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The Effect of Pentoxifylline on the Healing of Intestinal Anastomosis in Rats with Experimental Obstructive Jaundice

MUSTAFA CÖMERT[1], FERIT TANERİ[1], ERCÜMENT TEKİN[1], EMIN ERSOY[1], SELÇUK ÖKTEMER[1], ERHAN ONUK[1], ERSEL DÜZGÜN[2], and FERRUH AYOĞLU[3]

Departments of [1] General Surgery, [2] Biochemistry and [3] Public Health, Gazi University, Faculty of Medicine, Ankara, Turkey

Abstract The aims of this study were (1) to investigate the effect of experimental obstructive jaundice on the healing of intestinal anastomosis, and (2) to investigate the effect of pentoxifylline on the healing of intestinal anastomosis in rats with obstructive jaundice. Obstructive jaundice was induced in rats by the ligation and division of the common bile duct. Four days after this operation, either pentoxifylline or isotonic saline solution was administered intraperitoneally to these jaundiced rats and controls, and then intestinal anastomosis was performed. The concentrations of serum tumor necrosis factor α (TNF-α) and serum triglyceride of jaundiced and nonjaundiced rats were measured, and the quality of healing was evaluated by measuring the bursting preasure and hydroxyproline content of the anastomoses on the fifth and tenth days of anastomotic healing. Obstructive jaundice resulted in an impaired wound healing of the intestinal anastomosis in the rats. The administration of pentoxifylline to the jaundiced rats resulted in better anastomotic wound healing. The beneficial effects of pentoxifylline on anastomotic healing in rats with obstructive jaundice was attributed to its inhibitor effect on the endotoxin-induced TNF-α release from macrophages and monocytes, and the stabilizing effect on the neutrophils.

Key words Pentoxifylline · Obstructive jaundice · Intestinal anastomosis · Endotoxemia · Tumor necrosis factor α

Reprint requests to: M. Cömert, 9 Eylül Sokak No. 47/3, Topraklık, Ankara, Turkey
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Introduction

Obstructive jaundice results in a series of biochemical and pathologic changes which are associated with increased postoperative mortality and morbidity despite improvements in anesthesia and perioperative care.[1–4] Most frequent are postoperative infections and renal failure.[5] Based upon the clinical observations and experimental findings, it is also well known that the impaired wound healing and incisional herniae are much more common in obstructive jaundice. Wound dehiscence occurs in 2%–4% of jaundiced patients[6,7] and incisional herniae in 10% and 12.5%.[8,9] In various animal models, jaundice lowers the bursting strength of abdominal wounds[10–12] and adversely affects the migration of fibroblasts into experimental granulomas.[13]

High plasma bile acid levels, high plasma bilirubin levels, associated malignancies, and an impairment of the nutritional status were all suggested to be possible causes, but were not found to be involved in the pathogenesis of these complications due to obstructive jaundice. Especially in the last decade, another factor which was thought to play an important role in the pathogenesis of the enhanced morbidity and mortality in obstructive jaundice is the systemic and/or portal endotoxemia which is frequently observed in these patients.[14,15] Endotoxemia in patients with obstructive jaundice results from an increased absorption of gut-derived endotoxins[16] and a reduction in their clearance by the liver, thus permitting spillover into the systemic circulation.[17]

It has been demonstrated that the oral administration of lactulose[18] and bile salts[16] prevent the development of endotoxemia and subsequent death in experimental obstructive jaundice, and also reduces the incidence of postoperative renal failure in patients with jaundice.[19] Furthermore, it has also been shown that perioperative bile salt administration resulted in a significant increase in abdominal wound strength.[12] Such evidence supports

the hypothesis that endotoxemia may be the cause of the high morbidity, mortality, and delayed wound healing observed in patients with obstructive jaundice.

On the other hand, tumor necrosis factor α (TNF-α) or cachectin is a cytokine that is produced mainly by the macrophages and monocytes[20,21] and is thought to be the most important mediator responsible for the endotoxin effects.[22] Endotoxin remains the most potent stimulus known to induce TNF-α production and release from macrophages and monocytes.[23] Because of the regulatory effects of TNF-α on multiple different host defense mechanisms and inflammatory processes, it has been concluded to be a strategic and regulatory cytokine of the inflammation by some authors.[23]

The wound healing response can be divided into three distinct but overlapping phases: hemostasis and inflammation, proliferation, and maturation or remodeling.[24] The failure or a prolongation in one phase may result in either a delay of healing or a nonclosure of the wound.[25] Although there are some differences between the wound healing response of skin or soft tissue and the intestine, many components of the healing process are common to all tissues, such as the initial inflammatory response after injury, the deposition of new collagen, and the eventual maturation of the scar.[26] It is well known that obstructive jaundice causes a delay in the wound healing of an abdominal incision. However, only a few experimental studies on the healing of intestinal anastomosis in obstructive jaundice have been reported in literature. It was recently shown that obstructive jaundice in rats resulted in an impairment of anastomotic wound healing of the small intestine, which thus made it possible to decrease the endotoxemia, and also improve the intestinal wound healing with the administration of oral sodium taurocholate.[27] The present study investigated the effects of obstructive jaundice on the healing of intestinal anastomosis, and is the first study to investigate the effect of pentoxifylline on the healing of intestinal anastomosis in rats with obstructive jaundice.

Material and Methods

The study protocol was approved by the Ethics Committee of Gazi University Hospital. An experimental investigation was set up using Sprague-Dawley rats (Medical Research Laboratory of Gazi University) weighing 200–250 g. All of the operative procedures were performed under sterile conditions using intraperitoneal ketamine-HCl (Ketalar, Parke Davis, Morris Plains, NJ, USA) as the anesthetic agent (30 mg/kg body weight), and via a standard upper midline incision.

The rats were divided into four groups each of which consisted of 14 rats. Groups 1 and 2 were designed as obstructive jaundice groups, while groups 3 and 4 were established as control groups. In group 1, a bile duct ligation was performed; 4 days later, intestinal anastomosis was performed 30 min after 0.5 ml of isotonic saline solution was administered intraperitoneally. In group 2, a bile duct ligation was performed; 4 days later, intestinal anastomosis was performed 30 min after pentoxifylline (Trental, Hoechst, Istanbul, Turkey) was administered (50 mg/kg body weight) intraperitoneally. In group 3, a sham operation was performed; 4 days later, intestinal anastomosis was performed 30 min after 0.5 ml of isotonic saline solution was administered intraperitoneally. In group 4, a sham operation was performed; 4 days later, intestinal anastomosis was performed 30 min after pentoxifylline was administered (50 mg/kg body weight) intraperitoneally.

The bile duct ligation was performed according to the method of Lee[13] in groups 1 and 2. In the sham operation a silk ligature was placed around the common bile duct and then removed in groups 3 and 4. All intestinal anastomoses were performed in the standard manner. The small intestine was completely transected with a scalpel at a distance of 15 cm from the ileocecal valve without affecting the vascular supply. The bowel was anastomosed with eight inverting, single-layer, full-thickness sutures of 7-0 polypropylene. A magnifier was used while performing the anastomosis. The abdominal wall was closed in two layers. Postoperatively, the rats were allowed food and water ad libitum.

In each group, 14 animals were followed clinically, and the blood parameters and the parameters concerning the quality of anastomotic healing were measured on the fifth and tenth postoperative days of anastomotic healing.

Bursting Pressure of Intestinal Anastomoses

The bursting pressure of intestinal anastomoses was tested with sutures in place and without dissecting the adhesions, while the animals were under anesthesia. After the duodenum was transected completely, a subclavian catheter was placed into the duodenal lumen and tied with a silk suture. The terminal ileum was clamped just above to the ileocecal valve. Next, isotonic saline solution was infused at a rate of 2 ml/min into the lumen of the small intestine through the subclavian catheter by the use of an infusion pump with a digital pressure manometer (IVAC 770 Syringe Pump, Alaris Medical Systems, San Diego, CA, USA). While the saline solution was being infused, the intraluminal pressure of small intestine was observed on the screen of the infusion pump as millimeters of mercury. The highest pressure just before it started to decrease was recorded as the bursting pressure of intestinal anastomosis. The

mean ± SEM (standard error of the mean) value of the bursting pressure was calculated for each group.

Hydroxyproline Content of Intestinal Anastomosis

After the bursting pressure was tested and the blood samples were taken, the intestine was dissected along the mesenteric border and freed of any adhesions. The edges of anastomosis were excised, each strip being approximately 5 mm wide. The hydroxyproline content was estimated by the method of Jamall et al.,[28] and expressed as μg/g wet intestinal tissue.

Biochemical Investigations from the Blood

During the first operation in which the common bile duct was ligated, blood samples (0.5 ml) were taken for a TNF-α assay. On the fifth and tenth days of anastomotic healing, blood samples were taken for TNF-α, bilirubin, and triglyceride assays. The serum TNF-α concentrations were measured using the rat TNF-α enzyme-linked immunosorbent assay (ELISA) kit (Cytoscreen Immunoassay kit, BioSource International, Camarillo, CA, USA), which is commercially available. The assay had a lower detection limit of 15 pg/ml TNF-α.

The total serum bilirubin concentrations were measured by the method of Jendrassik-Graf and the triglyceride concentrations were measured by the method of glycerol-phosphate-oxidase (Technicon DAX-48 Random Access autoanalyzer, Miles, Tarrytown, NY, USA). Both of these parameters were expressed as mg/100 ml serum.

Statistical Analysis

We then determined whether or not any significant differences existed in all parameters between the groups on each postoperative day of anastomotic healing using Kruskal-Wallis one-way analysis. After that, if any significant differences were detected, the group showing the significant difference was analyzed by the Mann-Whitney *U*-test for the parameters. $P < 0.05$ was considered to indicate significance for all of the analyses.

Results

There was no weight loss in the postoperative period in the rats subjected to bile duct ligation. Two deaths were observed on the fourth day of anastomotic healing in group 1. Both anastomotic leakage and generalized peritonitis were found at necropsy in these rats. Two new animals were added to this group. No deaths were observed in groups 2, 3, or 4. All animals with bile duct ligation were obviously jaundiced within a few days of the operation. In addition, the jaundice was confirmed by measuring the serum bilirubin concentrations on the fifth and tenth days of anastomotic healing (Tables 1 and 2). No TNF-α was detected in the blood samples which were taken from the rats at the first operation.

Table 1. Plasma bilirubin, triglyceride, and tumor necrosis factor α (TNF-α) concentrations that were measured on the fifth day of anastomotic healing

	Mean bilirubin (mg/dl)	Mean TNF-α (pg/ml)	Mean triglyceride (mg/dl)
Group 1	5.03 ± 0.29[a]	155.20 ± 67.87[b]	169.57 ± 13.28[c]
Group 2	5.10 ± 0.17[a]	2.52 ± 2.52	95.57 ± 14.33
Group 3	0.84 ± 0.11	3.84 ± 3.84	61.71 ± 4.35
Group 4	0.87 ± 0.19	0.0 ± 0.0	67.57 ± 3.52

Values are mean ± SEM. Bile duct-ligated animals were significantly jaundiced. Plasma TNF-α and triglyceride concentrations were significantly elevated in group 1. With the pentoxifylline administration, plasma TNF-α and triglyceride concentrations were significantly reduced in the bile duct-ligated group (group 2)
[a] $P < 0.002$, [b] $P < 0.05$, [c] $P < 0.006$ by Mann-Whitney *U* statistical analysis

Table 2. Plasma bilirubin, triglyceride, and TNF-α concentrations that were measured on the tenth day of anastomotic healing

	Bilirubin (mg/dl)	Mean TNF-α (pg/ml)	Triglyceride (mg/dl)
Group 1	6.59 ± 0.27[a]	194.39 ± 65.45[b]	185.43 ± 17.64[a]
Group 2	6.03 ± 0.21[a]	2.91 ± 2.91	72.43 ± 5.09
Group 3	0.90 ± 0.12	2.19 ± 2.19	65.14 ± 4.51
Group 4	0.79 ± 0.17	0.0 ± 0.0	75.00 ± 5.21

Values are mean ± SEM. Bile duct-ligated animals were significantly jaundiced. Plasma TNF-α and triglyceride concentrations were significantly elevated in group 1. With the pentoxifylline administration, plasma TNF-α and triglyceride concentrations were significantly reduced in the bile duct-ligated group (group 2)
[a] $P < 0.002$, [b] $P < 0.02$, by Mann-Whitney *U* statistical analysis

Bursting Pressure and Hydroxyproline Content of the Anastomoses

The mean bursting pressure and the mean hydroxyproline content of the intestinal anastomoses in each group are shown in Tables 3 and 4. The bile duct ligation significantly lowered the bursting pressure and the hydroxyproline content of intestinal anstomosis both on the fifth and tenth days of anastomotic healing in group 1. The use of pentoxifylline resulted in a significant increase in both the bursting pressure and hydroxyproline content on the fifth and tenth days of anastomotic healing in group 2, when compared with group 1. De-

Table 3. Mean bursting pressure and hydroxyproline content values of the anastomoses on the fifth day of anastomotic healing

	Mean bursting pressure (mmHg)	Mean hydroxyproline content (μg/g wet tissue)
Group 1	84.85 ± 4.07[a]	6.43 ± 0.49[b]
Group 2	112.57 ± 6.14	8.66 ± 0.58
Group 3	112.86 ± 4.35	8.29 ± 1.01
Group 4	130.86 ± 5.60	9.64 ± 1.02

Values are mean ± SEM. Both the bursting pressure and hydroxyproline content values of anastomoses were significantly lower in group 1 when compared with the other groups
[a] $P < 0.006$, [b] $P < 0.05$, by Mann-Whitney U statistical analysis

Table 4. Mean bursting pressure and hydroxyproline content values of the anastomoses on the tenth day of anastomotic healing

	Mean bursting pressure (mmHg)	Mean hydroxyproline content (μg/g wet tissue)
Group 1	111.43 ± 5.74[a]	7.79 ± 0.66[b]
Group 2	195.14 ± 14.16	13.18 ± 1.51
Group 3	211.71 ± 15.32	15.06 ± 1.29
Group 4	206.73 ± 9.86	15.80 ± 1.65

Values are mean ± SEM. Both the bursting pressure and hydroxyproline content values of anastomoses were significantly lower in group 1 when compared with the other groups
[a] $P < 0.002$, [b] $P < 0.004$, by Mann-Whitney U statistical analysis

spite the fact that the use of pentoxifylline resulted in an increase in both the bursting pressure and the hydroxyproline content of anastomoses in rats undergoing a sham operation, the differences between groups 3 and 4 were not statistically significant.

Biochemical Investigations from the Blood

The mean values of the serum triglyceride and TNF-α concentrations from the blood samples which were taken on the fifth and tenth days of anastomotic healing are shown in Tables 1 and 2, respectively. On the fifth day of anastomotic healing, TNF-α was detected in four blood samples of the rats in group 1 (at concentrations between 55.70 and 386.40 pg/ml), in one blood sample of the rats in group 2 (at a concentration of 17.67 pg/ml), in one blood sample of the rats in group 3 (at a concentration of 26.86 pg/ml), and in none of the blood samples in group 4. On the tenth day of anastomotic healing, TNF-α was detected in five blood samples of the rats in group 1 (at concentrations between 44.79 and 395.59 pg/ml), in one blood sample of the rats in group 2 (at a concentration of 20.38 pg/ml), in one blood sample of the rats in group 3 (at a concentration of 15.31 pg/ml), and in none of the blood samples in group 4. The mean blood concentrations of TNF-α in group 1 were significantly higher than those in the other three groups on both the fifth and tenth days of anastomotic healing.

The mean serum triglyceride concentration in group 1 was significantly higher than in the sham-operated groups on the fifth and tenth days of anastomotic healing. The administration of pentoxifylline to the jaundiced rats lowered the serum triglyceride concentration.

Discussion

There have been numerous clinical and experimental studies done on the relationship between wound healing and jaundice. Although it is well known that obstructive jaundice causes an impaired wound healing of abdominal incisions, so far only a few studies have been done regarding the relationship between the healing of intestinal anastomosis and jaundice. Many components of the healing process are common to all tissues, such as the initial inflammatory response after injury, the deposition of new collagen, and the eventual maturation of the scar.[26] That is why the biochemical and pathologic changes that cause the impaired wound healing of abdominal incisions in obstructive jaundice may also result in an impaired healing of intestinal anastomosis.

The bursting pressure and the hydroxyproline content of intestinal anastomosis are objective parameters for evaluation of the quality and quantity of wound healing.[29] The results of a recent experimental study[27] demonstrated a reduction in the bursting pressure of intestinal anastomosis and tissue hydroxyproline concentration after a ligation of the bile duct in rats. The results of our study confirm these observations, but showing a significant reduction in the bursting pressure of the intestinal anastomosis and tissue hydroxyproline content in rats with jaundice on the fifth and tenth days of anastomotic healing when compared with those in the sham-operated groups. Our study is the only one thus far to investigate the effects of obstructive jaundice on the healing of intestinal anastomosis using a two-step experimental model. At the first operation, bile duct ligation was performed. Four days after this operation, when the jaundice became significant, intestinal anastomosis was performed. Thus, all the components of healing of intestinal anastomosis occurred in the significantly jaundiced rats.

Although the total amount of collagen present is not the only factor in the development of wound strength,[30] it is a valuable parameter that reflects the balance of the collagen metabolism in wound milieu.[29] In addition, the strength in healing wounds has been shown to correlate with increases in the amount of collagen.[31] Obstructive jaundice has been shown to reduce the number of fibroblasts present in healing wounds[11] and also reduces the

migration of reticuloendothelial cells and fibroblasts into the wound.[13]

Some researchers have tried to explain that impaired wound healing in obstructive jaundice is related to various factors such as high plasma bile acid levels, high plasma bilirubin levels, associated malignancies, and an impairment of the nutritional status. However, especially in the last decade, another factor which is thought to play an important role in the pathogenesis of the enhanced morbidity and mortality in obstructive jaundice is the systemic and/or portal endotoxemia frequently observed in these patients.[14,15] The relationship between obstructive jaundice, endotoxemia, and various postoperative complications is well known. For example, several clinical studies have suggested that endotoxins are related to the renal impairment frequently observed in jaundiced patients.[4,32] These observations were also confirmed by experimental studies.[16,33]

Similarly, endotoxemia in rats with obstructive jaundice decreased, and the impairment of abdominal wound healing was corrected by sodium taurocholate taken orally.[12] Such evidence suggests that the metabolic derangements which are related to endotoxemia, and resulted in such postoperative complications as renal failure, may also possibly be a cause of impaired wound healing in obstructive jaundice.

Endotoxins mainly stimulate the macrophages and monocytes to synthesize and release a cytokine which is called tumor necrosis factor type α.[20,21] After the injection of endotoxin, TNF-α appeared in the circulation within minutes, and reached peak levels after 2 h.[34,35] It has been shown that TNF-α administration to the rats resulted in similar clinical, matabolic, and histopathologic derangements, which were seen in the rats with endotoxic shock.[22] As a result, TNF-α is thought to be the principal cytokine for most endotoxin effects.

Recent evidence shows that TNF-α has a number of regulatory effects on the inflammatory processes and different cells which also play important roles in the wound-healing reaction.[36–44] In addition, the implantation of TNF-α in the rabbit cornea evoked an intensive inflammatory response which showed a large number of infiltrating leukocytes.[45] Based on such evidence, TNF-α is thought to be a strategic and regulatory cytokine of the inflammatory response.[23]

In conclusion, TNF-α evokes and enhances the inflammatory response, and the net effect of it on the collagen metabolism appears to be a downregulation. On the other hand, the detection of significant levels of TNF-α in the wound fluid[46] suggests that this cytokine may also play an important role in normal wound healing. Because of the various regulatory effects of TNF-α on inflammatory cells, and the detection of TNF-α within the healing wound during the first 3 days after being wounded, it was suggested that TNF-α might be an important mediator during the early phase of the healing process.[46]

Bemelmans et al.[47] reported that the majority of the mice undergoing an experimental bile duct ligation developed high circulating levels of TNF-α until the end of the study. In the present study, high levels of circulating TNF-α were detected in rats with obstructive jaundice on the fifth and tenth days of anastomotic healing. High concentrations of circulating TNF-α might result in an enhancement and prolongation of the inflammatory phase of healing, an increased collagen degradation by enhanced collagenase activity, a decrease in the degree of new collagen synthesis, and fibroblastic activity within the wound milieu, which thus might be the cause of impaired wound healing.

One of the clinical effects of TNF-α is the inhibition of systemic lipoprotein lipase activity, thus resulting in a hypertriglyceremia.[48] It was furthermore shown that TNF-α stimulates the de novo synthesis of triglycerides in the liver.[49] Some difficulties remain regarding the measurement of plasma endotoxin and TNF-α levels because of their very short plasma half-life.[34] Because plasma triglycerides remain elevated for at least 17 h after TNF-α stimulation,[49] they offer an indirect way to further study the possible involvement of endotoxins and/or TNF-α. This finding was supported and a relationship between the plasma triglyceride levels and mortality in rats with obstructive jaundice was also reported in another study.[50] In our experiments bile duct ligation resulted in higher levels of serum TNF-α and significantly higher plasma triglyceride concentrations in comparison with those in sham-operated rats. This finding supports the hypothesis that the measurement of the plasma triglyceride levels may be useful as an indirect parameter reflecting the TNF-α activity and/or endotoxemia.

Pentoxifylline is a methyl xanthine derivative which is currently approved in the United States for the treatment of patients with intermittent claudication due to chronic occlusive arterial disease. Our study is the first to investigate the effects of pentoxifylline on intestinal wound healing in rats with experimental obstructive jaundice. The mean bursting pressure and the hydroxyproline content of intestinal anastomosis were both significantly higher in the pentoxifylline-administered rats with obstructive jaundice than in the saline solution-administered ones. As a result, the administration of pentoxifylline to the jaundiced rats, just before intestinal anastomosis was performed, resulted in a better wound healing of anastomosis. It was reported that pentoxifylline effectively abolished the endotoxin-induced TNF-α production and release, in vitro[51–53] and in vivo.[53,54] There is evidence based on preclinical data that the sequelae of events provoked by endotoxin can be overcome, at least partially, by pentoxifylline.[55] This

drug directly inhibits various leukocyte functions such as neutrophil activation, superoxide anion production, and lysozyme degranulation.[56,57] In vivo, it was reported that pentoxifylline protected against the lethal effect of endotoxin[53,58] and also from endotoxin-induced lung injury[59] in different animal models of endotoxemia. These results were attributed by the authors to both the inhibitor effect of pentoxifylline on endotoxin-induced TNF-α production from mononuclear phagocytes and the neutrophil stabilizator effects of the drug. Because pentoxifylline administration to the jaundiced rats decreased the circulating TNF-α levels effectively and the plasma triglyceride concentrations were also significantly lower in comparison with those in the jaundiced rats not administered pentoxifylline, as an indirect indicator of the decreased TNF-α activity, the same mechanisms may also play a role in the improved healing of intestinal anastomosis in pentoxifylline-administered jaundiced rats.

Pentoxifylline is an approved drug for the treatment of various disorders in man. Since pentoxifylline inhibits the endotoxin-induced TNF-α production and release from mononuclear phagocytes, the efficacy of this drug on endotoxic shock is still being investigated in a number of studies. Because one of the causes of high postoperative complications in patients with obstructive jaundice might be due to increased endotoxemia and high circulating TNF-α levels, it should be kept in mind that pentoxifylline may have a beneficial effect in preventing such complications. We found that pentoxifylline improved the healing of intestinal anastomoses in rats with obstructive jaundice. Further studies to investigate the effects of pentoxifylline on other complications which are more common in patients with obstructive jaundice, such as renal and pulmonary complications, are thus called for.

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