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Beneficial effect of a traditional herbal medicine (inchin-ko-to) in postoperative biliary atresia patients

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Abstract Inchin-ko-to (ICKT) prevents Fas-mediated liver injury. This study evaluates the effect of ICKT on conventional markers of liver function (LF) and liver fibrosis in 18 postoperative biliary atresia (BA) patients aged 3 to 23 years with elevated glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), γ-glutamyl transpeptidase (γGTP) but normal serum total bilirubin (T-Bil) levels. ICKT (0.15 g/kg per day) was administered orally for 1 year. Serum GOT, GPT, γGTP, total bile acids (TBA), and T-Bil as markers of LF and hyaluronic acid (HA), prolyl hydroxylase (PH), procollagen III peptide (PIIIP), and type IV collagen as markers of liver fibrosis were measured before and after treatment in each patient and compared statistically. All patients tolerated ICKT well, and there were no side effects. The percentage of subjects who improved after ICKT was 45% for serum GOT, 72% for GPT, 72% for γGTP, 72% for TBA, 67% for HA, 40% for PH, 50% for PIIIP, and 23% for type IV collagen. Changes in the mean values of all serum markers were statistically significant (P < 0.01). It is concluded that long-term administration of ICKT in postoperative BA patients improves liver status as assessed by markers of LF and fibrosis.

Keywords Biliary atresia · Inchin-ko-to · Liver fibrosis

Introduction

In biliary atresia (BA) there is obliteration or discontinuity of the extrahepatic biliary system, resulting in obstruction of bile flow.

The initial surgical treatment for BA is the Kasai portoenterostomy. Unfortunately, the long-term success rate of the Kasai procedure is poor, and most patients either require liver transplantation (LT) or die from progressive liver disease [1].

We conducted a study of postoperative BA patients who were divided into three groups according to liver function (LF). Group I were jaundice-free and had normal LF and no evidence of severe cholangitis or portal hypertension. Group II were jaundice-free and had moderate liver dysfunction. Group III had severe liver dysfunction with jaundice [6]. Group II was most important because they were jaundice-free, had moderate liver dysfunction, and appeared well. As a result, they required careful out-patient follow-up. We have previously shown high levels of type IV collagen and procollagen III peptide (PIIIP) in group II patients compared with controls [5], indicating that these patients will have progressive fibrosis and eventually deteriorate and require LT, the fate of most group III patients. For this reason, group III is designated the unfavorable prognosis group.

Inchin-ko-to (ICKT) consists of spray-dried hot-water extracts of the following three medicinal herbs mixed in the ratios in parenthesis: Artemisiae capillaris spica (4.0), Gardenia fructus (3.0), and Rhei rhizoma (1.0). The drug has long been used in China and Japan as an anti-inflammatory, antipyretic, choleretic, and diuretic agent for liver disorders and jaundice and is now being manufactured as an approved ethical drug with standardized quality and quantities of ingredients in Japan. The drug has recently been reported to show a potent inhibitory effect on hepatocyte apoptosis in vitro [15] and in vivo [16]. This study evaluates the effect of ICKT administration on conventional markers of LF.
and fibrosis in group II postoperative BA patients, as they may deteriorate to end-stage cirrhosis.

Materials and methods

Eighteen postoperative BA patients aged 3 to 23 years with elevated glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and γ-glutamyl transpeptidase (γ-GTP) but normal serum total bilirubin (T-bil) levels were studied. All had been receiving ursodeoxycholic acid (UDCA, Tokyo Tanabe, Tokyo) for at least 1 year without improvement before ICKT treatment. Patients were treated with ICKT (0.15 g/kg per day) orally in addition to UDCA for 1 year. All subjects tolerated the drugs well and completed the study without difficulty.

Serum GOT, GPT, γ-GTP, total bile acids (TBA), and T-Bil were used as markers of LF and hyaluronic acid (HA), prolyl hydroxylase (PH), PIHP, and type IV collagen were used as markers of liver fibrosis and were measured before and after treatment in each patient. ICKT manufactured as TJ-135 (Tsumura, Tokyo) was used.

Peripheral-venous fasting whole blood was drawn with a sterile syringe, transferred to a centrifuge tube, allowed to clot for 30 min at room temperature, and then centrifuged at 1,500 rpm for 15 min at 4 °C. Samples were stored at −80 °C until they could be assayed. All specimens were taken after the subject had rested for at least 1 h. Serum GOT, GPT, γ-GTP, TBA and T-Bil activity were measured by routine methods. Serum HA, PH, and type IV collagen were measured with a commercial one-step sandwich ELIA kit (Fuji, Takaoka, Japan). Serum PIHP concentration was determined with a commercial radioimmunoassay kit (Hoechst, Tokyo).

All measurements were repeated three times in each patient, and the pre- and post-treatment values were expressed as the mean of the three measurements.

The outcome of ICKT treatment for each parameter was defined as follows: (1) Remission: the parameter became normal; (2) Partial remission: the parameter decreased by more than 50%; (3) Improvement: the parameter decreased by more than 25%; (4) No improvement: the parameter did not change; and (5) Progression: the parameter rose progressively. All subjects were investigated after obtaining parental informed consent to participate in this study. Results are expressed as mean values ± standard error. The paired Student t-test (2-tailed) was used to determine statistical differences between pre- and post-treatment clinical data. *P < 0.05 was considered statistically significant.

Results

All patients tolerated ICKT well, and there were no side effects.

Figure 1 shows the variation in various serum parameters before and after 1 year of ICKT treatment. After treatment, a significant decrease in the mean values of all serum markers was observed. GOT decreased from 90.6 ± 14.2 before ICKT treatment to 69.0 ± 12.5 IU/l (P = 0.0004), GPT from 98.8 ± 16.3 to 63.6 ± 13.9 IU/l (P = 0.0004), γ-GTP from 188.0 ± 41.6 to 115.0 ± 26.8 IU/l (P = 0.0026), TBA from 67.4 ± 14.6 to 35.8 ± 6.62 μmol/l (P = 0.0081), PH from 1.8 ± 0.19 to 1.3 ± 0.12 ng/ml (P = 0.0026), PIHP from 58.5 ± 3.90 to 48.6 ± 3.20 ng/ml (P = 0.0004), type IV collagen from 346 ± 54.1 to 275 ± 40.0 ng/ml (P = 0.0087), and HA from 61.4 ± 13.4 to 37.0 ± 9.07 ng/ml (P = 0.0048).

Figure 2 summarizes the outcome of ICKT treatment. Each bar is divided into regions proportional to the number of subjects exhibiting various ratings of drug effect. The percentage of subjects who had the ratings of “remission”, “partial remission”, or “improvement”