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A comparative study of the treatment outcomes in Alcoholic Liver Disease patients treated with Ursodeoxycholic acid and Methionine along with Abstinence (Placebo)

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ABSTRACT

Liver is extremely active organ in the body. Ethanol toxicity on liver is a function of duration of alcoholism, amount of daily intake of alcohol and patient's nutrition. Ethanol is oxidized in the liver to acetaldehyde--a compound considerably more toxic than ethanol itself. Despite small amount of alcohol dehydrogenase (ADH) found in gastric mucosa, the metabolism of ethanol in this site may have an important hepatoprotective effect. ATP synthesis rate is reduced in the liver cells when exposed to ethanol... ethanol is metabolised by two ways 1.Conversion of ethanol to acetaldehyde by Alcoholdehydrogenase. 2. Conversion of acetaldehyde to acetate by Acetaldeydrogenase. Chronic ethanol consumption does not influence ADH activity, but has a profound stimulatory effect on microsomal enzymes, in particular cytochrome CYP2E1. Alcohol increases the flow of blood in the portal and hepatic vascular resistance results increased portal pressure and collateral blood flow which causes the visceral bleeding in patients with alcoholic cirrhosis and portal hypertension. The aim of the study is to evaluate the outcome of ursodeoxycholic acid (300mg),methionine (400mg)and abstinence in the treatment of alcoholic liver disease and the objective is to achieve the following end points(primary end point -change from baseline in particular LFT parameter-albumin and CBP parameters such as PT and INR ratio)(secondary end point- effects of ursodeoxycholic acid and methionine on other LFT parameters such as total bilirubin, SGOT, SGPT along with changes in the above parameters in patients with abstinence.)The significance is though ursodeoxycholic acid and methionine drugs have well known effect on the liver function test parameters of SGOT and SGPT and total bilirubin, here we are assessing the effects of these two drugs in particular LFT parameter i.e albumin and CBP parameters i.e prothrombin and INR that may help us to know more about the drug's efficacy . In particular Liver function test parameters meant for the study are Bilirubin, SGOT, SGPT, Albumin. By assessing the particular parameters of the study, we concluded the following outcomes: At the end of the study, group 1 has shown 60% improvement, Group 2 has shown 50 % improvement from baseline to the end of the study. Group 3 has not shown much improvement when compared to the study medications i.e there is an overall improvement of only 30 % from baseline. By the end of the study scruitinizing all the laboratory parameters it is observed that of the three groups, group 1 and group 2 has better treatment outcomes than group 3 and hence it is concluded that medical intervention is more effective over complete abstinence and concluded that early medical intervention is a better option for better outcomes.

Keywords: Alcoholic liver disease, ursodeoxycholicacid, S-Adenosyl Methionine SGOT, SGPT, INR, Prothrombin.

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INTRODUCTION

Liver is extremely active organ in the body. It is the largest gland weighing between 3.17 and 3.66 pounds (lb), or between 1.44 and 1.66 kilograms (kg), the liver is reddish-brown with a rubbery texture.

The liver is classed as a gland and associated with many functions. It is difficult to give a number, as the organ is still being explored, but it is thought that the liver carries out 500 distinct roles. [1]

Liver disease can be defined as any disturbance of liver function that causes illness. The liver is responsible for many critical functions within the body. The loss of those functions can cause significant damage to the body. Liver disease is also referred to as a hepatic disease. Liver disease is a broad term that covers the potential problems which causes the liver to fail to perform its designated functions. Usually, more than 75% or three quarter of liver tissue needs to be affected before decrease in function occurs.[2]

Disease Spectrum:

Alcoholic fatty liver:

It is invariable if consumption exceeds 80g of alcohol per day. Effected hepatocytes occupied by the triglyceride accumulation but there is a normal liver function. It is reversible on abstinence.[3]

Alcoholic hepatitis:

Hepatocyte ballooning occurs due to increased intracellular water accumulation. Mallorys hyaline bodies are perinuclear eosinophilic inclusion bodies and are probably condensed and disorganized fragments of the cytoskeleton framework of the hepatocyte. These bodies are the characteristic of this condition. 15-20 years of excessive drinking estimated to develop alcohol hepatitis.[3]

Liver cirrhosis:

Liver cirrhosis is a irreversible damage of liver. It is a progressive parenchymal necrosis, regeneration and diffuses fibrosis, leading to disorganization of architecture of lobular throughout the whole liver. These nodules or lobules are called as pseudo lobules. This may be termed as micronodules or macronodules depending upon their size. Localized deficit such as nodular hyperplasia do not constitute cirrhosis because histological abnormality should involve the entire liver.[3]

Alcohol is a leading cause of liver disease. It is consumed in most regions of the world; two billion people worldwide consume alcoholic beverages. It is estimated that 76.3 million have a diagnosable alcohol use disorders by World Health Organization. It is responsible for over 2.5 million deaths every year and alcoholic liver disease (ALD) accounts for a large portion of alcohol related morbidity and mortality. Alcoholic liver disease is a spectrum of clinical illness and morphological changes that range from fatty liver to hepatic inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis).Alcohol is the world third largest risk factor for disease burden. Consumption of alcohol results in 2.5 million deaths each year.

Liver cirrhosis mortality in the world is 23.54% and it ranks 27th as a cause of death in the world majorly.

The World Health Organization (WHO) estimates that 140 million people worldwide suffer from alcohol dependency, causing damage to lives and economies. In India, 15 people die every day – or one every 96 minutes – from the effects of drinking alcohol, reveals by an India Spend analysis of 2013 National Crime Records Bureau (NCRB) data. Global status report on alcohol and health 2014 was released by WHO for India, Around 30% of total adult population consumes alcohol. 93% of alcohol consumes in the form of spirit. 7% in the form of beer and ≤1% in the form of wine. Highest alcohol consumption were found in Kerala (8 ltrs per annum) followed by Maharasthra and Punjab. 11% adult population in India indulged in heavy drinking or binge drinking.[4]

ATP synthesis rate is reduced in the liver cells when exposed to ethanol. Chronic alcohol consumption results in depressed activity of almost all mitochondrial complexes .This include decrease activity of cytochrome oxidase. Impaired proton translocation and electron transport, ATP synthesis complex is reduced and decreased cytochrome b content as a result energy metabolism is severely impaired and result in hepatic damage.[5]

Hypoxia also alteres the energy metabolism.The liver cells increases the oxygen uptake by chronic ethanol administration because of the need of its metabolism, which occurs in the centilobular area of the liver lobule which lead to the increased blood flow to the liver. But increasing blood flow do not match the requirements derived from metabolism of ethanol. Thus, the responsible for liver injury is centri lobular hypoxia.Hypoxia and high ethanol blood levels might ensure from the combination of increased oxygen demand and reduced perfusion .When the ethanol levels in the blood decline, it restore the lobular perfusion and injury.[5]

Oxidative stress:

Ethanol is metabolized by two steps:

1. Conversion of ethanol to acetaldehyde by Alcohol dehydrogenase.

2. Conversion of acetaldehyde to acetate by Acetal deydrogenase .

Acetaldehyde is toxic byproduct that damages the liver cells. Liver oxidative stress is increased through alcohol by generation of Reactive oxygen species (ROS) .In alcohol metabolism involves an excessive reduction of nicotinamide adenine dinucleotide (NAD) which causes the impairment in gluconeogenesis and metabolism to ketogenesis and fatty acid synthesis. Under normal circumstances reduction of NAD to NADH is regulated by cell kreb's cycle.[5]

Excessive alcohol consumption causes the shift and causing impairment of gluconeogenesis and diversion of metabolism to ketogenesis and fatty acid synthesis, NADH assume a reduced state of electron transport chain components in mitochondria. This results transfer of electrons to the molecular oxygen to generate the reactive oxygen species (ROS) as superoxide anion leading to the cell damage. NADH inhibition of β-oxidation leads to the accumulation of intracellular lipids, thus promoting steatosis. Excessive alcohol consumption leads to the induction of CYP2E1 which is the pathway of alcohol metabolism. The interaction of CYP2E1 with cytochrome reductase lead to the production of superoxide radicles, which results in leaks of electrons in the respiratory chain and ROS production. ROS produce in this cascade can react with iron and generates even more potent hydroxyl, ferryl, and perferryl radicles which perpetuate the liver damage.[5]

Immunological mechanism

By product of acetaldehyde by ethanol metabolism covalently bind to proteins and form adducts, antigenic which stimulate the immunological mechanisms which lead to the tissue injury. The expression of tumor necrosis factor –α (TNF –α), Interleukin (IL) –Iβ increased in alcoholic liver disease. while IL-6 and anti inflammatory cytokines decreased . These cytokines produce collagen leading to liver fibrosis by stimulating stellate cells and other way variety of substance like bacterial endotoxins such as lipopolysaccharides increase the intestinal permeability on intake of alcohol. At last it would characterized by necro-inflammation, apoptosis and fibrosis lead to liver disease i.e cirrhosis.[5]

Alcohol increases the flow of blood in the portal and hepatic vascular resistance results increased portal pressure and collateral blood flow which causes the visceral bleeding in patients with alcoholic cirrhosis and portal hypertension.[3]

Complications:

Chronic liver disease and exposure to hepatotoxic substances causes damage to normal liver tissue resulting in an inflammatory response and abnormal collagen secretion.

The initial result of this inflammation and collagen secretion is hepatic fibrosis. Fibrosis, defined as the excessive accumulation of proteins, such as collagen, in the liver's extracellular matrix, is currently considered a wound-healing response to chronic liver injury. If fibrotic liver disease advances, collagen bands progress to bridging fibrosis and eventually frank hepatic cirrhosis.[6]

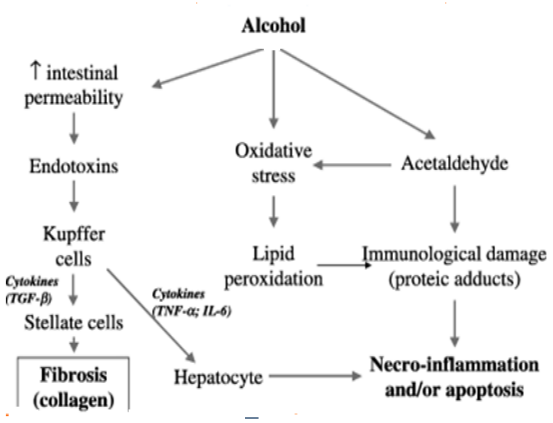

Figure -1: Pathophysiology of alcoholic liver disease

Ascites:

Ascites is a Greek word meaning water bag or wineskin. Ascites is the lymphatic fluid accumulation in the peritoneal cavity. It is the clinical presentation of cirrhosis. Formation of ascites is due to the splanchnic artial hypertension and decreased peripheral resistance due to severe portal hypertension and hepatic insufficiency. This results systemic hypotension which causes increased activity of sympathetic nervous system and renin-angiotensin–aldosterone system,that causes increased sodium and water retention and production of vasoconstrictor. This fluid accumulates in the abdominal cavity leading to the formation of ascites.[6]

Portal hypertension:

The classical symptom of portal hypertension is development of varices. Varices is the abnormal blood flow from the portal to systemic circulation, bypassing the liver. Varices causes portal venous system decompression and lead to return of blood to the systemic circulation. At any level of gastrointestinal tract varices occurs but the clinical significance route is through the left gastric vein development of esophageal varices. In cirrhotic patients there is a visceral bleeding when pressure in portal venous is more than 12mmhg which is greater than vena cava pressure. 25% to 40% of cirrhotic patients cause haemorrhage and 25% to 30% are risk of death in each episode of bleeding.Varices can be treated by decreasing the portal hypertension by pharmacological and surgical approaches.[6]

Hepatic encephalopathy:

Hepatic encephalopathy occurs with significant liver dysfunction with a reversible neuropsychiatric complication namely portosystemic shunting, metabolic dysfunction and alteration of blood brain barrier. Neurotoxic and neuroactive substance such as ammonia pass through the liver which is in disease condition and bypass the shunts then go directly to brain. Other substances like γ-amino butyric acid (GABA) and Glutamate are implicated in causing the hepatic encephalopathy. Trival lack of awareness, altered mental state to asterixis are the clinical feature of hepatic encephalopathy, even go to gross disorientation and coma. Symptoms like impaired judgment, altered personality, euphoria or anxiety occur in the lowgrade encephalopathy.[7]

Albumin:

Serum albumin often referred to simply as blood albumin is an albumin (a type of globular protein) found in vertebrate blood .

Serum albumin is produced by the liver, occurs dissolved in blood plasma in mammals. Albumin is essential for maintaining the oncotic pressure needed for proper distribution of body fluids between blood vessels and body tissues, without albumin, the high pressure in the blood vessels would force more fluids out into the tissues. It also acts as a plasma carrier by non specifically binding several hydrophobic steroid hormones and a transport protein for hemin and fatty acids. Too much or too little circulating serum albumin may be harmful.

Serum albumin is important blood volume by maintaining the oncotic pressure of the blood compartment. They also serve as carriers for molecules of low water solubility this way isolating their hydrophobic nature, including lipid soluble hormones, bile salts, unconjugated bilirubin , free fatty acids calcium , ions and some drugs like warfarin, phenobutazone, clofibrate and phenytoin .For this reason it is sometimes referred as a molecular taxi . Competition between drugs for albumin binding sites may cause drug interaction by increasing the free fraction of one of the drugs, thereby affecting potency.

Normal range of albumin in adults is 3.5 to 5 g/dl. If you have a lower albumin level, you may have malnutrition. It can also mean that you have liver disease or an inflammatory disease. Higher albumin levels may be caused by acute infections, burns, and stress from surgery or a heart attack. [8]

Functions:

Albumin functions primarily as a carrier protein for steroids, fatty acids, and thyroid hormones in the blood and plays a major role in stabilizing extracellular fluid volume by contributing to oncotic pressure (known also as colloid osmotic pressure) of plasma.

Synthesis:

Albumin is synthesized in the liver as pre proalbumin which has an N-terminal peptide that is removed before the nascent protein is released from the rough endoplasmic reticulum. The product ,proalbumin , is in turn cleaved in the Golgi vesicles to produce the secreted albumin. [8]

Child pugh scoring:

Child Pugh scoring is based on the values of lab parameters which include – total bilirubin in blood (mg/dl), serum albumin (mg/dl), Prothrombin and INR, Ascites, and stage of Hepatic encephalopathy. Child pugh score is used to grade the extent of liver damage.

Table-1: Child-Pugh Scoring.

Factor	1 point	2 points	3 points
Total bilirubin (mg/dl)	<34	34-50	>50
Serum albumin (g/L)	>3.5	28-35	<28
PT and INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Grades of child pugh score:

Table-2 Grades of liver cirrhosis with child pugh score.

Child-Pugh grade	Child-Pugh Score	Indicates
A	5-6	Well-functioning liver
B	7-9	Significant functional compromise
C	10-15	De-compensation of the liver

Laboratory Investigations:

The following lab investigations are usually performed to estimate the functionality of liver. Table-3.

Prothrombin Time:

Prothrombin is a protein made by the liver. Prothrombin helps blood to make normal clots. The "prothrombin time" (PT) is one way of measuring how long it takes blood to form a clot, and it is measured in seconds (such as 13.2 seconds). A normal PT indicates that a normal amount of blood-clotting protein is available.

When the PT is high, it takes longer for the blood to clot (17 seconds, for example). This usually happens because the liver is not making the right amount of blood clotting proteins, so the clotting process takes longer. A high PT usually means that there is serious liver damage or cirrhosis.Some patients take a drug called Coumadin (warfarin), which elevates the PT for the purpose of "thinning" the blood. This is not related to having liver disease because it is the Coumadin causing the PT to be high

Table-3 Lab Investigations usually performed to estimate liver functionality.

Laboratory test	Normal range	Disease Specific values
Bilirubin	0.3-1.2 mg/dl	>2 mg/dl
Aspartate aminotransferase(AST) SGOT	5-40 U/L	120U/L
Alanine aminotransferase (ALT) SGPT	7-56 U/L	>40 U/L
Prothrombine time (PT)	9.5-13 secs	> 13.5 secs
INR	1.0 or below	Greater than 1
Albumin	3.5-5.2 g/dl	<3 g/dl

INR (international normalized ratio):

International normalized ratio (INR) is blood-clotting test. It is a test used to measure how quickly your blood forms a clot, compared with normal clotting time.

A normal INR is 1.0. Each increase of 0.1 means the blood is slightly thinner (it takes longer to clot). INR is related to the prothrombin time (PT). If there is serious liver disease and cirrhosis, the liver may not produce the normal amount of proteins and then the blood is not able to clot normally. When your doctor is evaluating the function of your liver, a high INR usually means that the liver is not working as well as it could because it is not making the blood clot normally. [9]

Liver disease is the most likely diagnosis if the **AST** level is more than twice that of **ALT** , a ratio some studies have found in more than 80 percent of alcoholic liver disease patients. An elevated level of the liver enzyme **GGT** is another gauge of heavy alcohol use and liver injury.[10]

Treatment:

Conventionally, either Ursodeoxycholic acid or S-Adenosyl Methionine are being used as medical interventions in Alcoholic Liver Disease.

Ursodeoxycholic acid:

Ursodiol, a naturally occurring hydrophilic bile acid, derived from cholesterol, is present as a minor fraction of the total human bile acid pool. Oral administration of ursodiol increases this fraction in a dose related manner, to become the major biliary acid, replacing/displacing toxic concentrations of endogenous hydrophobic bile acids that tend to accumulate in cholestatic liver disease. In addition to the replacement and displacement of toxic bile acids, other mechanisms of action include cytoprotection of the injured bile duct epithelial cells (cholangiocytes) against toxic effects of bile acids, inhibition of apotosis of hepatocytes, immunemodulatory effects, and stimulation of bile secretion by hepatocytes and cholangiocytes. [11]

S-Adenosyl Methionine:

S-Adenosylmethionine (SAMe) is a natural substance present in the cells of the body. It is a direct metabolite of the essential amino acid L-methionine. SAMe plays a crucial biochemical role in the body by donating a one-carbon methyl group in a process called transmethylation. SAMe, formed from the reaction of L-methionine and adenosine triphosphate catalyzed by the enzyme S-adenosylmethionine synthetase, is the methyl-group donor in the biosynthesis of both DNA and RNA nucleic acids, phospholipids, proteins, epinephrine, melatonin, creatine and other molecules.[12]

Aims and Objectives:

Aim:

To evaluate the outcomes of Ursodeoxycholic acid(300mg), methionine(200mg) and abstinence in the treatment of alcoholic liver disease.

Objectives of the study:

To compare the following Endpoints:

Primary Endpoint-change from baseline in particular LFT parameter-albumin and CBP parameters such as PT and INR ratio.

SECONDARY ENDPOINT- effects of Ursodeoxycholic acid and methionine on other LFT parameters such as total bilirubin, SGOT, SGPT along with changes in the above parameters in patients with abstinence.

Significance:

Alcoholic liver disease is a major cause of mortality and morbidity worldwide.

Although the disease condition cannot be cured completely by alcohol abstinence due to very poor outcome, to improve patients quality of life, these drugs(ursodeoxycholic acidand methionine) were being used in the treatment of ALD patients widely.

Though ursodeoxycholic acid and methione drugs have well known effect on the liver function test parameters of SGOT and SGPT and total bilirubin, here we assessed the effects of these two drugs on specific LFT parameters i.e albumin and CBP parameters i.e prothrombin and INR that may help us to know more about the drugs efficacy.

Apart from the clinical management the abstinence(control group) was also included to observe for the changes in the particular parameters(LFT and CBP) in comparison with the patients treated with ursodeoxycholic acid and methionine.

MATERIALS AND METHODS:

Study Site:

GANDHI HOSPITAL:It is a 1200 beded government hospital located at secunderabad. The Gastroenterology department has both out - patient and in- patient department and the patient flow will be around 100 to 150 patients per day.70 cases are collected from here.

ASIAN INSTITUTE OF GASTROENTEROLOGY: It is a 1000 beded Super-speciality hospital located at Somajiguda Hyderabad. It has got both in-patient and out-patient department and the patient out flow will be around 40 to 50 per day.50 cases are collected from here.

Study design: Randomized, Observational, and prospective study.

Study duration:

The study is carried out over a period of 6 months, AUGUST 2018 TO FEBRUARY 2019.

Sample size: Total 120 subjects. (N=120)

GROUP -1: 40 subjects.

GROUP - 2: 40 subjects.

GROUP - 3: 40 subjects.

Ethical considerations:

The study was approved by Institutional Review Board.

Inclusion and Exclusion criteria:

Inclusion criteria:

- Patients diagnosed with alcoholic liver diseasein in-patient and out-patient department.
- Patients above 15 years of age.
- Male and female patients.
- Patients diagnosed with alcohol liver disease and CHILD PUGH SCORE below 10 (class B- Moderately severe liver disease) were included.

Exclusion criteria:

- Patients below 15 years of age.
- Patients who are diagnosed with grade 3 Cirrhosis.
- Patients with CHILD PUGH SCORE above 10 (class C-most severe liver disease) were excluded.

Source of data:

Review of patient records, laboratory data, direct communication with patients and their care takers.

Statistical analysis:

Base-line Mean values of all LFT parameters, End-point mean values of all LFT parameters, Percentage reduction in mean values from Base-line to End-point.

Parameters considered:

Demographics of patient.

Laboratory parameters includes –liver function test, complete blood picture,

In particular Liver function test parameters meant for the study are Bilirubin, SGOT, SGPT, Albumin.

In particular CBP parameters meant for the study are Prothrombin time and INR ratio.

Study procedure:

- Preparation of required documentation form for the case study of each person who were eligible for the study.
- The patients who reached the inclusion criteria are enrolled in the study.
- Both the in patients and out patients are reviewed on daily basis.
- The study has been explained to the patient / care takers.
- All the necessary information collected from patient record, laboratory data and documented.

- Their contact numbers were also been taken for the direct communication with patients and their care takers.
- Providing the medications and explaining regarding the dose to be administrated.
- Explained about the supportive care and diet for the patients of placebo group.
- Review of the data based on the requirement on time i.e for every 1 month upto 6 months .
- Interpretation of the data generated for seeking the result.
- All the above information was collected in properly designed data collection form, data were analyzed based on requirements.

Study Design:

A simple randomized study to evaluate the outcomes of ursodeoxycholicacid,S-adenosyl methionine and placebo in the treatment of alcoholic liver disease. During the screening, subjects who are willing to give consent will be evaluated for all the eligibility criteria.Eligible subjects clinically diagnosed with alcoholic liver disease and who are above 15 years of age and subjects with child pugh score below 10 (class B-moderate severe liver disease) were included in the study. Subjects fulfilling all the inclusion criteria and none of the exclusion criteria will be randomized on day 1.

Subjects were assigned into three groups i.e, Group 1, Group 2, Group 3. Group 1 subjects were assisted to administer Ursodeoxycholic acid 300 mg twice daily through oral route, Group were assisted to administer methionine 200mg twice daily through oral route and Group 3 were assisted to take the(abstinence) supportive care. All the three groups were advised to remain abstained from alcohol during the study period.

Subjects were assessed with LFT parameters such as bilirubin, SGOT, SGPT, albumin and CBP parameters such as prothrombin time and INR ratio. Adverse events and concomitant medications were assessed from baseline to end of the study/visit-6.

All the subjects were assessed for primary endpoint i.e, change from baseline in particular LFT parameter-albumin and CBP parameters such as PT and INR ratio, secondary endpoint i.e, effects of ursodeoxycholic acid and methionine on other LFT parameters such as total bilirubin, SGOT, SGPT along with changes in the above parameters in patients with abstinence.

RESULTS AND DISCUSSION:

The patients were included in the study from in-patient and out-patient department of gastroenterology.

All the subjects who fulfilled inclusion criteria are randomly assigned into 3 groups i.e Group 1(Ursodeoxycholic acid 300mg) Group 2 (Methionine 400 mg) and Group 3 (Abstinence)

The randomised subjects are explained about the project and asked for their consent to participate in the study.

Base line values of six parameters were noted:

Total bilirubin.

SGOT.

SGPT.

Albumin.

Prothrombin time.

INR ratio.

Later, the subjects were randomised based on child pugh score (below10). The group 1 and group 2 are prescribed with Ursodeoxycholic acid and Methionine respectively and group 3 were instructed to adhere to supportive care (Nutritional supplements and abstinence from alcohol). All the 3 groups were mandated to remain abstained from alcohol.

Subjects were instructed to come for a review on monthly basis for the assessment of the laboratory parameters upto 6 months from the date of inclusion in the study.

By assessing the particular parameters of the study, we concluded the following outcomes:

At the end of the study, group 1 has shown 60% improvement.

Group 2 has shown 50 % improvement from baseline to the end of the study.

Group 3 has not shown much improvement when compared to the study medications i.e there is an overall improvement of only 30 % from baseline.

Means of individual groups:

Group 1:

After assessing the overall LFT parameters

The baseline mean of Total bilirubin was found to be 2.9mg/dL and mean at the end of the study was found to be 1.1 mg/dL. At the end of the study period the percentage reduction of mean of total bilirubin was found to be 62 %.

The baseline mean of SGOT was found to be 98.2 U/L and mean at the end of study was found to be 45.4U/L and the percentage reduction in the mean of SGOT was noticed as 53.7% at the end of the study.

Baseline mean of SGPT was found to be 72.1U/L and the mean at the end of the study was observed as 49.1U/L. Percentage reduction in the mean of SGPT was found to be 31.9% by the end of the study.

Baseline mean of albumin was found to be 2.6 g/dL and the mean at the end of the study was observed as 3.7g/dL. Percentage increase in the mean of albumin was found to be 42.3 % from baseline at the end of the study.

Baseline mean of prothrombin time was found to be 21.3s and the mean at the end of the study was observed as 14s. Percentage reduction in the mean of prothrombin time was found to be 34.2 % from baseline at the end of the study.

Baseline mean of INR was found to be 1.5 and the mean at the end of the study was observed as 1.0. Percentage reduction in the mean of INR was found to be 33.3 % at the end of the study.

Group 2:

The baseline mean of Total bilirubin was found to be 3.44mg/dl and mean at the end of the study was found to be 1.70mg/dl. The percentage reduction in the mean of total bilirubin was found to be 50 % at the end of the study.

The baseline mean of SGOT was found to be 104.9U/L and mean at the end of study was found to be 57.43U/L. percentage reduction in the mean of SGOT was found to be 45.2% at the end of the study.

Baseline mean of SGPT was found to be 60.4U/L and the mean at the end of the study was observed as 46.8U/L. Percentage reduction in the mean of SGPT was found to be 23% at the end of the study.

Baseline mean of albumin was found to be 1.88g/dl and the mean at the end of the study was observed as2.8g/dl. Percentage reduction in the mean of albumin was found to be 49% at the end of the study.

Baseline mean of prothrombin time was found to be 16.9s and the mean at the end of the study was observed as13.5s. Percentage reduction in the mean of prothrombin time was found to be 20 % at the end of the study.

Baseline mean of INR was found to be 1.2 and the mean at the end of the study was observed as 0.9. Percentage reduction in the mean of INR was found to be 21.2 % at the end of the study.

Group 3:

The baseline mean of Total bilirubin was found to be 1.7mg/dl and mean at the end of the study was found to be 1.1mg/dl. percentage reduction in the mean of total bilirubin was found to be 37 % at the end of the study.

The baseline mean of SGOT was found to be 93U/L and mean at the end of study was found to be 64U/L. percentage reduction in the mean of SGOT was noticed as 31 % at the end of the study.

Baseline mean of SGPT was found to be 58.4U/L and the mean at the end of the study was observed as 40.6U/L. Percentage reduction in the mean of SGPT was found to be 30 % at the end of the study.

Baseline mean of albumin was found to be 2.1g/dl and the mean at the end of the study was observed as 2.7g/dl. Percentage increase of mean of albumin was found to be 28.5% at the end of the study.

Baseline mean of prothrombin time was found to be 16.7s and the mean at the end of the study was observed as 14.2s. Percentage reduction in the mean of prothrombin time was found to be 14 % at the end of the study.

Baseline mean of INR was found to be 1.2 and the mean at the end of the study was observed as 1.0. Percentage reduction of mean of INR was found to be 16 % at the end of the study.

To decrease the progress of the present condition the complete abstinence was instructed to patients of all the three groups, regardless of which some patients consumed alcohol without any confession but it was assessed by their laboratory parameters.

12% of patients in the group 1 and 8% of patients in group 2 and 5% of patients in group 3 have respectively reported a maximum of 2 episodes of drinking but they were permitted to stay in the study without further drinking. The measured outcomes were affected by these episodes of drinking.

Adverse Events:

As these drugs comes with a positive effect and less or more negative effect here few patients have experienced the adverse reactions.

There were no severe adverse events in either three groups. In Group1 (ursodeoxycholic acid), 2 patients complained of diarrhea, 3 patients complained of headache. In Group2 (methionine) no serious adverse events were reported. In Group3 (abstinence) 3 subjects complained of vomitings, 2 subjects complained of headache.

CONCLUSION

By the end of the study scruitinizing all the laboratory parameters it is observed thatof the three groups group 1 and group 2 has better treatment outcomes than group 3 and hence it is concluded that medical intervention is more effective over complete abstinence.

As Group 1 has shown 60% of improvement, Group 2 has shown 50% of improvement from baseline to end of the study period comparatively on the other hand complete abstinence has shown a poor improvement of 30% from baseline to the end of the study periods.

Considering all the above observed outcomes it is concluded that early medical intervention is a better option for better outcomes and among Ursodeoxycholic acid and methionine, Ursodeoxycholic acid was found to be better option for the treatment.

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ABBREVATIONS USED

1) AIDS-Acquired Immune Deficiency Syndrome
2) ALD-Alcoholic Liver Disease
3) ALT-Alanine Amino Transferase
4) AST-Aspirate Amino Transferase
5) ATP-Adenosine Triphosphate
6) CBP-Complete Blood Picture
7) CNS-Central Nervous System
8) DNA-Deoxyribo Nucleic Acid
9) GABA-Gamma Amino Butyric Acid
10) GGT-Gamma Glutamyl Transferase
11) IL-Interleukin
12) INR-International Normalized Ratio
13) LFT-Liver Functional Test
14) NAD-Nicotinamide Adenine Dinucleotide
15) NADH- Nicotinamide Adenine Dinucleotide Hydrogen
16) NCRB-National Crime Records Bureau
17) PBC-Primary Biliary Cirrhosis
18) PEG-Poly Ethylene Glycol
19) PT-Prothrombin Time
20) RNA-Ribonucleic Acid
21) ROS-Reactive Oxygen Species
22) SAM-S-Adenosyl Methionine
23) SGOT-Serum Glutamic Oxaloacetic Transaminase
24) SGPT-Serum Glutamic Pyruvic Transaminase
25) TNF-Tumor Necrosis Factor
26) UDCA-Ursodeoxycholic Acid
27) WHO-World Health Organization

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