Effects of Octreotide Acetate and *Saccharomyces Boulardii* on Bacterial Translocation in an Experimental Intestinal Loop Obstruction Model of Rats

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ALDEMİR, M., KÖKOĞLU, Ö.F., GEYİK, M.F. and BÜYÜKBAYRAM, H. *Effects of Octreotide Acetate and Saccharomyces Boulardii on Bacterial Translocation in an Experimental Intestinal Loop Obstruction Model of Rats.* Tohoku J. Exp. Med., 2002, **198** (1), 1-9 — Intestinal obstruction (IO) induces bacterial translocation (BT) due to mucosal disruption, motility dysfunction, and increased intestinal volume, leading to bacterial overgrowth. This study was conducted to investigate the effects of octreotide acetate (OA) and *Saccharomyces boulardii* (SB) on the BT and intestinal integrity in an animal model of intestinal loop obstruction (LO). Forty adult male Sprague-Dawley rats (250–300 g) were randomized into 4 groups containing 10 rats each. Complete IO was created in the distal ileum of rats by a single 3–0 silk suture (LO). Group Sham: Sham (Laparotomy only was performed in this group); group LO: LO; group OA: LO plus OA (100 µg/kg, at 0, 12 hours of obstruction); group (SB): LO plus SB (800 mg/kg/day, via orogastric and preoperative for 3 days). After 24 hours, samples of mesenteric lymph nodes (MLN), liver, spleen and blood were obtained and cultured. The terminal ileum specimens were examined histopathologically. There were no BT in group Sham, but BT was noticed totally in 31 (77.5%) cultures in group LO. This rate was reduced to 30% ($n=12$), 10% ($n=4$) in the groups OA and SB respectively. Bacterial translocations of MLN and the liver in group LO were significantly higher than those of groups OA and SB. Bacterial translocations of the both spleen and blood in group LO were significantly higher than those of groups OA and SB. The mean bacterial counts, colony-forming units per gram tissue (cfu/g), in the MLN, liver and spleen of group LO were found significantly higher than those of groups OA and SB. The mean villus height in group OA was significantly higher than that of group LO and it in the group SB significantly

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higher than those of groups LO and OA. The present experimental study has demonstrated that OA and SB may have protective effects against BT in mechanical bowel obstruction and additionally SB preserves intestinal mucosal integrity.

————— Intestinal obstruction; Bacterial translocation; Octreotide acetate; *Saccharomyces boulardii*

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Intestinal obstruction (IO) is a common disorder in surgical practice with significant morbidity and mortality. Under normal circumstances, the intestinal mucosa is a major barrier that functions to prevent bacteria colonizing the gut from invading systemic organs and tissues (Berg and Garlington 1979; Maejima et al. 1984). The passage of viable endogenous bacteria and their products across the intact intestinal mucosal barrier, disseminating to the mesenteric lymph nodes (MLN), peritoneal cavity, spleen, liver, and circulation, is defined as bacterial translocation (BT) (Akyildiz et al. 2000). BT is clinically important in such situations as hemorrhagic shock (Plaut et al. 1967; Savage et al. 1968; Baker et al. 1988), heavy burn (Maejima et al. 1984), endotoxemia (Deitch et al. 1987; Deitch 1988), trauma (Rush et al. 1988; Deitch 1989), impaired host immune defenses (Deitch et al. 1986), parenteral feeding (Alverdy et al. 1988), IO (Deitch et al. 1990; Sagar et al. 1995) and obstructive jaundice (Kuzu et al. 1999). IO induces BT due to mucosal disruption, motility dysfunction, and increased intestinal volume, leading to bacterial overgrowth (Akyildiz et al. 2000). BT induced by IO is suggested to be due to increased intestinal volume, leading to intestinal overgrowth with certain enteric microorganisms and intestinal mucosal damage (Reis et al. 1997).

The long-acting somatostatin analogue, octreotide acetate (OA), has been reported to have potent inhibitory effects on the gut, including inhibition of gastric, pancreatic, biliary, and intestinal secretions (Hurst and Modlin 1991). Somatostatin has been shown to decrease intestinal luminal volume and disten-

tion by inhibition of mucosal fluid and electrolyte secretion in an experimental model of closed loop obstruction (LO) (Mulvihill et al. 1988). *Saccharomyces boulardii* (SB) is non-pathogenic yeast, which exerts trophic effects on human and rat small intestinal mucosa (Buts et al. 1999). In this experimental study, we investigated the effects of OA and SB on BT in rats with LO.

METHODS

Animals

The Animal Ethics Committee of the Dicle University approved the study. Adult male Sprague-Dawley rats (250–300 g) were housed under constant temperature (22°C) and humidity, with 12 hours dark/light cycles and allowed tap water and rat pellets ad libitum before and after the operation.

Surgery

Forty rats were randomized into 4 groups containing 10 rats each. All rats were initially anaesthetized by intramuscularly injection of Ketamine (100 mg/kg) and xylazine (5 mg/kg). All procedures were performed under sterile conditions. The abdomen was opened through a smaller upper midline incision. The distal ileum was ligated with 3-0 silk suture 1 cm and 20 cm proximal to the ileocecal valve, obstructing the passage but not inhibiting the circulation of the vessels. Laparotomy was closed in one layer.

Treatments

Rats were divided in to 4 groups: Group Sham: Sham (Laparotomy only was performed

in this group); group LO: LO; group OA: LO plus OA (Sandostatin® ampul, Novartis, Switzerland). In this group, the animals received subcutaneous injections 1 ml of saline containing OA (100 µg/kg) at 0, 12 hours of obstruction; group 4 (SB): LO plus SB (Reflor saşe, Sanofi). In this group, the SB (800 mg/kg/day) was administered rats via orogastric before 36 hours of LO and continued for 3 days.

Sacrifice and collection of tissues

After a period of 24 hours, the animals were again anaesthetized. Samples of systemic blood, liver, spleen and MLN were taken for microbiological culture under sterile conditions. Segments of ileum were harvested for histopathologic examination. Liver and spleen and MLN were taken for microbiological culture. The animals were sacrificed by exsanguinations from the heart.

Bacterial translocation

Samples of blood were cultured aerobically using the BacTec™ Peds (Becton Dickinson, Diagnostic Instrument Systems, Sparks, MD, USA). Blood cultures were continuously monitored for 7 days. Positive cultures were plated out on appropriate media and species identified by seceptor microdilution and standard bacteriological techniques.

The mesenteric lymph nodes, spleen and right lobe of liver were removed and placed in preweighed sterile glass bottles containing sterile prerduced brain-heart infusion. The bottles were reweighed and tissue homogenates were prepared in 2 ml brain-heart infusion using sterile mortars and pestles. A portion (0.1 ml) of each of homogenates was cultured on blood agar, eosine metilen blue agar (EMB). All the plates were examined after 24 and 48 hours of incubation at 37°C. Individual colonies were identified and quantified as cfu/g.

Assessment of ileal villus heights

Following retrieval of the solid organs at

laparotomy, 3 cm segment of terminal ileum was removed. The bowel was stripped from its mesentery and each of the segments was opened along its length, rinsed in a cold solution. The specimens of terminal ileum were fixed in 10% formalin in 0.15 M phosphate buffer (pH 7.2), embedded in paraffin and then sections measuring 5 µm in thickness were cut. The specimens stained with hematoxylin and eosin and examined under the light microscope (Olympus BH-2, Tokyo). An independent pathologist who had no knowledge of the experimental groups from which the specimens were derived performed histological evaluation. Morphometric analysis was fulfilled using an eyepiece micrometer (Olympus). For each rat, 10 randomly chosen mucosal regions were traced and villus height (µm) was measured and the mean was calculated.

Statistical analysis

Biostatistical evaluation was made using analysis of Variance (one way-ANOVA) with Tukey HSD honestly significant test for post hoc multiple comparisons on an IBM-compatible personal computer using SPSS 10.0 software. A *p*-value of <0.05 was considered to be statistically significant.

RESULTS

Bacterial translocation

There was no death in any group during study. The effects of the treatments on BT are presented in Table 1. There were no BT in group Sham, but BT was noticed totally in 31 (77.5%) cultures in group LO. This rate was reduced to 30% (*n*=12), 10% (*n*=4) in the groups OA and SB respectively. The bacterial translocations in the group LO were significantly higher than those of the group Sham (*p*=0.000). The bacterial translocations of MLN and the liver in group LO were significantly higher than those of groups OA and SB (*p*<0.05 and *p*=0.001, respectively). Bacterial translocations of the both spleen and

blood in group LO were significantly higher than those of groups OA and SB ($p < 0.05$).

The predominant pathogens obtained from the MLN, liver and spleens were *Escherichia coli*, *Enterobacter cloaca* and *Klebsiella spp.* The type of bacteria most commonly obtained from the blood was *E. coli*. The average bacterial population levels of the groups are presented in Table 2. The mean cfu/g of MLN, liver and spleen in the LO were found significantly higher than those of groups OA and SB ($p = 0.000$).

Ileal villus heights

The mean villus height values of groups were shown Fig. 1. The mean ileal villus heights in the groups Sham, LO, OA and SB were 506.7 ± 17.7 , 317.4 ± 30 , 360.8 ± 27.2 and $480.5 \pm 14.1 \mu\text{m}$, respectively. Histopathologic examination of ileum specimens revealed a significant decrease in the heights of villi in groups LO and OA compared to group Sham ($p = 0.000$). However, there was no statistically difference between group SB and Sham for

mean villus height ($p > 0.05$). The mean villus height in group OA was significantly higher than that of group LO ($p = 0.001$). The mean villus height in the group SB was significantly higher than those of groups LO and OA ($p = 0.000$).

DISCUSSION

Intestinal motility, absorption, and secretion are altered after IO, but at what point the normal bacterial barrier function of the viable gut fails after IO is unclear. Deitch et al. (1990), in experimental study, reported that within 6 hours of intestinal ligation 1 cm proximal or distal to the ileocecal valve, bacteria had translocated to the mesenteric lymph nodes, and by 24 hours after IO, bacteria had spread to the liver, spleen, and blood stream. The primary role for bacteria and their products in inducing mucosal hypersecretion and alterations in intestinal blood flow is based on studies performed in both conventional and germ-free animals (Heneghan et al. 1981; Enochsson et al.

TABLE 1. The number of BT for each group

Groups	MLN (n =) ^a	Liver (n =) ^a	Spleen (n =) ^a	Blood (n =) ^a	Total BT n (%)
Group Sham	0/10	0/10	0/10	0/10	0
Group LO	9/10 ^b	8/10 ^b	7/10 ^b	7/10 ^b	31 (77.5)
Group OA	4/10 ^d	3/10 ^d	3/10 ^d	2/10 ^d	12 (30)
Group SB	2/10 ^c	1/10 ^c	1/10 ^d	0/10 ^d	4 (10)

^aPositive culture/total rat.

^b $p = 0.000$ vs. group Sham.

^c $p = 0.001$ vs. group LO.

^d $p < 0.05$ vs. group LO.

TABLE 2. The average bacterial population levels and villous heights of the groups

Groups	MLN (cfu/g) ($\times 10^4$)	Liver (cfu/g) ($\times 10^4$)	Spleen (cfu/g) ($\times 10^4$)
Group Sham	0	0	0
Group LO	180.1 ± 67.6^a	91 ± 55.2^a	33 ± 26^a
Group OA	2.4 ± 4.7	0.56 ± 1.2	0.97 ± 2
Group SB	1.4 ± 2.9	0.6 ± 1.8	0.1 ± 0.3

Data, mean $\pm$ s.d., ^a $p = 0.000$ compared with groups OA and SB.

Fig. 1. In the groups, values of mean villus height (μm).
 $p=0.000$, group sham compared with groups LO and OA.
 $p=0.000$, group SB compared with group LO.
 $p=0.001$, group OA compared with group LO.
 $p=0.000$, group SB compared with group OA.

1982). In our study, we determined that a significant increase in BT was in the MLN, liver, spleen and blood after 24 hours from intestinal LO and a significant reduction was in mean villus height in intestinal obstructed rats. Increase in this BT after LO may be due to ileal mucosal damage or disruption of the ecologic balance of the normal indigenous microflora.

The mechanisms of BT, after IO, include mechanical defenses, immunologic defenses, and the ability of the indigenous intestinal microflora to prevent colonization by exogenous pathogens or overgrowth by certain indigenous pathogens (Deitch 1988). In the small intestine, normal peristalsis prevents prolonged stasis of bacteria in close proximity to the intestinal mucosal and thereby reduces the change that any individual bacterium will have adequate time to penetrate the mucous layer and successfully adhere or attach to epithelium. Thus, peristaltic waves serve to continuously

wash bacteria through the intestinal tract. If this peristaltic clearing of bacteria is altered by mechanical obstruction, bacterial stasis will occur. Mechanical obstruction thus allows bacteria to remain in proximity to the epithelial cells for prolonged periods of time and increases their opportunity to penetrate the mucous layer and adhere directly to the epithelial mucosa (Plaut et al. 1967; Savage et al. 1968).

Under normal circumstances, the gut performs many functions, including the complex processes of digestion, selective absorption, and secretion. However, the gut contains bacteria and bacterial products that must be excluded as well as nutrients that must be absorbed. Therefore, the gut has developed a complex immune system that works in synchrony with local antibacterial barrier systems to prevent the escape of luminal contents. Although it is well recognized that intestinal motility, absorption, and secretion may be altered, it has been

recognized that the gut's immunologic and barrier functions may also fail (Ohman 1975; Roscher et al. 1988). Factors that promote the translocation of bacteria from the gastrointestinal tract in animal models include disruption of the ecologic balance of the normal indigenous microflora, resulting in bacterial overgrowth (Heneghan et al. 1981), impaired host immune defenses (Deitch et al. 1985), physical disruption of the gut mucosal barrier (Deitch et al. 1987), trauma (Deitch et al. 1989), endotoxemia (Deitch 1988), intra-abdominal abscess (Deitch et al. 1987), and shock (Plaut et al. 1967; Savage et al. 1968). In some experimental circumstances, bacteria translocating from the gut caused septicemia and death. In addition, indirect clinical evidence has accumulated indicating that the gut may be a reservoir for microorganisms causing systemic infections in man (Roscher et al. 1988; Steffen et al. 1988; Ohman 1975).

The long-acting somatostatin analogue, OA, has been reported to have potent inhibitory effects on the gut, including inhibition of gastric, pancreatic, biliary, and intestinal secretions (Hurst and Modlin 1991). Somatostatin has been shown to decrease intestinal luminal volume and distention by inhibition of mucosal fluid and electrolyte secretion in rabbits using an experimental model of closed LO (Mulvihill et al. 1988). OA has been reported to reduce intestinal transit (Veal et al. 2001). Veal et al. (2001) reported that OA had no influence on the level of BT in an experimental model of liver fibrosis. The rate of BT was significantly decreased with parenteral administration of OA to intestinal obstructed rats in our study. Positive cultures of MLN, liver, spleen and blood in group OA were significantly lower than those of group LO, but there was no statistically difference between group OA and group SB. Akyildiz et al. (2000) claimed that somatostatin analogues might have protective effects against BT in mechanical bowel obstruction. There is evidence that somatostatin or OA have a cyto-

protective role that may be important in gastric and duodenal ulceration (Mulvihill et al. 1986) and acetic acid-induced colitis in rats (Eliakim et al. 1993). However, Reis et al. (1997) determined that treatment with OA was found to be ineffective in reducing the incidence of BT, with no histopathological improvement in complete IO. In our study, mean villus height in group OA was higher than that of group LO, whereas it was lower than that of group SB. This showed that OA was not adequate on the preservation of mucosal integrity.

SB is non-pathogenic yeast, which has been used as both a preventive and therapeutic agent for the treatment of a variety of diarrheal diseases. The pharmacokinetic data demonstrate that SB reaches a steady-state concentration quickly and maintains a high stable level as long as the yeast is taken daily. Once the agent is discontinued, SB is quickly eliminated from the colon. Clinical trials studying antibiotics-associated diarrhea, nasogastric-tube alimentation diarrhea, *Clostridium difficile*-disease, acute diarrhea and chronic diarrhea in HIV-infected patients are reviewed (McFarland and Bernasconi 1993; Qamar et al. 2001). When SB was administered daily (0.8 g/kg oral) to rats, steady-state concentrations were achieved within a mean of 3 days and a constant level was maintained as long as oral dosing was continued (Blehaut et al. 1989). In our study also, SB was given orally rats in the group SB for 3 days before laparotomy.

Probiotics are nonpathogenic microorganisms that, when ingested, exert a positive influence on the health or physiology of the host. They can influence intestinal physiology either directly or indirectly through modulation of the endogenous ecosystem or immune system (Marteau et al. 2001). In vitro SB activates complement directly and fixes C3b. The phagocytosis of SB by mononuclear cells is complement dependent (Caetano et al. 1986). Oral ingestion of SB causes an increase in secretory IgA and secretory component in the small

intestines of rats (Buts et al. 1990). Rodrigues et al. (2000) determined that the yeast SB modulates the host immune responses with improving the resistance to enteropathogenic bacterial infections. SB has been tested in animal models of *C. difficile*-associated colitis and has been found to have a protective effect if challenged with either toxigenic *C. difficile* or purified toxin A or B (McFarland and Bernasconi 1993). Some toxinogenic strains of *C. difficile* may cause chronic enteropathies without colitis that may be improved by oral administration of SB (Buts et al. 1993). In an early study by Vidon et al. (1986) intestinal loops were surgically created in male Wistar rats and injected with either a 2 hours pre-incubated mixture of SB and cholera toxin or a mixture of cholera toxin and buffer (control loops). SB inhibited approximately 50% of the fluid and sodium secretion compared with loops treated with cholera toxin alone.

In rats, electron microscopic examination of duodeno-jejunal mucosa given SB (75 mg/d for 5 days) and mice (30 minutes to 24 hours) showed no invasion of SB into the mucosal layers, and no morphological changes of the villi or changes of crypt depth were noted (Buts et al. 1986). In a new experimental study, it has been claimed that SB is not useful in augmenting gut adaptation in animal model of short bowel syndrome (Kollman et al. 2001). However, Buts et al. (1999) determined that oral administration of SB soon after proximal enterectomy improved functional adaptation of the remnant ileum. In our study, positive cultures of MLN, liver, spleen and blood in group SB were significantly lower than those of group LO. Although ratio of BT (10%) in group SB was lower than that (30%) of group OA, there was not a significant difference between treatment groups. Mean villus height in group SB ($480.5 \pm 14.1 \mu\text{m}$) was significantly higher than those of groups OA ($360.8 \pm 27.2 \mu\text{m}$) and LO ($317.4 \pm 30 \mu\text{m}$). This showed that SB was adequate on the preservation of

mucosal integrity. Decreasing effects of SB on BT may be due to inhibition of overgrowth of pathogenic organisms and inhibition of the fluid-sodium secretion.

In conclusion, the present experimental study has demonstrated that OA and SB may have protective effects against BT in mechanical bowel obstruction and additionally SB preserves intestinal mucosal integrity.

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