ROLE OF LACTULOSE IN PREVENTING POSTOPERATIVE RENAL DYSFUNCTION IN PATIENTS WITH OBSTRUCTIVE JAUNDICE

A thesis submitted in partial fulfillment of the requirements for the degree of
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IN
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Based on the studies conducted at the
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Of
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March, 1999

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CERTIFICATE

This is to certify that the subject of this thesis “Role of Lactulose in Preventing Postoperative Renal Dysfunction in Patients with Obstructive Jaundice” is the results of the original investigative study undertaken by Dr. Uttam Krishna Shrestha under our guidance.

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DECLARATION

I hereby declare this thesis work on “Role of Lactulose in Preventing Postoperative Renal Dysfunction in Patients with Obstructive Jaundice” has not been submitted in candidature for any degree. I will have no objection for the availability of this thesis for photocopy and inter-library loans for outside organization.

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March 1999
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SUMMARY
1. SUMMARY

A prospective study was undertaken to assess postoperative renal dysfunction in patients with obstructive jaundice and to determine the effectiveness of lactulose in reducing its incidence. Forty-two patients undergoing surgery for obstructive jaundice (bilirubin level >100 µmol/l) were randomized in two groups. Those receiving preoperative lactulose (n=20), and a control group of patients receiving no specific treatment (n=22). All patients received intravenous fluid commencing 24 hours prior to surgery and all were given perioperative antibiotics. Blood urea, serum creatinine and creatinine clearance ($C_{24}$) measurements were performed on 2 days before surgery and on the first 3 days after operation. None of the patients developed postoperative acute renal failure. In both groups there were rise in blood urea and serum creatinine values postoperatively, but the changes were not statistically significant. The $C_{24}$ value in the control group dropped by 16 per cent whereas in lactulose group it was 10 per cent. It was statistically not significant (t=0.11, d.f.=40, P>0.05). Ten patients under control and six patients receiving lactulose were found to show >20 per cent fall in mean $C_{24}$ following operation, which was statistically not significant ($\chi^2=1.1$, d.f. =1, P>0.05). These findings suggest that, with preoperative hydration, electrolyte correction and perioperative antibiotics, the incidence of postoperative renal dysfunction in patients with obstructive jaundice can be reduced, and is not altered by the administration of preoperative oral lactulose.
INTRODUCTION
2. INTRODUCTION

Jaundice due to obstruction of the biliary system usually demands surgical relief. Frequently, diagnosis and management are relatively simple but cases of considerable complexity occur and, if the patient is inappropriately managed, the problems are compounded. Jaundiced patients undergoing either invasive diagnostic or therapeutic procedures have an increased risk of subsequent morbidity and mortality compared with those without jaundice. The high morbidity and mortality may in part be due to hyperbilirubinaemia, malnourishment and malignancy. However, some perioperative complications are due to endotoxaemia, which results from an increased absorption of gut-derived endotoxins and a reduction in their clearance by the liver.

Acute renal failure following biliary tract surgery was first reported by Clairmont and Von Haberer in 1911, and Helwig and Schutz’s description of a liver and kidney syndrome in early 1930s intensified the interest. This has implications for other specialties in an analysis of patients. In one renal unit 12 per cent of those receiving treatment for acute renal failure had undergone preceding biliary tract surgery. The realization of the renal dysfunction as a significant problem in patient with obstructive jaundice has led researches to hypothesize various pathophysiological mechanism and development of new therapeutic strategy, but renal dysfunction remains persistent problem in hepatobiliary practice.

Surgical procedures in patients with obstructive jaundice are associated with higher rate of postoperative renal dysfunction; this has changed little over the past three decades despite advances in anaesthesia and perioperative care. The frequency of postoperative renal impairment in some studies are as high as 60 per cent, while that of acute renal failure varies from 4 to 18 per cent, with a mean of 9 per cent. Approximately 80 per cent of those who develop
renal failure die\textsuperscript{6-8}. In contrast, postoperative renal failure in individuals without jaundice is rare. In one series of 2348 patients undergoing biliary tract surgery only 3 died from renal failure\textsuperscript{9}. In view of this several therapies have been introduced, including the administration of mannitol, bile salts, lactulose, dopamine and preoperative biliary drainage. Despite these regimens, postoperative renal impairment in patients with obstructive jaundice appears to be a persistent clinically significant problem.

In Nepal, we do not have any study conducted in the past regarding renal impairment postoperatively in obstructive jaundiced cases. So, we do not have any data to compare with results in the western countries. Certainly due to late presentation of the patients to hospitals we do have more cases of renal impairment who has undergone surgery for relief of biliary obstruction. Not only in renal function impairment but there may also be more sepsis and impair wound healing in them.

Tribhuvan University Teaching Hospital is a tertiary hospital where we get referrals from all over the country. This is more true in cases of obstructive jaundice patients, because of availability of diagnostic and therapeutic tools in our hospital. As we have ultrasound, fluoroscopy, endoscopic retrograde cholangio-pancreaticography (ERCP) and we also have facilities for radiological intervention like percutaneous transhepatic cholangiogram (PTC) and drainage. Some cases are referred here for diagnostic purposes while others are for diagnostic as well as therapeutic purposes. Because of these facts, we get more number of jaundiced patients for surgery.

Since Wardle and Wright\textsuperscript{10} demonstrated an association between systemic endotoxaemia and renal failure in obstructive jaundice, endotoxin has been increasingly implicated in the pathophysiology of complications seen in jaundiced patients. It is postulated that in obstructive jaundice there are two major contributing factors in the development of endotoxaemia. First, the
absence of bile salts in the gastrointestinal tract means a loss of their antiendotoxin effect, resulting in a large pool of endotoxin in the large bowel that can be absorbed into the portal circulation\textsuperscript{2,11}. Second, impairment of hepatic Kupffer cell phagocytic function in obstructive jaundice allows spill over of gut-derived endotoxin into the systemic circulation. Systemic endotoxaemia may then activate the inflammatory response, leading ultimately to impairment of organ function. Considering this as a burning issue there has been several strategies introduced to overcome renal dysfunction in jaundiced patients and we have taken lactulose as a substance given preoperatively to reduce the renal function impairment.
REVIEW OF LITERATURE
REVIEW OF LITERATURE

3.1. HISTORICAL ASPECT

According to the Greeks, “the disease of jaundice gets its name (icterus) from an animal of yellow colour. The disease occurs after prolonged ingestion or after the drinking of purgative drugs that remains within the body without being driven off. Symptomatic jaundice is the change to a yellow colour which first appears and is particularly noticeable in the whites of the eyes, the hollow of the soles, and the veins under the tongue. Moreover, the bowel fails to move, or whitish and clay stools occur and the urine is thick and saffron coloured. There is also a bitter taste in the mouth, thirst, loss of appetite, itching and dryness of the body, often the liver is swollen.”

Five centuries BC Hippocrates noted that “in jaundice, it is a bad sign if the liver hardens”. Although he had almost certainly recognized the hard, irregular liver and jaundice accompanying metastatic liver disease, it is true that in biliary tract obstruction long periods of jaundice accompanied by a palpable liver and compromise liver function are associated with an increase in morbidity and mortality after operation\textsuperscript{12}.

Pain, jaundice, and fever with rigors occurring together constitute the Charcot’s triad and indicate acute cholangitis. In 1877, he published this classical triad as typical findings of common bile duct stone\textsuperscript{13}.

The finding of a palpable gall bladder in the presence of obstructive jaundice suggests malignant obstruction to the biliary tree (Courvoisier’s law) and is most commonly due to carcinoma of the head of the pancreas. However, failure to palpate the gallbladder does not necessarily exclude malignant disease. In addition, it is possible to have a palpable distended gallbladder in
the presence of gallstones where one obstructs the common bile duct and another is impacted in Hartmann’s pouch or cystic duct resulting in an empyema (or mucocele) of the gall bladder. Courvoisier was the first to remove a stone successfully from the common bile duct on 21st January 1890\(^{13}\). He published his finding “of 187 cases, a shrivelled gall bladder was found in 70/87 with stones in common bile duct and distention in 92/100 from other causes.”

Occurrence of renal failure was first described by Clairmont and Von Haberer, in 1911, after surgery of obstructive jaundice in five patients. All of them died from acute renal failure. Since then many reports have been published regarding hepatorenal syndrome including pathogenesis of acute renal failure. The exact mechanism is not yet clearly understood.

### 2.2. RENAL DYSFUNCTION IN OBSTRUCTIVE JAUNDICE

Many studies have strongly suggested that there is a close association between liver and kidney disease. The term “hepatorenal syndrome” has been used to describe association between kidney and liver disease in patients dying of uremia after biliary tract surgery or acute liver failure. Although jaundice is not a prerequisite for this condition, there is an incidence of acute renal failure after surgery in patients with obstructive jaundice\(^{14}\). The term “hepatorenal syndrome” has since been redefined and is now reserved for patients with liver disease who develop renal dysfunction in the absence of any other known cause of renal failure\(^{4}\). In contrast to renal failure associated with acute tubular necrosis, the hepatorenal syndrome is characterized by the functional nature and inherent reversibility of the renal disorder which has been suggested or proved by the virtual absence of abnormalities on light microscopy in the post-mortem kidneys\(^{15,16}\), by the disappearance after death
of vasospastic changes demonstrated during life with angiography, and by occasional spontaneous recoveries from the complication. The kidneys of patients dying from acute renal failure showed histopathological changes similar to those observed in hypovolaemic shock. Good renal function has been achieved in kidneys procured from donors with hepatorenal syndrome, and conversely, renal function has recovered in patients with hepatorenal syndrome after successful orthotopic liver transplantation.

3.2.a. RENAL FUNCTION AND PATHOGENESIS OF RENAL FAILURE IN OBSTRUCTIVE JAUNDICE

The pathological changes within the kidney following the development of renal failure are quite non-specific and vary from relatively few histological changes to acute tubular necrosis, with glomerular and peritubular fibrin deposition. A number of factors have been implicated as aetiology of renal dysfunction. The factors that have been implicated are renal haemodynamics and body fluid disturbances, bacterial translocation from gut, endotoxaemia, disturbances of coagulation, decreased reticuloendothelial phagocytic capacity and hyperbilirubinaemia.

Alteration in renal blood flow or glomerular filtration rate (GFR) in obstructive jaundice has been addressed by many investigators, but remains controversial. In an experiment of bile duct ligation in dogs, Dawson observed that renal blood flow and glomerular filtration rate remained unchanged. This was supported by Zambraski and Dunn’s study. But some other studies reported mild degree of reduction in renal blood flow and glomerular filtration rate. In addition to possible changes in total renal blood flow, intrarenal cortical distribution of blood flow has been shown to be altered after bile duct ligation.
Bomzone and Kew\textsuperscript{21} concluded that catecholamines, rather than the renin and angiotensin system mediated the decrease in renal blood flow and redistribution of blood flow away from the outer cortex. However, it has been shown that renal nerve ablation does not prevent the decrease in renal blood flow after bile duct ligation\textsuperscript{6}. Change in intrinsic vascular reactivity could result in enhanced vascular tone and decreased renal flow, though sympathetic tone or catecholamine levels may not be increased. These effects suggest that any effect of jaundice or the renal vascular response to norepinephrine may be modulated by a separate effect on renal prostaglandin. There are similar findings in bile duct ligated experimental dogs where there was significant increase in renal production of prostaglandin E\textsubscript{2} and prostaglandin I\textsubscript{2}\textsuperscript{22}. These studies have found normal renal blood flow and GFR after bile duct ligation but administration of indomethacin caused a decrease in prostaglandin production resulting in a marked decrease in both renal blood flow and GFR. Zambraski and Dunn\textsuperscript{22} have noted redistribution of cortical blood flow with a relative increase in superficial cortical flow after prostaglandin inhibition with indomethacin.

The studies have shown that jaundice induces change in both renal and systemic vascular activity. There is decrease in vascular contractile responses and an increased endothelial derived relaxation factor (EDRF) found in obstructive jaundice\textsuperscript{23}. It has been stated that one of the causes inducing systemic hypotension is an excess in the amount of EDRF. There may be a relationship between the reported tendency to develop hypotension and the apparent predisposition to the development of acute renal failure in jaundiced patient. The amount of haemorrhage required to induce hypovolaemic shock was much less for jaundiced dogs than for non-jaundiced controls\textsuperscript{14}.

It is appreciated that, as a result of preoperative fluid depletion, jaundiced patients were more prone to the effect of hypovolaemic than non-jaundiced patients. Reduction in plasma volume in rats following common bile duct
ligation was supported by Oms *et al.*\(^{24}\) by the study of the fluid compartments within the body by using multi-isotope dilution techniques in bile duct ligated rats. They observed an initial reduction in the overall volume of extracellular fluid followed by 15 per cent fall in the plasma volume. The cause of volume depletion is appeared to be hypodipsia in association with impaired renal concentration of urine. They have also studied in human with similar reports.

At present, the pathogeneses of extracellular fluid depletion is not fully understood. Some studies point towards humoral mediators, such as atrial natriuretic peptide (ANP)\(^{24}\). ANP is known to cause natriuresis to counter the action of water and sodium retaining hormones, to inhibit the thirst mechanism and to produce peripheral vasodilatation\(^{25}\). There is an increase in rabbit plasma ANP levels following common bile duct ligation, and this was associated with increase in the sodium and water retaining hormones, aldosterone, renin and ADH. Why ANP levels are inappropriately increased in the presence of a depleted extracellular space is not known. Perhaps release of ANP, triggered by complete biliary obstruction, may be a primary event leading to isotonic extracellular volume depletion through hypodipsia, decreased appetite for sodium, and increased renal water and sodium losses. Neurogenic pathways from the liver to organs known to contain or release ANP (central nervous system, right atrium) may be involved but hepatic denervation did not prevent increased natriuresis after common bile duct ligation in dogs\(^{26}\). ANP could be present in the liver and be released to the general circulation as a consequence of an increase in biliary or portal venous pressure following bile duct ligation.

We are now beginning to understand that the gastrointestinal tract is not a passive organ and that gastrointestinal dysfunction is not limited to only ileus or gastrointestinal bleeding. Instead, it is becoming increasingly clear that the gastrointestinal tract and its contents, including bacteria and their products such as endotoxin, may influence other organ systems and alter patient outcome. The gastrointestinal tract has important endocrine, immunologic,
metabolic and barrier functions in addition to its role in nutrient absorption. Many investigators have documented that portal and systemic endotoxaemia are relatively common events in patients with obstructive jaundice. Although other explanations are possible, most investigators believe that it is the lack of bile salts reaching the intestinal lumen in patients with obstructive jaundice that results in the increased absorption of endotoxin into the portal circulation. The role of endotoxin is further supported by studies showing that preoperative treatment with oral bile salts prevent endotoxaemia and that, in patients so treated, postoperative renal function is maintained.

There has been increasing evidence that gut-derived endotoxins are the prime cause of renal dysfunction in obstructive jaundice. The effects of endotoxin are most likely to be mediated by the action of various cytokines. Cytokines are capable in altering renal haemodynamics and they have direct toxic effect on the kidney. They may alter renal haemodynamics by inducing a state of hypotension with concomitant release of vasoconstrictors and by redistributing intrarenal blood flow away from the renal cortex. The toxic effect of cytokines on the kidney may be secondary to their procoagulant activity, with induction of intravascular coagulation.

The Kupffer cells play an important role in removing any microorganisms in the portal blood, in inactivating endotoxin, and in clearing macromolecules or immune complexes. They also play a role in the removal of fibrin and fibrin complexes of high molecular weight in states associated with intravascular coagulation. Studies have shown impairment of Kupffer cell phagocytic function in obstructive jaundice, which promote spillover of endotoxin into the systemic circulation with subsequent development of systemic complications.

Indeed in both endotoxaemia and other states of disseminated intravascular coagulation, blockade of the reticuloendothelial system may result in renal cortical necrosis. Again intravascular coagulation is a dynamic process.
whereby procoagulant activity is countered by fibrinolysin and the latter may be impaired in obstructive jaundice\textsuperscript{34}. Since endotoxaemia is related to the onset of renal failure in patients with obstructive jaundice\textsuperscript{3}, there have been studies conducted on the functional activity of the Kupffer cells on the liver in the several types of liver diseases\textsuperscript{3}.

Studies have shown that one of the main predictive factors of postoperative renal impairment and deaths is the presence of an increased preoperative level of serum bilirubin\textsuperscript{35}. Whether bile or its constituents have a direct toxic effect on kidney has to be investigated. Some investigators postulate that impairment of mitochondrial function by bilirubin results not only in decreased hepatic reserve as measured by glucose tolerance curve but in reduced renal function as well. It has been noted that mitochondrial sequestration of bilirubin occurs only when bilirubin distribution exceeds the binding capacity of albumin, which corresponds to \textit{in vivo} concentration of bilirubin of \textgreater{}20mg/dl and albumin \textless{}3g/dl\textsuperscript{36}. Bilirubin has been shown to uncouple mitochondrial oxidative phosphorylation\textsuperscript{37}. Dawson\textsuperscript{38} has suggested that bilirubin may also induce renal ischaemia, but this effect has not been reproduced in other studies\textsuperscript{39}. Overall, there is insufficient evidence to implicate bilirubin in the pathogenesis of renal failure associated with obstructive jaundice.

\section*{3.2.b. RISK ASSESSMENT AND THERAPEUTIC STRATEGIES IN OBSTRUCTIVE JAUNDICE}

The recognition of renal dysfunction as a significant problem in patients with obstructive jaundice has led to the development of various theories about its pathogenesis and, based on these, to several proposed therapeutic strategies. Some of which have been widely used. The risk of postoperative morbidity
and mortality in jaundiced patients is considerably higher than in non-jaundiced patients.

**THERAPEUTIC STRATEGIES**

**Antiendotoxin therapy**

**Lactulose:** Lactulose, a commercially available synthetic disaccharide (galactoside-fructose), is used in the treatment of constipation and in the prevention of hepatic encephalopathy. Its exact mechanism of action in reducing endotoxaemia is not known but it may prevent endotoxaemia either by reducing or altering the gut flora, thereby reducing the endotoxin pool available for absorption, or by a direct effect on endotoxin itself\(^4^0\). It may reduce the availability of colonic endotoxin for absorption by its laxative effect\(^4^1\). Many of the toxic effects of endotoxin are mediated via the release from macrophages of effector substances such as tumour necrosis factor\(^4^2\), and lactulose has been shown to modify this macrophage response\(^4^3\). It reduces endotoxin-related mortality and improves survival in bile duct-ligated rats\(^4^0\), and a number of human studies have shown that preoperative administration of oral lactulose protects renal function in patients with obstructive jaundice\(^3^0,4^0\). However, lactulose often produces diarrhoea, sometimes distressing, limiting its clinical usefulness.

**Bile salts:** Bile acids and salts have detergent properties and the endotoxin lipopolysaccharide molecule is susceptible to this action *in vitro*\(^4^4\). In normal individuals significant systemic absorption of intact endotoxin is limited by emulsification or dissociation into non-toxic subunits\(^4^5\). It has been suggested that the gut of patients with obstructive jaundice has depleted bile salts, which results in larger pool of endotoxin available for absorption into the portal circulation\(^2\). Kocsar *et al.*\(^4^6\) showed that oral replacement of the bile salts
reduces endotoxin absorption and mortality. The effect of bile salts on the gut flora is less certain.

In humans, the study of bile salts supplement has produced conflicting results. In Cahill’s study in 1983\textsuperscript{29}, patients receiving 48 hours prior to surgery had no portal or systemic endotoxaemia and none had evidence of renal impairment postoperatively. This was supported by more recent study of Pain \textit{et al.}\textsuperscript{30}. However, Gawley and Colleagues\textsuperscript{47}, who also used sodium deoxycholate observed impaired renal function, despite a reduction in endotoxaemia. Thompson \textit{et al.}\textsuperscript{48} found no significant difference in endotoxaemia, renal function, morbidity and mortality between bile salt treated and control group. Theoretically, more than 95 per cent of sodium deoxycholate is absorbed in the terminal ileum, leaving only a small portion to reach into the colon\textsuperscript{49}. This means that only a small proportion actually reaches the major source to endotoxin\textsuperscript{1}, which is a major theoretical criticism of preoperative bile salt administration.

\textbf{Other antiendotoxin strategies}

Endotoxaemia has been stated as one of the causes of renal dysfunction in obstructive jaundice patients\textsuperscript{50}. Animal experiment of preoperative large bowel irrigation\textsuperscript{51} and administration of antiendotoxic compounds, such as polymixin B\textsuperscript{52} or taurolidine\textsuperscript{53} has shown some promise. A study of polymixin B in humans with obstructive jaundice has not proven to be beneficial\textsuperscript{54}. Till now there have no clinical trials using taurolidine in jaundiced patients, nor have there been any studies examining endotoxin antibodies in relation to obstructive jaundice and renal dysfunction\textsuperscript{4}. 
**Biliary drainage**

A high serum bilirubin in jaundiced patients undergoing surgery is recognized as a predictor of morbidity and mortality and is associated with an increased frequency of renal insufficiency, septic complications and postoperative haemorrhage\textsuperscript{55}. Wait and Kahng\textsuperscript{6} postulated that, lowering bilirubin levels preoperatively might be beneficial. “External drainage” diverts bile away from the gastrointestinal tract whereas “internal drainage” returns bile in the gastrointestinal tract.

Gouma and co-workers\textsuperscript{56}, using a rat model, showed that endotoxaemia associated with biliary obstruction was reduced after internal drainage but was unaffected after external drainage. Percutaneous external biliary drainage has been criticized for being susceptible to local septic complications, which may account for persistent endotoxaemia. Other known complications resulted in a study are bleeding, bile leakage, sepsis and catheter dislodgment. Diamond and Rowlands, using modified form of external biliary drainage in a sterile model, demonstrated that both internal and external drainage are equally capable of reversing endotoxaemia\textsuperscript{57}.

Returning bile to the gastrointestinal tract has been assumed to be of benefit and in animal models has reduced postoperative endotoxaemia, renal impairment and mortality\textsuperscript{58}. Internal biliary drainage has also been considered to be important in the recovery of mononuclear phagocyte function\textsuperscript{59}. Whether the reversal of endotoxaemia has any significant benefit in preventing perioperative renal dysfunction is not entirely clear. Smith et al.\textsuperscript{60}, however, demonstrated an improvement in renal function and fewer surgical complications in patients who had preoperative internal drainage. Percutaneously placed stents were subject to the same local complications as those associated with percutaneous external techniques. The result was that the overall incidence of associated morbidity negated any potential benefit.
Speer et al.\textsuperscript{61} have demonstrated a lower thirty-day mortality rate for endoscopic stenting method of decompressing the biliary tract compared with the percutaneous technique and this method avoids the complications associated with percutaneous insertion. Although some studies have revealed fewer postoperative complications in patients who have undergone preoperative endoscopic internal drainage\textsuperscript{62}, principally a reduced incidence of biliary infection, bacteraemia and intraoperative bleeding, there are no specific data relating to renal function. A definitive answer about the efficacy of biliary drainage in preventing renal impairment requires further controlled trials\textsuperscript{4}.

**Perioperative dopamine administration**

Dopamine, an endogenous catecholamine, has a role of selective dilatation of renal vessels increasing renal blood flow, sodium excretion and glomerular filtration rate\textsuperscript{63}. These effects may be reproduced clinically by the infusion of low-dose dopamine hydrochloride (2-5 \( \mu \text{g kg}^{-1}\text{min}^{-1} \)); this also causes mesenteric, coronary and intracerebral vasodilatation. Intravenous dopamine infusion is currently used to maintain renal perfusion and urinary output in critically ill patients and those with sepsis\textsuperscript{63}. This treatment also reduces incidence of renal impairment in patients undergoing liver transplantation. Parks et al.\textsuperscript{64} conducted a study to assess renal dysfunction in patients with obstructive jaundice and found that perioperative dopamine administration (starting at induction of anaesthesia and continuing for 48 hours after operation) does not alter the incidence of postoperative renal dysfunction in jaundiced patients.
Mannitol

Mannitol is a sugar that is freely filtered by the glomeruli into the tubular fluid where it acts as an osmotic diuretic\textsuperscript{65}. The perioperative use of intravenous mannitol to protect renal function is widespread, with 84 per cent of consultant surgeons in the UK using it as some stage in the management of the jaundiced patients\textsuperscript{66}. The protective effect of mannitol in preventing deterioration in function in the ischaemic kidney was noted by many surgeons. Perioperative mannitol administration was advocated by Dawson in 1965 and has become the most widely used therapeutic strategy. The theoretical basis is that mannitol acts as an osmotic diuretic, increasing tubular production of urine so preventing occlusion by renal casts. The second basis is, as it passes through the renal tubule, mannitol may exert an osmotic effect and so prevent endothelial cell swelling\textsuperscript{67}. Third, it has been shown to increase renal blood flow. Fourth, it is an effective radical scavenger\textsuperscript{68}.

Despite its widespread popularity, however, treatment with mannitol has been subjected to only a single prospective trial, which not only failed to demonstrate any significant benefit but also showed deterioration in renal function from the preoperative to the postoperative stage, which was actually greater in patients receiving mannitol\textsuperscript{69}. It also precipitated electrolyte disturbances. In their study mannitol group received 50g mannitol one hour before induction of anaesthesia which was continued for 2 days after surgery. Although, mannitol is able initially to improve the parameter, which is, monitored clinically, i.e. urine output, it might ultimately do harm and precipitate renal impairment\textsuperscript{69}.
Preoperative rehydration

Research has concentrated on control of fluid balance. Jaundiced patients are often fasted for prolonged periods before surgery for radiological investigations. In addition, animals and patients with obstructive jaundice have a depleted extracellular fluid volume, thought to be due to hypodipsia, and an impaired ability to concentrate urine, possibly mediated via an increase in atrial natriuretic peptide. Such a predisposition to hypotension would be in keeping with the pathological changes of focal tubular necrosis that are often found in the kidneys when renal failure occurs in association with obstructive jaundice. Such a hypovolaemic state may be exacerbated by administration of an osmotic diuretic like mannitol. This has led to the concept of preoperative volume expansion, which in recent clinical studies have shown decreases in incidence of postoperative renal dysfunction and renal failure. It seems prudent that careful control of fluid and electrolyte balance in addition to volume expansion before surgical, endoscopic or radiological intervention may substantially reduce renal dysfunction and might prevent it almost completely.
AIM OF THE STUDY
4. AIM OF THE STUDY

The aim of the study was:

- To assess the role of preoperative lactulose in preventing postoperative renal dysfunction in obstructive jaundice.
PATIENTS AND METHODS
5. PATIENTS AND METHODS

A prospective study was carried out from March 1997 to April 1998 in the Department of Surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. The total period of study was fourteen months. The cases were randomized in two groups. Patients in study group received lactulose whereas control group did not. Forty-five patients were entered into the study at least 3 days before surgery. All patients had a plasma bilirubin level $>100 \, \mu\text{mol/l}$. Patients with previous history of renal or parenchymal liver disease or who had been given a general anaesthesia in preceding six weeks were excluded. Three patients failed to comply with the protocol requirements and were excluded: 2 had inappropriate sample collection, one underwent laparotomy alone for carcinoma of the gall bladder with metastasis. The remaining forty-two patients were evaluated. Twenty patients received preoperative oral lactulose and twenty-two remained as control. All the biochemical tests were carried out in the Biochemistry Lab, Tribhuvan University Teaching Hospital.

PREOPERATIVE MANAGEMENT

All patients admitted were evaluated with detailed history and physical examination in order to know about the existence of exclusion criteria in patients. In addition to diagnostic investigations and those required for assessment of fitness for general anaesthesia, serum bilirubin, serum protein, serum transaminases, alkaline phosphatase and prothrombin time were estimated in all patients two to three days prior to surgery. According to need of patient’s, the diagnostic tools used were ultrasonography of abdomen, ERCP, percutaneous transhepatic cholangiogram and CT scan.
Preoperative assessment of renal function included estimation of blood urea, serum creatinine and 24-hour endogenous creatinine clearance rate ($C_{24}$). The tests were carried out two days prior to surgery and on first 3 consecutive 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. Renal failure was defined as a urine volume <400 ml/24 hr. and associated with a rising plasma urea and creatinine level. Serum electrolytes were estimated in all cases when renal function tests were performed.

Blood urea was estimated by Diacetyl monoxime, serum creatinine by Jaffe reaction, serum bilirubin by Malloy and Evelyn method, transaminases by Retimann and Franklin method, serum protein by Biuret method and prothrombin time by one stage method (using thromboplastin).

Oral lactulose, 30 ml 6 hourly was given for 3 days before surgery. In a patient who developed troublesome or frequent diarrhoea (>4 times per 24- hrs), the subsequent dose of lactulose thereafter were halved.

Preoperative hydration was started 24 hours prior to surgery. All were infused 50 ml/kg of intravenous fluid (5% dextrose and normal saline) in that period. All of them received antibiotics according to surgeon’s choice on the day of hydration, which was continued at least a week after surgery. Electrolytes imbalances, if exist, were corrected. All of them were given vitamin $K_1$ (10 mg intra-muscular or intravenous) for 3 or more days for the correction of prothrombin time. Patients with haemoglobin <10 gm per cent were corrected with whole blood transfusion.
INTRAOPERATIVE MANAGEMENT

Urine output during surgery was noted. Regular blood pressure was recorded and amount of blood loss was noted. Operative findings, procedure done and time taken for surgery were recorded.

POSTOPERATIVE MANAGEMENT

According to requirement of patients care, they were either transferred to Intensive Care Unit or Post-Operative Ward for immediate postoperative care. Accurate 24-hr. urine output was recorded with strict maintaining of input and output chart. Antibiotics started preoperatively were continued for a week or more as deemed necessary.

Renal functions were assessed on first three consecutive postoperative days. Values of urea, creatinine and C24 were recorded. All patients were monitored for development of any complication till the day of discharge. Total hospital stay of every patient was recorded.

STATISTICAL ANALYSIS

Postoperative change in urea, creatinine and C24 were compared in same group using ‘paired t test’, whereas for comparison of changes in C24 in two different groups were made with ‘unpaired t test’. Comparison of incidences of renal function impairment was made with $\chi^2$ test. P value of less than 0.05 was considered as significant.
RESULTS
6. RESULTS

Forty-two patients with obstructive jaundice were taken for study. There were 17 males and 25 females, and their age ranged from 16 to 70 years (mean 42±14 years). The mean duration of jaundice at the time of presentation was 6.1±5.8 weeks, ranging from 1 to 26 weeks (Table-I).

The commonest cause of obstructive jaundice was choledocholithiasis (50%) followed by carcinoma head of pancreas (19%) (Table-II). Other patients with minimally elevated bilirubin (<100 µmol/l), who were not included in this study, were caused by common bile duct stones. CBD exploration with or without cholecystectomy was the commonest operative procedure in obstructive jaundice. Among 18 patients operated for periampullary carcinoma, 9(50 per cent) underwent curative surgery with Whipple’s procedure, whereas others had undergone palliative by-pass surgery (Table-III).

The operation time ranged from 75 to 300 minutes (mean 150±92 min). The duration of hospital stay ranged from 12 to 58 days (mean 24±10 days).

Preoperative bilirubin level ranged from 110 to 637 µmol/l. The transaminases values were normal or minimally elevated, except in those with late presentation. The alkaline phosphatase levels were invariably raised and total protein levels in both groups were within normal limits (Table-IV). Three patients in lactulose group developed frequent diarrhoea but all of them tolerated when the remaining doses were halved.

The preoperative blood urea level ranged from 2.2 to 6.9 mmol/l (mean 4.5±1.7 mmol/l) and serum creatinine from 50 to 151 µmol/l (mean 71±20.1
µmol/l). The mean \(C_{24}\) was \(66\pm21\) ml/min (ranged from 27 to 111 ml/min). Three patients in control group and two patients in lactulose group had evidence of preoperative renal dysfunction (\(C_{24}<40\) ml/min). But among them only one in control group had postoperative renal impairment. Remaining four patients had increase in \(C_{24}\) level by 40 to 80 per cent. Overall the \(C_{24}\) value in the control group dropped from a mean of \(65.1\pm20.5\) ml/min before surgery to \(54.4\pm22.4\) ml/min after surgery (16 per cent decrease). In the group receiving lactulose the \(C_{24}\) value dropped from \(66.8\pm21.7\) ml/min to \(60.0\pm20.4\) ml/min (10 per cent decrease) (Table-V). To compare the drop of \(C_{24}\) in two groups, statistical analysis was done applying ‘unpaired t test’ and difference in change was found to be statistically not significant (\(t=0.11,\) d.f.=40, \(P>0.05\)). None of the patients in both groups developed acute renal failure postoperatively.

Among 22 patients in control group, 10 patients had \(C_{24}\) dropped postoperatively by more than 20 per cent whereas 8 patients had less than 20 per cent drop and 4 had increased \(C_{24}\) value. In lactulose group, out of 20 patients 6 had \(C_{24}\) value dropped by more than 20 per cent postoperatively. Ten had minimal decreased \(C_{24}\) value and 4 had increased in \(C_{24}\) value (Table-VI). When these two groups were compared to know whether there is significant renal function impairment or not, statistical analysis failed to show any significant difference (\(\chi^2=1.1,\) d.f.=1, \(P>0.05\)).

The most frequent complication noted was wound infection in 18 patients (43 per cent). Other complications noted were respiratory tract infection, diarrhoea, anastomotic leak, urinary tract infection, gastrointestinal bleeding, ascitic fluid leak, subphrenic abscess and prolonged ileus (Table-VII). One patient died in second week after Whipple’s procedure. There was anastomotic leak with wound infection and finally died due to septicaemia. One each after Whipple’s procedure and common bile duct exploration were gravely ill and were taken home by patients parties, and these two cases were
included in mortality. Both of them had presented late with poor nutritional status preoperatively. The one who had undergone common bile duct exploration also had significantly poor liver function.
Table – I : Age and sex distribution of patients and duration of jaundice.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 22)</th>
<th>Lactulose group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>16 – 70 (40±15)</td>
<td>24 – 68 (40±13)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>8:14</td>
<td>9:11</td>
</tr>
<tr>
<td>Jaundice duration (weeks)</td>
<td>1 – 26 (6.4±6.5)</td>
<td>1 – 26 (5.6±6.5)</td>
</tr>
</tbody>
</table>

Values given are (mean ± standard deviation)
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group (%)</td>
</tr>
<tr>
<td>Choledocholithiasis with or without Cholelithiasis</td>
<td>12(54.5)</td>
</tr>
<tr>
<td>Carcinoma head of pancreas</td>
<td>4(18.2)</td>
</tr>
<tr>
<td>Carcinoma ampulla of Vater</td>
<td>2(9.1)</td>
</tr>
<tr>
<td>Chlangiocarcinoma</td>
<td>4(18.2)</td>
</tr>
<tr>
<td>Bile duct stricture (Postoperative)</td>
<td>-</td>
</tr>
<tr>
<td>Mirizzi’s syndrome</td>
<td>-</td>
</tr>
<tr>
<td>Hydatid cyst (ruptured in bile duct)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>22(100.0)</td>
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Table – III : Operative procedures performed to relieve biliary obstruction

<table>
<thead>
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<th>Operative procedure</th>
<th>No. of patients</th>
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</thead>
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<tr>
<td></td>
<td>Control group (%)</td>
</tr>
<tr>
<td>Common bile duct exploration with or without cholecystectomy</td>
<td>10(45.5)</td>
</tr>
<tr>
<td>Whipple’s procedure</td>
<td>4(18.2)</td>
</tr>
<tr>
<td>Cholecysto – jejunostomy + jejuno-jejunostomy</td>
<td>3(13.6)</td>
</tr>
<tr>
<td>Hepatico-jejunostomy + jejuno-jejunostomy</td>
<td>3(13.6)</td>
</tr>
<tr>
<td>Cholecystectomy + choledocho-duodenostomy</td>
<td>2(9.1)</td>
</tr>
<tr>
<td>Cholecystectomy + peroperative cholangiogram</td>
<td>-</td>
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<tr>
<td>Total</td>
<td>22(100.0)</td>
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</tbody>
</table>
Table – IV : Preoperative liver function tests

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 22)</th>
<th>Lactulose group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (µmol/l)</td>
<td>110 – 637 (293±148)</td>
<td>110 – 612 (259±157)</td>
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<tr>
<td>Alkaline phosphatase (units/l)</td>
<td>126 – 444 (229±118)</td>
<td>110 – 488 (196±121)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (units/l)</td>
<td>16 – 70 (38.4±17)</td>
<td>17 – 210 (45±20)</td>
</tr>
<tr>
<td>Alanine aminotransferase (units/l)</td>
<td>13 – 93 (39±27)</td>
<td>19 – 197 (46±19)</td>
</tr>
<tr>
<td>Protein (g/l)</td>
<td>45 – 90 (62±13)</td>
<td>58 – 77 (65±6)</td>
</tr>
<tr>
<td>Prothrombin time (sec.)</td>
<td>13 – 18 (15±1)</td>
<td>13 – 18 (15±1)</td>
</tr>
</tbody>
</table>

Values given are (mean ± standard deviation)
Table – V : Summary of the preoperative and postoperative results of renal functions and their comparison.

A. Control group

<table>
<thead>
<tr>
<th>Mean of variables</th>
<th>Preoperative (mean of 3 days)</th>
<th>Postoperative (mean of 3 days)</th>
<th>Paired t values</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea (mmol/l)</td>
<td>2.2 – 6.9 (4.4±1.2)</td>
<td>1.9 – 12.4 (5.5±3.4)</td>
<td>1.26</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>60 –151 (79.8±19.2)</td>
<td>53 – 162 (98.2±39.5)</td>
<td>1.95</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Creatinine clearance (C₂₄ ml/min)</td>
<td>29.5 – 95.9 (65.1±20.5)</td>
<td>22.5 – 117.0 (54.4±22.4)</td>
<td>1.93</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

B. Lactulose group

<table>
<thead>
<tr>
<th>Mean of variables</th>
<th>Preoperative (mean of 3 days)</th>
<th>Postoperative (mean of 3 days)</th>
<th>Paired t values</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea (mmol/l)</td>
<td>2.6 – 6.5 (4.7±1.6)</td>
<td>2.0 – 15.0 (5.1±2.8)</td>
<td>0.46</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>50.0 – 105.0 (60.0±21.0)</td>
<td>59.0 – 201.0 (87.2±29.5)</td>
<td>1.24</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Creatinine clearance (C₂₄ ml/min)</td>
<td>27.6 – 111.6 (66.8±21.7)</td>
<td>20.7 – 97.0 (60.0±20.4)</td>
<td>1.74</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values given are (mean ± standard deviation)
Table – VI : Overall incidence of postoperative renal function impairment

<table>
<thead>
<tr>
<th></th>
<th>Renal function impaired</th>
<th>Renal function not-impaired</th>
</tr>
</thead>
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<tr>
<td>Control group</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>(n = 22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactulose group</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>(n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>26</td>
</tr>
</tbody>
</table>

P value > 0.05
### Table VII: Complications and their frequency

<table>
<thead>
<tr>
<th>Complications</th>
<th>Control group n = 22 (%)</th>
<th>Lactulose group n = 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>10(45.0)</td>
<td>8(40.0)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>-</td>
<td>3(15.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3(13.5)</td>
<td>-</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>2(9.0)</td>
<td>-</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1(4.5)</td>
<td>1(5.0)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>-</td>
<td>1(5.0)</td>
</tr>
<tr>
<td>Ascitic fluid leak</td>
<td>1(4.5)</td>
<td>-</td>
</tr>
<tr>
<td>Subphrenic abscess</td>
<td>-</td>
<td>1(5.0)</td>
</tr>
<tr>
<td>Prolonged ileus</td>
<td>-</td>
<td>1(5.0)</td>
</tr>
<tr>
<td>Death (*)</td>
<td>2(9.0)</td>
<td>1(5.0)</td>
</tr>
</tbody>
</table>

Some patients had more than one complication

(*): One case in control group was discharged on request in terminal stage and one in lactulose group was taken home by family who was also in terminal stage. Both of them are included in mortality.
Table VIII: Mortality and acute renal failure in patients with obstructive jaundice.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of patients</th>
<th>Overall mortality rate (%)</th>
<th>Acute renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al.</td>
<td>1960</td>
<td>350</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Dawson</td>
<td>1965</td>
<td>103</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Braasch and Gray</td>
<td>1977</td>
<td>279</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Allison et al.</td>
<td>1979</td>
<td>24</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Pitt et al.</td>
<td>1981</td>
<td>155</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Wittenstein et al.</td>
<td>1981</td>
<td>170</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Dixon et al.</td>
<td>1983</td>
<td>373</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Blamey et al.</td>
<td>1983</td>
<td>89</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Armstrong et al.</td>
<td>1984</td>
<td>120</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Gundry et al.</td>
<td>1984</td>
<td>50</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Keighley et al.</td>
<td>1984</td>
<td>118</td>
<td>10</td>
<td>6</td>
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<tr>
<td>Bouillot et al.</td>
<td>1985</td>
<td>176</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Pain et al.</td>
<td>1991</td>
<td>102</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Govil et al.</td>
<td>1993</td>
<td>32</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Parks et al.</td>
<td>1994</td>
<td>23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Present series</td>
<td>1999</td>
<td>42</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Total or mean</td>
<td></td>
<td>2206</td>
<td>13.6</td>
<td>7.3</td>
</tr>
</tbody>
</table>
DISCUSSION
7. DISCUSSION

Surgical procedures in patients with obstructive jaundice are known to be associated with higher incidences of complications than those in non-jaundiced patients. This is based on both clinical experience and several studies in animal and man documenting a higher incidence of renal dysfunction, sepsis, coagulation disturbance and impaired wound healing in jaundice.

Cholelithiasis is very common disease in our country. Cholecystectomy is one of the commonest operations performed in our hospital, which is equally true for other hospitals. Mostly, common bile duct stones are secondary stones. Hence, stones in common bile duct comprises of 50 per cent cases of obstructive jaundice in this study.

Renal impairment is extremely common in the presence of obstructive jaundice with 60 to 75 per cent of patients having a fall in operative glomerular filtration rate (GFR). In our study, about 80 per cent in both groups had a fall in their GFR postoperatively, which is consistent with above findings.

Dawson 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 more than 20 per cent as a criterion of renal impairment. In Dawson’s study, the C$_{24}$ value in control group dropped from mean of 92.7±8.2 ml/min before surgery to 56.5±7.4 ml/min after surgery (39 per cent decrease). In the group receiving mannitol the C$_{24}$ value dropped from 70±10.9 ml/min to 15±4.1 ml/min (78 per cent decrease). There was a statistically significant difference between two groups. Contrary to this result, Pain et al. had shown increase in postoperative C$_{24}$ value. In their study, the C$_{24}$ value in control group rose from mean 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 C24 value rose from 53.4±21.6 ml/min to 61.5±22.1 ml/min (15 per cent increase). But there was no statistically significant difference between two groups. In our study, though there was more drop in postoperative C24 value in control group than in lactulose group, they were found to be statistically not significant. In control group postoperative C24 drop was 16 per cent (from 65.1±20.5 ml/min preoperatively to 54.4±22.4 ml/min postoperatively) and in lactulose group there was drop of C24 by 10 per cent (from 66.8±21.7 ml/min to 60±20.4 ml/min).

In a study conducted by Pain et al.,30 they have shown that in patients who had normal renal function before surgery, postoperative renal impairment was more common ($\chi^2$=8.1, d.f.=2, P<0.02) in the control group than in those treated by preoperative lactulose or bile salts. In our study, though per cent drop of C24 is more in control group than in lactulose group, the postoperative renal function impairment was not significantly different in two groups ($\chi^2$=1.1, d.f.=1, P>0.05).

The most striking finding in the present series is that not a single patient developed acute renal failure postoperatively. This is similar to a study conducted by Parks et al.,64 in contrary to other series reporting 4 to 18 per cent acute renal failures (Table-VIII). This may be because of preoperative strict attention to fluid, electrolytes and use of perioperative antibiotics.

The other modalities have also been tried to improve postoperative renal function, but none of them showed promising results to be accepted as standard means for controlling renal dysfunction. Gawley et al.,47 used preoperative oral bile salts, Parks et al.,64 used perioperative dopamine infusion and Gubern et al.,69 used perioperative mannitol as measures to control renal dysfunction. All the results showed no renal function improvement in postoperative cases of patients with obstructive jaundice.
The incidence of wound infection and other septic complications after biliary surgery is high, but significantly reduced by the use of prophylactic antibiotics\textsuperscript{73}. In our study, we used cefazoline(or ciprofloxacin) plus metronidazole perioperatively. In spite of use of perioperative antibiotics, we have very high incidence of wound infection (43 per cent) compared to 6 per cent in a study by Pain \textit{et al.}\textsuperscript{30}. It is also true that wound infection is also common in other abdominal surgeries, especially related to malignant and chronically debilitating diseases.

The overall mortality in patients with obstructive jaundice undergoing surgery ranged from 0 to 27 per cent (Table-VIII). Present study had mortality of 7 per cent (3 out of 42). Two of them were followed by very major surgery for malignancy (Whipple’s procedure) and one of them for bile duct stones, who presented very late with high bilirubin level and deranged liver functions.
CONCLUSION
8. CONCLUSION

The fall in the incidence of postoperative renal impairment and no incidence of renal failure with or without lactulose, was the result of strict attention to the preoperative hydration, electrolyte correction, perioperative use of antibiotics and preoperative correction of coagulation abnormality. Thus, all jaundiced patients undergoing surgery or percutaneous and endoscopic procedures should be properly managed preoperatively.
BIBLIOGRAPHY
9. **BIBLIOGRAPHY**


APPENDIX
APPENDIX

Data collection

Case no. :
In Patient no. :
Patient’s name :
Age :
Sex : Male / Female
Marital status :
Religion :
Occupation :
Address :
Group :
   A. Control
   B. Lactulose

Date of admission :
Date of discharge :
Duration of stay (days) :

CHIEF COMPLAINTS

Pain abdomen :
Fever :
   Chills / rigors
Jaundice : 
Duration : 
Itching : 
Urine colour : 
Stool colour : 
Other complaints :

PERSONAL HISTORY
Smoking :
Alcohol :

PAST ILLNESSES
A.
B.
C.

PHYSICAL EXAMINATION
general
Nutrition :
Body weight :
Jaundice :
Anaemia :
Lymph nodes :
Oedema :

Dehydration :

Pulse :

Blood pressure :

Temperature :

Respiratory rate :

**abdominal examination**

Liver :

Gall bladder :

Spleen :

Kidneys :

Ascites :

External genitalia :

Per rectum findings :

Others :

**respiratory system**

Breath sounds :

Added sounds :

**cardiovascular system**

Heart sound :

Murmurs :

Other sounds :
**central nervous system**

Higher mental function :

Memory :

Orientation :

Cranial nerves :

Motor function :

Sensory function :

**INVESTIGATIONS**

Blood :

Haemoglobin :

WBC :

Total :

Differential : N L E M B

ESR :

B.T. :

C.T. :

Serum :

Sugar :

Na and K :

Urine :

Chest x–ray :

ECG :
<table>
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<tr>
<th>Test</th>
<th>Preoperative (2 days before surgery)</th>
<th>Postoperative</th>
<th>day 1</th>
<th>day 2</th>
<th>day 3</th>
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<td>Renal function test</td>
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</tr>
<tr>
<td>Urea</td>
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<td>Creatinine</td>
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<td>C24</td>
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<td>Urine (ml/24hr)</td>
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<td>Liver function test</td>
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<tr>
<td>Bilirubin</td>
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<td>Serum protein</td>
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PREOPERATIVE PREPARATION

I/V fluids : 
Vitamin K : 
Antibiotics : 
Others : 

OPERATIVE DETAILS

Diagnosis : 
Operative procedure : 
Findings : 
Operative duration : 

POSTOPERATIVE MORBIDITY AND MORTALITY

Complications : 
Death (cause) : 

HISTOPATHOLOGICAL REPORT