

THE EFFECT OF URSODEOXYCHOLIC ACID AS A CONSERVATIVE TREATMENT OF SECONDARY COMMON BILE DUCT STONES IN PREPARATION FOR LAPAROSCOPICAL CHOLECYSTECTOMY

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Abstract

Calculus cholecystitis with secondary bile duct stones is a surgical problem that solved by many surgical/conservative options. In our study we use oral Ursodeoxycholic acid as a medical dissolution therapy for secondary common bile duct stones in preparation for cholecystectomy. The study aimed to see the effects of ursodeoxycholic acid on biliary stone dissolution in our locality.

A prospective study on twenty one patients presented with calculus cholecystitis and CBD stones from January 2010 to January 2011 involved in this study, they received oral Ursodeoxycholic acid (ursogall, UDCA) in a dose of 300 mg twice daily p.o over period of four to six weeks & some of them repeat course of treatment.

During the period of observation, seventeen patients respond to medical treatment showed decrease or absence of jaundice and four patients show no response.

It is concluded that: This study illustrate that we can use bile acids as medical dissolution treatment in some indicated patients with CBD stones, there is a chance of conservative treatment to be a way of treating patients with obstructive jaundice due to common bile duct stones, although the number of patient is small owing to the natural occurrence of such cases all over the world and we are lacking the standard facilities of identical research equipment and the comparative differentiation between diseased patients and control cases ; our results need further research with big number of patients and more elements of investigations.

Introduction

The extra hepatic bile ducts consist of the right and left hepatic ducts, the common hepatic duct, the cystic duct, and the common bile duct or choledochus¹. The common bile duct enters the second portion of the duodenum through a muscular structure, the sphincter of Oddi¹. The common bile duct is about 7 to 11 cm in length and 5 to 10 mm in diameter.

Choledocholithiasis: Common bile duct stones may be small or large, single or multiple, and are found in 6 to 12% of patients with stones in the gallbladder. The incidence increases with age. About 20 to 25% of patients above the age of 60 with symptomatic gallstones have stones in the common bile duct as well as in the gallbladder. The vast majority of duct

stones in western countries are formed within the gallbladder and migrate down the cystic duct to the common bile duct. These are classified as secondary common bile duct stones, in contrast to the primary stones that form in the bile ducts. The secondary stones are usually cholesterol stones, whereas the primary stones are usually of the brown pigment type. The primary stones are associated with biliary stasis and infection and are more commonly seen in Asian populations. The causes of biliary stasis that lead to the development of primary stones include biliary stricture, papillary stenosis, tumors, or other (secondary) stones^{1,2}.

The bile: Composed mainly of water & electrolytes (97%), bile salts (2%),

protein, lipid, bile pigments (1%); the PH of it is neutral or alkaline. The bile salts are primary & secondary; the primary bile salts are cholate & chenodeoxycholate synthesized in liver from cholesterol, they conjugate there with taurine & glycine which acts within bile as anion that balanced by sodium, Bile salts excreted into bile by hepatocytes & aid in digestion & absorption of fats in intestines in which 80% of conjugated bile acids are absorbed in terminal ileum; the remainder is deconjugated by gut bacteria forming secondary bile acids. The secondary bile acids (deoxycholate & lithocholate) which are absorbed in colon, transported to the liver, conjugated & secreted into bile; 95% of bile acids pool reabsorbed & returned via the portal venous system to liver (enterohepatic circulation)¹.

Proving diagnosis of cholelithiasis and choledocholithiasis can be facilitated by abdominal ultrasonography documenting stones, sludge, degree of inflammatory process around the gall bladder wall and stones in the bile ducts, and it is regarded as the prime cost effective, flexible and the standard initial non-invasive technique for the diagnosis in jaundiced patient^{1,2}. More sophisticated measures of diagnosis are computed tomography, magnetic resonance cholangiography which providing excellent anatomical details has sensitivity and specificity of 95%, 98% respectively^{1,2}. Endoscopic cholangiography is the gold standard for diagnosing common bile duct stones. It has the distinct advantage of providing a therapeutic option at the time of diagnosis. In experienced hands, cannulation of the ampulla of Vater and diagnostic cholangiography are achieved in over 90% of cases, with associated morbidity of less than 5% (mainly cholangitis and pancreatitis). An endoscopic ultrasound is less sensitive, but can be done in nearly every patient without associated complications¹.

Treatment strategy for choledocholithiasis: The treatment is mostly surgical,

though sporadic cases of CBD stones resolved spontaneously and may pass silently into the gut canal without any clinical complications¹. Variable surgical methods are present depending on the extent of the disease, presence of complications, chronicity of the disease. Nevertheless, many pharmacological substances were attempted as conservative treatment to resolve jaundice due to choledocholithiasis²⁻⁵.

Surgical treatment: Patients with symptomatic gallstones and suspected CBD stones undergoing either preoperative endoscopic cholangiogram or intraoperative cholangiogram which reveals CBD stones¹. If endoscopic cholangiography reveals stones: sphincterotomy and ductal clearance of stones followed by laparoscopic cholecystectomy. If intraoperative cholangiogram positive then do laparoscopic common bile duct exploration via cystic duct or with formal choledochotomy allows stones to be retrieved in the same setting¹. If expertise and/or the instruments for laparoscopic common bile duct exploration are not available, the patient scheduled for endoscopic sphincterotomy on the following day⁵⁻¹².

If choledochotomy performed; a T-tube is left in place and T-tube cholangiogram performed before removal. Retained stones can be retrieved after T-tube matured (2-4 weeks) by endoscopic basket removal¹. A contact dissolution therapy had been tried for the last decades for non-extractable common bile duct stones, by infusion of chemical substances into the biliary system via a T-tube or naso-biliary drain which can cause partial or complete stone dissolution such as mono-octanion, methyl tert-butyl ether (MTBE) and 1% EDTA/bile acid solution have been tried; because of serious side effects of these solutions they are abandoned from treatment of common bile duct stones and relied on oral bile acid therapy as a safe medical dissolution therapy. It should not be forgotten that the open approach always

remain as final option when others modalities have failed, electrohydrolic lithotripsy, extracorporeal shockwave lithotripsy, laser lithotripsy, and dissolving solutions have especial indications and more clinical trial in this area must be performed¹²⁻¹⁹.

Medical treatment: From many pharmaceutical preparations available all over the world, since anciently, oral bile acid are regarded as one of the most effective dissolvant preparation of common bile duct stones. Now that the treatment of biliary disorder is no longer the private estate of the surgeons; it behoves all who endeavor to treat patients with gallstones, calculus cholecystitis, biliary dyskinesia and papillary stenosis to develop a better understanding of the complex physiological processes².

Gallstone dissolution with bile acids (ursodiol) is useful for cholesterol gallstones & they act by: a- depresses secretion of cholesterol into bile (major effect)³⁻⁹. b- Expands the bile acids pool and increase bile acids secretion (minor effect)³⁻⁹.

Ursodeoxycholic acid (ursodiol, ursogall, UDCA)^{3,9}: is naturally occurring bile acid that makes up less than 5% of the circulating bile salt pool in humans³. After oral administration, it is absorbed (50-70%), conjugated in the liver with glycine or taurine, and excreted in the bile^{3,10}. Conjugated ursodiol undergoes extensive enterohepatic recirculation³. The serum half life is approximately 100 hours. With long term daily administration, ursodiol constitutes 30-50% of the circulating bile acid pool³. UDCA can be used to dissolve cholesterol gallstones; it supplements the bile acid pool and thus improve the solubility of cholesterol in bile.

Pharmacodynamics Ursodiol is used for the dissolution of cholesterol gallstones³⁻⁶. The solubility of cholesterol in bile is determined by the relative proportions of bile acids, lecithin, and cholesterol³⁻⁶. Although prolonged ursodiol therapy expands the bile acid pool, this does not

appear to be the principal mechanism of action for dissolution of gallstones³⁻⁶. Ursodiol decreases the cholesterol content of bile by reducing hepatic cholesterol secretion³⁻⁶. Ursodiol also appears to stabilize hepatocyte canalicular membranes possibility through a reduction in the concentration of other endogenous bile acids or through the inhibition of immune-mediated hepatocyte destruction³.

Clinical use of Ursodeoxycholic acid: Approved by FDA in 1988A, Ursodiol is used for dissolution of small cholesterol gallstones in patients with symptomatic gallbladder disease who refuse cholecystectomy or who are poor surgical candidates at a dosage of 8-13 mg/kg/day and it is also effective for the prevention of gallstones in obese patients undergoing rapid weight loss therapy^{3,7}. Several trials demonstrate that ursodiol 13-15 mg/kg/day is helpful for patients with early stage primary biliary cirrhosis, reducing liver function abnormalities and improving liver histology³. In half of patients gallstones recurs within 5 years³⁻⁷. **Adverse Effects:** Ursodiol is practically free of adverse effects³⁻⁷. Bile salt-induced diarrhea is uncommon. Unlike its predecessor, chenodeoxycholate, ursodiol has not been associated with hepatotoxicity³⁻⁷. In UK, UDCA at low dose of 8-12 mg/kg daily is licensed as treatment for gall stones²². The drug has no carcinogenic, no mutagenic effect, no effect on fertility¹⁰.

Patients and methods

This study is randomized prospective study done on twenty one patients involved and observed through the period from the first of January 2010 to the first of January 2011. The age of patients range from 18-82 years (average 50), nineteen patients were females (90.47%), two were males (9.52%) (Table I&II). Appointed and scheduled for laparoscopic cholecystectomy, and for a reason or while waiting for surgery i.e. laparoscopic cholecystectomy jaundice developed, to

start with, jaundice was mild with slight upper abdominal pain in most of the patients which can be explained by passage of some stones from the gall bladder into the common bile duct (C.B.D) and impacted there causing partial or complete obstruction and thence painful jaundice; this scenario was triggered by all the patients involved in the study as early anorexia, nausea, with or without vomiting, tinge of jaundice in their eyes sclera and proved by the researcher by detailed clinical history and physical examination with various documentary investigations involving simple laboratory tests like liver function tests, abdominal ultrasonography and ending by abdominal computed tomography (C T scan) and magnetic resonance imaging (MRI and MRCP) to prove the condition of obstructive jaundice caused by CBD stone.

The clinical presentations that the researcher depends upon were colicky abdominal pain (biliary colick), jaundice, fever / rigor, and dyspepsia.

The investigational variables that were rely on were detailed liver function tests especially serum bilirubin (Total, direct, indirect), aspartate transaminase (AST) and alkaline phosphatase (Alph).

All patients underwent serial ultrasonographic examination as needed according to the progress of natural history of the disease and the response to the medical (conservative) treatment.

All of the patients send for either abdominal CT scan or MRI/MRCP, but only five patients did the examination (23%) and six patients (28%) underwent MRI-MRCP. All twenty one patients were followed up closely and meticulously for the progress of the disease with thorough review and assessment of the clinical condition.

All patients were given oral bile acid Ursodeoxycholic acid (UDCA), ursogall, in the form of capsules 300 mg twice daily before meal over a period of four to six weeks, hoping that gallstones and

especially C.B.D stones would be dissolved in preparation for laparoscopic cholecystectomy and thus minimizing very much the extent of the trauma to the patients represented by C.B.D exploration. Some of those patients needed a repetition course of the drug to get better successful results.

Five patients (23%) who were presented with fever, rigor and pain demanded primary admission to the hospital to treat the acute condition to prevent complications and then discharged home to complete the treatment after initial response observed upon thence; all other patients were treated as an outpatient bases.

During the course of the treatment; all patients were informed about the possible complications from both the disease and the used drug is UDCA; if any, the duration course of the treatment keeping in mind that most of the patients disliked and refused undergoing C.B.D exploration surgery and its extent of trauma hoping and waiting for the results of conservative medical treatment.

Three patients (14.2%) showed partial response to the medical treatment ,two of them were lost from further action of follow up; the third was underwent surgery for C.B.D exploration.

Two patients (9.5%) showed no response to treatment, one of them repeated a second course of the treatment with complete response over another six weeks; the other one underwent surgery (choledochotomy). Table II, so four patients were excluded from the final results and only 17 patients were the complete responders.

Results

During the period of observation and follow up; twenty out of twenty one patients (95%) were presented with upper abdominal pain (i.e. biliary colick).

Fever with or without rigor were found in only five patients (23%), clinical jaundice in all patients (100%) with duration of

illness ranging from 1 day–6 weeks. Table III. All of the patients (100%) underwent liver function tests which revealed elevated TSB in all of them (100%) with direct hyperbilirubinemia, elevated liver enzymes in eight patients (38%).

As a first line of imaging test, all patients were sent for abdominal ultrasound study emphasizing on gastrobiliary system revealing gall stones (multiple tiny, few stones, sludge or thick walled gall bladder) and dilated C.B.D in all of them (100%) with impacted stones ranging size of < 1 cm.

As far as two patients were lost from follow up and the other two show no

response, so four patients regarded as patients with no response and 17 patients were complete the course of medical treatment with ursodeoxycholic acid successfully, one of them with a repeated course of treatment.

The overall complete response to target of the study showed 17 patients (81%), 16 patients with initial complete response and one with retreatment ending with complete absence of clinical jaundice and normalization of liver function tests with re-imaging by U/S study which showed relative decrease in C.B.D. diameter and absence of stone shadow in it. Tables VI&V.

Table I: Age distribution

Average	Minimum	Maximum
50%	18 years	82 years

Table II: Gender distribution

MALES	FEMALES
19(90.47%)	2(9.52%)

Table III: Clinical data

Clinical data	NO. (%)
Biliary colic	20(95%)
Jaundice	21(100%)
Fever & rigor	5(23%)
↑TSB	21(100%)
↑liver enzymes	8(38%)

21(100%)	U/S
5(23%)	CT
6(28%)	MRC

Table IV: Results of study

Percentages	Number percentages	Patients
	21	total
76.3%	16	initial complete response
14.2%	3 (2 of them lost + 1 treated surgically)	partial response
9.5%	2 (1 repetition of the medical course of treatment with successful dissolution + 1 treated surgically)	no response
	2	patient treated surgically

Table V: Final results of the study

Percentages	Number percentages	Patients
81%	17 (16 + 1 from retreated)	Target complete response
19%	4 (2 lost + 1 partial+1 from non responders)	No response
	21 patients	Total number

Discussion

Gallstone diseases, cholecystitis with CBD stones impaction and its complications are one of the commonest digestive diseases in the world¹.

Having discussed this problem and other problems of biliary diseases manifested by jaundice due to stones (i.e. surgical jaundice); the general idea that would be clearly evident will be a surgical intervention to relieve jaundice which is regarded one of major clinical problems and surgically it is considered among the first surgical top emergencies which is usually associated with many complications and dangerous sequels if not treated promptly by explorative surgery in the right way without any delay after a short period of initial supportive resuscitation aiming to optimize the clinical status of the patient and his /her fitness to a super major surgery; but always; there is a hope in the way of minimizing trauma as possible.

In our study we have tried to decrease trauma of surgery in patients known to have calculus cholecystitis whether acute or chronic and have given appointment for a laparoscopic cholecystectomy but incidentally developed obstructive jaundice by passage of some of gall stones into the common bile duct From this introduction and because of the fact that all our patients (twenty one) were acutely presented and seeking a medical advice ;this point is very helpful in the medical treatment that we talk about giving a good results because chronicity of the disease complicate its fate and may end in treatment failure or a need for a longer period of conservative treatment may reach up to five years and decliment of success rate to less than 20% as other

studies stated^{4,5}. Other reasons implicated in our study is that some patients refuse surgery with massive trauma and a long hospital stay ,and some other patients were elderly and unfit for such major surgical trauma.

So twenty one patients were challenged to a conservative medical treatment receiving UDCA (ursogall) orally in the form of capsule 300 mg twice daily before meals over period of 4-6 weeks; some of them needed to repeat the course of treatment after partial response showing a total complete response in 17 patients with complete dissolution (81%), 2 out of 21 patients show partial responses (14.2%) and then lost, one patients show no response (9.5%) although in world there is no use of drug dissolution therapy alone for treatment of CBD stones which usually combined with endoscopic techniques and other direct dissolution methods, we will discuss and compare our results with these studies since the feasibility of oral bile acids as a dissolution therapy for gall stones.

There are some published figures for successful dissolution of common bile duct stones using chenodeoxycholic acid (CDCA) alone in a dose of 750 mg /day, Iser et al.(1975)³ show complete disappearance in 1 out of 4 patients, Barbara et al.(1976)⁴ showed complete dissolution in 3 out of 8 patients, Bateson et al.(1978)⁵ showed complete dissolution in 1 out of 10 patients, Thistle et al. (1978)⁶ showed complete dissolution in 5 out of 11 patients, Sue et al. (1981)⁷ showed complete dissolution in 3 out of 13 patients, although they used chenodeoxycholic acid primarily at early years; the subsequent studies preferred Ursodeoxycholic acid over cheno-

deoxycholic acid because of less side effects, more potent dissolution, less effect on liver enzymes⁸.

Dr. Gianfranco Salvioli and his colleagues from Modena in Italia (1979) C, described the results of random allocation, double masked trial in 28 patients with uncomplicated biliary stones, half of whom (14) were treated with 12 mg /kg Ursodeoxycholic acid (UDCA) in three divided doses while other half received placebo; seven of the 14 patients treated with UDCA showed complete disappearance of stones in 6,8,24 months observation, only one show a partial response while all of patients that received placebo showed no evidence of gallstones dissolution, this study is important in that it established the feasibility of oral dissolution therapy for stones in the biliary tree in reasonable number of patients, the authors have confirmed that bile acids treatment can lead to dissolution and or disintegration /disappearance of CBD and biliary tree stones. Swobodnik W, Janowitz P et al¹⁰, studied the effect of ursodeoxycholic acid on recurrence prevention of choledochal calculi after endoscopic sphincterotomy was evaluated in 46 patients, whose bile duct stones had been removed endoscopically, 22 patients received 500 mg of Ursodeoxycholic acid once a day, 24 patients received placebo, one recurrent stone could be detected in the ursodeoxycholic acid treated group 19 months after endoscopy, whereas 4 recurrent stones occurred in the placebo group about 16 months after endoscopy.

In a study use combination therapy of gallbladder stones using extracorporeal shock waves and bile acids¹¹, 97 patients with radiolucent gallbladder stones (total diameter less than or equal to 3 cm) and intact gallbladder function were found suitable for extracorporeal shock wave lithotripsy, disintegration of gallstones was achieved in 92 of the 97 patients (95%). CDCA and UDCA were used as adjuvant litholytic therapy, the therapeutic

results were evaluated cumulatively in 90 patients after follow up of 10 months; 46 patients (80%) with solitary stone up to 20 mm in diameter had stone free gallbladder, whereas other patients with stones measures of 2-3cm and multiple gallstones show only 28% gallbladder free stones.

KW Somerville, et al (1985)¹², studied the effect of medical dissolution therapy on stones in common bile duct in thirty one patients with radiolucent common bile duct stones received medical treatment, 19 patients had Roachol, a terpene preparation, 8 of them (42%) achieving complete stone disappearance within 3 to 48 months, fifteen (including 3 of the above) took Roachol with bile acid (chenodeoxycholic acid) for 3 to 60 months; 11(73%) achieved complete dissolution within 18 months, they conclude that oral dissolution therapy with Roachol and bile acids should be considered when endoscopic sphincterotomy or surgery is not feasible.

GA Kenneth Johnson et al. study 1993¹² revealed treatment of non extractable CBD stones after sphincterotomy with combined UDCA plus end prosthesis in 22 patients in whom biliary stent kept for unextractable stones, 10 of them were treated with UDCA and 12 of them with stent only; nine of the ten show complete clearance in contrast that none of the 12 had complete clearance¹².

Ilyas Tuncer and his colleagues (2003)¹³, test the effect of UDCA on radiolucent gallstones and concludes that after 12 months of treatment, stone dissolution was found in 6 (37.5%) of 16 patients compared to control (13) patients who show no dissolution of stones during period of observation by ultrasound¹³. In a research article published in 1975 Oliver James and his colleagues, showed the effect of chenodeoxycholic acid CDCA 1g daily was administered to 10 patients with gallstones and three patients with biliary stricture and recurrent cholangitis; 4 gallstones show diminution or dis-

appearance of stones including one patient whose stone was in common bile duct¹⁴. Zuain M et al (1982)¹⁵; obtained a gallstone dissolution rate of (83%) with UDCA plus chenodeoxycholic acid combination in 12 months¹⁵, whereas Petroni et al¹⁶; found the rate to be 30% with the same combination in 24 months while Tazuma A et al found a 70% stone dissolution rate of multiple stones and 25% of solitary stones at the end of 12 months in patients treated with UDCA¹⁷.

In the UK Ursodeoxycholic acid at a dose of 8-12 mg/kg daily is licensed as a treatment for gallstones¹⁸. Whilst there is no evidence that Ursodeoxycholic acid reduces biliary symptoms in patients awaiting cholecystectomy it may have a role in reducing the size of common bile duct stone which would otherwise irretrievable endoscopically, UDCA at a dose of 500 mg/day has been shown to reduce the risk of stones forming in the gallbladder when given to patients undergoing obesity surgery¹⁸.

In a review article by Abolfazl shojaiefard et al¹⁹, several types of solutions that are used for dissolving gallstones (table 5) and CBD stones, these solutions have few toxic side effects and do not cause irritation of the biliary tree, every dissolution therapy will last for several weeks, the use of UDCA and chenodeoxycholic acid has only been shown to dissolve cholesterol containing

gallstones, continuing therapy with UDCA appeared to prevent recurrence of gallbladder microlithiasis, methyl-ter-butyl-ether (MTBE) is an excellent cholesterol solvent but it is toxic to liver and duodenal mucosa, Katsinelos et al. suggested that UDCA does not seem to contribute to the reduction in stones size or stones fragmentation during the endoprosthetic procedure¹⁹.

There is one published study by Venneman NG et al in 2006²⁰ they conclude that ursodeoxycholic acid does not reduce biliary symptoms in highly symptomatic patients awaiting cholecystectomy²⁰.

Conclusion and recommendations:

- 1) This study illustrate that we can use bile acids as medical dissolution treatment in some indicated patients with CBD stones.
- 2) There is a chance of conservative treatment to be a way in treating patients with obstructive jaundice due to common bile duct stones.
- 3) Although the number of patient is small owing to the natural occurrence of such cases all over the world and we are lacking the standard facilities of identical research equipment and the comparative differentiation between diseased patients and control cases; our results need more future research with big number of patients and more elements of investigations.

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