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Original Article

A Prospective Observational Study on Assessment of Risk Factors, Complications and Clinical Efficacy of Hepatoprotectives and Antimicrobials in Treatment of Liver Diseases at Tertiary Care Teaching Hospital in Telangana

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ABSTRACT

Background: The liver serves a variety of essential purposes, making it the most important organ. Chronic liver disease (CLD) has a wide range of etiologies, including toxins, alcoholism, infections, autoimmune illnesses, and hereditary problems. Patients are initially asymptomatic, as the disease progresses, signs like jaundice, icterus, pedal oedema, and abdominal distension can be seen. Liver functioning tests are used to assess liver disease progression. Liver disease may result in problems such as portal vein hypertension (PH). The treatment is to stop the disease and its associated complications from getting worse. For the treatment, a comprehensive strategy involving hepatoprotectives and antibacterial medications is required. **Materials and Methods:** This is a prospective observational study with the sample size of 200 patients. Patients were selected by simple random sampling. Then the patients were categorized according to their disease condition and collected data was analysed using suitable methods. **Results:** According to our research, chronic alcoholics have a higher risk of getting hepatitis and alcoholic fatty liver disease. The greatest treatment for liver disease is alcohol abstinence, which can be started as soon as possible. Avoiding alcohol will increase survival at all stages of the illness. Thiamine and ursodeoxycholic acid are the two hepatoprotectives that are most usually advised, followed by rifaximin and L-ornithine and L-aspartate (LOLA). **Conclusion:** Our research found that within the first week of treatment, serum bilirubin levels, aspartate transaminase levels, and alanine transaminase levels significantly decreased in people receiving hepatoprotective medications. The pharmacist is crucial for better therapeutic management based on the patient's stage and condition.

Keywords: Risk factors, Complications, Alcoholic liver diseases, Hepatoprotectives, Antimicrobials.

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INTRODUCTION

The liver is the most significant organ in the human body. It is located in the upper right quadrant of the stomach and has regenerative capability. The liver has many vital functions like transportation of waste, production of albumin and other proteins to maintain osmotic pressure, synthesis of cholesterol and lipoproteins, which facilitate lipid transportation, metabolism of carbohydrates, which involves the storage of glycogen and gluconeogenesis, which controls blood glucose levels, processing hemoglobin to utilize the iron it contains, and the liver converts hazardous ammonia to urea. The liver's primary role is to metabolize medicines, toxic compounds, and other xenobiotics. The liver prevents infections by producing immunological components, eliminating microorganisms from the bloodstream, and regulating blood coagulation.[1]

Etiology of Liver Diseases

There are numerous etiologies which contribute to Chronic Liver Disease (CLD), including toxins, alcoholism, infections, autoimmune diseases, and genetic issues. Cirrhosis, the final stage of CLD, is marked by anatomical disruption, the formation of many nodules, rearrangement of the circulatory system, neovascularization, and the deposition of extracellular matrix. Alcoholic Liver Disease (ALD) is the most common disease

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worldwide. When a patient quits drinking alcohol, ALD is reversible. Chronic alcoholics develop thiamine deficiency, which leads to Wernicke-Korsakoff syndrome.[2]

The present leading cause of liver disease in the world due to changes in lifestyle is Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis; these are related to metabolic syndrome like Obesity, Hyperlipidemia, and Diabetes Mellitus sometimes it will progress to liver fibrosis. The other predominant cause of liver damage is due to viral hepatitis B, C, and D infections among which Hepatitis C has various genotypes. A very small percentage of the population is affected by inherited liver diseases such as Alpha-1 antitrypsin deficiency, which causes Neonatal jaundice; Hereditary Hemochromatosis; Wilson disease; and Gilbert syndrome. The other most important etiological factor which contributes to causes the Drug Induced Liver Failure (DIL) especially patients who are on poly pharmacy, chronic medication Antiretroviral (ARV), Antitubercular Therapy (ATT), Antiepileptic Drugs (AED), Paracetamol is the most misused.[3,4]

Clinical Manifestations of liver diseases

A clinical manifestation of liver diseases is atypical because initially patients are asymptomatic but upon disease progression we can observe symptoms like jaundice, icterus, pedal oedema, abdominal distension and ascites.

Complications of liver diseases

Progressive liver disease may lead to complications like, Portal vein Hypertension (PH) (portal venous pressure over 7 mmHg). Esophageal variceal hemorrhage is the life-threatening complication of CLD which needs immediate medical attention.[5]

As the disease aggravates liver will lost its synthesis capacity and produce less number of clotting factors and this may leads to coagulopathy. Hepatic Encephalopathy (HE) is the condition resulted due to inability of liver to detoxify the toxic by-products like ammonia; increased ammonia concentrations can affect consciousness, can occur in nearly 50% of CLD patients.[6]

Some metabolic pathway end products and enzymes that are particularly susceptible to abnormalities could be used as biochemical indicators of liver malfunction. Serum Bilirubin (SB), alanine amino transferase, aspartate amino transferase, ratio of amino transferase, alkaline phosphatase, gamma glutamyl transferase, 5′ nucleotidase, ceruloplasmin, and fetoprotein are a few examples of biochemical indicators.[7]

The goal of treatment is to prevent the illness and its effects from progressing. A comprehensive approach is necessary for the treatment of liver issues.[8,9] Initially treatment plan involves hepatoprotectives combined with broad-spectrum antibiotics, followed by specialized antibiotics following a culture test. When the precipitating factor is treated with medicines like Rifaximin and Lactulose, patients with hepatic encephalopathy typically get better.[10,11]

MATERIALS AND METHODS

Study Design: This study is a prospective observational study.

Inclusion criteria: Includes patient's age above 20 years who are diagnosed with all types of liver diseases.

Exclusion criteria: Patients of age under 20 years and patients not willing to participate.

Sample size: *N*=200.

Study period: The study was performed over a period of 6 months from October 2022 to march 2023.

Study location: Tertiary care teaching hospital, Khammam.

Study Procedure: This study was conducted after Institutional Ethics Committee (IEC) approval then the patients were selected for the study by simple random sampling. Then the patients were categorized according to their disease condition.

Source of data

Patient case sheets and patient interview about their alcohol consumption, previous health problems, and co-morbidities.

Past medical history, present medical history.

Physical examination and lab investigations.

Severity of disease will be assessed by child pugh score.

Assessing factors

Risk factors, complications, Clinical efficacy of antimicrobial and hepatoprotectives agent.

Statistical plan: The statistical analysis will be carried out by Microsoft Office Excel and Graph Pad Prism 8.

Monitoring Parameters: Liver Functioning Tests (LFT), Ultrasonography (USG)

Scales used to assess the severity of Liver Diseases

The Child-Pugh score evaluates complications with the help of parameters like bilirubin, albumin, ascites, encephalopathy and Prothrombin Time (PT) is depicted in Table 1.[12]

Class A (score 5-6): Good hepatic function.

Class B (score 7-9): Moderately impaired hepatic function.

Class C (score 10-15): Advanced hepatic dysfunction.

RESULTS AND DISCUSSION

The total study population is 200, with 172 males and 28 females, which we have categorized using different parameters like age groups, alcoholic status, social habits was depicted in Table 2.

Table 1: Variable points for each criterion based on increasing severity.

Parameters	1 point	2 points	3 points
Encephalopathy	None	Grade I and II	Grades III and IV
Ascites	None	Slight	moderate
Bilirubin	under 2 mg/mL	2 to 3 mg/mL	over 3 mg/mL
Albumin	>3.5 mg/mL	2.8 to 3.5 mg/mL	<2.8 mg/mL
Prothrombin Time	<4 sec	4 to 6 sec	>6 sec
Frequently INR	with INR<1.7	INR 1.7 to 2.2	INR>2.2

Table 2: Age-Gender, Alcoholic status of study population.

Age Group	Males	Females	Total	Alcoholics	Non-Alcoholics	Alcohol and smoking
20-40	64 (32)	5(2.5)	69 (34.50)	60 (30)	09 (4.5)	12 (6)
41-60	62 (31)	12(6)	74 (37)	68 (34)	06 (3)	23 (3)
61-80	40 (20)	11(5.5)	51(25.50)	46 (23)	05 (2.5)	05 (2.5)
81-100	6 (3)	0 (0)	6 (3)	06 (3)	00 (0)	02 (1)
Total	172(86)	28(14)	200 (100)	180 (90)	20 (10)	42 (21)

Table 3: Risk factors noticed in our study.

Risk factors		Number
Alcohol		180 (90)
Genetic causes	Crigler-najjar syndrome	01 (0.5)
	Gilbert syndrome	01 (0.5)
Drug induced liver disease	usage of AED's (Anti-epileptic drugs)	04 (2)
	usage of ART (Anti-retroviral therapy)	04 (2)
	usage of ART and AED's	01 (0.5)
	usage of ATT (Anti-tubercular therapy)	01 (0.5)
	usage of Azithromycin	01 (0.5)
	usage of Paracetamol	01 (0.5)
Herbal medicine induced liver disease	Herbal medicine	04 (2)
Other Factors	Hepatitis A virus	02 (1)
Total		200 (100)

Categorisation of residence with gender

To assess the incidence of liver diseases, we have categorised the residents by gender and observed that there are 67 males in rural areas and 105 males in urban areas. Females were 14 in both urban and rural areas.

According to our study, the 41-60 age groups [37%] is at greater risk of developing liver diseases because of their lifestyle, social habits, and other causes, followed by the 20-40 age group [34.50%]. Our results are similar to those of the study conducted by Lischner MW *et al.*[13] According to our study findings, males [86%] are at more risk of developing ALD. Females who had a drinking habit were also more vulnerable to developing alcoholic liver disease. Many studies concluded that, compared to males, females will develop liver disease at a very young age and with less alcohol consumption. The development of gender-specific susceptibility to alcohol hepatotoxicity in females has been linked to lower gastric alcohol dehydrogenase levels, which slow down alcohol's first-pass metabolism, higher gut permeability, which raises endotoxin levels after consuming alcohol and causes more aggressive oxidative stress and inflammation, and higher body fat content.[14,15]

Social habit status of study population

In our study, 180 patients were identified as alcoholics, with 163 men and 17 women, and 42 patients were also smokers. Alcoholic liver disease remains the leading cause of morbidity and mortality in India.[16] Alcoholic liver diseases develop in chronic alcoholics who routinely consume significant amounts of alcohol. Only the correct history of alcohol consumption, fever, jaundice, ascites, high WBC (White Blood Cells), AST400 IU/mL, and an elevated AST: ALT ratio can be used to diagnose alcoholic hepatitis.[17] For

ALD patients; a liver biopsy is suggested to rule out hepatocellular carcinoma. The general consensus is that the urban population [59%] has a higher chance of acquiring liver disease, particularly ALD, which can be prevented by reducing alcohol intake. ALD in India was concerning, which could cause issues including a strain on health care costs and socioeconomic position. According to our study, alcoholism (80.72%) is the main risk factor for all forms of liver disorders.

We found two rare hereditary and genetic liver disorders with a 1% incidence rate. Smoking and tobacco use were discovered to have a statistically significant connection with chronic liver disease among narcotic and psychotropic drug abusers who had ever consumed alcohol. Lin *et al.* discovered similar outcomes in their research.[18] In our study, we observed that people taking herbal medicine like Tamarind leaf extract decoction prepared by local tribes for various diseases, especially for jaundice, without following any sterilization and hygiene practices had caused liver abscesses, these results are presented in Table 3.

Table 4: Multiple Risk Factors wise distribution.

Multiple risk Factors	Number of cases
Alcohol and AED	2
Alcohol and ART	2
Alcohol and ATT	1
Alcohol and Azithromycin	1
Alcohol and Hepatitis	2
Alcohol and Crigler-najjar syndrome	1
Alcohol and herbal medicine ingestion	2
Total	24

Multiple risk Factors

Multiple risk factors observed in our study are alcoholism, polypharmacy, and the fact that patients taking anti-tuberculosis and anti-retroviral drugs had the risk of developing Drug-Induced Liver Injury (DILI), and in our study, we observed 24 cases of Drug-Induced Liver Injury (DILI) is depicted in Table 4. However, the incidence of adverse events, medication withdrawal, the severity of the drug-induced injury, when it will occur, and the indicators of liver function are unpredictable and need further studies and explanation.[19]

Diseases diagnosed

The majority of the patients in this study were diagnosed with alcoholic liver disease (43.50%), chronic liver disease (17%), liver cirrhosis (9%), Drug-induced liver diseases (7.5%), and alcoholic hepatitis (5%) followed by decompensated liver disease (2.5%) is depicted in Table 5.

Complications Assessed

A total 354 complications were seen in 200 patients as shown in Figure 1, many patients developed multiple complications, ascites was shown to be the most likely complication linked with liver disease in our study, followed by portal HTN. The issue that has to be addressed is that serious side effects, such as hepatic encephalopathy carry a higher chance of developing neurological symptoms, which could exacerbate the illness. We observed that diabetes mellitus and hypertension were the most associated comorbidities with liver disease that lead to metabolic syndromes and worsen the condition.

Assessment of Severity by Child-Pugh Score

In our study, the child-pugh score was used to determine the severity of the liver disease, and we found that the majority of

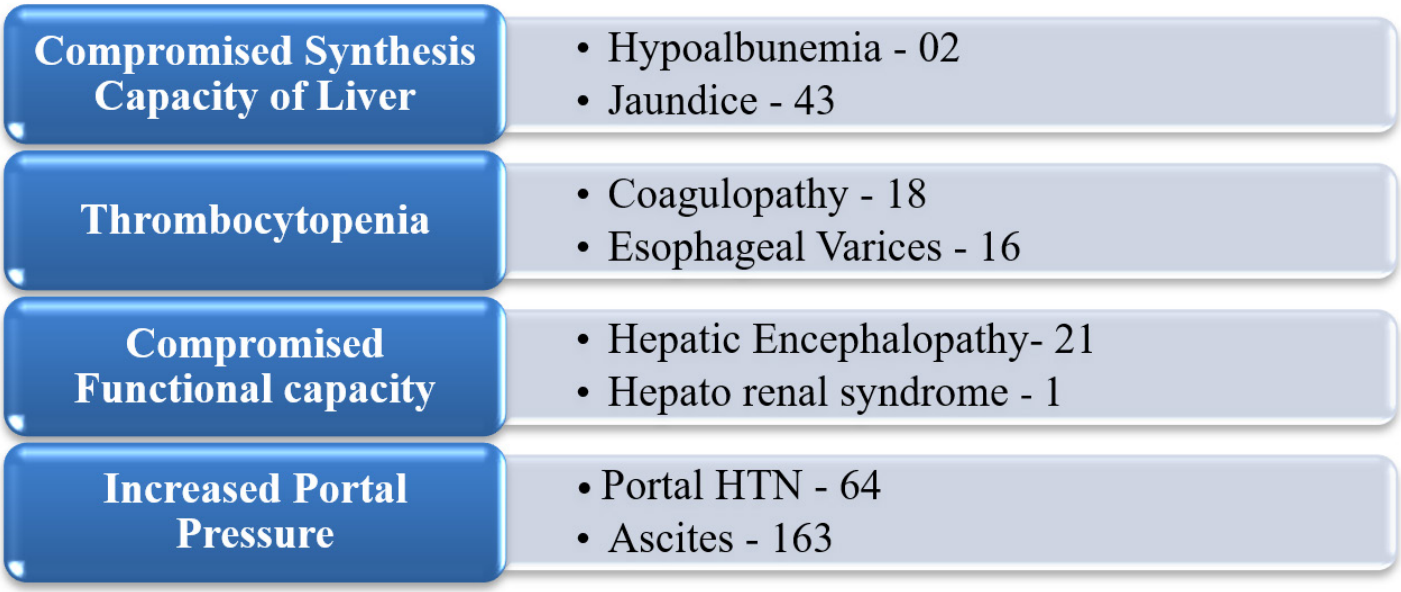

Figure 1: List of complications assessed.

cases had advanced hepatic dysfunction (67.5%), which may have been caused by a late diagnosis of the illness, followed by moderately impaired hepatic dysfunction (28.5%) good liver function was found in 4% of cases and it is depicted in Figure 2.

Utilizing Hepatoprotective Agents

The most commonly used hepatoprotective agent was thiamine, followed by ursodeoxycholic acid as shown in Figure 3. As we discussed, hepatic encephalopathy is the most dangerous complication, and it can be prevented by treating it with thiamine supplements. The majority of people with hepatic coagulopathy have vitamin K deficiency, and vitamin K is necessary for the activation of clotting factors II, VII, IX, and X. Patients taking vitamin K supplements for liver disease reported better coagulation.

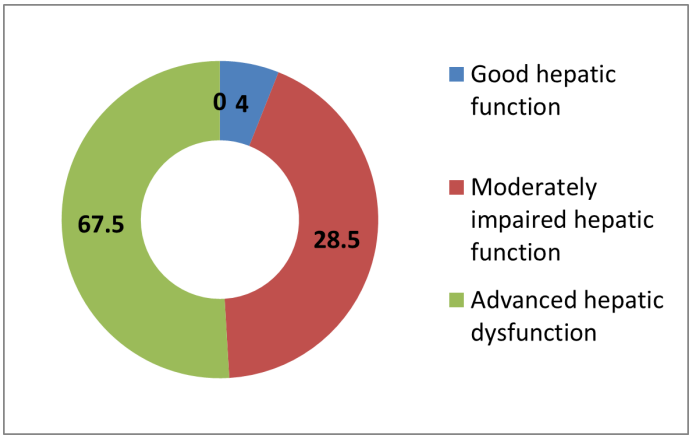

Figure 2: Categorisation of severity of Liver diseases.

Rifaximin at 550 mg twice daily decrease the hepato encephalopathy by reducing ammonia generation by eliminating colonic bacteria. Rifaximin-treated patients showed a marked reduction in the number and length of acute Hepatic Encephalopathy (HE) hospitalizations. Rifaximin is currently the most extensively used drug due to its slow systemic absorption, broad antibacterial spectrum, and few side effects.[20,16]

Table 5: Diseases diagnosed.

Disease diagnosed	Number of cases
Acute hepatitis.	2 (1)
Alcoholic hepatitis.	10 (5)
Alcoholic liver disease.	87 (43.5)
Chronic liver disease.	34 (17)
Cirrhosis of liver.	18 (9)
Decompensated chronic liver disease.	5 (2.5)
Drug induced liver diseases.	15 (7.5)
Haemangioma of the liver.	1 (0.5)
Herbal medicine induced liver disease.	14 (7)
Jaundice.	2 (1)
Liver abscess.	6 (3)
Liver carcinoma.	1 (0.5)
Non-alcoholic liver disease.	2 (1)
Rare genetic disorder associated with liver disease.	2 (1)
Viral hepatitis.	1 (0.5)
Total	200 (100)

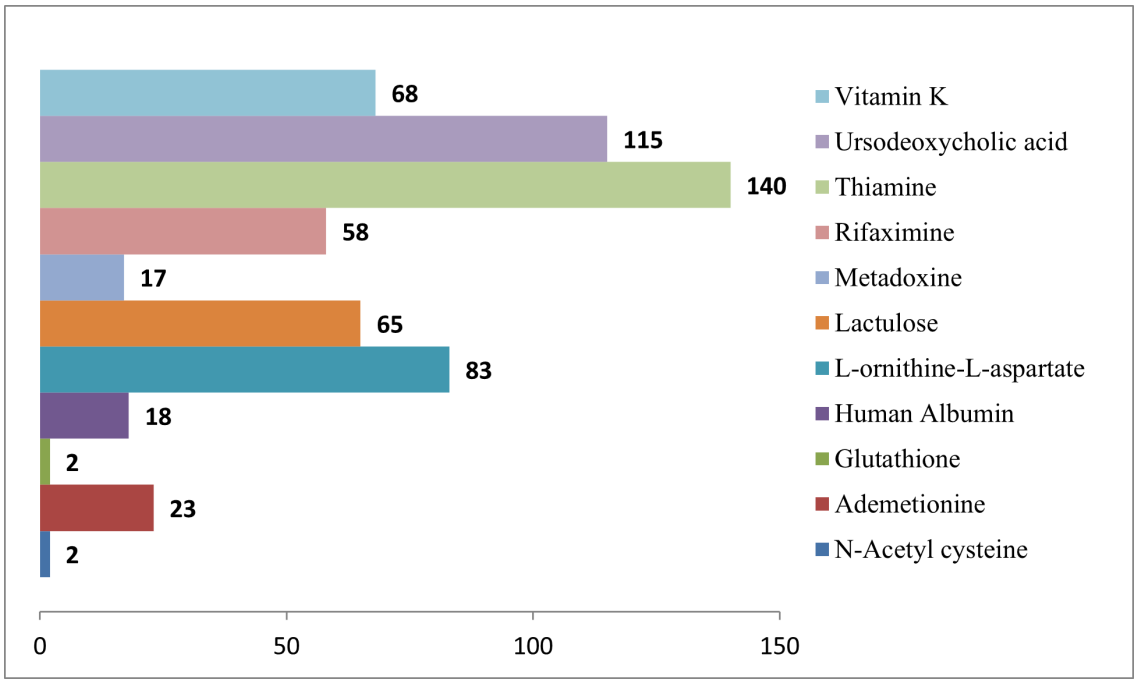

Figure 3: Number of Hepatoprotectives Used.

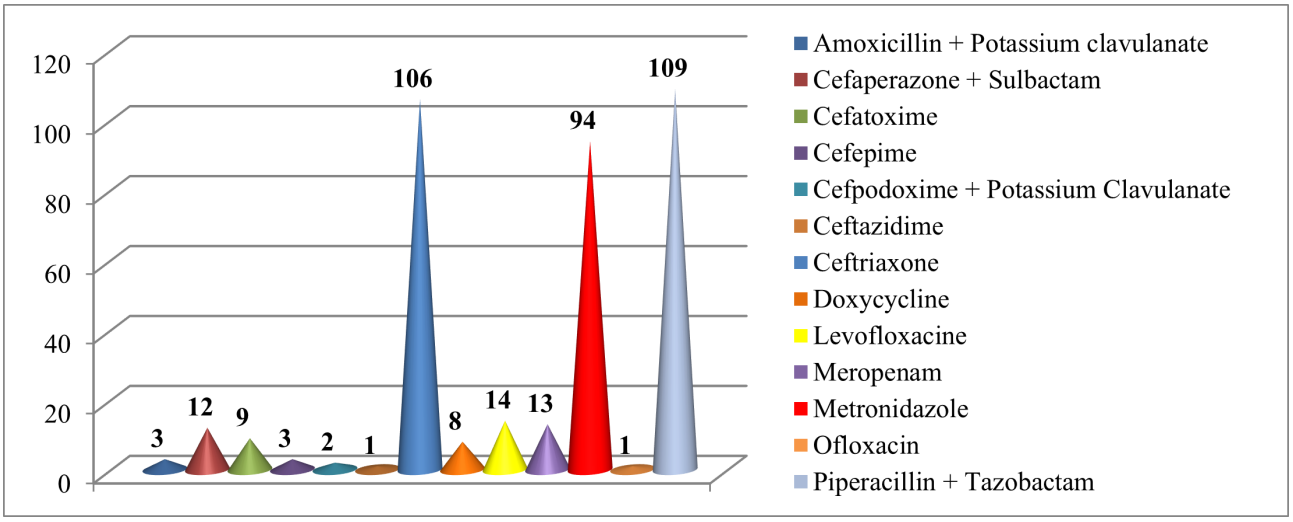

Figure 4: Most commonly used antimicrobial drugs in our study.

Table 6: Statistical analysis of efficacy of hepatoprotectives and anti-microbial agents.

Hepatic Enzymes	Before Treatment	After Treatment	Percentage Reduced (%)	*p*-Value	Significant
AST	179.36	75.736	57.77	0.00417	Yes
ALT	130.81	63.021	51.82	0.0001	Yes
SB	7.13095	3.00875	57.81	0.0001	Yes

Clinical portal-systemic encephalopathy can be prevented and treated with lactulose. Lactulose, which prevents intestinal ammonia synthesis, is used to treat hepatic encephalopathy, which is brought on by elevated ammonia levels. It works primarily by making the gut more acidic and reducing intestinal ammonia synthesis and absorption.[21] L-Ornithine L-Aspartate (LOLA), one of the best ammonia-lowering drugs, showed good efficacy in treating hepatic encephalopathy. The three drugs together with the other hepatoprotective drugs used in the study are often recommended in medical settings.

Utilization of Antimicrobial Drugs

The most prescribed antimicrobial drugs for liver diseases are piperacillin + tazobactam, metronidazole, and ceftriaxone. Combinational antibiotics were prescribed to treat peritonitis, liver infections, and other complications of liver diseases, the chosen antibiotics have a maximum safety profile in liver-impaired patients as depicted in Figure 4.

Efficacy of hepatoprotective agents and antimicrobial drugs in liver diseases

A student *t*-test was used to evaluate the therapeutic efficacy of hepatoprotective drugs and antimicrobial therapy. When the patients were admitted, we recorded their liver enzymes such as Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Serum Bilirubin (SB). The liver enzyme measurements were taken once again after 7 days. We have shown that pharmacological effectiveness was demonstrated by the reduction of AST values by 57.77%, ALT levels by 51.82%, and SB values by 57.81%. P values were discovered to be significant was shown in Table 6.

Limitations and Strengths

This study was constrained to only one region with specific district populations, we cannot extrapolate these results to a large group of population but we are confident the same will reflect with the majority of the population, the sampling in this study was not biased and we considered alcoholics as a cohort. Further studies have to be performed to understand the alcohol at various concentrations available in the market.

CONCLUSION

Our research shows that chronic alcohol users are more likely to develop Alcoholic fatty liver disease and Hepatitis. The most typical form of liver disease is alcoholic liver disease. Males are more likely than females to develop liver failure, which may be related to male's higher alcohol consumption.

Ascites, the most common complication, followed by Portal hypertension, have been demonstrated to be significantly influenced by the duration of alcohol consumption.

Beginning lifestyle changes like avoiding alcohol consumption will increase survival at all stages of the illness, alcohol withdrawal is the best course of action for liver disease.

The patient's care is concentrated on the nature and severity of the ailment, as well as dietary support and alcohol abstinence. The antibiotics that are most frequently used in liver failure cases are Piperacillin+Tazobactam combinational drug which has a good safety profile.

To improve liver function hepatoprotectives are also administered to patients to prevent complications. The two hepatoprotectives most frequently recommended are Thiamine, and Ursodeoxycholic acid followed by Rifaximine and LOLA. According to our study, individuals taking hepatoprotective drugs resulted in a significant drop down in hepatic impairment biomarkers.

The pharmacist is crucial for better therapeutic management based on the patient's stage and condition of liver disease, as well as for managing and addressing any unintended side effects. The pharmacist plays a vital role in designing the rationalized dosage regimen in liver failure patients to minimize the toxicity due to the inability of the liver to metabolize the drugs. Sincere efforts have been made to counsel the patients about the negative impacts of alcohol use on their health, families, and social well-being through our work.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTIONS

Jaya and Nikhil contributed by designing the study protocol, study design, and preparing the manuscript. Mounika, Deepthi, and Jharna were involved in the data collection form design and data collection. Chinnaeswaraiah coordinated with Mounika in analysing, and interpreting the results.

ABBREVIATIONS

AST: Aspartate aminotransferase; **ALT:** Alanine aminotransferase; **SB:** Serum bilirubin; **LOLA:** L-ornithine- L-aspartate; **HTN:** Hypertension; **DILI:** Drug-induced liver injury. **INR:** International normalized ratio; **LOLA:** L-ornithine- L-aspartate; **HTN:** Hypertension; **DILI:** Drug-induced liver injury.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted after obtaining approval from the Institutional Ethics Committee and following protocol which protects the safety and privacy of study participants, study coordinators obtained signatures on the informed consent form explained in the local language.

SUMMARY

Liver diseases and treatment options available are complex, we assessed the efficacy and safety of hepatoprotectives and antimicrobials used in liver diseases to provide the best clinical outcome to patient and to improve their quality of life. This study provides data on alcohol and its complications on the health of chronic alcoholics in specific regions of Telangana which serves as a significant manual for society.

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