

Prevention of postoperative renal dysfunction in patients with obstructive jaundice: a multicentre study of bile salts and lactulose

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The role of preoperative lactulose and bile salts in the prevention of postoperative renal failure in patients with obstructive jaundice has been evaluated in a prospective randomized trial. One hundred and two patients undergoing surgery for obstructive jaundice (bilirubin >100 µmol/l) were randomized into three groups: those receiving preoperative oral lactulose (n=35), those receiving oral sodium deoxycholate (n=32) and a control group of patients receiving no specific treatment (n=35). All patients received intravenous fluids commencing the night before surgery. One patient in the control group and none in the treatment groups developed postoperative renal failure. Postoperative deterioration of renal function in patients with normal preoperative function was significantly more common in the control group than in the treatment groups ($\chi^2=8.1$, d.f.=2, $P<0.02$). The incidence of renal failure and impairment was lower in this control group than that reported in previous studies. This may be due to the introduction of adequate preoperative hydration. Additional protection occurs by the preoperative administration of either lactulose or sodium deoxycholate.

Patients with obstructive jaundice have an increased incidence of postoperative renal failure^{1,2}. Systemic endotoxaemia, resulting from increased absorption of intestinal endotoxin into the portal blood^{3,4} and its spillover into the systemic blood due to impaired removal by the hepatic reticuloendothelial system^{5,6}, may be important aetiological factors. Preoperative oral bile salts and lactulose have been shown in preliminary studies^{7,8} to reduce systemic endotoxaemia and to protect postoperative renal function. A prospective randomized multicentre study has been performed to evaluate these agents.

Patients and methods

One hundred and fourteen patients from six hospitals were entered into the study at least 3 days before undergoing surgery for relief of obstructive jaundice. All patients had a plasma bilirubin level >100 µmol/l. Patients about to undergo preoperative percutaneous external or endoscopic internal drainage, with a previous history of renal or parenchymal liver disease, or who had been given a general anaesthetic in the preceding 6 weeks were excluded. Twelve patients (three controls, three in the lactulose group and six in the bile salt group) failed to comply with the protocol requirements and were withdrawn: seven had inadequate sample collection, three underwent non-operative relief of jaundice and two underwent laparotomy alone.

The remaining 102 patients were evaluated. Thirty-five patients received preoperative oral lactulose, 32 patients received preoperative oral sodium deoxycholate, and 35 patients acted as controls and received neither treatment. All patients received preoperative intravenous fluids commencing the night before surgery. Patients were given perioperative mannitol and antibiotics according to the preference of the individual surgeon.

A comparison of the three groups is shown in Table 1. Patients receiving lactulose were older and had a higher mean bilirubin level than patients in the other groups. Diagnoses and operative details are shown in Table 2.

Lactulose

Oral lactulose (Duphalac®, Duphar Labs Ltd., UK), 30 ml 6-hourly,

was given for 3 days before surgery. The final dose was administered within 12 h of surgery. If a patient developed troublesome or frequent diarrhoea (>4 times per 24 h) the subsequent dose of lactulose was omitted and doses thereafter were halved.

Bile salts

Sodium deoxycholate, the bile salt with the greatest antiendotoxic action⁹, was used in this study. Sodium deoxycholate (Kochlight Ltd., UK) was made up into 250 mg capsules. Patients received 500 mg by mouth 8-hourly for 2 days before surgery. The final dose was given within 12 h of surgery.

Table 1 Patient details

	Control group (n=35)	Lactulose group (n=35)	Bile salt group (n=32)
Age (years)			
Mean	69(10)	74(8)	66(11)
Range	54-86	32-86	42-86
Sex (M:F)	24:11	25:10	24:9
Jaundice duration (days)	22 (13)	21(14)	20(12)
Diabetes (n)	1	3	4
Bilirubin (µmol/l)	317(156)	358(165)	270(110)
Alkaline phosphatase (units/l)	711(313)	584(256)	623(363)
Transaminase (aspartate aminotransferase) (units/l)	146(63)	129(61)	121(118)
Albumin (g/l)	33.1(6)	31.2(8)	34.0(6)
Haemoglobin (g/dl)	12.3(1)	12.3(2)	12.6(2)
Preoperative blood transfusion (n)	1	2	2
White cell count (10 ⁹ /l)	9.1(3)	8.5(3)	9.7(5)
Perioperative mannitol (%)	71	51	59
Perioperative antibiotics (%)	89	97	94

Values given are mean(s.d.) unless otherwise stated

Table 2 Diagnoses and operative details

	Control group (n=35)	Lactulose group (n=35)	Bile salt group (n=32)
Diagnosis			
Carcinoma of the pancreas	21	28	14
Malignant duct obstruction	3	2	7
Carcinoma of the gallbladder	3	1	0
Cholelithiasis	6	3	8
Benign bile duct stricture	0	0	3
Pancreatitis	2	1	0
Operative details			
Palliative bypass	26	31	19
Pancreatectomy	0	1	0
Stent insertion	3	0	5
Exploration common bile duct	6	3	8
Operative duration (min)*	98(35)	97(32)	113(39)
Presence of liver metastases (%)	31	20	9

* Values given are mean(s.d.)

Renal function

Serial 24 h endogenous creatinine clearance measurements (C_{24}) were performed on the 2 days before surgery and on the first 3 days after operation. Impairment of renal function was defined as a preoperative C_{24} value of <40 ml/min associated with a raised plasma urea and creatinine level, or a >20 per cent fall in mean C_{24} value after operation^{7,8,10}. Renal failure was defined as a urine volume <400 ml/24 h associated with a rising plasma urea and creatinine level.

Statistical analysis

Comparison of changes in creatinine clearance were made with analysis of variance. Comparisons of the incidences of renal impairment were made with the χ^2 test.

Results

Twelve patients (34 per cent) had modification of lactulose dosage because of diarrhoea. Sodium deoxycholate doses were omitted in two patients (6 per cent) because of vomiting and in one patient (3 per cent) because of epigastric discomfort.

Mortality and morbidity

There were five postoperative deaths (within 30 days of operation) in the control group, five in the group receiving lactulose and one in the group receiving bile salts. Causes of deaths and complications are shown in Table 3. Renal failure was not a principal cause of death in any patient. Twenty-six per cent of patients had postoperative septic complications and 5 per cent had postoperative gastrointestinal haemorrhage.

Renal failure

One patient in the control group, who had preoperative renal impairment (C_{24} = 38.3 ml/min), developed postoperative renal failure (urine output 320 ml/24 h). This responded to supportive therapy and he was eventually discharged home on the 46th day after operation. No patient receiving lactulose or bile salts developed postoperative renal failure.

Renal impairment

The incidence of preoperative and postoperative renal impairment is shown in Table 4. In patients who had normal renal function before surgery postoperative renal impairment was more common (χ^2 = 8.1, d.f. = 2, P < 0.02) in the control group than in the two treated groups (Table 4). Overall the C_{24} value in the control group rose from a mean(s.d.) of 63.4(24.2) ml/min before surgery to 64.5(27.7) ml/min after surgery (2 per cent increase). In the group receiving lactulose the C_{24} value rose from 53.4(21.6) ml/min to 61.5(22.1) ml/min (15 per cent increase). In the group receiving bile salts the C_{24} value rose from 63.5(21.1) ml/min to 68.0(19.9) ml/min

(7 per cent increase). There were no statistically significant differences between or within groups.

Discussion

An overall 9 per cent incidence of renal failure has been reported in patients with obstructive jaundice^{1,2}. In this study only one patient (<3 per cent) in the control group developed renal failure and this resolved. Dawson¹¹ found that in non-jaundiced patients undergoing surgery the maximum fall in C_{24} level after operation was 22.8 per cent. We therefore used a mean postoperative C_{24} fall of >20 per cent as a criterion of renal impairment. The incidence of impairment in the control group was 34 per cent compared with over 50 per cent in the control groups of our earlier studies^{3,7,8}. This may be due to the fact that all patients, including the control group, received preoperative intravenous fluids starting at least the day before surgery. Williams *et al.*¹² observed that fatal acute postoperative renal failure in jaundiced patients was preceded by a period of hypotension. The postoperative mortality rate fell from 13 to 7 per cent if patients were routinely transfused before surgery. Two possible explanations for this response are a reduction in peripheral vascular resistance^{13,14} and a fall in total body water¹⁵ associated with obstructive jaundice.

In patients who had normal preoperative renal function there was a significantly (P < 0.02) greater incidence of postoperative renal impairment in the controls compared with the treated groups (Table 4). Additional protection of renal function can be provided by lactulose or bile salts. We have previously shown that lactulose and sodium deoxycholate

Table 3 Postoperative mortality and morbidity (number of patients)

	Control group (n=35)	Lactulose group (n=35)	Bile salt group (n=32)
Deaths			
Myocardial infarction	5	5	1
Chest infection	—	2	—
Anastomotic leak	3	1	1
Recurrent jaundice	—	1	—
Carcinomatosis	—	1	—
Cardiac failure	1	—	—
Major complications			
Gastrointestinal bleed	5*	1	3*
Septicaemia	3	1	1
Subphrenic abscess	1	—	2
Pancreatitis	—	—	1
Biliary fistula	1	—	—
Cerebrovascular accident	1	—	—
Renal failure	1	—	—
Minor complications			
Respiratory infection	6	7	6*
Urinary tract infection	1	4	4
Wound infection	1	2	1
Diarrhoea	3	—	3
Prolonged ileus	—	1	—
	1	—	—

* Some patients had more than one complication

Table 4 Overall incidence of preoperative and postoperative renal impairment

	Control group (n=35)	Lactulose group (n=35)	Bile salt group (n=32)
Preoperative alone	7	10	6
Preoperative and postoperative	4	4	3
Postoperative alone	8*	1	2

* P < 0.02 control group versus lactulose and bile salt groups

reduce the incidence of portal and systemic endotoxaemia in patients with obstructive jaundice undergoing surgery^{7,8}. Measurement of endotoxins in plasma is a difficult technique requiring great care in obtaining, treating and assaying samples. Because this was a multicentre study these points could not be controlled adequately; therefore measurements were not undertaken.

Lactulose, a commercially available synthetic disaccharide, is used in the treatment of constipation and for the prevention of hepatic encephalopathy. Lactulose reduces endotoxaemia in parenchymal liver disease¹⁶⁻¹⁸, and in a non-randomized study of patients with obstructive jaundice lactulose was shown to reduce endotoxaemia and protect against postoperative renal failure⁸. The mechanism of action is unknown. It has a direct antiendotoxic action *in vitro* and in animals^{8,19} but this is more modest than that of bile salts⁹. It may reduce the availability of colonic endotoxin for absorption by its laxative effect²⁰ and its alteration of colonic bacterial flora²¹. If lactulose is absorbed from the intestine of jaundiced patients it may exert a systemic action. Many of the toxic effects of endotoxin are mediated via the release from macrophages of effector substances such as tumour necrosis factor²², and lactulose has been shown to modify this macrophage response²³.

Bile salts are detergents and inactivate the endotoxin molecule *in vitro*²⁴⁻²⁶. The presence of bile within the intestinal lumen reduces endotoxin absorption into the portal blood. Endotoxin absorption is increased in obstructive jaundice³ or following external biliary drainage²⁷, but endotoxin absorption is reduced if oral bile salts are administered³, or if internal biliary drainage is performed²⁸.

The choice of the correct bile salt appears to be important. In patients with obstructive jaundice oral sodium deoxycholate prevents both portal and systemic endotoxaemia and protects postoperative renal function⁷. Chenodeoxycholic acid is less effective¹⁰ and ursodeoxycholic acid confers no benefit²⁸. Sodium deoxycholate has the greatest detergent activity, and has the most effective antiendotoxic action *in vitro* and *in vivo*⁹.

The incidence of postoperative renal failure in patients with obstructive jaundice is reduced by adequate preoperative hydration. Preoperative administration of lactulose or sodium deoxycholate confers additional protection. Lactulose is widely available and safe, but in the doses used in this study may cause diarrhoea requiring dose reduction. Sodium deoxycholate is not commercially available. Clinical experience of its use is limited, but no serious side-effects have been observed.

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