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# Comparative Efficacy of Five Indigenous Compound Formulations in Patients of Acute Viral Hepatitis

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## INTRODUCTION

Viral hepatitis, a major public health problem throughout the world, occurs in both epidemic and endemic forms in India[1]. Despite rapid advances in modern scientific medicine, there is no specific treatment available for this disease. A number of indigenous agents are claimed to be useful for treatment of liver disorders including viral hepatitis[2]. We selected five commonly available indigenous compound formulations viz., Arogyavardhini, Hepax, Valiliv, Kamalahar forte and Liv.52 (See Tables 1, 2, 3, 4 and 5 for composition). In our another study, these agents were found beneficial in a model of hepatocellular jaundice in albino rats. This is the report of comparative efficacy of these agents in patients of acute viral hepatitis.

## PATIENTS AND METHODS

Patients of viral hepatitis, referred to Naidu Hospital, Pune, were included in the study, which extended from June 1985 to June 1987. Two hundred and forty eight consecutive adult cases were randomised, after obtained informed written consent. The diagnosis of acute viral hepatitis was established by history, clinical examination and liver function tests. Patients with history of jaundice for more than 4 weeks before admission, chronic alcohol consumption etc. (See Table 4) were excluded.

Treatment was started within 24 hours after admission. The drugs were given in the form of 2 capsules twice daily for 14 days. Placebo capsules containing 500 mg of dextrose each, were administered in the same manner. Patients were asked to take these capsules at least one hour before food. No dietary restrictions were imposed, but patients with severe anorexia and vomiting were treated with intravenous glucose. Likewise bed rest was not imposed. Vitamin K was administered to the patients with prothrombin concentrations less than 30% of normal, as estimated by prothrombin time. No other drugs, except B complex vitamins, were allowed.

The following information was obtained before starting treatment, twice in first week and then at weekly intervals for next three weeks: state of patient's well-being and loss of appetite, presence of any nausea, vomiting, fever, pruritus, rash, joint pains, abdominal discomfort, tiredness, colour of urine, hepatic tenderness and enlargement and some of the liver functions tests [serum bilirubin (normal value $\leq$ 0.8 mg/dl), SGPT $\leq$ 25 iu/l), SGOT ($\leq$ 20 iu/l), alkaline phosphatase (3-13 KAU/dl) and prothrombin concentration ($\geq$ 60%). Estimations of body weight, haemoglobin, WBC count (total and differential), serum protein total (6.3-7.9 g/dl), albumin (3.7 - 5.3 g/dl) and globulin (1.8 - 3.6 g/dl)] and routine urine examination were done initially and then at the end of four weeks. Hepatitis B surface antigen (HbsAg) was determined at the beginning and at monthly intervals, if positive, by counterimmunoelectrophoresis. The sera were cross-checked for HbsAg by RPHA. The clinical features were scored with the help of an arbitrary scoring system viz., absent 0, mild 1, moderate 2 and severe 3. Side effects, likely to be due to the treatment were also recorded. For those patients, who were discharged before the end of four weeks, evaluation was continued on out-patient basis. Compliance to therapy was assessed by direct questioning.

Patients were followed up at monthly intervals for a total period of six months from the day of admission. The data were analysed by student's unpaired '*t*' test, de Jonge's trend analysis and Fisher's exact test.

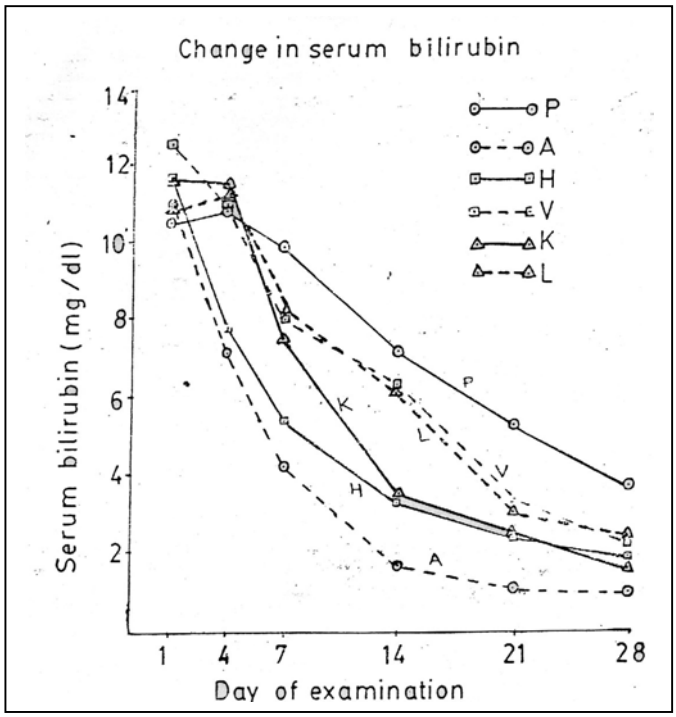
**RESULTS**

Two hundred forty eight patients were included in the study. Out of these thirty four patients were excluded from the analysis for reasons mentioned in Table 7.

Thus, 214 patients remained in the trial and received Arogyavardhini (n=30), Hepax (n=20), Valiliv (n=23), Kamalahar forte (n=19), Liv.52 (n=34) and Placebo (n=88). The clinical and laboratory details of these patients are summarised in Tables 8 and 9 respectively. There was no significant difference in the various groups on entry in the study.

Table 10 outlines the results of treatment. Treatment with all agents was associated with significantly ($p$<0.05) less loss in body weight and rapid clinical recovery, as compared to placebo. This was most prominent in patients treated with Arogyavardhini. In drug treated patients, there was significantly ($p$<0.05) rapid biochemical recovery, as suggested by short time required for 50% decline in serum bilirubin levels . Again this was more marked in those treated with Hepax and Arogyavardhini. By the end of four weeks, 83 to 90% of patients treated with Arogyavardhini and Hepax and recovered in contrast to 63 to 74% in those treated by other agents.

The changes in serum levels of bilirubin during the study period of four weeks are shown in Figure 1. There was a more rapid ($p$<0.05) decline in the serum bilirubin levels in all drug-treated patients. It was evident from seventh day of treatment with all agents except Arogyavardhini and Hepax, with which the effect began as early as 4$^{th}$ day. The effects were persistent for a week after stopping treatment. Changes in SGPT levels and in serum levels of alkaline phosphatase were similar to those in serum bilirubin.




There was no significant change in other parameters viz., serum proteins, SGOT, prothrombin time and clearance of HbsAg etc.

Eight patients from placebo and six patients on drugs had relapse of hepatitis (during fourth (n=8) and seventh (n=6) week respectively), from which they recovered unevenfully. No relapse was observed in those treated with Arogyavardhini and Hepax.

Side effects likely to be due to treatment were recorded in all the groups. These were minor, like diarrhoea, epigastric pain, skin rash etc., and discontinuation of the drug was not required. The incidence of side effects was comparable in all the groups.

During the follow-up, 79 patients dropped out from the study at various time intervals, remaining 135 patients (drugs - 82 and placebo - 53) were followed for a period of six months. Seroconversion from HbsAg positively was noticed in one patient treated with Arogyavardhini and two patients on

Hepax, at the end of one month. This was not statistically significant as compared to placebo treatment. Similarly none of the drugs had any significant effect on the incidence of HbsAg carrier state, however the number of cases of hepatitis B in each group was very small.

## DISCUSSION

The results show a more rapid clinical as well as biochemical recovery from acute viral hepatitis during treatment with all agents in this study. Although administration of steroids leads to clinical improvement and lowering of serum bilirubin, this is often associated with troublesome side effects and high relapse rate[3]. Previous studies have demonstrated better clinical improvement in patients of viral hepatitis treated with Liv.52,[4] Arogyavardhini[5] and Stimuliv[6]. However, the biochemical recovery was unaltered. Besides this, the patient were not followed up to study the effect of drug treatment, if any, on the relapse rate and incidence carrier state in type B hepatitis.

In this study, we have noticed that none of these agents was beneficial in patients of acute viral hepatitis positive for HbsAg. Although the number of patients studied is too small, treatment with Hepax/Arogyavardhini might accelerate the seroconversion in such cases and deserves further study in hepatitis B. The relapse rate and incidence of carrier state were also not modified by any of the preparations studied.

In contrast to this, HbsAg negative patients showed beneficial effects with all treatment, especially with Arogyavardhini and Hepax. The dramatic decrease in total serum bilirubin, evident from 4$^{th}$ day of treatment suggests that these agents might be enhancing bilirubin clearance by stimulating either hepatic or extrahepatic clearance of bilirubin. One of the main ingredients of these preparations viz., *Picrorrhiza kurroa* has been reported to exert such action[7]. *Andrographis paniculata* and *Tinospora cordifolia* have been reported to possess hepatoprotective action[8,9]. There are few reports regarding the pharmacological activity of other ingredients present in these formulations. Hence, it is not possible to comment upon their inclusion. To our knowledge, this is the first report of comparative efficacy of indigenous compound formulations in patients of acute viral hepatitis. The results suggest rapid clinical and biochemical recovery with drug treatment in HbsAg negative patients.

The administration of indigenous compound formulations like Arogyavardhani was found beneficial in patients of acute viral hepatitis. There was a rapid clinical and biochemical recovery, most marked in those treated with Arogyavardhini and Hepax. The beneficial effects were restricted to HbsAg negative patients. The relapse rate and incidence of carrier state were not modified. Further studies are necessary to determine the role of such agents in patients with severe hepatitis, type B hepatitis population groups pregnant women, old age etc.


## ABSTRACT

Viral hepatitis is a major public health problem in our country. However, as yet, specific treatment is not available. Many indigenous agents are claimed to be beneficial, although controlled studies are only few. We studied five indigenous compound formulations viz., Arogyavardhini, Hepax, Valiliv, Kamalahar forte and Liv.52, in 214 patients of acute viral hepatitis admitted to Naidu Hospital, Pune. The patients were randomly allocated to receive either the indigenous compound formulation or placebo. Response to treatment was assessed by regular clinical examination and periodic estimation of liver function tests viz., serum bilirubin, SGPT, serum alkaline phosphatase etc. Adverse effects, likely to be attributed to drug treatment were recorded and HbsAg status was also assessed. Treatment with all agents, especially Arogyavardhini and Hepax, accelerated clinical and biochemical recovery in HbsAg negative patients.


**Table 1: Composition of Arogyavardhini**

| Ingredient | Quantity |
|---|---|
| Mercury | 2 mg |
| Sulphur | 2 mg |
| Loha bhasma | 2 mg |
| Tamra bhasma | 2 mg |
| Abhrak bhasma | 2 mg |
| Triphala churna | 4 mg |

| | |
|---|---|
| Shilajeet | 6 mg |
| Guggul (*Commiphora mukul*) | 8 mg |
| Chitrakamal churna | 8 mg |
| Kutaki churna | 36 mg |
| Decoction of *A. indica* | 128 mg |
| Total (Approx.) | 200 mg |

**Table 2: Composition of Hepex (500 mg)**

| Ingredient | Quantity |
|---|---|
| *Plumbago zeylanica* (Chitraka) | 30 mg |
| *Picrorrhiza kurroa* (Kali kutki) | 30 mg |
| *Piper nigrum* (Kali mirch) | 30 mg |
| *Zingiber officinale* (Sunthi) | 30 mg |
| Carbonate of soda (Sajikhar) | 30 mg |
| *Phyllanthus emblica* (Amla) | 25 mg |
| *Terminalia chebula* (Haritaki) | 25 mg |
| Calcium hydroxide (Chuna) | 25 mg |
| Pearl ash (Papadkhar) | 275 mg |

**Table 3: Composition of Valiliv (250 mg)**

| Ingredient | Quantity |
|---|---|
| Arogyavardhini | 60 mg |
| *Picrorrhiza kurroa* | 15 mg |
| *Terminalia chebula* | 15 mg |
| *Eclipta alba* | 30 mg |
| Solanum nigrum | 15 mg |
| Kanthaloha bhasma | 15 mg |
| *Capparis spinosa* | 15 mg |
| *Fumaria parviflora* | 15 mg |
| *Tamarix gallica* | 10 mg |
| *Embelia ribes* | 15 mg |
| Somnathi tamra | 45 mg |

**Table 4: Composition of Kamalahar forte (250 mg)**

| Ingredient | Quantity |
|---|---|
| *Cichorium intybus* | 25 mg |
| *Solanum nigrum* | 50 mg |
| Mineral salts | 75 mg |
| Mandura bhasma | 20 mg |
| *Terminalia arjuna* | 20 mg |
| *Achyranthes aspera* | 16 mg |
| *Tinospora cordifolia* | 10 mg |
| *Tephrosia purpurea* | 12 mg |
| *Boerhavia diffusa* | 5 mg |
| *Emblica officinalis* | 5 mg |
| *Terminalia chebula* | 3 mg |
| *Andrographis paniculata* | 3 mg |
| *Berberis aristata* | 3 mg |
| *Plumbago zeylanica* | 3 mg |

**Table 5: Composition of Liv.52 (275 mg)**

| Ingredient | Quantity |
|---|---|
| *Capparis spinosa* | 65 mg |
| *Cichorium intybus* | 65 mg |
| *Solanum nigrum* | 32 mg |
| *Cassia occidentalis* | 16 mg |
| *Terminalia arjuna* | 32 mg |
| *Achillea millefolium* | 16 mg |
| *Tamarix gallica* | 16 mg |
| Mandura bhasma | 33 mg |

**Table 6: Exclusion Criteria**

1. Duration of jaundice > 4 weeks
2. H/o chronic alcoholism
3. H/o intake of hepatotoxic drugs
4. Age <14 years, > 50 years
5. Pregnancy
6. Signs of hepatic coma/precoma
7. Serum alkaline phosphatase ≥ 30 KAU/dl
8. Associated major illness like diabetes mellitus, renal disease etc.

**Table 7: Drop-outs from the study**

| Reason | | Number |
|---|---|---|
| 1. | Developed coma/precoma | 11 |
| 2. | Non-compliance with therapy | 12 |
| 3. | Did not complete 4 weeks observation period | 11 |
| | Total | 34 |

**Table 8: Clinical features of entry**

| Feature | Arogya-vardhini | Hepax | Valiliv | Kamalahar forte | Liv.52 | Placebo |
|---|---|---|---|---|---|---|
| Age (years) | 28.40 ± 5.60 | 26.45 ± 7.70 | 26.60 ± 9.10 | 30.05 ± 10.94 | 23.40 ± 8.50 | 28.11 ± 9.31 |
| Sex (M/F) | 17/13 | 15/6 | 13/10 | 12/7 | 22/12 | 66/22 |
| Weight (Kg) | 46.40 ± 9.32 | 51.50 ± 10.25 | 49.70 ± 11.30 | 52.10 ± 10.25 | 50.80 ±10.70 | 49.06 ± 10.98 |
| Duration of illness (days) | 13.23 ± 5.65 | 11.20 ± 5.03 | 9.80 ± 4.10 | 13.10 ±5.00 | 10.25 ± 4.25 | 11.33 ± 4.91 |
| Severity of illness (score) | 15.10 ± 4.46 | 16.25 ± 3.50 | 16.50 ± 3.70 | 15.80 ± 4.25 | 15.45 ± 4.60 | 14.96 ± 4.54 |

Figures are mean ± SD, No significant difference between the groups.

**Table 9: Biochemical profile on entry**

| Parameter | | Arogya-vardhini (n=30) | Hepax (n=20) | Valiliv (n=23) | Kamalahar forte (n=19) | Liv.52 (n=34) | Placebo (n=88) |
|---|---|---|---|---|---|---|---|
| Serum bilirubin (mg/dl) | | 11.00 ± 5.91 | 11.72 ± 6.50 | 12.50 ± 6.80 | 11.60 ± 6.80 | 10.85 ± 6.20 | 10.49 ± 6.01 |
| SGPT (iu/l) | | 117.18 ± 86.19 | 125.35 ± 57.67 | 140.00 ± 60.20 | 130.52 ± 60.14 | 130.50 ± 65.20 | 120.55 ± 74.22 |
| Serum alkaline phosphatase (KAU/dl) | | 16.56 ± 5.75 | 16.90 ± 6.01 | 17.30 ± 9.50 | 16.34 ± 6.10 | 15.80 ± 8.25 | 17.37 ± 8.12 |
| Serum proteins (g/dl) | Total | 6.40 ± 0.72 | 6.56 ± 0.80 | 6.90 ± 1.10 | 6.54 ± 0.87 | 6.60 ± 0.84 | 6.81 ± 0.85 |
| | Albumin | 4.08 ± 0.36 | 4.12 ± 0.41 | 4.40 ± 0.60 | 4.14 ± 0.44 | 4.20 ± 0.42 | 2.53 ± 0.47 |
| | Globulin | 2.32 ± 0.40 | 2.44 ± 0.41 | 2.50 ± 0.60 | 2.40 ± 0.44 | 2.40 ± 0.42 | 2.59 ± 0.43 |
| HbsAg status | By CIE (+ve/-ve) | 5//25 | 6/14 | 6/17 | 5/14 | 8/26 | 25/63 |
| | By RPHA (+ve/-ve) | 10/20 | 10/20 | 9/14 | 8/11 | 14/20 | 39/49 |

Figures are mean ± SD, No significant difference between the groups.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| Table 10: Response to treatment | | | | | | |
|---|---|---|---|---|---|---|
| Parameter | Arogya-vardhini (n=30) | Hepax (n=20) | Valiliv (n=23) | Kamalahar forte (n=19) | Liv.52 (n=34) | Placebo (n=88) |
| Weight loss (kg) | 1.08 ± 0.23* | 1.00 ± 0.86* | 1.30 ± 0.90* | 1.13 ± 0.89* | 1.25 ± 0.95* | 2.15 ± 1.10 |
| Time for clinical recovery (days) | 7.90 ± 3.29** | 11.40 ± 6.68* | 14.00 ± 7.10* | 12.51 ± 6.86* | 12.70 ± 7.18* | 20.17 ± 9.70 |
| Time for 50% fall in serum bilirubin (days) | 6.80 ± 2.79* | 6.47 ± 3.03* | 7.90 ± 2.40* | 8.12 ± 3.90* | 8.46 ± 3.54* | 15.05 ± 8.70 |
| Time for biochemical recovery (days) | 20.06 ± 6.29** | 23.79 ± 8.28* | 21.00 ± 3.90* | 25.10 ± 10.55* | 36.40 ± 14.10 | 54.17 ± 9.35 |
| No recovered (by 28 days) (%) | 25 (83.33)* | 18 (90)* | 16 (69.50)* | 12 (63.16)* | 25 (73.53)* | 39 (55.68) |
| Relapsing hepatitis | – | – | 2 | 1 | 3 | 8 |
| HbsAg conversion (by one month) per patients followed | 1/5 | 2/6 | 0/6 | 0/5 | 0/8 | 0/25 |
| HbsAg +ve at the end of six months per patients followed | 0/5 | 0/3 | 0/6 | 1/4 | 3/8 | 2/14 |
| Side effects (No. of patients) | 3 | 3 | 4 | 3 | 3 | 9 |
| *$p$<0.05, **$p$<0.01 = Compared to placebo. | | | | | | |

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