The Effect of Ursodeoxycholic Acid and Piperacillin-Tazobactam on Acute Renal Failure Associated with Obstructive Jaundice in Experimental Models

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ÖZET

Sıçanlarda oluşturulan deneysel tıkanma sarılığı modelinde urseodeoksikolik asit ve piperasilin tazobaktamın akut böbrek yetmezliği üzerine etkisi

Amaç: Tıkanma sarılığı ile ilişkili akut böbrek yetmezliği, fizyopatolojisi ve tedavisi henüz tam olarak aydınlatılmamış olan ve hala klinik önemini koruyan ciddi bir tablodur. Yapılan birçok çalışmada, endotoksemi ve bununla tetiklenen sepsisin bu tablonun ortaya çıkma sürecinde kilit role sahip olduğu gösterilmiştir. Çalışmamızda, sıçanlarda oluşturulan deneysel tıkanma sarılığı modellerinde ursodeoksikolik asit ve piperasilin-tazobaktamın böbrek hasarı üzerine etkilerini araştırdık.

Gereç ve Yöntem: Toplam 40 erkek Spraque-Dawley cinsi sıçan rastgele seçilmiş on denekten oluşan 4 eşit gruba bölündü. Birinci grup kontrol grubu olarak kabul edildi ve bu gruba sadece şam laparotomi uygulandı. Diğer üç gruptaki deneklerin tümünde laparotomiyi takiben ortak safra kanalı bağlanarak tıkanma sarılığı oluşturuldu. Birinci ve 2. gruba işlem sonrasında hiçbir ek tedavi verilmezken, 3. gruba enteral ursodeoksikolik asit tedavisi ve 4. gruba parenteral piperasilin-tazobaktam tedavisi uygulandı. İşlemden sonraki 14. günde sakrifiye edilen deneklerden alınan kan örneklerinden böbrek fonksiyonu parametreleri, karaciğer fonksiyonu parametreleri, endotoksin düzeyleri belirlenirken, alınan böbrek dokusu örnekleri de histopatolojik incelemeye tabii tutuldu.

Bulgular: Üçüncü ve 4. gruptaki deneklerde saptanan endotoksin düzeyi, kontrol grubuna kıyasla anlamlı düzeyde yüksek ve 2. gruba kıyasla anlamlı düzeyde düşük bulundu. Üre ve kreatinin düzeylerinin kontrol grubu haricindeki gruplarda kontrol grubuna kıyasla anlamlı düzeyde yüksek olduğu saptandı. Histopatolojik incelemede, kontrol grubu haricindeki tüm gruplarda anlamlı düzeyde şiddetli ve yaygın renal tubuler nekrozun varlığı tespit edildi.

Sonuç: Sıçanlarda oluşturulan deneysel tıkanma sarılığı modellerinde, ursodeoksikolik asit ve piperasilin-tazobaktamın tıkanma sarılığı ile ilişkili akut böbrek yetmezliği üzerinde istatistiksel açıdan anlamlı bir etkiye sahip değildir.

Anahtar kelimeler: Tıkanma sarılığı, böbrek yetmezliği, endotoksemi, ursodeoksikolik asit, piperasilin-tazobaktam

ABSTRACT

The effect of ursodeoxycholic acid and piperacillin-tazobactam on acute renal failure associated with obstructive jaundice

Objective: Acute renal failure associated with obstructive jaundice is still a major clinical problem, and has yet not been completely understood. Many studies showed that one of the most important features of the process was endotoxemia and subsequent sepsis. We investigated the effects of ursodeoxycholic acid and piperacillin-tazobactam on acute renal failure associated with obstructive jaundice.

Material and Methods: Forty male Spraque-Dawley rats were divided into four equal groups. First group was considered to be control group, and had only sham laparotomy. Obstructive jaundice models were created by ligation of the common bile duct in other three groups. Second group had no treatment; third group had enteral ursodeoxycholic acid treatment; fourth group had parenteral piperacillin-tazobactam treatment. Tissue and blood samples were obtained for the assessment of biochemical and histopathological parameters.

Results: Endotoxin levels of treatment groups were significantly lower than the jaundiced group without treatment, but were significantly higher than control group. Histopathological examination revealed obvious renal tubular necrosis in all groups but in control group.

Conclusion: Neither ursodeoxycholic acid nor piperacillin-tazobactam has a statistically significant impact on development of acute renal failure associated with obstructive jaundice.

Key words: Obstructive jaundice, renal failure, endotoxemia, ursodeoxycholic acid, piperacillin-tazobactam

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INTRODUCTION

Acute renal failure associated with obstructive jaundice (ARFAWOJ) is a well-known clinical entity that increases morbidity and mortality rates of patients who undergo a surgical intervention for obstructive biliary tract diseases (1). Six decades ago, the clinicians named the kidney pathology associated with obstructive jaundice "cholemic nephrosis". Since 1911, when two German surgeons, Clairmont and von Haberer, first described this entity, the incidence of ARFAWOJ has not decreased significantly in spite of considerable improvements in perioperative care of surgical patients (2,3).

The pathophysiological mechanism of ARFAWOJ is still enigmatic; however, most of the related studies

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have pointed out the very possible role of endotoxemia and subsequent sepsis (4-8). As we too believe that endotoxemia is the key factor in developing ARFAWOJ, we investigated the effect of ursodeoxycholic acid (UDCA) and piperacillin-tazobactam (PT) on the prevention of ARFAWOJ in this experimental study.

MATERIAL AND METHODS

Forty male Spraque-Dawley rats weighing 150-350 g were provided by Experimental Medicine and Animal Laboratory at Cerrahpasa Medical Faculty, The University of Istanbul, Istanbul, Turkey. The subjects were treated according to institutional guidelines, and the study was approved by the Ethical Committee of Cerrahpasa Medical Faculty. The subjects were fed with standard laboratory food and ordinary water, and kept in standard cages in room temperature.

The subjects were randomly divided into four equal groups. The first group (I) (n=10) was control group, and had only sham laparotomy; the second group (II) (n=10) had their common bile duct ligated, and had no treatment; the third group (III) (n=10) had their common bile duct ligated, and also had enteral UDCA treatment via a orogastric feeding tube; the fourth group (IV) (n=10) had their common bile duct ligated, and also had parenteral PT treatment via intramuscular route.

All of the subjects were anesthesized with 20 mg/kg Ketamine (Ketalar, Pfizer) administered intraperitoneally. Ketamine anesthesia was supported with inhalation anesthesia with ether if needed. Abdominal skin was shaved, and disinfected with povidone-iodine. A longitudinal midline incision was preferred for laparotomy. Portal hilus was identified, and common bile duct was dissected and isolated. In the first group, no additional procedure was carried out, whereas in the other groups, the common bile duct was ligated twice with 4/0 silk suture, and was sectioned. Laparotomy was closed with 4/0 silk suture in continous fashion by mass closure technique. All of the subjects were administered 5 cc subcutaneous 5% dextrose solution, and were put into a warm incubator for recovery.

A single dose of 25 mg/kg UDCA (Ursofalk, Falk) was administered to all subjects in Group III through an orogastric tube, and 2.000 mg/kg PT (Tazocin, Wyeth) divided into 3 equal doses via intramuscular route was administered to all subjects in Group IV from the first post-operative day to 14th post-operative day.

The subjects have been observed for stigmata of obstructive jaundice such as the darkening of urine and discoloration of ears. All of the subjects were sacrificed via cervical dislocation on the 14th post-operative day. A thoracoabdominal incision was made, and blood sample was obtained from heart with a syringe, and the kidneys were harvested for histopathological examination.

Blood samples were collected in test tubes containing EDTA, and were immediately transferred to biochemistry laboratory. The samples were centrifuged at 4.000 rpm for 20 minutes at 4°C. After the seperation of the plasma, urea, creatinine, total bilirubin, and alkaline phosphotase levels were detected by Olympus A4-800 otoanalyzers utilizing Diasis kits. The rest of the plasma was frozen at -70°C for the assessment of endotoxin levels.

Frozen samples were first diluted to 1/10 with Reagent-Water solution, and 1 ml of this dilution was moved into sterile borosilicate tube. The tube was kept in boiling water for 2 minutes and in water at 70°C for 15 minutes. Then endotoxin level was assessed by gel clot method utilizing Limulus Amebocyte Lisate kit (Endosafe KTA).

The kidney samples were collected in glass boxes containing 10% formaline. The tissue samples taken from the kidneys were dehyrated by automatic casting machine (Shandon) containing increasing concentrations of alcohol, acetone, xylene, and parafine at 60°C. The samples were divided into 3-5μ sections by microtome, and were deparafinized with xylene in incubator at 60°C. Then these sections were dehyrated with decreasing concentrations of alcohol, and were stained with hematoxylene-eosine. All of the prepared samples were examined under light microscopy. Totally five parameters were used for the evaluation of the samples: 1. degeneration in renal tubular epithelial cells; 2. straightening in renal tubular epithelial cells; 3. nuclear enlargement in renal tubular epithelial cells; 4. necrosis in renal tubular epithelial cells; 5. neutrophilic infiltration.

A histopathological scoring system was designed for the comparison of the results. All of the parameters were ranked from 0 to 3 according to their severities and generalities (Table 1).

Table 1: Histopathological scoring system.

	0	1	2	3
Severity	-	slight	moderate	severe
Generality	-	focal	moderate	diffuse

Among the histopathological parameters, renal tubular necrosis and nuclear enlargement were considered to be more spesific for acute tubular necrosis. Degeneration and straightening in renal tubular epithelial cells were included as determinants of renal tubular cells in pre- and post-necrotic process. Neutrophilic infiltration was used to differentiate whether the pathological process was acute or chronic.

Twelve rats were dropped out from the study. Of these, three died due to anesthetic complications, and six died within the postoperative course. The rest three were excluded from the study because the findings of obstructive jaundice has not been observed within the three postoperative days. Of note, none of the subjects in control group developed signs of obstructive jaundice. All of twelve rats were replaced by randomly selected new rats, and none of the new subjects were needed to be dropped out.

All of the biochemical and histopathological parameters were evaluated with ANOVA and Tukey's HSD Test, Kruskal-Wallis Test, and Mann-Whitney U Test by SPSS for Windows 10.0 statistical program software. A p value of <0.05 was accepted to be significant for all results.

RESULTS

The values and the comparison of biochemical parameters are demonstrated in Table 2 and 3. Total bilirubin and alkaline phosphatase levels in control group were significantly lower than the other groups ($p<0.0001$); besides, clinical findings of jaundice have not been observed in control group. Group II, III and IV also had significantly different levels of total bilirubin and alkaline phosphatase with Group III having the lowest values among them ($p<0.0001$ for each).

Urea and creatinine levels were significantly lower in control group when compared with the other groups ($p<0.0001$). Group II had significantly higher levels of urea and creatinine than the other groups ($p<0.0001$). However, there were no significant differences between urea and creatinine levels of Group III and IV ($p>0.05$).

Endotoxins were not detected in blood samples of control group. Group II had significantly higher endotoxin levels than Group III ($p<0.0001$) and Group IV ($p<0.002$). Endotoxin levels were found to be significantly lower in Group III when compared with Group IV ($p<0.023$).

The comparison of severities and extent of histopathological parameters of each group is shown in

Table 2: The results of biochemical parameters and endotoxin levels.

Group	Urea Mean±SD	Creatinine Mean±SD	Total bilirubin Mean±SD	Alkaline phosphatase Mean±SD	Endotoxin Mean±SD
1	32.10±3.14	0.37±0.04	0.39±0.05	135.20±7.16	0.0
2	75.39±4.10	1.91±0.15	4.60±0.27	333.50±19.62	12.90±3.38
3	55.69±3.08	1.33±0.20	3.39±0.37	222.10±10.09	6.00±0.01
4	53.54±6.79	1.49±0.09	3.91±0.17	250.30±18.25	7.33±1.00

Table 3: The comparison of biochemical parameters and endotoxin levels.

Groups	Urea	Creatinine	Total bilirubin	Alkaline phosphatase	Endotoxin
1-2	<0.0001*	<0.0001*	<0.0001*	<0.0001*	-
1-3	<0.0001*	<0.0001*	<0.0001*	<0.0001*	-
1-4	<0.0001*	<0.0001*	<0.0001*	<0.0001*	-
2-3	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
2-4	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.002*
3-4	<0.716	<0.057	<0.0001*	<0.001*	<0.023*

Table 4: The comparison of groups according to the severity of histopathological parameters.

	Group 1-2	Group 1-3	Group 1-4	Group 2-3	Group 2-4	Group 3-4
1	<0.0001*	<0.015*	<0.023*	<0.280	<0.280	<0.481
2	<0.315	<0.315	<0.315	<0.481	<0.481	<0.315
3	<0.0001*	<0.002*	<0.015*	<0.315	<0.089	<0.280
4	<0.0001*	<0.015*	<0.015*	<0.089	<0.481	<0.315
5	<0.015*	<0.015*	<0.023*	<0.280	<0.063	<0.481

Table 5: The comparison of groups according to the extent of histopathological parameters.

	Group 1-2	Group 1-3	Group 1-4	Group 2-3	Group 2-4	Group 3-4
1	<0.002*	<0.015*	<0.002*	<1.000	<0.063	<1.000
2	<0.315	<0.315	<0.315	<0.481	<0.481	<0.089
3	<0.0001*	<0.002*	<0.002*	<0.089	<0.089	<0.089
4	<0.002*	<0.015*	<0.002*	<1.000	<0.481	<0.315
5	<0.002*	<0.015*	<0.023*	<1.000	<1.000	<1.000

Table 4 and 5.

Both severity and extent of straightening in renal tubular epithelial cells were similar in all groups (p>0.05 for each).

Both severity and extent of the other four histopathological parameters were significantly slighter in control group when compared with other groups (p<0.007 for each); however, there were no significant differences between Group II, III, and IV (p>0.05 for each).

DISCUSSION

Obstructive jaundice is universally accepted as a negative perioperative factor which markedly increases morbidity and mortality rates (9,10). Renal failure is one of the most important consequence of obstructive jaundice as clearly demonstrated by many studies reported within the last three decades, and is the particular cause of developing complications (11). Since the exact physiopathological mechanism of ARFAWOJ has not been identified yet, clinicians have been trying to interfere with some well-known responsible factors such as hypovolemia, hypotension, myocardial dysfunction, oxidative stress, and endotoxemia (12-16). The effects of obstructive jaundice on kidneys are summarized in Figure 1.

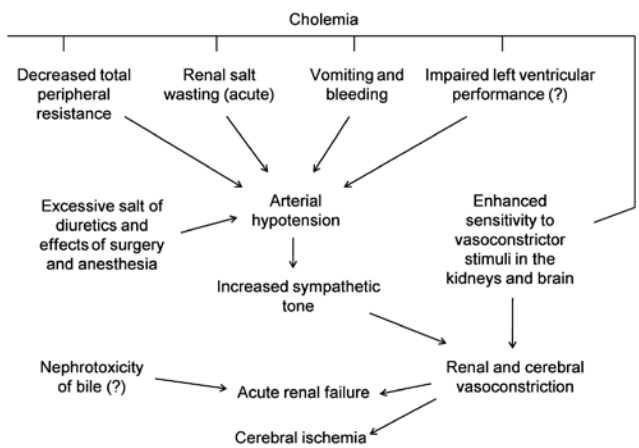

Figure 1. Physiopathological mechanism of ARFAWOJ.

Some authors suggested that ARFAWOJ could be attributed to impaired immune function and high incidence of systemic endotoxemia (17,18,19). Previous studies demonstrated that increased intestinal permeability due to obstructive jaundice resulted in translocation of bacteria and endotoxins to mesenteric lymph nodes, portal circulation, and liver (7,20). In addition, impaired clearance of endotoxins by Kuppfer's cells, and altered systemic immunity contributes to the escape of endotoxins into systemic circulation, which leads to release of proinflammatory cytokines, and subsequent gut-derived sepsis (21-24). Morover, functions of both hepatic and extrahepatic reticuloendothelial system were found to be compromised in several experimental studies (25,26,27). Likewise, Papakoustas et al. found that endotoxin levels were similar in portal and systemic circulation indicating the diminished filtering activity of the liver (28). The other responsible factors for the development of ARFAWOJ such as hypovolemia, hypotension, myocardial dysfunction, oxidative stress, may either be aggrevated by sepsis or be directly the consequences of sepsis.

Bile salts were demonstrated as an important part of immunological, biological and mechanical barriers of bowel in numerous studies (29-41). Several mechanisms have been identified about the effects of UDCA on target organs: 1. the protection of hepatocytes that have already been injured by the disease process; 2. the stimulation of impaired bile secretion; 3. the stimulation of detoxification of hydrophobic bile salts; 4. the modification of intestinal flora; 5. the elimination of endotoxins revealed as a consequence of the destruction of luminal bacteria with surfactan-like effect (6,16,42).

UDCA (3α, 7β-dihydroxy-5β-cholanic acid) is accepted as an effective drug in the treatment of chronic cholestatic liver diseases, and is the only drug to have FDA approval for the treatment of primary biliary cirrhosis. There are numerous studies demonstrated the beneficial effects of UDCA on liver function tests

in cholestatic liver diseases (43,44). Normally, it is a component of human bile composition, and constitutes 3% of all bile salts.

The administration of prophylactic antibiotics is recommended in patients with obstructive jaundice in means of reducing the septic complications; however, there is no consensus about which antibiotic should be used, and how long it should be lasted (45-48). PT is a combination of a semi-synthetic antibiotic, piperacillin, and a potent beta-lactamase inhibitor, tazobactam. Piperacillin is a member of the ureidopenicillins which are a group of penicillins active against Gram (-) bacteria (particularly Pseudomonas Aeruginosa) and tazobactam is a sulfone derivative of triazolylmetilpenicillanic acid which is a potential inhibitor of both plasmid- and chromosome-mediated beta-lactamases. The estimated dosage of piperacillin-tazobactam combination is 2.000 mg/kg/day in rats.

Piperacillin-tazobactam has potential bactericidal activity against Gram (+), Gram (-) and anaerobic bacteria. The combination is only effective when administered parenterally.

In fact, neither oral bile salts which were shown to have beneficial effects nor antibiotic prophylaxis is routinely used as a part of treatment in patients with obstructive jaundice in the perioperative course by most of the surgeons in practice unless an invasive procedure is carried out. Of note, synbiotic therapy was also proven to have beneficial effects in the peri-operative management of jaundiced patients (49).

Endotoxemia seems to be inevitable in obstructive jaundice, since all of the groups except the control group in the study were found to have endotoxemia. UDCA-treatment group, however, had significantly lower endotoxin levels than PT-treatment group. This finding emphasizes the efficacy of bile salts as a part of intestinal barrier. Higher endotoxin levels detected in PT-treatment group could be attributed to possible increase in the amount of luminal endotoxins due to the destruction of luminal bacteria by the direct effect of PT. Nonetheless, significantly lower endotoxin levels were found in PT-treatment group when compared to jaundiced group without treatment, as were in UDCA-treatment group.

Numerous previous studies demonstrated that the administration of oral bile salts minimized or even prevented ARFAWOJ (16,42,50). Histopathological results in our study conflict with the previous studies, since histopathological indicators of renal tubular necrosis were found to be significantly higher in UDCA- and PT-treatment groups when compared with the control group. Furthermore, statistically similar results of jaundiced groups suggest that both treatments fail to prevent or even minimize renal damage. Our conflicting data may be due to the multifactorial nature of ARFAWOJ, as the present study spesifically focused on endotoxemia. Besides, we also wonder what would be the results in an additional group which recieved a combined UDCA and PT treatment.

Neither ursodeoxycholic acid nor piperacillin-tazobactam has a statistically significant impact on development of acute renal failure associated with obstructive jaundice.

REFERENCES

1. Wait RB, Kahng KU. Renal failure complicating obstructive jaundice. Am J Surg 1989: 157; 256-263.
2. Allison ME, Prentice CR, Kennedy AC, Blumgart LH. Renal function and other factors in obstructive jaundice. Br J Surg 1979: 66; 392-397.
3. Wittenstein BH, Giacchino JL, Pickleman JR, et al. Obstructive jaundice: the necessity for improved management. Am Surg 1981: 47; 116-120.
4. Wardle EN. Endotoxinaemia and the pathogenesis of acute renal failure. Q J Med 1975: 44; 389-398.
5. Inan M, Sayek I, Tel BC, Sahin-Erdemli I. Role of endotoxin and nitric oxide in the pathogenesis of renal failure in obstructive jaundice. Br J Surg 1997; 84: 943-947.
6. Wardle EN, Wright NA. Endotoxin and renal failure associated with obstructive jaundice. Br Med J 1979; 4: 472-474.
7. Deitch EA, Sittig K, Li M, Berg R, Specian RD. Obstructive jaundice promotes bacterial translocation from the gut. Am J Surg 1990; 159: 79-84.
8. Bailey ME. Endotoxin, bile salts and renal function in obstructive jaundice. Br J Surg 1976; 63: 773-778.
9. Greig JD, Krukowski ZH, Matheson NA. Surgical morbidity and mortality in one hundred and twenty-nine patients with obstructive jaundice. Br J Surg 1988; 75: 216-219.
10. Sewnath ME, Karsten TM, Prins MH, Rauws EJ, Obertop H, Gouma DJ. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. Ann Surg 2002; 236: 17-27.
11. Wilkinson SP, Moodie H, Stamatakis JD, Kakar VV, Williams R. Endotoxemia and renal failure in cirrhosis and obstructive jaundice. Br Med J 1976; 11: 1415-1418.
12. Padillo FJ, Briceño J, Cruz A, Chicano M, Naranjo A, Vallejo J, et al. Randomized clinical trial of the effect of intravenous fluid administration on hormonal and renal dysfunction in patients with obstructive jaundice undergoing endoscopic drainage. Br J Surg 2005; 92: 39-43.
13. Padillo FJ, Puente J, Gómez M, et al. Improved cardiac function in patients with obstructive jaundice after internal biliary drainage: hemodynamic and hormonal assessment. Ann Surg 2001; 234: 652-656.
14. Cruz A, Padillo FJ, Tunez I, et al. Melatonin protects against renal oxidative stress after obstructive jaundice in rats. Eur J Pharmacol 2001; 425: 135-139.

15. Kucuk C, Sozuer E, Ikizceli I, et al. Role of oxygen free radical scavengers in acute renal failure complicating obstructive jaundice. Eur Surg Res 2003; 35: 143-147.
16. Cahill CJ. Prevention of postoperative renal failure in patients with obstructive jaundice-the role of bile salts. Br J Surg 1983; 70: 590-595.
17. Clements WD, Parks R, Erwin P, Halliday MI, Barr J, Rowlands BJ. Role of the gut in the pathophysiology of extrahepatic biliary obstruction. Gut 1996; 39: 587-593.
18. Parks RW, Halliday MI, McCrory DC, et al. Host immune responses and intestinal permeability in patients with jaundice. Br J Surg 2003; 90: 239-245.
19. Clements WD, Erwin P, McCaigue MD, Halliday I, Barclay GR, Rowlands BJ. Conclusive evidence of endotoxaemia in biliary obstruction. Gut 1998; 42: 293-299.
20. Scopa CD, Koureleas S, Tsamandas AC, et al. Beneficial effects of growth hormone and insulin-like growth factor I on intestinal bacterial translocation, endotoxemia, and apoptosis in experimentally jaundiced rats. J Am Coll Surg 2000; 190: 423-431.
21. Vane DW, Redlich P, Weber T, Leapman S, Siddiqui AR, Grosfeld JL. Impaired immune function in obstructive jaundice. J Surg Res 1988; 45: 287-293.
22. Clements WD, Halliday MI, McCaigue MD, et al. Effects of extrahepatic obstructive jaundice on Kupffer cell clearance capacity. Arch Surg 1993; 128: 200-205.
23. Kuzu MA, Kale IT, Cöl C, Tekeli A, Tanik A, Köksoy C. Obstructive jaundice promotes bacterial translocation in humans. Hepatogastroenterology 1999; 46: 2159-2164.
24. Assimakopoulos SF, Scopa CD, Vagianos CE. Pathophysiology of increased intestinal permeability in obstructive jaundice. World J Gastroenterol 2007;13: 6458-6464.
25. Ozcelik MF, Pekmezci S, Kabasakal L, Cansız T, Ozker K. Reticuloendothelial system functions in obstructive jaundice. Ulusal Cerrahi Dergisi 1993; 9:86-91.
26. Ball SK, Grogan JB, Collier BJ, Scott-Conner CE. Bacterial phagocytosis in obstructive jaundice: a microbiologic and electron microscopic analysis. Am Surg 1991; 57: 67-72.
27. Tuncer U, Karahan S, Guclu ME, Gursel C, Gurel N, Agacfidan A. The effect of internal drainage procedures on cellular immunity in an experimental model of extrahepatic cholestasis. Ulusal Cerrahi Dergisi 1992; 8: 242-245.
28. Papakostas C, Bezirtzoglou E, Pitiakoudis M, Polychronidis A, Simopoulos C. Endotoxinemia in the portal and the systemic circulation in obstructive jaundice. Clin Exp Med 2003; 3: 124-128.
29. Sano T, Ajiki T, Takeyama Y, Kuroda Y. Internal biliary drainage improves decreased number of gut mucosal T lymphocytes and MAdCAM-1 expression in jaundiced rats. Surgery 2004; 136: 693-699.
30. Ogawa A, Tagawa T, Nishimura H, et al. Toll-like receptors 2 and 4 are differentially involved in Fas dependent apoptosis in Peyer's patch and the liver at an early stage after bile duct ligation in mice. Gut 2006; 55: 105-113.
31. Arai T, Yoshikai Y, Kamiya J, et al. Bilirubin impairs bactericidal activity of neutrophils through an antioxidant mechanism in vitro. J Surg Res 2001; 96: 107-113.
32. Brown WR, Kloppel TM. The liver and IgA: immunological, cell biological and clinical implications. Hepatology 1989; 9: 763-784.
33. Kloppel TM, Hoops TC, Gaskin D, Le M. Uncoupling of the secretory pathways for IgA and secretory component by cholestasis. Am J Physiol 1987; 253: 232-240.
34. Wells CL, Jechorek RP, Erlandsen SL. Inhibitory effect of bile on bacterial invasion of enterocytes: possible mechanism for increased translocation associated with obstructive jaundice. Crit Care Med 1995; 23: 301-307.
35. Assimakopoulos SF, Vagianos CE, Patsoukis N, Georgiou C, Nikolopoulou V, Scopa CD. Evidence for intestinal oxidative stress in obstructive jaundice-induced gut barrier dysfunction in rats. Acta Physiol Scand 2004; 180: 177-185.
36. Bron PA, Marco M, Hoffer SM, Van Mullekom E, de Vos WM, Kleerebezem M. Genetic characterization of the bile salt response in Lactobacillus plantarum and analysis of responsive promoters in vitro and in situ in the gastrointestinal tract. J Bacteriol 2004; 186: 7829-7835.
37. Bertok L. Physico-chemical defense of vertebrate organisms: the role of bile acids in defense against bacterial endotoxins. Perspect Biol Med 1977; 21: 70-76.
38. Parks RW, Stuart Cameron CH, Gannon CD, Pope C, Diamond T, Rowlands BJ. Changes in gastrointestinal morphology associated with obstructive jaundice. J Pathol 2000;192:526-532.
39. Toledo A, Yamaguchi J, Wang JY, Bass BL, Turner DJ, Strauch ED. Taurodeoxycholate stimulates intestinal cell proliferation and protects against apoptotic cell death through activation of NF-kappaB. Dig Dis Sci 2004; 49: 1664-1671.
40. Yamaguchi J, Toledo A, Bass BL, Celeste FA, Rao JN, Wang JY, Strauch ED. Taurodeoxycholate increases intestinal epithelial cell proliferation through c-myc expression. Surgery 2004; 135: 215-221.
41. Yang R, Harada T, Li J, Uchiyama T, Han Y, Englert JA, Fink MP. Bile modulates intestinal epithelial barrier function via an extracellular signal related kinase 1/2 dependent mechanism. Intensive Care Med 2005; 31: 709-717.
42. Evans HJ, Torrealba V, Hudd C, Knight M. The effect of preoperative bile salt administration on postoperative renal function in patients with obstructive jaundice. Br J Surg 1982; 69: 706-708.
43. Leuschner U, Leuschner M, Sieratzki J, Kurtz W, Hubner K. Gallstone dissolution with ursodeoxycholic acid in patients with chronic active hepatitis and two years follow-up. A pilot study. Dig Dis Sci 1985; 30: 642-649.
44. Miyaji K, Akiyama T, Ito M, Urokawa T, Shimaji Y. The effect of ursodeoxycholic acid on liver functions in patients with chronic liver disease. A double blind study in one institution and the study on the effect on hepatic blood flow. Rinsho to Kenkyu 1976; 53: 1395-1403.
45. Oussoultzoglou E, Jaeck D. Patient preparation before surgery for cholangiocarcinoma. HPB 2008; 10: 150-153.
46. Togo S, Tanaka K, Morioka D, et al. Usefulness of granular BCAA after hepatectomy for liver cancer complicated with liver cirrhosis. Nutrition 2005; 21: 480-486.
47. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg 2002; 137: 174-180.
48. Nagino M, Nimura Y, Kamiya J, et al. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. Hepatology 1995; 21: 434-439.
49. Sugawara G, Nagino M, Nishio H, et al. Perioperative synbiotic treatment to prevent postoperative infectious complications in biliary cancer surgery: a randomized controlled trial. Ann Surg 2006; 244: 706-714.
50. Acarli KS, Ozacmak ID, Uysal V, Kurtoglu M, Ozgur M. The effect of oral bile salts on etiopathogenesis of acute renal failure developing in experimental model of extrahepatic cholestasis. Ulusal Cerrahi Dergisi 1988; 4: 17-22.