Original Research Paper

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General Surgery

COMPARISON OF COMBINATION THERAPY OF URSODEOXYCHOLIC ACID AND SILYMARIN VERSUS URSODEOXYCHOLIC ACID ALONE IN GALLSTONE DISSOLUTION AND IMPROVEMENT IN LFT PARAMETERS.

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ABSTRACT

Background: Ursodeoxycholic acid (UDCA), a secondary bile acid had been used since decades for dissolution of cholesterol gallstones and biliary sludge. UDCA reduces the cholesterol saturation of bile by inhibiting the rate limiting enzyme HMG-coA reductase, leading to gradual dissolution of gallstones. Another molecule; 'Silymarin', an extract of milk thistle seed, containing a mixture of flavonolignans also used for increasing bile flow in ductules, favouring its use in biliary sludge and dissolution of gallstones. Since there are few studies comparing Ursodiol and Silymarin in dissolution of gallstones, this study is done to evaluate the efficacy of ursodiol alone versus combination of ursodiol-silymarin in gallstone dissolution.

Material And Methods: In this observational study over a time of 6 months, 40 patients of radiologically proven gallstone (< 2 cm), were randomly allocated into 2 groups of 30 patients each. One group received Ursodiol 600 mg/d (Group A) while the other received a combination of Ursodiol-Silymarin (Group B). Both groups were treated for 6 months and re-investigated thereafter by USG for gallstone; also LFT parameters were compared.

Result: Group B patients showed a better reduction in both number and mean size of gallstones after 6 months; whilst Group A patients showed an inferior reduction in these parameters. The result of Group B population was significantly better than Group A.(p<0.0.5).LFT was also better improved in Group B patients.

Conclusion: Combination therapy of Ursodiol-Silymarin is better than Ursodiol alone in gallstone dissolution in addition to its hepatoprotective effect.

KEYWORDS : Combination therapy, Ursodiol, Silymarin.

INTRODUCTION:

Gallstone disease represents a major issue in healthcare system and one of the most common hepatobiliary disease, if we consider the number of cholecystectomies done for the same which are performed annually[1] . Gallstone disease is a complex disorder where both environmental and genetic factors contribute to the susceptibility to the disease. Risk factors include age, gender, genetic factors, parity and dietary factors. Gallstones are classified as cholesterol, pigment and mixed stones. More than 90% of gallstones are Cholesterol stone and are formed within the gallbladder. Majority of Acute calculous cholecystitis can be managed non-operatively in about 85% cases, while 15% cases need index surgery. Most of the Chronic calculous cholecystitis need surgery in order to prevent major complications like biliary colic, pancreatitis, empyema or CBD stones.

The use of UDCA in the treatment of liver diseases dates back to the traditional Chinese medicine. For centuries, the Chinese drug "*shorea spp*.", derived from the bile of adult black bears, has been used to cure various hepatobiliary disorders[2] . Only at the beginning of the 20th century, UDCA identified from polar bear bile by Hammarsten , a swedish research worker, who named this uncharacterized bile acid as Ursocholeinic acid. Twenty years later, in 1927, Shoda, from Okayama University, isolated UDCA from bear bile imported from China, succeeded in crystallizing it and then called it by its present name, *i.e*., Urso-deoxycholic acid. Makino et al clearly demonstrated that treatment with UDCA resulted in dissolution of cholesterol gallstones[3].

Ursodiol markedly decreases biliary cholesterol saturation by 40%-60%, by inhibition of cholesterol absorption in the intestine and cholesterol secretion into bile, by inhibiting HMG coA reductase. Moreover, it is known that UDCA decreases toxicity of bile acids which damage cell membranes and cause cholestasis. Since Makino et al first reported gallstone dissolution with UDCA, it has been used above all in the treatment of gallbladder cholesterol stones as an alternative to cholecystectomy. Candidates for UDCA treatment should have cholesterol-enriched gallstones < 20 mm in diameter and a patent cystic duct. The recommended dose of UDCA for gallbladder stones is 8-10 mg/kg per day. A dissolution rate of 30%-60% has been reported, although the initial gallstone diameter has been shown to be the most important factor affecting the dissolution rate. A clinical study demonstrated complete disappearance of small stones (< 5 mm) with UDCA treatment after 6 months. Silymarin is a plant derived molecule with its active ingredient as Silybinin that increases the bile flow and thus capacitates the flow of small stones into the GI tract and also inhibits the stasis of bile within the GB that favours calculi formation. Additionally, Silymarin also have hepatoprotective role, hence improving LFT parameters particularly Alkaline Phosphatase and liver enzymes.

MATERIAL AND METHODS:

Source of data: Gallstone patients seen in Surgery OPD PJMCH Dumka.
Type of study: An observational type.
Place of study: PJMCH Dumka, Jharkhand.
Period of study: August 2020 to January 2021
Sample size: 40 patients.

Inclusion Criteria:

Patients of 18-60 years of age with radiologically proven gallstones with size < 2 cm without any other concomitant gallbladder disease and those willing only for medical management.

Exclusion Criteria:

Patients with gallstone of size > 2cm and with other disease like Ca GB, CBD stones etc; and those who are willing for surgery.

Plan Of Analysing Data:

40 patients were taken in the study and their USG reports and LFT parameters are being recorded before starting the treatment.

Evaluation Of Result:

40 patients were randomly allocated into 2 groups of 20 patients each. *Group A* consist of those who received UDCA 600 mg/day alone for 6 months; while *Group B* consist of those who received a combination therapy of UDCA and silymarin for 6 months.

Both pre and post treatment USG were performed along with LFT in order to compare the parameters of gallstone configuration (size reduction, number reduction, biliary sludge, status of inflammation etc); and parameters of LFT in both the groups. These statistical data are compared in both the groups and then the p value is derived using *Analystat*, a computer based application software, and then conclusion is made.

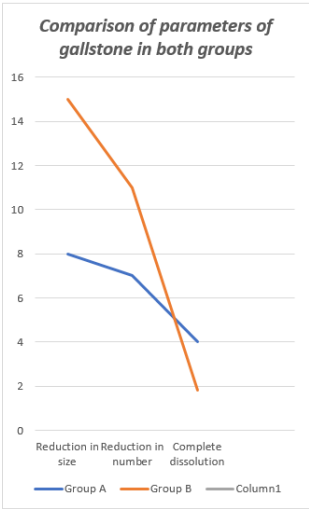
OBSERVATION AND RESULT:

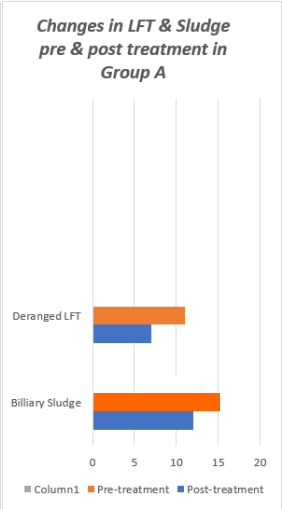
There was a significant reduction in both size and number of gallstones post treatment in Group B patients ie; those receiving UDCA (600 mg/day) with silymarin(UDILIV-SL) in comparison to Group A patients.

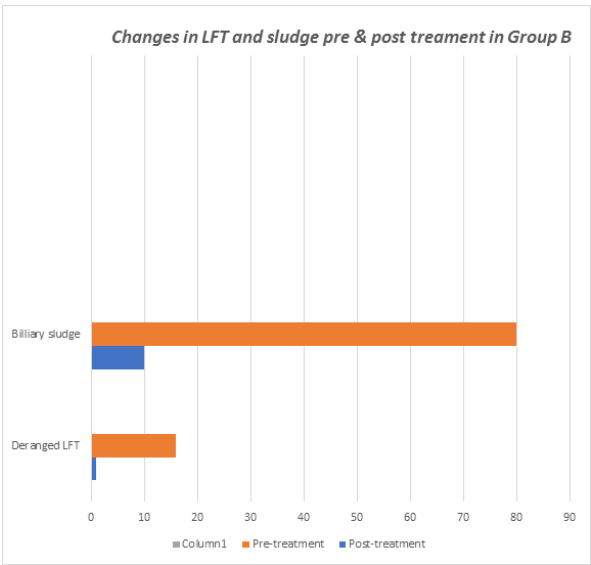
In *Group A*, there is reduction in size of gallstones in 8/20 ie; in 40% patients in post treatment USG. In the same group, there is reduction in number of stones in 7/20 ie; 35% patients. Complete dissolution is also

seen in 4/20 ie; 20% patients over 6 months of treatment. Concomitant biliary sludge that was seen in 15/20 ie;75% patients in pre-treatment USG, was only seen in 12/20 ie; 60% patients in post-treatment USG. In parameters of LFT, there is mild reduction in liver enzymes seen in 10/20 ie; 50% patients.

In *Group B*, there is significant reduction in size of gallstones in 15/20 ie; 75% patients. The mean reduction in number is seen in 11/20 ie; 55% patients. Complete dissolution of calculi is seen in 9/10 ie; 45% patients over 6 months of treatment. In about 16/20 ie; 80% patient, biliary sludge was seen in pre-treatment USG, that was significantly reduced up to 2/20 ie; 10% patients seen in post-treatment USG, hence proving the use of silymarin in facilitating increased flow of bile in biliary tree. In LFT status, there is a significant improvement seen in liver enzymes in 16/20 ie; 80% patients; hence proving its hepatoprotective role and prevention of gallstone and calculi induced obstructive changes, when used for 6 months.







DISCUSSION:

In this study, patients who received UDCA alone in dose of 600 mg/day for 6 months showed an inferior result in all parameters ie; reduction in size and number of calculi, complete dissolution, sludge and deranged LFT; than those who received a combination therapy of Ursodiol and Silymarin for same duration.

UDCA in its therapeutic dose of 8-10 mg/kg/day exerts its role mainly by inhibiting HMG-coA reductase, a rate limiting enzyme in cholesterol formation, hence decreasing cholesterol absorption and formation which subsequently decreases cholesterol enucleation and hence calculi formation.

Also, UDCA exerts its role by many ways ie; choleretic, alteration of bile acid pool, anti-inflammatory, antiapoptotic, immunomodulation and increases cell integrity. These are the possible mechanism by which UDCA exerts its role in decreasing gallstone formation.

Silymarin with its active constituent like silibinin-isosilibinin exerts its excellent role in gallstone dissolution, decreasing sludge and increasing biliary flow in IHB and EHB ducts[4]. Silymarin, a standardized extract obtained from seeds of Silybum marianum, is widely used in treatment of liver diseases. Seeds of S. marianum have been shown to treat liver and gall bladder disorders, including hepatitis, cirrhosis and jaundice and to protect the liver from certain poisonings. Moreover, its antioxidative, anti-lipid peroxidative, antifibrotic, anti-inflammatory, immunomodulatory, anti-carcinogenic and anti-atherosclerotic activities were also reported. Silymarin prevents liver damage by maintaining the integrity of plasma membrane, thereby suppressing the leakage of enzymes, and thus helps to maintain deranged liver enzymes observed in the study.[5] Silymarin is also known to reduce intracellular Ca2+ levels induced by ter butyl hydroperoxide in rat hepatocytes, suggesting that the hepatoprotective effect of silymarin is not only due to the inhibition of lipid peroxidation but also modulation of intracellular calcium levels. The ability to maintain calcium flux may be due to either silymarin's effect as an antioxidant by reducing intracellular free radical levels and/or some direct effect on mitochondria through modulation of mitochondrial calcium ion channels. The elevated levels of liver enzymes such as AST and ALT found in liver injuries and chronic diseases are reduced significantly after silymarin for 6 months. The synergistic effect of Ursodeoxycholic acid and silymarin is seen to decrease biliary sludge, improve deranged LFT and to exert a hepatoprotective role.[6]

CONCLUSION:

Use of Combination therapy ie; Ursodiol and silymarin for 6 months had been observed as an alternative to cholecystectomy and superior to Ursodiol alone, in terms of both therapeutic efficacy and cost effectivity. Use of combination therapy had been related to a significant reduction in size, number, sludge, complete dissolution and improvement in deranged LFT better than ursodiol alone.

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