: 187-192.
12. Kuzu MA, Kale IT, Col C. Obstructive jaundice promotes bacterial translocation in humans. Hepatogastroenterology 1999; 46: 2159-2164.
13. Slocum MM, Sittig KM, Specian RD. Absence of intestinal bile promotes bacterial translocation. Am J Surg 1992; 58: 305-310.
14. Mainous M, Xu D, Lu Q. Oral TPN induced bacterial translocation and impaired immune defences are reversed by refeeding. Surgery 1991; 110: 277-284.
15. Deitch EA, Xu D, Naruhn MB. Elemental diet and IV-TPN-induced bacterial translocation is associated with loss of intestinal mucosal barrier function against bacteria. Ann Surg 1995; 221: 299-307.
16. Helton WS, Garcia R. Oral prostaglandin E2 prevents gut atrophy during intravenous feeding but not bacterial translocation. Arch Surg 1993; 128: 178-184.
17. Berg RD, Wommack E, Dietch EA. Immunosuppression and intestinal bacterial overgrowth synergistically promote bacterial translocation. Arch Surg 1988; 123: 1359-1364.
18. Bjorneklett A, Hoverstad T, Hovig T. Bacterial overgrowth. Scand J Gastroenterol 1985; 20: 123-132.
19. Deitch EA, Xu D, Qi L. Bacterial translocation from the gut impairs systemic immunity. Surgery 1991; 109: 269-276.
20. Marshall JC. The ecology and immunology of the gastrointestinal tract in health and critical illness. J Hosp Infection 1991; 19: 7-17.
21. Berg RD. Bacterial translocation from the gastrointestinal tract. Trends Microbiol 1995; 3: 149-154.
22. Deitch EA, Bridges W, Baker J. Hemorrhagic shock-induced bacterial translocation is reduced by xanthine oxidase inhibition or inactivation. Surgery 1988; 104: 191-198.
23. Greenberg R, Haddad R, Kashtan H. The effects of somatostatin and octreotide on experimental and human acute pancreatitis. J Lab Clin Med 2000; 135: 112-121.
24. McKay CJ, Imrie CW, Baxter JN. Somatostatin and somatostatin analogues -are they indicated in the management of acute pancreatitis?. Gut 1993; 34: 1622-1626.
25. Paran H, Klausner J, Siegal A. Effect of somatostatin analogue octreotide on experimental pancreatitis in rats. J Surg Res 1996; 62: 201-206.
26. Turkcapar AG, Ersoz S, Gur U. The effect of octreotide on bacterial translocation from the gut. An experimental study. Int Surg 1995; 80: 264-266.
27. Tocchi A, Costa G, Lepre L. The influence of somatostatin on bacterial translocation. Panminerva Med 2001; 43: 11-14.
28. Raptis SA, Ladas SD. Therapy of acute pancreatitis with somatostatin. Scand J Gastroenterol 1994; 207: 34-38.
29. Buchler MW, Binder M, Friess H. Role of somatostatin and its analogues in the treatment of acute and chronic pancreatitis. Gut 1994; 35: 15-19.
30. Andriulli A, Leandro G, Clemente R. Meta-analysis of somatostatin, octreotide and gabexate mesilate in the therapy of acute pancreatitis. Aliment Pharmacol Ther 1998; 12: 237-245.
31. Ladas SD, Raptis SA. Conservative treatment of acute pancreatitis: The use of somatostatin. Hepatogastroenterology 1992; 39: 466-469.
32. Juvonen PO, Alhava EM, Takala JA. Gut permeability in patients with acute pancreatitis. Scand J Gastroenterol 2000; 35: 14-18.
33. de Souza L, Sampietre SN, Figueiredo S. Bacterial translocation in acute pancreatitis. Experimental study in rats. Rev Hosp Clin Fac Med Sao Paulo. 1996; 51: 116-20.
34. Sahin M, Yol S, Ciftci E. Does large-bowel enema reduce septic complications in acute pancreatitis? Am J Surg. 1998; 176: 331-334.