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ORIGINAL RESEARCH ARTICLE OPEN ACCESS

AN OPEN LABLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF VALILIV® CAPSULES IN THE PATIENTS WITH VIRAL HEPATITIS

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ABSTRACT

Liver is a vital organ play a major role in metabolism and excretion of xenobiotics from the body. Liver cell injury is generally caused by various toxic chemicals (certain anti-biotic, chemotherapeutic agents, carbon tetrachloride (CCl4), thioacetamide (TAA) etc.), excessive alcohol consumption and microbes is well-studied. The available synthetic drugs to treat liver disorders in this condition also cause further damage to the liver. Hence, Herbal drugs have become increasingly popular and their use is wide-spread. Herbal medicines have been used in the treatment of liver diseases for a long time so the maintenance of a healthy liver is get possible. Current open labeled study of Valiliv capsule a preparation of extract of *Kutki* (Picrorrhiza kurroa) and *bhui-awala* (Phyllanthus niruri) in capsule form was studied in a cases of acute viral hepatitis cases caused due to HAV for the period of 12 week in a dose of 2 capsules BID. Highly significant results even after 4 week of treatment in biochemical parameters of billirubin, ALT, AST, WBC indicates the significance hepatoprotective effect of the therapy with highly significant difference in clinical parameters like anorexia, pain in abdomen etc. without causing any untoward effect during the therapy.

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INTRODUCTION

Hepatitis, a general term referring to inflammation of the liver, may result from various causes, both infectious (ie, viral, bacterial, fungal, and parasitic organisms) and noninfectious (e.g, alcohol, drugs, autoimmune diseases, and metabolic diseases). In the United States, viral hepatitis is most commonly caused by hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). These three viruses can all result in acute disease with symptoms of nausea, abdominal pain, fatigue, malaise, and jaundice (Wasley *et al.,* 2006). Additionally, acute infection with HBV and HCV can lead to chronic infection.

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Patients who are chronically infected may go on to develop cirrhosis and hepatocellular carcinoma (HCC). Further more, chronic hepatitis carriers remain infectious and may transmit the disease for many years (Previsani and Lavanchy, 2014). The term viral hepatitis can describe either a clinical illness or the histologic findings associated with the disease. Acute infection with a hepatitis virus may result in conditions ranging from subclinical disease to self-limited symptomatic disease to fulminant hepatic failure. Adults with acute hepatitis A or B are usually symptomatic. Persons with acute hepatitis C may be either symptomatic or asymptomatic (ie, subclinical). Typical symptoms of acute hepatitis are fatigue, anorexia, nausea, and vomiting. Very high aminotransferase values (>1000 U/L) and hyperbilirubinemia are often observed. Severe cases of acute hepatitis may progress rapidly to acute liver failure, marked by poor hepatic synthetic function. This is

often defined as a prothrombin time (PT) of 16 seconds or an international normalized ratio (INR) of 1.5 in the absence of previous liver disease. Typical cases of acute HAV infection are marked by several weeks of malaise, anorexia, nausea, vomiting, and elevated aminotransferase levels. Jaundice develops in more severe cases. Some patients experience a cholestatic hepatitis, marked by the development of an elevated alkaline phosphatase (ALP) level, in contrast to the classic picture of elevated aminotransferase levels. Other patients may experience several relapses during the course of a year. Less than 1% of cases result in fulminant hepatic failure (FHF). HAV infection does not persist and does not lead to chronic hepatitis. Hepatitis A virus (HAV) infection usually is mild and self-limited, and infection confers lifelong immunity against the virus. Overall mortality is approximately 0.02% (Centers for Disease Control and Prevention, 2014); in general, children younger than 5 years and adults older than 50 years have the highest case-fatality rates. Older patients are at greater risk for severe disease: Whereas icteric disease occurs in fewer than 10% of children younger than 6 years, it occurs in 40-50% of older children and in 70-80% of adults with HAV. Three rare complications are relapsing hepatitis, cholestatic hepatitis, and fulminant hepatitic failure (FHF). Hepatitis A causes an acute illness that does not progress to chronic liver disease. Therefore, the role of screening is to assess immune status in people who are at high risk of contracting the virus, as well as in people with known liver disease for whom hepatitis A infection could lead to liver failure (Guidelines For Viral Hepatitis Surveillance and Case Management; Longo *et al.,* 2013). There are no specific medications to cure or treat hepatitis A virus. Most treatments are focused on ameliorating the symptoms of the disease, such as resting frequently, eating small meals in order to reduce the nausea, and elimination of alcoholic beverages. However those who have been exposed to an infected person may be given hepatitis A immunoglobulin, which may prevent infection. Liver cell injury caused by various toxic chemicals (certain antibiotics, chemotherapeutic agents, carbon tetrachloride (CCl4), thioacetamide (TAA) etc.), excessive alcohol consumption and microbes is well studied. The synthetic drugs in practice has side effect on lungs and sometimes may fatal to liver. Hence, to avoid this herbal drugs have become increasingly popular. Herbal medicines have been used in the treatment of liver diseases for a long time.

MATERIALS AND METHODS

This was an open labeled study involving the patients of acute viral hepatitis. Each patient is screened and enrolled according to proper inclusion and exclusion criteria mentioned in protocol which was approved by ethics committee of Ashwin rural ayurved college and hospital manchii hill, dist. Ahmadnagar, where this study was carried out. Also CRF (case report form), patients consent form was submitted and approved by ethics committee.

Inclusion and Exclusion Criteria: Patients age between 18 and 65 years. Diagnosis of acute viral hepatitis A (<1 month) as manifested by a combination of the following symptoms: jaundice, dark-colored urine, light-colored stools, fever, anorexia, nausea, vomiting, abdominal discomfort, abdominal pain or heaviness or feeling of pressure in right hypochondrium. Increase in serum ALT level than upper limit of normal. Increase in Albumin level than upper limit of normal. Subject has given written informed consent. The subject is able and willing to undertake all study-required procedures and has the ability to take oral medications. Obvious history of drug-induced acute hepatitis. Compensated liver diseases. Exclusion criteria included Subjects < 18 years of age. Subjects with positive anti-HAV anti body. Other conditions, which in the opinion of the investigators, makes the patient unsuitable for enrollment or could interfere with his/her participation in, and completion of, the protocol (e.g. severe mental illness). The subject is currently participating in any clinical trial (marketed product or otherwise), or has done so within 30 days or 5 half-lives (whichever is longer) prior to screening visit. Treatment with any investigational drug within 30 days of entry to this protocol. Non-response to previous treatment for chronic viral hepatitis. Use of prohibited medication. Suspicion or evidence that the subject is not trustworthy and reliable. Suspicion or evidence that the subject is not able to make a free consent or to under-stand the information in this regard.

Evaluation Criteria: In HAV patients with specific etiologies resolution of clinical signs and symptoms. Significant reduction or normalization of ALT, AST, CRP and ESR. Significant reduction or normalization of total and direct bilirubin. Symptom resolution & return to normal physical activity Incidence, severity and duration of Adverse Events.

About The Investigational Product: In vestigational product Valiliv capsule is a technology based Ayurvedic product in a form of encapsulated pellets. This was derived from the extracts of *Kutki* (Picrorrhiza kurroa) 50 mg and *Bhui awala* (Phyllanthus niruri) 500 mg. dose of 2 capsules BID was advised to the patients enrolled in the study for the period of 12 week with initial screening period of 3 days.

Overall Study Design: It is an open labeled, prospective design in patients with viral hepatitis. Adult male or female subjects between & including the ages of 18 to 65 years, with confirmed diagnosis of viral hepatitis are selected. The patients who are eligible to participate, by inclusion & exclusion criteria, have provided a written informed consent at the screening visit.

Screening Visit: There will be a screening period of 3 days. The laboratory reports will be reviewed for eligibility. After the assessment, patients who fulfill all the eligibility criteria will be provided a diary card & trained the pt. about how to fill the diary & also provide rescue medication. Symptom score assessments & adverse events & also the rescue medication use will be recorded by the patient in the daily diary. Following procedures will be done at screening visit.

Visit V1 (End of week 4): The patients who are eligible will enter in 12 weeks active treatment period. The patients who entered into the treatment period will be given VALILIV CAPSULES. The patients will administer the first dose of their allocated Investigational product (IP) at clinic & remain under observation during & after 30 minutes of dosing. Thereafter, they are allowed to take the medicine to home for further doses. A new diary will be provided to patients to record symptom score, use of study medication, rescue & any adverse events. Follow up visits will be scheduled at 4, 8 & 12 weeks after enrollment. A window period of ± 2 days will be allowed for each follow up visit. All visits will be scheduled between 9.00 am to 1.00 pm. A window period of ± 1 hour is acceptable at subsequent visits after screening.

Reporting of adverse events, routine hematological & biochemical tests, physical examination & vital signs will assess safety. Following procedures will be done:

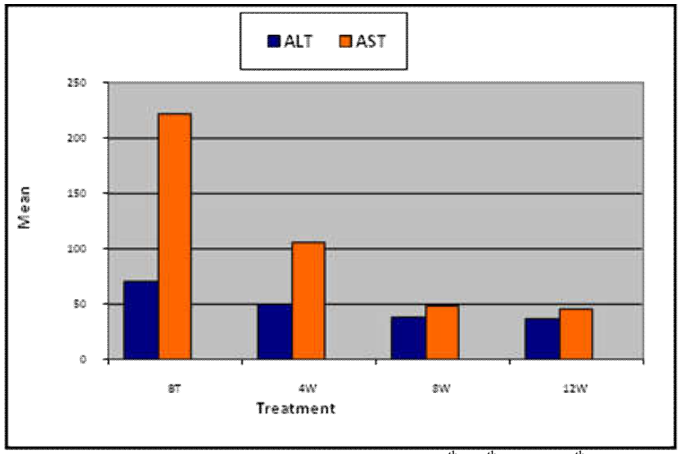
Follow up Visits: Follow up visits will be scheduled at 4, 8 & 12 weeks after start of treatment. A window period of ± 2 days will be allowed for each follow up visit. All visits will be scheduled between 9.00am to 1.00 pm. A window period of ± 1 hour is acceptable at subsequent visits after screening. Reporting of adverse events, routine hematological & biochemical tests, physical examination & vital signs will assess safety. Following procedures will be followed at the scheduled visits.

Adverse Events: All adverse events reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to confirm the reason for withdrawing.

Statistical Analysis: Statistical analysis is done using paired't' test for paired data within group. The criteria for statistical significance was $p<0.05$. Descriptive statistics are presented for all measurements of efficacy. Categorical data are summarized and presented using frequency tables of counts, histograms, and percentages. Continuous variables are summarized and presented as means, standard deviation, medians, and ranges.

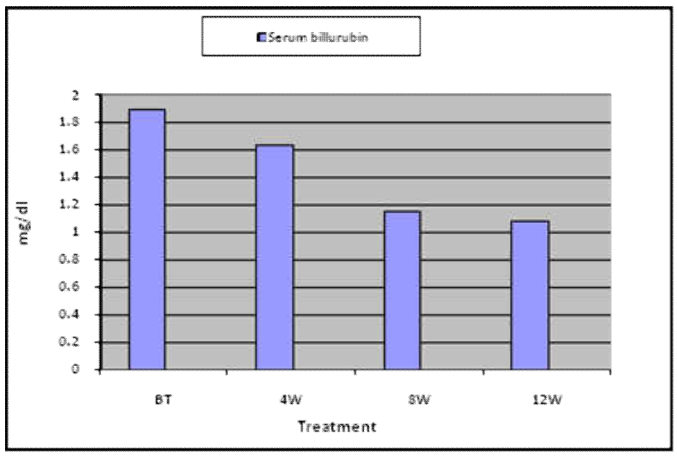
RESULTS

Total 97 patients were screened according to criteria for the trial out of which 88 patients (50 male and 38 females) were enrolled in the study who fits in accordance with inclusion and exclusion criteria and started consuming the investigational product. Out of these data of 63 patients (44 male and 19 female) were available for final analysis as remaining patients have dropped out due to non follow up. Efficacy: In ALT and AST highly significant result was observed after 4th, 8th and 12th week of treatment. Whereas significant result was observed after 4th week of treatment in billirubin levels which was highly significant after 8th and 12th week of treatment.



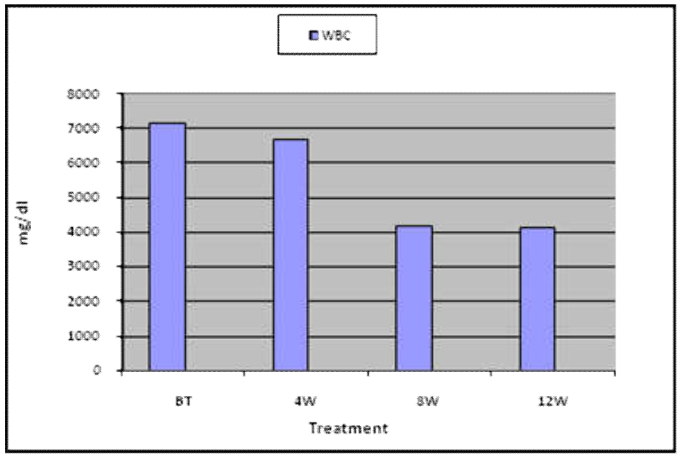
**highly significant result was observed after 4th, 8th and 12th week of treatment.

Graph 1: ALT & AST



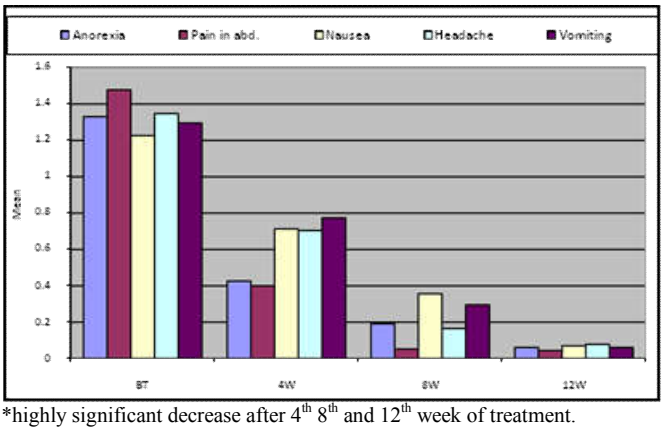
**Significant after 4th week and highly significant result after 8th and 12th week of treatment.

Graph 2: Serum billirubin



**Significant decrease after 4th week and very significant after 8th and 12th week of treatment.

Graph 3: WBC



**highly significant decrease after 4th 8th and 12th week of treatment.

Graph 4: Clinical symptoms

In case of WBC significant decreased was observed after 4th week of treatment and very significant after 8th and 12th week of treatment. In subjective parameters of Anorexia, pain in abdomen, nausea, headache and vomiting highly significant difference was observed in mean symptom score after 4th, 8th and 12th week of treatment, which proves better symptomatic results in clinical symptoms of viral hepatitis. Safety: Significant improvement was observed in clinical symptoms assessed and the essential investigations done. No abnormality

or any type of adverse reactions is noted. Other investigations assessed for safety also doesn't shows any significant changes. Hence Validly is safe at all these regards.

DISCUSSION

In viral hepatitis, which is a chronic and progressive ailment, the aim of therapy is mainly conservative – to conserve the function, to arrest or retard degeneration and destruction of liver and, above all, to bring symptomatic relief to the patient. The ideal drug is not yet available for the treatment of liver disorders. The use of a drug ought to be measured against parameters like efficacy, tolerance, incidence of side effects, safety during prolonged use and the cost factor. The most important role of Valiliv is in the maintenance of remission of disease activity and in the prevention of relapse of the disease. The overall improvement was noticed in patients was highly significant. The improvement of subjective symptoms such as anorexia, weakness, pain in abdomen, nausea, vomiting etc. At the time of completion of treatment period these patients were able to go back without any discomfort such as pain, nausea, vomiting etc. With the dose of 2 capsules B.I.D. For the patients of viral hepatitis for 12 week duration suggests following outcomes. A highly significant result after 4th week in ALT and AST indicates that Valiliv capsules has good activity in repairing inflammatory damage to hepatocytes. This may be due to anti-inflammatory activity of *Bhui-awala and Kutki*. Aqueous extract of *Bhui awala* has well reported hepatoprotective activity and possible mechanism may involve its antioxidant activity. Significant difference after 4^{th} week in bilirubin level indicates that Valiliv capsule is good in checking and improving balance between production and removal of pigments in the body. This is possibly due to detoxification effects of *kutki and bhui awala* because of their bitter principles. In case of statistically highly significant result in mean scores of Albumin before treatment and after 4^{th}, 8^{th} and 12^{th} week indicates that Validly capsules significantly improves hepatic protein metabolism which can be directly co-related with osmotic pressure, nutritional balance and in maintaining good hormonal balance. Also significant decrease in mean WBC count after 4^{th} week and very significant after 8^{th} week and highly significant after 12^{th} week indicates that Validly capsule is effective in reducing infective and inflammatory pathologies of liver and decreasing the viral load. A part from these hematological parameters highly significant difference in mean symptoms score of various clinical symptoms of anorexia, headache, vomiting, abdominal pain, weakness and nausea indicates that Validly capsules has good result in decreasing associated symptoms of viral hepatitis and increasing quality of life of the patients within few week time. Treatment with Validly capsules for 12 week time doesn't produce any untoward effects, which suggest good palatability of the drug and no significant difference in basic parameters like BP, BSL etc. proves that Validly capsules are completely safe.

Conclusion

Thus from these observations one can say that the drug has got a definite beneficial role to play in Viral hepatitis and allied conditions particularly in relieving clinical symptoms like anorexia, pain in abdomen. etc. and decreasing bio-chemical parameters of ALT, AST, WBC. And can be given very safely as it is almost free from toxic effects. It is concluded that validly has definite anti-inflammatory and hepatoprotective effect.

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