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**Clinical trial with traditional Chinese medicine intervention of tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment for chronic hepatitis B liver failure**

Li HM *et al*. Clinical Intervention with “TTKESC” for CHBLF

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**Abstract**

**AIM:** To study the clinical efficacy for treating chronic hepatitis B liver failure (CHBLF) with traditional Chinese medicine (TCM) intervention of tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment (TTKESC).

**METHODS:** We designed the study as a randomized controlled clinical trial. Registration number of Chinese Clinical Trial Registry: ChiCTR-TRC-12002961. A total of 144 patients with CHBLF were enrolled in this study. Participants were randomly assigned to three groups in a 1:2:1 ratio: (1) modern medicine control group (MMC group, 36 patients); (2) group of “tonifying qi and detoxifying” (“TQD” group, 72 patients); and (3) “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” group (“TTKESC” group, 36 patients). Treatments were as follows: MMC group was given the general internal medicine treatment; “TQD” group was given the TCM formula of “tonifying qi and detoxifying” on the base of general internal medicine therapy; “TTKESC” group was given the TCM formula of “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” (“TTKESC”) on the base of general internal medicine treatment. Every participant received treatment for 8 wk. Follow up was 48 wk. The primary efficacy endpoint was fatality rate. Secondary endpoints were some virological and biochemical indicators. One way-ANOVA and *t* test were performed to estimate the outcomes.

**RESULTS:** After 48 wk of post-treatment follow up, the fatality rates in MMC group, “TQD” group and “TTKESC” group were 51.61%, 35.38% and 16.67%, respectively, and which were statistically significant differences across the three groups (*P* = 0.010). No significant differences in hepatitis B virus (HBV) DNA levels as well as prothrombin activity (PTA) levels could be observed among the three groups (*P* > 0.05). “TTKESC” group had a significantly higher mean serum total bilirubin(TBIL) level than did MMC subjects (339.40 ± 270.09 *vs* 176.13 ± 185.70, *P* = 0.014); albumin (ALB) levels were significantly increased in “TQD” group as well as “TTKESC” group compared with MMC group (31.30 ± 4.77 *vs* 28.57 ± 4.56; 30.72 ± 2.89 *vs* 28.57 ± 4.56, respectively, *P* < 0.05); there were no significant differences in alanine transaminase(ALT) levels among three groups (*P* > 0.05). Safety data showed that there was only one case appeared stomachache in “TQD” group and one case appeared gastrointestinal side effects in “TTKESC” group.

**CONCLUSION:** The “TTKESC” strategy had obviously improved survival in CHBLF, and make liver tissue reconstructed as well as liver function restored.

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**Key words:** Clinical study; “Tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment”(TTKESC); Liver regeneration; Treatment of integrated traditional and western medicine; Chronic hepatitis b liver failure

**Core tip:** We designed a randomized controlled clinical trial to observe the effect of the TCM intervention of “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” (“TTKESC”) for treating chronic hepatitis B liver failure. This clinical study showed that the fatality rate in the group with treatment of “TTKESC” was significantly lower than did in other two groups (16.67% *vs* 51.61%; 16.67% *vs* 35.38%,respectively, *P* = 0.010), and the effect mechanism may be related to the promotion of liver regeneration and repair through effecting stem cells and it’s microenvironment.

Li HM, Ye ZH, Zhang J, Gao X, Chen YM, Yao X, Gu JX, Zhan L, Ji Y, Xu YL, Zeng YH, Yang F, Xiao L, Sheng GG, Xin W, Long Q, Zhu QJ, Shi ZH, Ruan LG, Yang LY, Li CC, Wu HB, Chen SD, Luo XL. Clinical trial with TCM intervention of “TTKESC” for chronic hepatitis B liver failure. *World J Gastroenterol* 2014; In press

**INTRODUCTION**

The fatality rate in patients with chronic hepatitis B liver failure (CHBLF) can reach up to 70%, and the survivors also have very high recurrence rates[1]. In recent years, the fatality rate of CHBLF has been significantly reduced[2] by the treatment of integrated traditional and western medicine. Our previous studies[3-5] have shown that treating with the TCM formula called “TTKESC” (“tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment”) can promote liver regeneration and repair liver damage through regulating stem cells and it’s microenvironment[6]. In this study, we designed a randomized controlled clinical study to evaluate the clinical efficacy of the TCM intervention of “TTKESC” for CHBLF.

**MATERIALS AND METHODS**

***Study design***

We conducted a randomized and controlled clinical trial for CHBLF between January 2007 and July 2013 at 6 medical sites (Hubei Provincial Hospital of TCM, Wuhan Medical Treatment Center, Wuhan No.1 Hospital, Wuhan No.7 Hospital, Wuhan Hospital of TCM) in Hubei province of China. The Ethics Committee of Hubei Province Hospital of Traditional Chinese Medicine reviewed and approved the protocol and consent forms before the study (Approved No. of ethic committee: 2006001). All participants signed written informed consent forms before enrollment. A total of 144 participants confirmed with CHBLF were randomized intothree groups by computer random number generation program. The three groups-modern medicine control group (MMC group),control group of integrated traditional and western medicine (“TQD” group) as well as “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” group (“TTKESC” group), were randomized in a 1:2:1 ratio. Because some patients hadn’t completed the study according to the plan (5 cases in the MMC group and 7 cases in “TQD” group), 12 cases were excluded in the study and 132 cases (112 men and 20 women) were involved in the statistical analysis finally. Figure 1 showed the disposition of the study participants. Baseline characteristics were similar among the three groups (Table 1).

***Patient enrollment***

Patients who were diagnosed as CHBLF were enrolled. Chronic liver failure (CLF) and acute-on-CLF (ACLF) are two most common types of CHBLF. All participants were admitted to hospitals, where they could be quarantined and observed. Patients who fulfilled all of the following criteria were included two parts.

First of all, the participants should need the diagnostic criteria of CHBLF according to diagnostic and treatment guidelines for liver failure[7] in 2006, and the details were as follows: CLF is defined as liver function progressively dysfunction or decompensation based on hepatic cirrhosis. Patients who fulfilled the following criteria were diagnosed with CLF: Patient with ascites or other manifestations of portal hypertension; patient with/without hepatic encephalopathy; TBIL levels increased and/or ALB levels reduced; patient with coagulation disorders (PTA ≤ 40％). ACLF is defined as the main clinical manifestations of short-term acute hepatic decompensation based on the history of chronic liver disease, and it can be divided into early stage, middle stage, late stage. And patients who fulfilled the following criteria were diagnosed with the early stage of ACLF: Patient with extreme fatigue and serious digestive symptoms (significant anorexia, vomiting, or abdominal distension); patient with progressive deepening jaundice (TBIL ≥ 171 μmol/L, or TBIL Daily rised ≥ 17.1 μmol/L); patient with bleeding tendency (30% < PTA < 40%); patient without hepatic encephalopathy or significant ascites. When patient's condition appeared further development based on the early stage and needed one of the following can be diagnosed with the middle stage of ACLF: Patient with hepatic encephalopathy (≤ Ⅱ-degree) and/or significant ascites; patient with obvious bleeding tendency(hemorrhagic spot or ecchymosis) and 20% < PTA ≤ 30%. When patient's condition appeared further development based on the middle stage and needed the following items can be diagnosed with the late stage of ACLF: Patient with intractable complications (hepatorenal syndrome, upper gastrointestinal bleeding, serious infections, serious electrolyte imbalance, *et al*); patient with hepatic encephalopathy (≥ Ⅲ degree); patient with severe bleeding tendency (*e.g.* Ecchymoses of injection sites), and PTA ≤ 20%.

Second, patient should be a volunteer who had signed the information consent firm. Patients who fulfilled one of the following criteria were excluded: Patient had acute hepatic failure; patient had chronic hepatic failure occured with other disease except chronic hepatitis B; patient was a lactating or pregnant woman; patient had primary hepatocellular carcinoma; patient was a drug user; patient was complicated by other severe systematic diseases or mental diseases; patient had positive reaction of anti-HIV; patient was complicated with cytomegalovirus, EB virus ,or other hepatotropic virus infection; patient had attended other clinical studies in last three months; patient with poor compliance, and could not guarantee to complete the protocol; patient was complicated with severe cerebral edema, severe infectious , type 1 hepatorenal syndrome, or massive hemorrhage of gastrointestinal tract, *et al*.

***Treatment***

MMC group was treated with general internal medicine treatment, including basic treatment, symptomatic and supportive treatment plus antiviral therapy. The drugs we used in MMC group for CHBLF mainly included Compound Glycyrrhizin For Injection (80-160 mg, once daily, intravenous drip), Reduced glutathione for injection (1.2 g, once daily, intravenous drip), *N*-acetylcysteine (4.0 g, once daily, intravenous drip), and Hepatocyte Growth-promoting Factor for Injection(100-160 mg, once daily, intravenous drip). This was also a vital treatment to prevent and treat complications (*e.g.* hepatic encephalopathy, cerebral edema, hepatorenal syndrome, infection, hemorrhage of digestive tract). The need for antiviral therapy was determined by attending physicians. If the reaction of HBV DNA was positive, nucleoside drugs was given for antiviral therapy, such as lamivudine tablets, adefovirdipivoxil tablets, entecavir tablets or telbivudine tablets. Table 2 showed that there was no difference among the three groups of using nucleoside drugs (*P* = 0.153).

“TQD” group was given the TCM formula of “tonifying qi and detoxifying” (“TQD”) on the base of general internal medicine therapy. The composition of the TCM formula of “TQD” (Table 3) was as follows: zhihuangqi (honey-fried Astmgali Radix praeparata cum melle) 30 g, huzhang (Polygoni Cuspidati Rhizoma Et Radix) 30-60 g, fuling (Poria) 30 g, danshen(Salviae Miltiorrhizae Radix Et Rhizoma) 30 g, yimucao (Leonuri Herba) 30 g, zhuling (Polyporus) 20 g, chaobaizhu (stir-baked Rhizoma Atractylodis Macrocephalae) 30 g, yinchen( Artemisiae Scopariae Herba) 30-60 g, zhizi(Gardeniae Fructus) 12 g, huangqin (Scutellariae Radix) 6 g, dahuang (Rhei Radix et Rhizoma) 10 g, and gancao (Glycyrrhizae Radix Et Rhizoma) 6 g.

The TCM formula of “TQD” can be changed according to different symptoms: (1) adding chenxiang (Aquilariae Lignum Resinatum) 6 g or laifuzi (Raphani Semen) 30 g on the TCM formula of “TQD” for patients with severe abdominal distension; (2) adding jiaomaiya (charred Hordei Fructus Germinatus) 10 g, jiaoshanzha (charred Crataegi Fructus) 10 g, jiaoshenqu (charred Medicated Leaven) 10 g, or jineijin (Gigeriae Galli Endothelium Corneum) 20 g for patients with poor appetite; (3) adding jiangbanxia (Pinelliae Rhizoma Praeparatum cum Zingibere et Alumine) 15 g, chenpi (Citri Reticulatae Pericarpium)15 g,orzhuru(Bambusae Caulis In Taenias) 15 g for patients with nausea and vomiting; (4)adding chaoyiyiren (stir-baked Coicis Semen) 30 g for patients with diarrhea or loose stools; (5) adding mudanpi (Moutan Cortex) 20 g and qinjiao (Gentianae Macrophyllae Radix) 20 g for patients with skin itch; (6) adding baimaogen (Imperatae Rhizoma) 15 g and zicao (Arnebiae Radix) 30 g for patients with epistaxis, teeth bleed or skin ecchymosis; and (7) adding Chinese patent drug of “chidantuihuang soluble granules” (SFDA Approval No. Z20010176, Hunan Jiuzhitang Co., Ltd.), 10 g orally 3 times daily with tepid water for patients with severe jaundice; *et al*.

“TTKESC” group was given the TCM formula of “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” (“TTKESC”) on the base of general internal medicine treatment. The TCM formula of “TTKESC” (Table 4) was mainly composed of following herbs: shudihuang (Rehmanniae Radix Praeparata) 15-30 g, yinchen (Artemisiae Scopariae Herba) 30-60 g, wuweizi (Schisandrae Chinensis Fructus) 10-15 g, jianghuang(Curcumae Longae Rhizoma) 3-6 g, gancao (Glycyrrhizae Radix Et Rhizoma) 9-12 g, shanyao (Rhizoma Dioscoreae) 15 g, gouqizi (Fructus Lycii) 15 g, shanzhuyu (Fructus Corni) 15 g, tusizi (Cuscutae Semen) 10 g, fuling (Poria) 30 g, mudanpi (Moutan Cortex) 10 g, zexie (Alismatis Rhizoma) 10 g.

The TCM formula of “TTKESC” can be modified according to different symptoms: (1) adding binglang (Arecae Semen) 10 g and dafupi (Arecae Pericarpium) 10 g for patients with abdominal distension; (2) adding jiaoshenqu (charred Medicated Leaven) 10 g, dangshen (Codonopsis Radix) 15 g or chaobaizhu (stir-baked Rhizoma Atractylodis Macrocephalae) 10 g for patients with poor appetite; (3) adding jiangbanxia (Pinelliae Rhizoma Praeparatum cum Zingibere et Alumine) 15 g or zhuru (Bambusae Caulis In Taenias) 15 g for patients with nausea and vomiting; (4) adding ganjiang (Zingiberis Rhizoma) 10 g, huanglian (Coptidis Rhizoma) 6 g, huangqin (Scutellariae Radix) 10 g for patients with diarrhea or loose stools; (5) adding qiancao (Rubiae Radix et Rhizoma) 15 g for patients with epistaxis, teeth bleed or skin ecchymosis; and (6) subtracting shudihuang (Rehmanniae Radix Praeparata) from the TCM formula of “TTKESC” and adding dahuang (Rhei Radix et Rhizoma) 6 g plus zhizi (Gardeniae Fructus) 10 g for patients with thick and greasy yellow tongue coating; *et al*.

All Chinese Medicine in the study was provided by Hubei Tianji Chinese Herbal Sliced Medicine Co.,Ltd. And the results of quality testing met safety standards in China. According to a traditional TCM decoction method, each unit of TCM formula yielded 260 ml of decoction, 130mL orally each time and twice a day with warm-taken decoction.

Every participant in 3 groups should experience 8 wk treatment and 48 wk follow up.

***Study assessments***

The primary efficacy endpoint was fatality rate from randomization to the follow-up visit. Secondary endpoints were some virological and biochemical indicators at baseline and after 8 wk treatment, such as levels of HBV DNA, prothrombin activity (PTA), serum total bilirubin (TBIL), albumin (ALB) and alanine transaminase (ALT). Using real-time PCR for testing HBV DNA. Specialized technicians used Germany AMAX-200 type automatic coagulation analyzer (paramagnetic particle method) and the corresponding control sera and reagents for detecting PTA. Using Toshiba 120 automatic biochemical analyzer and ancillary reagents to detect levels of TBIL, ALB and ALT.

***Statistical analysis***

All analyses were performed using the SPSS for Windows, version 19.0. Data were expressed as mean ± SD.*χ*2 test was used for numeration data. We also used one way-ANOVA for the data of among groups and *t* test for the data between two groups. A *P* value less than 0.05 was considered statistically significant.

***Safety***

The two TCM formulas in the study had used frequently before study and few appeared serious adverse events. There were only two cases appeared untoward effect. One case appeared stomachache in “TQD” group and one case appeared nausea and vomiting in “TTKESC” group.

**RESULTS**

***Response on fatality rate***

After 8 wk of treatment and 48 weeks of follow up, Figure 2 showed that the fatality rates in MMC group, “TQD” group and “TTKESC” group were 51.61%, 35.38% and 16.67%,respectively; the fatality rate among three groups was significant (*P* < 0.05); the fatality rate was lowest in “TTKESC” group (16.67%); the fatality rate in “TTKESC” group was significantly lower than MMC group (16.67% *vs* 51.61%, *P* = 0.002) and “TQD” group (35.38% *vs* 16.67%, *P* = 0.046).

***Response to HBV DNA***

The results of HBV DNA returning negative as well as HBV DNA decreasing by two or more than two logarithmic ratio were considered positive. In contrast, the results were negative. After 8 wk of treatment, Table 5 showed that there was no significant difference in the rusults of HBV DNA among three groups (*P* > 0.05).

***Biochemical response***

From Table 6, we see the results as follows: After 8 wk of treatment, there was no statistically significant in PTA levels (*P* > 0.05); TBIL levels in “TTKESC” group was statistically significant compared with MMC group after treatment (339.40 ± 270.09 *vs* 176.13 ± 185.70, *t* = -2.552, *P* = 0.014); ALB levels in “TQD” group and “TTKESC” group significantly increased compared with MMC group(31.30 ± 4.77 *vs* 28.57 ± 4.56, *t* = -2.389, *P* = 0.019; 30.72 ± 2.89 *vs* 28.57 ± 4.56, *t* = -2.378, *P* = 0.021). Moreover, there was no significant difference in ALT levels among three groups after treatment (*P* > 0.05).

**DISCUSSION**

Drugs and alcohol are the major pathogenic factors of liver failure in Occident[8], but the hepatitis B virus is the major cause of liver failure and usually develops chronic CHBLF in China. CLF and ACLF are two common types of CHBLF. The pathogenesis of CHBLF is complex, the mechanism by which has so far not been fully elucidated. Currently, it is considered that the interaction between viral factors and host factors leads to CHBLF. The virus factors mainly include virus genotype, the level of viral replication, virus mutation and so on; Host factors include biological genetic features, immunopathological mechanisms of injury, mechanisms of abnormal liver regeneration and repair, *et al*[9,10].

CHBLF is a serious disease, often accompanied by various complications and high fatality. To date, modern medicine is still ineffective in the treatment of CHBLF, just symptomatic and supportive therapy. However, in recent years, the fatality rate decreased significantly-the majority reported that 30% to 50%[2]. All patients in the study had taken the same general internal medicine treatment and some patients were also given antiviral drugs, but Table 1 showed there was no significant difference in antiviral drug usage of three groups (*P* > 0.05). The primary efficacy endpoint (fatality) of this clinical study showed that the fatality of CHBLF in taking the integrated traditional and western medicine program guided with the TCM formula of “TTKESC” was significantly decreased compared with MMC group and the group with TCM formula of “TQD” (16.67% *vs* 35.38% and 16.67% *vs* 51.61%, *P* < 0.05). Furthermore, the level of ALB in “TTKESC” group with treatment of “TTKESC” was also significantly increased compared with MMC group (30.72 ± 2.89 *vs* 28.07 ± 4.56, *P* = 0.021), indicating that “TTKESC” treatment has a good effect on CHBLF.

We believe that the imbalance between liver damage and liver regeneration is an important mechanism (heavy damage and insufficient regeneration) for CHBLF. The key of treatment is to adjust the balance between liver damage and liver regeneration by reducing/preventing liver damage, maintaining normal liver regeneration/regulating abnormal liver regeneration. Liver regeneration is the vitality of patients with liver failure, if damaged liver cannot regenerate in normally and timely, then the patient will die; if damaged liver can normally regenerate within the effective time and restore its normal structure and function, then the patient can survive[11,12].

The new TCM formula of “TTKESC” is proposed after our in-depth study. And the formula of “TTKESC” for treating CHBLF can reduce liver damage through affecting stem cells and it’s microenvironment(liver stem cells[13,14], bone marrow stem cells[3,5,15-18],brain marrow stem cells[19-22], *et al*.) to promote normal regeneration, inhibit abnormal regeneration, then restoring the balance between damage and regeneration, finally the patients' liver tissue and liver function in a certain extent can be reconstructed and restored, thereby reducing the fatality and improving the patients' quality of life.

Our previous preclilical studies have shown that “TTKESC” can improve the conversion rate of bone marrow stem cells differentiating into liver cells, and the molecules mechanism may be through affecting gene expression profile of liver tissue[3,5,15,23]. We used the “MSG-regeneration-rat” model[24] to explore the relevant contact between liver regeneration and senior central nervous system/hypothalamus-hypophysis-liver axis/nerve-endocrine-immune net, and the results revealed that the treatment of “TTKESC” played a bidirectional regulation role in the process of liver regeneration, which was beneficial for liver damage recovering in orderly[20,21,25-29].

The clinical study did not use a double-blind observation as well as a multi-center observation of different regions, and therefore may cause bias results of trial. Furthermore, it is necessary to use a large sample, multi-center, randomized, controlled, double-blind clinical trial methods to provide more competing evidence in the future.

**comments**

***Background***

Chronic hepatitis B liver failure (CHBLF) is a major cause of death in patients with viral hepatitis, accompanied by high fatality. However, we found that the fatality rate of CHBLF has been significantly reduced with the treatment of integrated traditional and western medicine.

***Research frontiers***

In recent years, Ministry of Science of China had set up “the National Key Technology R and D Program” and “Key Projects in the National Science and Technology Pillar Program during the Twelfth Five-year Plan Period” to organize national experts of Chinese medicine and Western medicine for joint research. It will make the greatest efforts to reduce the fatality and further explore the mechanism through studying the prevention and treatment programs of integrative medicine, which will be an important area of ​​research and academic hotspot of major infectious diseases.

***Innovations and breakthroughs***

Fatality rate in patients with CHBLF was the primary efficacy endpoint of evidence-based medicine. In the study, the fatality of CHBLF in the group of “TTKESC” was significantly decreased compared with the MMC group and the group of “TQD” (16.67% *vs* 35.38% and 16.67% *vs* 51.61%, *P* < 0.05).Liver regeneration and repair is a key pathophysiological mechanisms of patients with CHBLF survived. In the past, the academic community had always emphasized the importance of promoting liver regeneration process. However, we found that the dysfunction of liver regeneration was an important pathogenesis of patients with CHBLF through the study, which will hinder the function of liver tissue reconstruction and recovery. Futhermore, the treatment with “TTKESC” played a bidirectional regulation role in the process of liver regeneration, which may be an important mechanism for reducing the fatality rate in patients with CHBLF.

***Applications***

The clinical study provide a certain level of evidence based medicine. And the program is effective and feasible, with some clinical value. In the further, a large sample, multi-center, double-blind, randomized and controlled study should be conducted, in order to provide a higher level of evidence based medicine and in-depth study the mechanism of preventing and treatment CHBLF by regulating liver regeneration.

***Terminology***

“TTKESC”: “Tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment”; “TQD”: “Tonifying qi and detoxifying”. CHBLF: Chronic hepatitis B liver failure; Bidirectional regulation: Promoting normal liver regeneration and inhibiting abnormal liver regeneration

***Peer review***

The study design was good, data collection and interpretation are sound. The statistical analyses were appropriate. It is a great finding to reduce the fatality of CHBLF by regulating the mechanism of liver regeneration and repair, which has important scientific significance and clinical value, and it is necessary to further study.

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**Table 1 Baseline characteristics of patients *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **MMC group (*n =* 31)** | **“TQD” group (*n =* 65)** | **“TTKESC” group (*n =* 36)** | ***P* value** |
| age, yr, mean ± SD | 43.71 ± 9.85 | 44.94 ± 12.64 | 46.69 ± 11.86 | 0.580 |
| Male | 29 (93.55) | 51 (78.46) | 32 (88.89) | 0.114 |
| Course of disease, yr, mean ± SD | 9.87 ± 10.93 | 8.74 ± 8.48 | 10.03 ± 9.21 | 0.753 |
| Chronic liver failure | 15 (48.39) | 35(53.85) | 14(38.89) | 0.354 |

MMC group: modern medicine control group; TQD: tonifying qi and detoxifying; “TTKESC” group: “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” group.

**Table 2 antiviral therapy in groups *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Nucleoside drugs** | **MMC group (*n =* 31)** | **“TQD” group (*n =* 65)** | **“TTKESC” group (*n =* 36)** |
| Not using nucleoside drugs | 21 (67.74) | 55 (84.62) | 27 (75.00) |
| Using nucleoside drugs  | 10 (32.26) | 10 (15.38) | 9 (25.00) |
| Lamivudine  | 12 (38.71) | 30 (46.15) | 12 (33.33) |
| Adefovir  | 0 (0.00) | 5 (7.69) | 4 (11.11) |
| Telbivudine  | 2 (6.45) | 6 (9.23) | 1 (2.78) |
| Entecavi  | 6 (19.35) | 12 (18.46) | 5 (13.89) |
| Lamivudine combined adefovir  | 1 (3.23) | 1 (1.54) |  5 (13.89) |
| Entecavir combined adefovir  | 0 (0.00) | 1 (1.54) | 0 (0.00) |

There was no difference among the three groups of using nucleoside drugs in the study (*P*=0.153). MMC group: modern medicine control group; TQD: tonifying qi and detoxifying; “TTKESC” group: “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” group.

**Table 3 TCM formula of “tonifying qi and detoxifying” group**

|  |  |  |
| --- | --- | --- |
| **English translation** | **Chinese pinyin** | **Dosage** |
| Honey-fried radix astragaliseu hedysari | zhihuangqi | 30 g |
| Rhizoma polygoni cuspidati | huzhang | 30-60 g |
| Poria | fuling | 30 g |
| Radix salviae miltiorrhizae | danshen | 30 g |
| Herba leonuri | yimucao | 30 g |
| Polyporus umbellatus | zhuling | 20 g |
| Stir-baked rhizoma atractylodis macrocephalae | chaobaizhu | 30 g |
| Herba artemisiae scopariae | yinchen | 30-60 g |
| Fructus gardeniae | zhizi | 12 g |
| Radix scutellariae | huangqin | 6 g |
| Radix et rhizomarhei | dahuang | 10 g |
| Radix glycyrrhizae | gancao | 6 g |

**Table 4 TCM formula of “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” group**

|  |  |  |
| --- | --- | --- |
| **English translation** | **Chinese Pinyin** | **Dosage** |
| Radix rehmanniae preparata | Shudihuang | 15-30 g |
| Herba artemisiae scopariae | Yinchen | 30-60 g |
| Fructus schisandrae chinensis | Wuweizi | 10-15 g |
| Rhizoma curcumae longae | Jianghuang | 3-6 g |
| Radix glycyrrhizae | Gancao | 9-12 g |
| Rhizoma dioscoreae | Shanyao | 15 g |
| Fructus lycii | Gouqizi | 15 g |
| Fructus corni | Shanzhuyu | 15 g |
| Cuscutae semen | Tusizi | 10 g |
| Poria | Fulin | 30 g |
| Moutan cortex | Mudanpi | 10 g |
| Alismatis rhizoma | Zexie | 10 g |

**Table** **5 Response on hepatitis B virus DNA** **after 8-wk treatment *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Groups** | ***n*** | **Negtive** | **Positive** |
| MMC group  |  6 | 3 (50.0) | 3 (50.0) |
| “TQD” group | 17 | 4 (23.5) | 13 (76.5) |
| “TTKESC” group |  6 | 2 (33.3) | 4 (66.7) |

Normal range of HBV DNA (FQ-PCR): < 1.0 x 103 copies/ml. Positive: HBV DNA returned negative or decreased by two or more than two logarithmic ratio. MMC group: modern medicine control group; TQD: tonifying qi and detoxifying; “TTKESC” group: “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” group. HBV: hepatitis B virus.

**Table 6 Response on biochemical indicators after 8-wk treatment (mean ± SD)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Time** | ***n*** | **PTA** | ***n*** | **TBIL (μmol/L)** | ***n*** | **ALB (g/L)** | ***n*** | **ALT (IU/L)** |
| MMC group | Before treatment | 28 | 26.80 ± 10.91 | 30 | 326.29 ± 210.47 | 28 | 28.07 ± 4.56 | 30 | 202.00 ± 249.20 |
|  | After treatment | 18 | 43.14 ± 18.60 | 21 | 176.13 ± 185.70 | 21 | 28.57 ± 4.56 | 21 | 39.90 ± 30.19 |
| “TQD” group | Before treatment | 61 | 32.50 ± 12.15 | 65 | 314.04 ± 160.20 | 65 | 29.54 ± 4.75 | 65 | 254.80 ± 424.32 |
|  | After treatment | 55 | 43.59±22.08 | 63 | 242.54 ± 229.05 | 63 | 31.30 ± 4.77c | 63 |  78.70 ± 161.80 |
| “TTKESC” group | Before treatment | 36 | 28.63 ± 11.28 | 36 | 369.13 ± 198.06 | 36 | 27.82 ± 4.52 | 36 | 189.52 ± 241.97 |
|  | After treatment | 30 | 32.55 ± 15.58 | 33 | 339.40 ± 270.09a | 33 | 30.72 ± 2.89e | 33 |  70.12 ± 82.23 |

Normal range: PTA: 80%-120%; TBIL: 3.4-20.5 μmol/L; ALB: 35-55 g/L; ALT: 0-46 IU/L. a*P* < 0.05 *vs* MMC group; c*P* < 0.05 *vs* MMC group, e*P* < 0.05 *vs* MMC group. MMC group: modern medicine control group; TQD: tonifying qi and detoxifying; “TTKESC” group: “tonifying the kidney to promote liver regeneration and repair by effecting stem cells and it’s microenvironment” group; PTA: Prothrombin activity; TBIL: Serum total bilirubin; ALB: Albumin; ALT: Alanine transaminase.