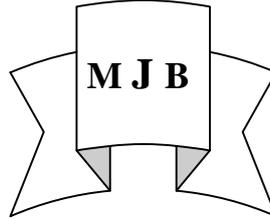


The Immediate Biochemicalresponse after Relieving Large Bile Duct Obstruction

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Abstract

- Ninety six patients with large bile duct obstruction were admitted to the surgical ward in the specialized teaching hospital for gastro-enterology and hepatology between January 2002 and march 2004
 - Each of them was offered a therapeutic procedure (surgical or otherwise), that successfully drained his/her obstructed biliary system.
 - Each of them was assessed clinically and biochemically before and after that therapeutic procedure and the follow-up continued for 10 days to assess the immediate clinical and biochemical responses.
 - Most of the clinical and biochemical parameters chosen for the assessment improved towards normality during the observation period.
 - Aberrant results were noticed, specified, and analyzed, in order to understand the underlying pathological factors leading to them.
 - The results were discussed.
- Recommendations were suggested to improve postoperative assessment of such patients.

الخلاصة

- الاستجابة المختبرية المباشرة بعد فتح أنسداد القنوات الصفراوية الكبرى
١. ست وتسعين مريضاً مصاباً بأنسداد القنوات الصفراوية الكبرى تم إدخالهم الى مستشفى علاج أمراض الجهاز الهضمي والكبد التعليمي ، في الفترة الممتدة بين كانون الثاني ٢٠٠٢ و آذار ٢٠٠٤ .
 ٢. كل منهم خضع لأجراء علاجي (بالجراحة أو بغيرها) نجح في بزل جهازه الصفراوي المسدود.
 ٣. كل حالة تم تقييمها سريريا و مختبريا قبل وبعد الأجراء العلاجي وتم متابعة المرضى للعشرة أيام التي تلت ذلك مباشرة، لتقييم أستجابتهم المختبرية المباشرة.
 ٤. في معظم الحالات تم ملاحظة تحسن النتائج المختبرية نحو حدودها الطبيعيه خلال فترة المتابعه.
 ٥. النتائج التي شذت عن ذلك تم ملاحظتها وتقييمها لفهم العوامل المرضيه المسببه لها.
 ٦. تمت مناقشة كل النتائج التي تم الحصول عليها في سياق البحث.
- أقترحت بعض التوصيات لتحسين مستوى المتابعه السريره والمختبريه (بعد العلاجي) للمرضى.

Introduction

Jaundice from the French “jaune” meaning yellow – Lord Cohn of Birkenhead, professor of medicine, University of Liverpool. Jaundice is a syndrome, the hallmark of which is yellowish discoloration of the tissues owing to the accumulation bilirubin (conjugated water soluble or unconjugated). It has varied etiology and mechanisms.

Jaundice can be detected clinically when the serum bilirubin exceeds 40 mmol /L[1-3]

The various mechanisms alone or in combination, that lead to the hyperbilirubinaemia are:

1. Excessive bilirubin production; haemolysis, ineffective erythropoiesis, etc.
2. Impaired uptake and transport by the hepatocytes.
3. Failure of conjugation.
4. Impaired secretion of conjugated bile into the bile canaliculi.
5. Impairment of bile flow subsequent to secretion by the hepatocytes. [2]

Cholestatic jaundice:

It is the type of jaundice that result from impaired bile flow to the duodenum subsequent to secretion of conjugated bilirubin into the bile canaliculi.

Cholestatic jaundice can be “intrahepatic” when it may be:

- Functional: e.g. drugs, hepatitis, etc.
- Organic: due to obstruction to the intrahepatic biliary tree.

On the other hand cholestatic jaundice can be “extrahepatic” which also known as “large bile duct obstruction” and this type is nearly always the result of organic disease e.g. ductal calculi, pancreaticobiliary cancer. ...etc.[2,3]

Causes of surgical jaundice (large bile duct obstruction):

1. Ductal calculi
2. Gallstones
3. Pancreatic and biliary malignancy
4. Non-malignant strictures
5. External compression of the bile duct by lymph nodes and tumour masses

Parasitic infestation of the biliary tract.[1,4,5]

Clinical manifestations of large bile duct obstruction:

Calculi within the common duct may be present for many years without causing symptoms. Usually the symptom complex consists of colicky pain in the right upper quadrant radiating to the right shoulder with intermittent jaundice (which is characteristic for ductal stones)

accompanied by pale stools and dark urine. If obstruction is complete, jaundice progresses but is rarely intense. The gallbladder is usually not distended because of associated inflammation (Courvoisier's law). In patients with ascending cholangitis charcot's triad of fever, abdominal pain and jaundice are characteristic. [5]

Patients with bile duct carcinoma characteristically present with the recent onset of jaundice, pale stools, and dark urine. Jaundice is usually preceded by pruritis. Almost all patients have significant weight loss with loss of appetite. Half of the patients have abdominal pain. Cholangitis may result from obstruction, and the gallbladder is palpable in one third of the patients with distal lesions[5,6].

Pancreatic head cancers may produce obstructive jaundice when they are still small and curable. Painless jaundice is uncommon (13%), while 75% present with obstructive jaundice, weight loss, and deep-seated abdominal pain (which may be referred to the back), jaundice is usually progressive, associated with itching, cholangitis is uncommon (10%), and the gallbladder is palpable in 25% of the patients.[5,7- 9]

Intrabiliary rupture of a hydatid cyst present with classic triad of biliary colic, jaundice and urticaria.[5]

Biochemical features of large bile duct obstruction:

1. Conjugated hyperbilirubinaemia.
2. Elevation of the alkaline phosphatase, 5-nucleotidase, gamma-glutamyl transpeptidase.
3. Minimal or no elevation of the serum transaminases.
4. The presence of conjugated bilirubin in the urine.
5. Elevation of serum cholesterol and bile acids levels (although they are not routinely measured). [2 ,10]

The Aim of the Study

Is to achieve the following purposes:-

1. To assess the clinical and biochemical response of our patients after successful relief of their large bile duct obstruction , to analyze the results , tabulate them , and to compare them with those fixed in literatures and textbooks.
2. To answer the following questions:
 - What is the best tool to assess the success of our operation /intervention to relieve large bile duct obstruction?
 - Whether it is the clinical or the biochemical arm of the assessment that

is most reliable and how frequent they should be ordered postoperatively

- What is the explanation of any aberrant or unexpected results obtained and whether or not active measures should be undertaken as a response?
- What are the difficulties encountered during the accomplishment of this study that limit our full assessment?

Patients and Methods

Ninety six (96) patients with large bile duct obstruction were followed up prospectively for 2 years & 4 months (between January 2002 and March 2004), each patient was evaluated clinically and biochemically, on admission to the surgical ward (in the specialized teaching hospital for gastroenterology and hepatology) and being treated successfully and their cholestatic jaundice was relieved ,they were followed for 10 days after their surgery / intervention using the clinical parameters of abdominal pain , jaundice , fever , itching and loss of appetite , and the biochemical parameters of total serum bilirubin , serum albumen , alkaline phosphatase,

AST ,ALT ,....to assess their response to the surgical or interventional endoscopic solutions offered to solve their problem.

Each of the clinical parameters chosen was assessed daily and for the abdominal pain , jaundice and itching ; the terms ,(mild ,moderate and severe)were used for scoring, and for the appetite ,the terms , (same ,much improved) ,were used.

The biochemical parameters were assessed every other day starting on “day one” postoperatively up to day ten. The normal values used in the hospital lab. are used in this study, and the S.I. units were used except for the serum bilirubin level ;when mg/dl was used for easier interpretation.

Results

1. age & sex incidence :

The 96 patients included in this study were picked randomly & the only criteria to let them be part of the study is that they are victims of large bile duct obstruction caused by benign & /or malignant pathologies. They were 65 males & 31 female table 1.

Sex	31-40	41-50	51-60	61-70	71-80	Total
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Males	2(12.5%)	6(16.6%)	3(13.5%)	0(20.8%)	4(4.2%)	5(67.7%)
Females	1(6.25%)	5(5.2%)	5(6.25%)	7(7.3%)	7(7.3%)	11(32.3%)
total	3(18.8%)	11(21.8%)	9(19.8%)	7(28.1%)	11(11.5%)	16(100%)

Table 1: age & sex categories

2-Aetiology

The main aetiological factors in this study were malignant lesions 64 cases(66.5%),while the benign lesions 32 cases (33%) of the causative factors (mainly ductal

stones, benign strictures, and intrabiliary rupture of a hydatid cyst).

Both categories are shown in details in table 2 :

Sex	Ductal stones	Benign strictures	Caecal pancreas	Periampullary ca	Extra-Hepatic Cho. Ca	Pancreatic mass with stones	Rupture hydatid	Total
Males	14	3	35	2	2	4	5	65
<i>Females</i>								

Table2: Etiology of obstructive jaundice

Malignant lesions were commoner in the older age groups in contrast to the benign lesions which were commoner

in the young / middle age groups as shown in table 3

Table 3 Aetiology according to age group

Age group	30-55(both M&F)	55-80(bothM&F)	total
malignant	13 (13.5%)	51 (53%)	64
benign	21 (21.9%)	11 (11.5%)	32

Most of the patients (90 out of 96 i.e. 93.8%) were recognized to have intra and/or extrahepatic bile ducts dilatations using abdominal ultrasound scanning (though more than once in some of them) .

Cases of ductal calculi are usually referred from the medical dept. after being diagnosed either to have a big stone (> 1.5 cm) or after doing E.R.C.P. with failure to extract smaller stones.

M.R.C.P. and C.T-scanning were used to verify obscure or borderline cases and they were used in 15 and 8 cases successively especially in pancreatic carcinomas and cholangiocarcinomas.

Positive fine needle aspiration cytology(FNAC) or endoscopic biopsy was available as a positive tissue diagnosis preoperatively in a minority of cases only.

3.Treatment : two major categories were applied :

a. Operative management:

The majority of the cases admitted to the surgical ward were dealt with

surgically, and they were either benign lesions (mostly choledocholithiasis ,ductal injuries / strictures or ruptured hydatid cysts) ,in which other non-operative modalities fail to achieve reopening or bypassing obstructed biliary passages ,or failure to extract big stones (> 1.5 cm) stones by endoscopic stone extraction.

Otherwise malignant lesions are either resected hoping for the cure (using Whipple's pancreaticoduodenectomy) or they were bypassed surgically for inoperable pancreatic head carcinomas and periampullary tumors.

b. Non operative management.

Some of the above cases (benign & malignant) were managed by the interventional endoscopic maneuvers (endoscopic stone extraction or endoscopic biliary drainage using nasobiliary tube drains or stenting). & this is either to make the next step easier (e.g: endoscopic stone extraction is followed by laparoscopic cholecystectomy) or to relieve their cholestatic jaundice when they are unfit for general anesthesia & major surgery.

Table 4 Management of benign and malignant cases

Type	Interventional endoscopy	surgery	Total
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Malignant causes	4(4.2%)	60(62.5%)	64
Benign causes	12(12.5%)	20(20.8%)	32

(4) follow-up : biochemical response :

The initial pre-operative /intervention levels of T.S.B. were higher in the malignant group .

Initial values higher than 10mg/dl (170mmol/l) were recorded in

(A) Total serum bilirubin level: (with direct and indirect fractionation):

35 cases (33 in the malignant group and 2 in the benign group),and such levels were associated with pancreatic head tumors larger than 4 cm, or a disease duration longer than 2 months

Table 6 No. of cases with the specified pre-operative T.S.B. levels

cause	< 5 mg/dl	5-10 mg/dl	> 10 mg/dl	total
benign	19	11	2	32
malignant	6	25	33	64

Total serum bilirubin levels is one of the important biochemical parameters used to assess the validity of surgery (or endoscopic intervention) to relieve cholestatic jaundice.

The majority of our patients showed gradual steady decline in their T.S.B. levels, being faster and reaching back to the normal levels at the end of the observation period in cases of ductal stones or intrabiliary ruptured hydatid cysts, while those who had pancreatic tumors larger than 4 cm in diameter ,or those with prolonged illness showed a slower decline in their

T.S.B. levels ,and a high percentage of them

(> 80%) never regain their normal T.S.B. levels at the end of the observation period in spite of the observed marked decline as compared to the pre-operative levels.

A striking observation was to notice that 5 cases (single benign intrabiliary rupture of a hydatid cyst and 4 malignant cases) ,showed slightly elevated initial T.S.B. levels. post-operatively as compared with the pre-operative levels. This observation formed 3.1% of the benign cases and

6.3% of the malignant cases and this was noticed in the serum samples taken in the immediate post operative

morning followed by gradual decline in the successive readings.

Table 7 No.s and percentages of cases with initial elevated TSB levels.

type	Cases with increased initial TSB	% of the same type	% of the total	<i>P value</i>
benign	1	3.1 %	1 %	
<i>malignant</i>	4	6.3 %	4.2%	

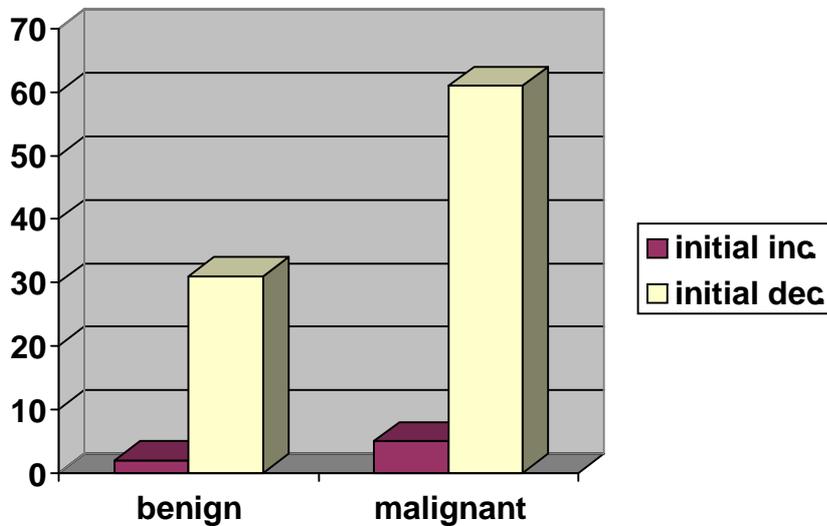
(B) Serum alkaline phosphatase:

Pre operative/ intervention levels of serum alkaline phosphatase were higher in the malignant group as compared as those caused by benign pathologies .

Cases associated with severe hyperbilirubinaemia with T.S.B. levels > 10 mg/dl were associated with an increment in the serum alkaline phosphatase levels of 3 folds or more the upper normal values. While ductal stones cases were usually associated with an increase that is less than twice the upper normal limit .

The decline in S. alk. Phosph. Levels was an important marker for successful

drainage of the biliary system. The majority of our cases showed gradual decline in the serum level of this enzyme apart from 2 cases in the benign group and 5 cases in the malignant group which showed an initial single high reading (higher than the pre operative level) followed by gradual decline back to the normal levels during the observation period in the benign group ,while the majority of the malignant group showed slower decline especially those with large pancreatic masses , prolonged illnesses, or those with high initial T.S.B. levels (> 10 mg / dl = >170 mmol / l).



This scale shows the relative % of cases with an initial increase in the alkaline phosphatase level.

(C) A.S.T. and A.L.T. serum levels:
(Aspartate and Alanine amino transferases)

the majority of our patients with large bile duct obstruction showed normal or slightly increased levels of either of these 2 enzymes especially ALT ,even in cases which are serologically positive for hepatitis B or C (4 cases) . those with normal levels were checked only once post operatively and no obvious changes were observed ,while those with mild increase in one of the transaminases.., all returned to the normal levels following the successful treatment of their problem.

(D) P.T. and P.T.T (prothrombin time and partial thromboplastin times)

57 of our patients (60%) showed prolonged P.T.(and to a lesser extent a prolonged P.T.T.) especially those with extreme elevation of T.S.B. levels , such changes were more marked in patients with hypoproteinaemia, anemia, and those with prolonged illness (more than 8 weeks).

Such coagulopathies were corrected prior to any intervention using vitamin K , plasma , and cryoprecipitate, and they were checked post operatively.., to be found returning to normality after successful intervention.

When a bleeding tendency developed post operatively for one reason or another a full coagulation profile was obtained.

(E) Total serum protein and serum albumen:

most of our patients showed a reasonable level of total serum protein and serum albumin , few cases ; one of the benign group (when the liver was involved by multiple hydatid cysts with intrabiliary rupture) and 6 cases in the malignant group (especially those with prolonged illness , pancreatic head masses larger than 4 cm, and those with multiple liver secondaries, and severe anemia),showed hypoproteinaemia . when such cases were scheduled for surgery ,their protein level was corrected prior to any intervention using plasma and human albumen intravenously. Serum protein level (even in such patients) improved after the successful drainage of their biliary systems.

Discussion

(1) age and sex incidence:

1. To compare our results with the published ones ,we find that the prevalence of gallstones in females is approximately twice that of the male population in the western countries [1,10,11].

Our study showed that the males outnumber the females.

2. Contrary to gallbladder cancer there a slight preponderance of males (1.5:1) in malignant bile duct tumors with the

peak incidence in the sixth decade [11],and the incidence of pancreatic cancer (mostly ductal adenocarcinoma) is 10/100000 of the population in the U.K., it is a disease of the aging with the average age of death in men being 74 and in women 79 ,and it affect both to the same degree.

In our study 13.5% of the malignant lesions affects patients younger than 55 years and this high percentage was noticed in our country during possibly related to local carcinogens used in weapons during the last 3 successive wars.

3.The specialized teaching hospital for gastroenterology and hepatology is a tertiary referral center ,which receives selected patients from different parts of Iraq ,that's why the age and sex incidence in its patients does not match exactly with that of the community and rather represent those patients who need the specialized procedures of this center and do not represent random sampling for each disease entity.

(2) The etiology:

The surgical ward receives patients in whom surgery is indicated either intending for curative resection, or when other palliative measures fail, to relieve large bile duct obstruction by a bypass procedure.

The major bulk of the ductal calculi are dealt with in the medical ward and only referred to the surgical ward when other interventional endoscopic or radiological fail to offer successful drainage of the biliary system . This may explain the relative smaller number (18 cases) in comparism for example with the large number of cases with carcinoma of the head of pancreas (55 cases ,7 of them are associated with ductal stones at the same time).

Hydatid disease is still our local problem and 9 cases represent “somewhat” the relative incidence of such complication as intrabiliary rupture of the hydatid cyst.

(3) The treatment modality:

The majority of patients referred to the surgical ward were offered surgery. 4 Whipple' spancreaticoduodenectomies were done for resectable pancreatic head cancers or periampullary carcinomas . Most of the rest of pancreatic head carcinomas are either locally advanced or disseminated and they were bypassed surgically using the transactional roux en y choledocho- jejunostomy procedure for biliary bypass. Patients who are friable or with co morbid diseases were referred to the endoscopy unit where

they were offered an endoscopic stenting (4 cases).

Three periampullary tumors were locally resected transduodenally with free margin by histopathology and when these are added to the 4 Whipple's, this makes the percentage of resectable tumors

11.7%, and since 90-95% of pancreatic carcinomas are unsuitable for resection at the time of presentation [12] , so our percentages are approximate to those fixed for the U.K. taking into consideration the selected nature of our referred patients.

The strategy to deal with ductal stones < 1.5cm is endoscopic sphincterotomy and stone extraction followed by laparoscopic

Cholecystectomy, this was done in 8 of our 18 cases, and the rest are either harboring large or multiple stones, or a trial for endoscopic stone extraction had failed. Surgical exploration of the CBD plus cholecystectomy will be the solution for such patients.

Management of benign strictures was either by surgical drainage using a dilated proximal segment of the CBD to construct the bilioenteric bypass, or through the use of the endoscopic stenting.

(4) biochemical response :

The serum levels of bilirubin (with direct and indirect fractionation), and alkaline phosphatase are 2 most important parameters to assess of biliary drainage in cases of large bile duct obstruction in addition to the clinical parameters .

there were 2 major observations in this study :

- The slower decrease in the serum level of those two biochemical parameters in the malignant group (especially cases of large pancreatic head tumors , prolonged illness, and those with suboptimal liver functions).
- The striking few cases with initial higher values of both TSB and serum alkaline phosphatase levels followed by gradual decline .

To understand those two observations we should know that:

(A). "in the majority of cases of cholestatic jaundice , plasma bilirubin begins to fall promptly after insertion of a drainage catheter or an internal biliary bypass procedure and this is accompanied by clinical improvement . However, the return of hepatocyte function to normal is not instantaneous " [13]

(B). Thompson et al stated that the return of hepatocytes function was not seen until 6 weeks after relief of

obstruction and the time taken to recover did not correlate well with other standard pre operative liver function tests nor with post operative changes in these tests. [14]

(C). Kayama et al have also suggested that preoperative biliary decompression may have to be continued for at least 6 weeks to allow recovery of hepatocellular function. [15]

Higashino and Nagakawa found that These apply to uncomplicated biliary obstruction , but other factors such as infection of the obstructed biliary tract result in impaired liver activities after the relief of biliary obstruction, so a pre existing cholangitis may be a significant complicating factor [16]

(D). Moreover in patients with severely impaired hepatic function following longstanding biliary obstruction , one should anticipate slow bilirubin clearance as well as impairment of the more subtle forms of hepatocyte function for many weeks after biliary decompression.

(E). Localized edema at the site of bilioenteric bypass may predispose to the initial high values recorded in few cases , otherwise technical errors should be expected but the successive

decline in the serum levels of bilirubin and alkaline phosphatase with the clinical improvement of these patients proved that the bypass was patent.

(F). The effect of the several combinations of drugs used before, during , and after any procedure to relieve large bile duct obstruction(including antibiotics, analgesics, anaesthetics, vitamin K, H2-blockers & proton pump inhibitors, in addition to whole blood & plasma which were given once they were needed), all should have their impact on the biochemical response obtained from such patients

Conclusions

- Large bile duct obstruction is an organic extra hepatic type of cholestatic jaundice.
- The a etiological factors were of 2 major categories: benign & malignant
- Therapeutic modalities offered in the surgical ward were mainly operative, but the use of interventional endoscopy & radiology were used when indicated.
- Patients were followed biochemical & the result of such follow up were verified according to each category of patients

- Successful relief of large bile duct obstruction should mean improvement in all the clinical& the biochemical criteria.

- Slower responses noticed in the more advanced malignant lesion with longer illness duration & explanations were tried to be given for such responses.

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