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RESEARCH ARTICLE

ROLE OF DISSOLUTION THERAPY IN THE MANAGEMENT OF ASYMPTOMATIC CHOLELITHIASIS

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ABSTRACT

Background and Objectives: Symptomatic gallstones are easy to treat, unfortunately however asymptomatic gallstones are as easy to treat. This creates a problem for health care planners in the form of the financial implications involved, since asymptomatic gallstones are even more common than gallstones associated with symptoms and require no surgical intervention, while the funds diverted towards dealing with them drains the health care establishment of much needed funds in an era of costly health care. In this review we attempt to clarify the fact that asymptomatic gallstones need no intervention in most cases, thereby saving the patient unnecessary surgery and the health care establishment costs, both in the financial form and in manpower.

Materials and Methods: This study is based on 25(twenty-five) patients came at RIMS, Ranchi with Gallstone disease on the period of April 2015 to September 2016. Patients who can benefit from this treatment are those who have small gallstones may be less than 1.5cm in diameter and which have high cholesterol content.

Results and Conclusion: My data confirm that UDCA can dissolve radiolucent gallstones even at 4 mg/kg, a dose which after 6 months of treatment induced stone reduction or disappearance in 33% of patients. The success rate improved at the higher doses, 50% of patients showing partial or complete dissolution with 8 mg/kg and 65%with 12 mg/kg. Therefore, I conclude that there is a relationship between the dose employed, over the range of 4-12 mg/kg, and the response in terms of stone dissolution at 6 months.

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INTRODUCTION

Calculous disease of the biliary tract is the general term applied to diseases of the gallbladder and biliary tree that are a direct result of gallstones. Gallstone disease is the most common disorder affecting the biliary system. The true prevalence rate is difficult to determine because calculous disease may often be asymptomatic. There is great variability regarding the worldwide prevalence of gallstone disease. High rates of incidence occur in the United States, Chile, Sweden, Germany, and Austria. The prevalence among the Masai peoples of East Africa is 0% whereas it approaches 70% in Pima Indian women. Asian populations appear to have the lowest incidence of gallstone disease. In the United States, approximately 10–15% of the adult population has gallstones, with approximately one million cases presenting each year. Gallstones are the most common gastrointestinal disorder requiring hospitalization. The annual cost of gallstones in the United States is estimated at 5 billion dollars.

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Cholelithiasis (Gallstones) may be smaller than a grain of sand or larger than a golf ball. Gallstones are concretions that form in the biliary tract, usually in the gallbladder. According to the American Medical Association 80% of gallstones are caused by hardened cholesterol. These are believed to form when there is too much cholesterol in the gallbladder. Other stones are caused by too much bilirubin or too little bile salts. Gallstones develop insidiously, and they may remain asymptomatic for decades. Migration of a gallstone into the opening of the cystic duct may block the outflow of bile during gallbladder contraction. The resulting increase in gallbladder wall tension produces a characteristic type of pain (biliary colic). Cystic duct obstruction, if it persists for more than a few hours, may lead to acute gallbladder inflammation (acute cholecystitis).

MATERIALS AND METHODS

Patients who can benefit from this treatment are those who have small gallstones may be less than 1.5cm in diameter and which have high cholesterol content. As is said earlier this therapy suits only for cholesterol stones. Patients who have

calcified gallstones or those stones consisting of bile pigments and those who are obese may not benefit from this therapy. It is said that only 30% of the patients may be suitable to undergo this treatment or even lower as compliance poses a major problem. In addition to this the treatment may continue to two years and very expensive cost.

DISCUSSION

Ursodeoxycholic acid treatment is associated with distinct changes in fasting biliary lipid composition. Ursodeoxycholic acid feeding reduces the relative concentration of cholesterol in gallbladder bile. Furthermore, the observation that this treatment did not influence the total concentration of biliary lipids, which is an important factor in determining the cholesterol-holding capacity of bile, permits the conclusion that ursodeoxycholic acid unsaturates gallbladder bile. For the first time, data on lipid concentration and cholesterol saturation in hepatic bile during treatment with ursodeoxycholic acid were obtained. The finding that ursodeoxycholic acid made fasting hepatic bile unsaturated in all patients studied is probably of great importance in explaining why this bile acid is effective in dissolving gallstones. The change seen with ursodeoxycholic acid was even more impressive than that previously demonstrated for chenodeoxycholic acid. Similar to the findings seen with chenodeoxycholic acid therapy, the ratios between cholesterol and bile acids, and between cholesterol and phospholipids were clearly reduced in fasting bile during ursodeoxycholic acid treatment. It is thus reasonable to speculate that ursodeoxycholic acid, like chenodeoxycholic acid, leads to a reduction of cholesterol secretion in the fasting state. A diminished biliary cholesterol output during stimulated bile secretion has recently been demonstrated during treatment with both bile acids.

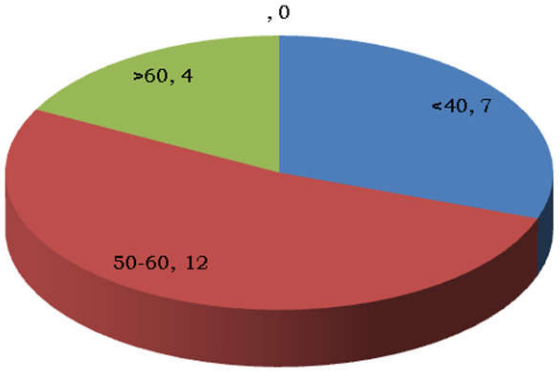
However, the mechanism behind these effects may not be the same for the two bile acids. The reduction in cholesterol saturation of hepatic bile during chenodeoxycholic acid treatment appears to be linked to a reduced activity of hepatic microsomal HMG CoA reductase. Under the higbly standardized conditions employed , no significant influence on HMG CoA reductase activity was observed during ursodeoxycholic acid feeding. Thus, Maton *et al*. (1 0) reported that feeding ursodeoxycholic acid for 1-6 months resulted in a 40% decrease in HMG CoA reductase activity. Their doses were lower (4.5-7.2mgkg-lday-') and their patients were generally somewhat overweight compared to those in the present study. Furthermore, the untreated gallstone patients in their report had increased HMG CoA reductase activities compared to controls, so treatment with ursodeoxycholic acid actually only "normalized" enzyme activity in these patients. We have been unable to find an increased HMGCoA reductase activity in nonobese, normolipidemic patients with cholesterol gallstones, and the patients studied by Maton *et al*. may thus not be fully comparable to those investigated in the present report. Salen *et al*. recently reported a reduction of hepatic HMG CoA reductase activity in two gallstone patients treated with ursodeoxycholic acid for 1 year. On the other hand, Carulli *et al*. found that 1 week of ursodeoxycholic acid treatment stimulated HMG CoA reductase activity in gallstone patients. In the study of Carulli *et al*., there was no change in the composition of biliary lipids, and it is therefore doubtful if the patients had reached a metabolic steady state. Thus, in the nonobese, normolipidemic patient with cholesterol seen during ursodeoxycholic acid does not appear to be linked to a reduced hepatic cholesterol synthesis. Therefore, although we cannot exclude the possibility of a relatively small decrease of reductase activity in some patients during ursodeoxycholic acid treatment, the present results are in contrast to the clear reduction of HMG CoA reductase activity seen during chenodeoxycholic acid therapy under similar experimental conditions. Further support for this concept is gained by the fact that during chenodeoxycholic acid treatment, but not during ursodeoxycholic acid treatment (present study), there was a positive correlation between hepatic bile saturation and HMG CoA reductase activity.

If suppression of cholesterol biosynthesis in the liver is not a major mechanism of action of ursodeoxycholic acid, how can one explain its remarkable effects on biliary lipids?

First, the inflow of cholesterol from the intestine may be inhibited. The poor cholesterol-solubilizing capacity of ursodeoxycholic acid may, when it becomes the major bile acid secreted, result in areduced absorption and a diminished transport of cholesterol to the liver. Some evidence for this mechanism has been presented, but it is not yet clear whether a reduced cholesterol uptake may reduce cholesterol secretion. Thus, beta-sitosterol and neomycin, which block cholesterol uptake, did not change biliary lipid composition significantly.
Second, ursodeoxycholic acid treatment could lead to a reduced degradation of endogenous, cholesterol- containing lipoproteins. Find any increase in total plasma cholesterol or triglyceride, nor in plasma LDL or HDL cholesterol. In contrast to chenodeoxycholic acid treatment, there was no reduction of plasma (VLDL) triglycerides. Recent data also give some evidence for an increase of LDL cholesterol and LDL/HDL cholesterol ratio during chenodeoxycholic acid therapy. As such changes are definitely unwanted with regard to long-term risk for development of ischemic heart disease, the present finding that ursodeoxycholic acid treatment lowered plasma LDL and HDL cholesterol levels slightly without affecting the LDL/HDL ratio may have some clinical implications in the choice between these two bile acids. However, further controlled studies are needed to confirm and expand these observations.

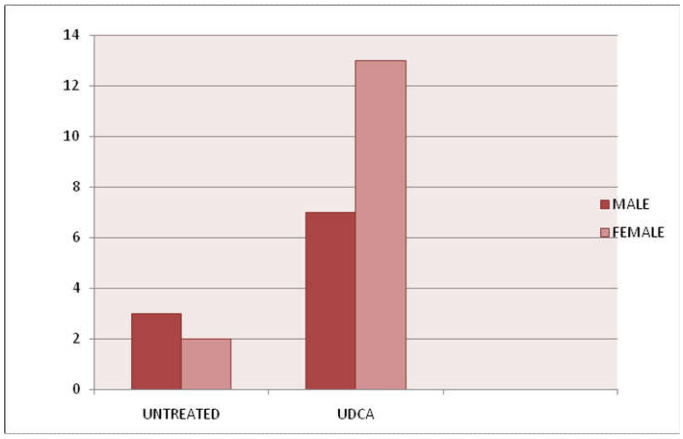
Observation

This is based on the study of 25(twenty-five) patients came at RIMS, Ranchi with Gallstone disease.



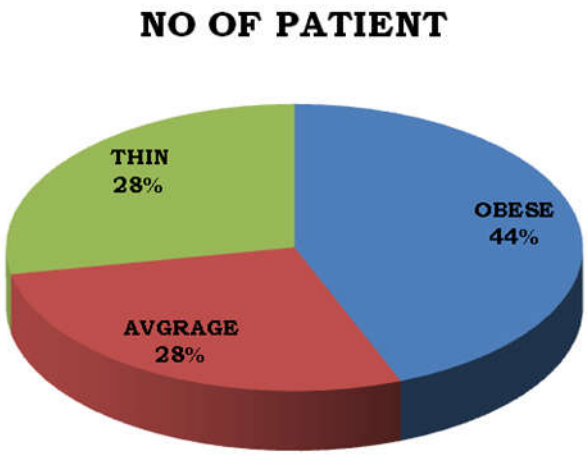
Age group	No. of patients
<40	7
50-60	12
>60	4

Treatment



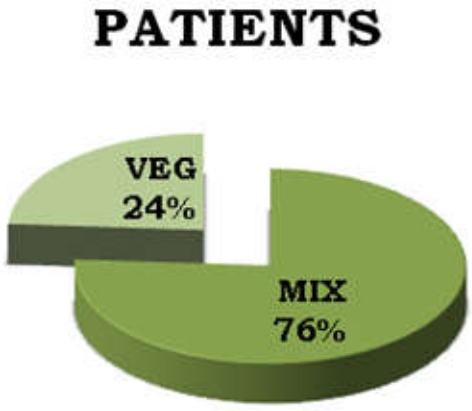
	Male	Female
Untreated	3	2
Taking-UDCA	7	13

BODY BUILT



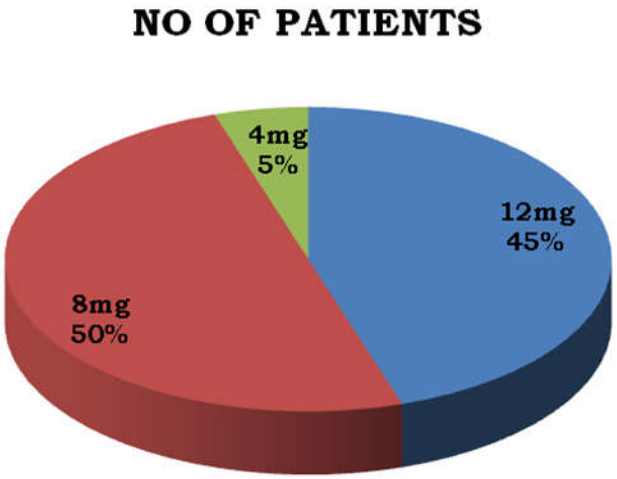
Body built	No. of patients
Obese	11
Avrage	7
Thin	7

Diet



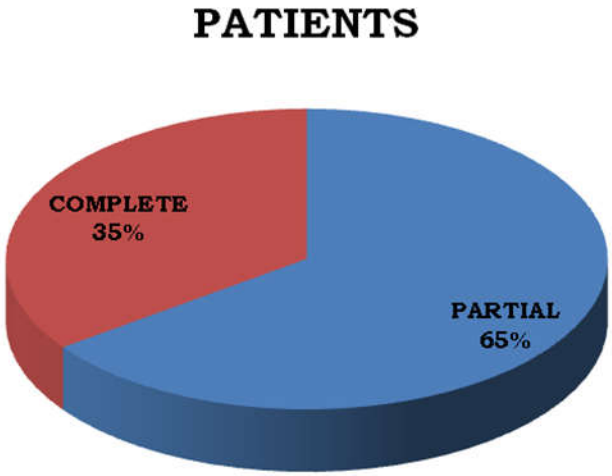
Diet	Patients
Mix.	19
Veg.	6

Dosage



Dosage	No. of patients
12mg	9
8mg	10
4mg	1

Dissolution of stone



Dissolution of stone	No of patient
Partial	13
Complete	7

Conclusion

My data confirm that UDCA can dissolve radiolucent gallstones even at 4 mg/kg, a dose which after 6 months of treatment induced stone reduction or disappearance in 33% of patients. The success rate improved at the higher doses, 50% of patients showing partial or complete dissolution with 8 mg/kg and 65%with 12 mg/kg. Therefore, I conclude that there is a relationship between the dose employed, over the range of 4-12 mg/kg, and the response in terms of stone dissolution at 6 months. Though biliary lipids were not studied in this investigation, the dose-dependent effects of UDCA in our patients might be explained by differences in cholesterol saturation at the different doses employed. In fact, it is generally accepted that bile must be unsaturated with cholesterol for gallstone dissolution to occur (Iser *et al.,* 1975) and the fall in the saturation index has been shown to be dose-

dependent during treatment with 5-15 mg/kg UDCA of non-obese patients with gallstones (Bateson *et al.,* 1980, Maton *et al.,* 1977). With 4 mg/kg, bile became unsaturated with cholesterol in only about half the patients (Bateson *et al.,* 1980; Salen *et al.,* 1980, Thistle *et al.,* 1978b; Weis *et al.,* 1978), whereas desaturation was achieved in almost all of those treated with 10-12 mg/kg (Bateson *et al.,* 1980, Maton *et al.,* 1977). Furthermore the degree of unsaturation was more marked with the higher doses (Bateson *et al.,* 1980; Maton *et al.,* 1977; Trotman *et al.,* 1975). Major factors besides bile desaturation which influence dissolution are stone composition and size. As far as composition is concerned, only stones mainly made up of cholesterol respond favourably to bile salt therapy.

Selection of patients is based on the stones' appearance in X-rays, but it has been shown that about 15% of radiolucent stones are not cholesterol (Trotman *et al.,* 1975), and one would therefore expect that the maximum success rate will not exceed 85%. When the sub-groups of patients with small and medium size stones are considered, the response rate approximated this theoretical maximum only with the dose of 12 mg/kg. Some of the patients have additional benefits in regular bowel habits, particularly when it was prescribed in higher dose. At the other extreme, no response was seen in patients with larger stones treated with the lower dose. Furthermore, 6 months may be too short period of treatment for a change in stone size to be seen by X-rays, even if some dissolution has occurred. The overall efficacy of the higher dose of UDCA compares favourably with that reported for12-15 mg/kg of COCA (Barbara *et al.,* 1976; Oanzinger *et al.,* 1980, Gerolami *et al.,* 1977; Thistle *et al.,* 1978a), which induces side-effects in a rather large proportion of patients. On the contrary, UDCA was well tolerated by all the subjects who completed the study. From a practical point of view, doses of at least 8 mg/kg should be employed for patients with stones of small size and 12 mg/kg should be given to patients with stones of medium or large size.

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