

# 太衝 및 陽池의 電針이 實驗적으로 誘發된 白鼠의 肝保護效果에 미치는 影響

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## Hepatoprotective effects of Electro-Acupuncture at Taechung (LR3) and Yangji (TE4) on experimental liver injury in rats

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### Abstract

**목적**: 본 연구는 太衝 및 陽池穴에 대한 電鍼이 galactosamine을 이용한 백서의 肝毒性을 실험적으로 유발시킨 모델에서 豫防效果를 알아보고자 혈청중의  $\gamma$ -GTP, GOT, GPT, LDH, total bilirubin, total cholesterol, triglyceride의 변화를 관찰하였다.

**방법**: 간독성은 각 군들은 간독성을 유발하지 않고 무처치한 정상군, 간독성을 유발하고 난 후 무처치한 대조군, 각각 10 Hz, 50 Hz, 100 Hz 전침을 20일간 10회 시행한 후 간독성을 유발한 Pre 10, Pre 50, Pre 100군 등으로 분류하였다.

**결과**: 太衝陽池穴에 대한 電鍼 治療의 豫防效果에서는 Pre 10군에서는  $\gamma$ -GTP, GOT, GPT, total cholesterol, triglyceride이 Pre 50군에서는  $\gamma$ -GTP, GOT, GPT, LDH, total bilirubin, total cholesterol 이, Pre 100군에서는  $\gamma$ -GTP, GOT, LDH, total bilirubin, total cholesterol이 대조군에 비해 감소하였다.

**결론**: 위의 결과를 종합해보면 간독성에 대하여 太衝陽池穴의 電鍼을 시행한 모든 군에서 간기능과 지질대사에서 간손상에 대한 유의한 예방효과를 나타내었다.

**Key words**: 간 독성, 전침, 예방효과, 태충, 양지

## I. Introduction

Acupuncture is an oriental ancient therapeutic method, and has been used for the treatment of patients with various diseases from old times.

The theory of meridians and acupuncture points is the basic theory of acupuncture therapy.

The science of meridians expounds the routes that connect different parts of the body based on the clinical application of acupuncture points. Meridians not only connect all parts of the body, but also coordinate their functions, they also influence various complicated pathological changes and adjust the states of the viscera.

Galactosamine (GalN) is a hepatotoxin that induces liver injury through the formation of the

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highly reactive hydroxyl radical lipid peroxidation and damage to the cell membrane<sup>1)</sup>. It has been used as an animal model of fulminant hepatic failure to develop artificial liver support, and it can be commonly seen at human viral hepatitis<sup>2,3)</sup>.

Recent reports on the study of acupuncture are as follows.

*Liu et al*<sup>4)</sup> reported effects on the reduction of biochemical and pathological parameters of liver injury after acupuncture, and *Lin et al*<sup>5)</sup> reported the prevention of ANIT-induced hyperbilirubinemia and cholangitis. *Huang et al*<sup>6)</sup> and *Chakrabarti et al*<sup>7)</sup> reported the improvement of the hepatic metabolism and promoting the membrane transport action in endotoxic shock and the hepatic functions on the liver in rats. *Shimoju-Kobayashi et al*<sup>8)</sup> reported increases of hepatic glucose output in responses to electro-acupuncture (EA) stimulation.

In this study we investigated hepatoprotective effects of EA at Taechung (LR3)-Yangji (TE4) on the GalN-induced liver injury in rats.

## II. Materials & Methods

### 1. Animals

Male Sprague Dawley rats (Damil Science Co., Korea) weighing 160±10 g were used for the experiment. Each animal was housed at a controlled temperature (22±3 °C) and was maintained under light-dark cycles, each cycle consisting of 12 hr of light and 12 hr of darkness (lights on from 09:00 to 19:00 hr) with food (Pellet, Samyang, Korea) and water made available *ad libitum*. The experimental procedures were performed in accordance with the animal care guidelines of the

NIH and the Korean Academy of Medical Sciences.

### 2. Liver injury and electro-acupuncture

To induce liver injury in the experimental animals, a single intraperitoneal injection of GalN (400 mg/kg in saline : Sigma Chemical Co., St. Louis, MO, USA) was given to each animal, while animals of the normal group received equivalent amounts of normal saline.

In the EA groups, EA treatment was given to each animal every other day 10 times for 20 days at 1 time per 2 days on bilateral acupuncture points. The needles were then connected to the Dual Impedance Research stimulator (Harvard, USA) and were electrically stimulated at 1 mV intensity, 1 msec duration during 5 minutes.

Before 20 days in liver injury, as treatment to study hepatoprotective effects, four stainless steel 0.5 mm diameter needles (3-0.5, Haenglim, Korea) were acupunctured at a point corresponding to LR3 and TE4 in rats.

LR3 is located on the dorsum of foot, in the depression distal to the junction of the first and second metatarsal bones, when the palm is turned upward, TE4 is in the depression at the point on the transverse crease of the wrist dorsum crossed with the vertical interstice between the third and fourth metacarpal bones. When the knee is flexed, LR 8 is in the depression above the medial end of the transverse popliteal crease, posterior to the medial epicondyle of the femur.

### 3. Groups

Animals are divided into 8 groups ( $n=8$  in each

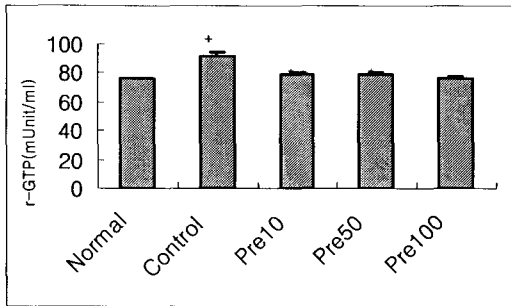


Fig. 1. Hepatoprotective effect of electro-acupuncture at Taechung (LR3) and Yangji (TE4) on serum  $\gamma$ -GTP in liver injury rats induced by D-galactosamine. Normal, not liver injury-induced and not treated group. Control, the liver injury-induced and not treated group. Pre10, before the liver injury-induced electro-acupuncture with 10Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre50, before the liver injury-induced electro-acupuncture with 50Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre100, before the liver injury-induced electro-acupuncture with 100Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Results are shown as mean  $\pm$ S.E. +,  $p < 0.05$  as compared with the corresponding data of normal group. \*,  $p < 0.05$  as compared with the corresponding data of control group.

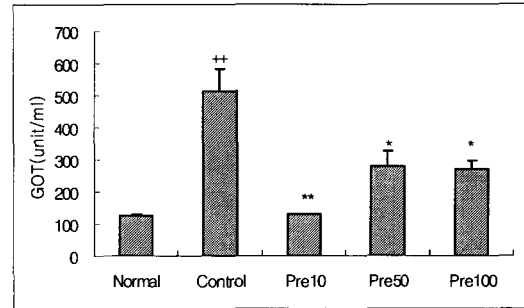


Fig. 2. Hepatoprotective effect of electro-acupuncture at Taechung (LR3) and Yangji (TE4) on serum GOT in liver injury rats induced by D-galactosamine. Normal, not liver injury-induced and not treated group. Control, the liver injury-induced and not treated group. Pre 10, before the liver injury-induced electro-acupuncture with 10 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 50, before the liver injury-induced electro-acupuncture with 50 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 100, before the liver injury-induced electro-acupuncture with 100 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Results are shown as mean  $\pm$ S.E. ++,  $p < 0.01$  as compared with the corresponding data of normal group. \*,  $p < 0.05$ , \*\*,  $p < 0.01$  as compared with the corresponding data of control group.

group). Normal group is not liver injury-induced and not treated, Control group is the liver injury-induced and not treated.

The Pre 10, Pre 50, Pre 100 groups executed by the hepatoprotective treatment are carried out electro-acupuncture at LR3-TE4 with each 10 Hz, 50 Hz, 100 Hz electrical stimulation before the liver is injury-induced.

#### 4. Assays of serums

Rats are sacrificed by the decapitation after final treatment, and then blood samples collected from the stump are put at a room temperature to

allow coagulation. Then serums are immediately centrifuged at 5,000 rpm for 10 minutes, and they are collected and stored at  $-70^{\circ}\text{C}$  for  $\gamma$ -GTP, GOT, GPT, LDH, total bilirubin, total cholesterol, and triglyceride.

The activity of  $\gamma$ -GTP is measured using diagnostic kits (AM158-K, Asan, Korea) at 635 nm by the spectrophotometer (Unikon922, Kontron, Italy). That of other parameters in serum without  $\gamma$ -GTP is determined using diagnostic kits by the photometer (5010, Robert Riele GmbH & Co. Germany): GOT (GOT-SL Kit at 340 nm, ELITech, France); GPT (GPT-SL Kit at 340 nm, ELITech, France); total bilirubin (T. bilirubin-SL

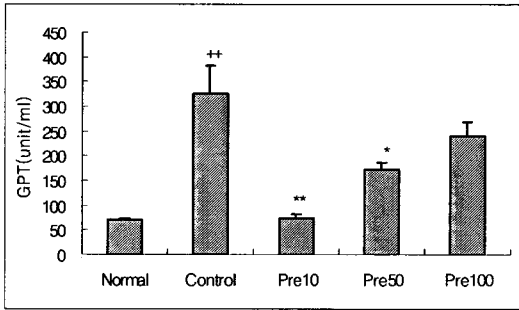


Fig. 3. Hepatoprotective effect of electro-acupuncture at Taechung (LR3) and Yangji (TE4) on serum GPT in liver injury rats induced by D-galactosamine. Normal, not liver injury-induced and not treated group. Control, the liver injury-induced and not treated group. Pre 10, before the liver injury-induced electro-acupuncture with 10 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 50, before the liver injury-induced electro-acupuncture with 50 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 100, before the liver injury-induced electro-acupuncture with 100 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Results are shown as mean±S.E. ++,  $p < 0.01$  as compared with the corresponding data of normal group. \*,  $p < 0.05$ , \*\*,  $p < 0.01$  as compared with the corresponding data of control group.

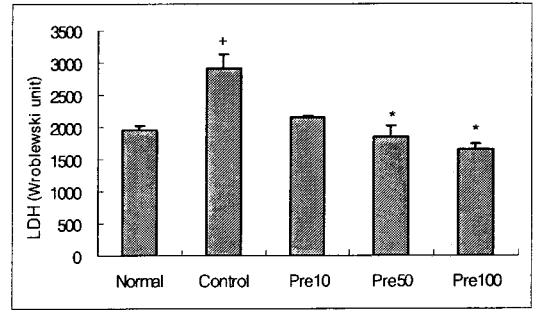


Fig. 4. Hepatoprotective effect of electro-acupuncture at Taechung (LR3) and Yangji (TE4) on serum LDH in liver injury rats induced by D-galactosamine. Normal, not liver injury-induced and not treated group. Control, the liver injury-induced and not treated group. Pre 10, before the liver injury-induced electro-acupuncture with 10 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 50, before the liver injury-induced electro-acupuncture with 50 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 100, before the liver injury-induced electro-acupuncture with 100 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Results are shown as mean±S.E. +,  $p < 0.05$  as compared with the corresponding data of normal group. \*,  $p < 0.05$  as compared with the corresponding data of control group.

Kit at 546 nm, ELITech, France); LDH (LDH-SL Kit at 340 nm, ELITech, France); total cholesterol (T. cholesterol-SL Kit at 546 nm, ELITech, France); triglyceride (Triglyceride -SL Kit at 505 nm, ELITech, France).

## 5. Data Analysis

Data are analyzed using SPSS 10.0.5 for Windows (SPSS Inc. USA) by student t-test. Results are expressed as mean ± standard error (S.E.). Differences are considered significant for  $p < 0.05$ .

## III. Results

### 1. Effects of EA on $\gamma$ -GTP in serums

The  $\gamma$ -GTP was  $75.8 \pm 0.27$  mUnit/ml in the normal group,  $91.1 \pm 3.88$  mUnit/ml in the control group,  $78.5 \pm 1.52$  mUnit/ml in the Pre10 group,  $79.2 \pm 1.72$  mUnit/ml in the Pre 50 group and  $76.8 \pm 1.65$  mUnit/ml in the Pre 100 group.

These observations indicate that the control group is significantly increased as compared with normal group ( $p < 0.05$ ), and that Pre 10, Pre 50 and Pre 100 groups are significantly decreased on the  $\gamma$ -GTP in serums to be compared with the

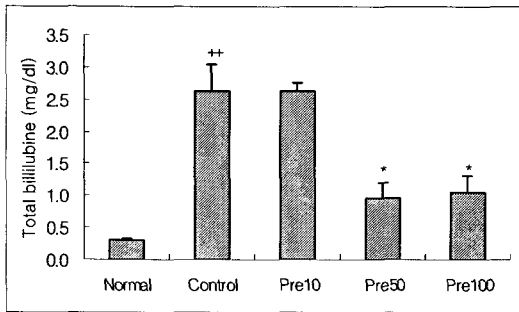


Fig. 5. Hepatoprotective effect of electro-acupuncture at Taechung (LR3) and Yangji (TE4) on serum total bilirubin in liver injury rats induced by D-galactosamine. Normal, not liver injury-induced and not treated group. Control, the liver injury-induced and not treated group. Pre 10, before the liver injury-induced electro-acupuncture with 10 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 50, before the liver injury-induced electro-acupuncture with 50 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 100, before the liver injury-induced electro-acupuncture with 100 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Results are shown as mean±S.E. ++,  $p < 0.01$  as compared with the corresponding data of normal group. \*,  $p < 0.05$  as compared with the corresponding data of control group.

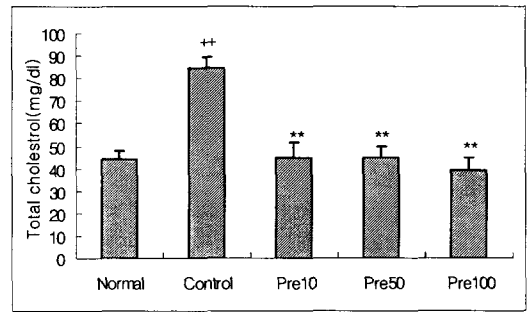


Fig. 6. Hepatoprotective effect of electro-acupuncture at Taechung (LR3) and Yangji (TE4) on serum total cholesterol in liver injury rats induced by D-galactosamine. Normal, not liver injury-induced and not treated group. Control, the liver injury-induced and not treated group. Pre 10, before the liver injury-induced electro-acupuncture with 10 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 50, before the liver injury-induced electro-acupuncture with 50 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 100, before the liver injury-induced electro-acupuncture with 100 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Results are shown as mean±S.E. ++,  $p < 0.01$  as compared with the corresponding data of normal group. \*\*,  $p < 0.01$  as compared with the corresponding data of control group.

control group ( $p < 0.05$ )(Fig. 1).

## 2. Effects of EA on GOT in serum

The GOT was  $128.2 \pm 3.50$  unit/ml in the normal group,  $512.9 \pm 68.91$  unit/ml in the control group,  $132.0 \pm 0.31$  unit/ml in the Pre 10 group,  $276.5 \pm 48.26$  unit/ml in the Pre 50 group and  $269.5 \pm 25.37$  unit/ml in the Pre 100 group.

These observations indicate that the control group is significantly increased as compared with normal group ( $p < 0.01$ ), and that Pre 10 ( $p < 0.01$ ), Pre 50 ( $p < 0.05$ ) and Pre 100 ( $p < 0.05$ ) groups are significantly decreased on the GOT in serums to

be compared with the control group (Fig. 2).

## 3. Effects of EA on GPT in serum

The GPT was  $72.1 \pm 2.10$  unit/ml in the normal group,  $326.0 \pm 65.61$  unit/ml in the control group,  $72.5 \pm 9.24$  unit/ml in the Pre 10 group,  $171.4 \pm 15.46$  unit/ml in the Pre 50 group and  $239.5 \pm 30.31$  unit/ml in the Pre 100 group.

These observations indicate that the control group is significantly increased as compared with normal group ( $p < 0.01$ ), and that Pre 10 ( $p < 0.01$ ) and Pre 50 ( $p < 0.05$ ) groups are significantly decreased on the GPT in serums to be compared with

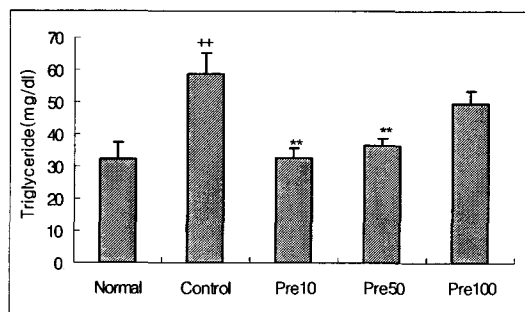


Fig. 7. Hepatoprotective effect of electro-acupuncture at Taechung (LR3) and Yangji (TE4) on serum triglyceride in liver injury rats induced by D-galactosamine. Normal, not liver injury-induced and not treated group. Control, the liver injury-induced and not treated group. Pre 10, before the liver injury-induced electro-acupuncture with 10 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 50, before the liver injury-induced electro-acupuncture with 50 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Pre 100, before the liver injury-induced electro-acupuncture with 100 Hz electrical stimulation at bilateral acupuncture point of LR3-TE4. Results are shown as mean±S.E. ++,  $p < 0.01$  as compared with the corresponding data of normal group. \*\*,  $p < 0.01$  as compared with the corresponding data of control group.

the control group (Fig. 3).

#### 4. Effects of EA on LDH in serum

The LDH was  $1962.8 \pm 64.22$  Wroblewski unit in the normal group,  $2903.0 \pm 230.87$  Wroblewski unit in the control group,  $2153.3 \pm 16.29$  Wroblewski unit in the Pre 10 group,  $1854.6 \pm 156.68$  Wroblewski unit in the Pre 50 group and  $1660.8 \pm 77.90$  Wroblewski unit in the Pre 100 group.

These observations indicate that the control group is significantly increased as compared with normal group ( $p < 0.05$ ), and that Pre 50 and Pre 100

groups are significantly decreased on the LDH in serums to be compared with the control group ( $p < 0.05$ )(Fig. 7).

#### 5. Effects of EA on Total bilirubin in serum

The total bilirubin in serum was  $0.3 \pm 0.02$  mg/dl in the normal group,  $2.6 \pm 0.41$  mg/dl in the control group,  $2.6 \pm 0.12$  mg/dl in the Pre 10 group,  $1.0 \pm 0.23$  mg/dl in the Pre 50 group and  $1.1 \pm 0.25$  mg/dl in the Pre 100 group.

These observations indicate that the control group is significantly increased as compared with normal group ( $p < 0.01$ ), and that Pre 50 and Pre 100 groups are significantly decreased on the total bilirubin in serums to be compared with the control group ( $p < 0.05$ )(Fig. 5).

#### 6. Effects of EA on Total cholesterol in serum

The total cholesterol was  $44.0 \pm 3.60$  mg/dl in the normal group,  $84.6 \pm 4.95$  mg/dl in the control group,  $44.8 \pm 6.96$  mg/dl in the Pre 10 group,  $44.5 \pm 5.44$  mg/dl in the Pre 50 group and  $39.3 \pm 5.16$  mg/dl in the Pre 100 group.

These results suggest that the control group is significantly increased as compared with normal group ( $p < 0.01$ ), and that Pre 10, Pre 50 and Pre 100 groups are significantly decreased on the total cholesterol in serums to be compared with the control group ( $p < 0.01$ )(Fig. 6).

#### 7. Effects of EA on Triglyceride in serum

The triglyceride was  $32.0 \pm 5.44$  mg/dl in the normal group,  $58.6 \pm 6.78$  mg/dl in the control group,

32.7±2.94 mg/dl in the Pre 10 group, 36.7±1.82 mg/dl in the Pre 50 group and 49.6±3.88 mg/dl in the Pre 100 group.

These observations indicate that the control group is significantly increased as compared with normal group ( $p<0.01$ ), and that Pre 10 and Pre 50 groups are significantly decreased on the triglyceride in serums to be compared with the control group ( $p<0.01$ )(Fig. 7).

#### IV. Discussion

In recent years, carbon tetrachloride( $\text{CCl}_4$ ) and GalN are well known for highly toxic chemical materials inducing the liver injury and the toxic effects of them on the liver have been steadily reported for years.

$\text{CCl}_4$  treatment inducing fatty liver, is manifested histologically as hepatic steatosis, centrilobular necrosis, and cirrhosis. Hepatic steatosis of the liver is a multifactorial phenomenon which is thought to be caused by a blockage of lipoprotein secretion<sup>9)</sup>, impaired synthesis or peroxidation of phospholipids<sup>10,11)</sup>, and the toxic effects of free alkyl radicals on cell membranes<sup>12,13)</sup>, and disturbances in methylation reactions<sup>14)</sup>.

GalN treatment induce the features of acute hepatitis in rats. The toxic effect of GalN is connected with an insufficiency of UDP-glucose and UDP-galactose and the loss of intracellular calcium homeostasis. These changes affect cell membranes and organelles and the synthesis of proteins and nucleic acids<sup>15)</sup>. After GalN application, the location of proteoglycans is changed in the rat liver<sup>16)</sup>. GalN also inhibits the energy metabolism of hepatocytes<sup>17)</sup>.

The special acupuncture points (Yuan-Source, Five acupuncture points) retain reflecting the pathological changes of the viscera and they are clinically used to diagnose and treat the disorders of the related viscera and organs.

LR3 is used in the clinical treatment of liver disease, headache, vertigo, redness, and swelling pain of eyes, glaucoma, nearsightedness, apoplexy, epilepsy, infantile convulsion, irregular menstruation, vomiting, hiccup, stomachache, and flaccidity<sup>18)</sup>.

TE4 is commonly used in the clinical treatment of tinnitus, deafness, sore throat, flaccidity and bi-syndrome of the upper limbs and diabetes<sup>18)</sup>.

So this study is designed to investigate hepatoprotective effects of EA at LR3-TE4 on GalN-induced liver injury in rats.

When the liver cell plasma membrane is damaged, varieties of enzyme normally located on the cytosol are released into the bloodstream<sup>19)</sup>. The serum levels of the  $\gamma$ -GTP, GPT, GOT, and total bilirubin, the markers of liver enzymes, are employed as important indicators of liver damage<sup>4,5,19-21)</sup>. Lactate dehydrogenase (LDH) is one of the important enzymes in diagnosis of specific organ diseases. Vertebrate tissues and serums contain the characteristic distributions of the LDH isozymes<sup>22,23)</sup>.

In this study, the control group significantly shows a decrease of markers of liver enzymes in serum.

On the hepatoprotective effect of EA at LR3-TE4, Pre 10 group is significantly decreased on the  $\gamma$ -GTP, GOT and GPT in serums to be compared with the control group, and Pre 50 group is de-

creased on the  $\gamma$ -GTP, GOT, GPT, LDH, and total bilirubin, and Pre 100 group is decreased on the  $\gamma$ -GTP, GOT, LDH, and total bilirubin.

These results support that all of EA groups are effective on markers of liver enzymes, which concern liver functions in serums, in GalN-induced liver injury in rats. Hence, these data suggest that electro-acupuncture treats and prevents the enzyme disorder of liver injury.

The evaluation of the concentration of serum lipids was reported by many investigations after toxic liver damage in rats<sup>24,25</sup>. In this study, the control group significantly shows an increase of concentration of serum lipids.

On the hepatoprotective effect of EA at LR3-TE4, Pre 10 group is significantly decreased on total cholesterol, and triglyceride in serums to be compared with the control group, and the Pre 50 group is decreased on total cholesterol, and triglyceride, and the Pre 100 group is decreased on total cholesterol. These results support that the EA has especially preventive effect on lipid metabolism progression in GalN-induced liver injury in rats by the decrease of concentration of serum lipid agents such as cholesterol and triglyceride. These results support that the EA has effect of treatment on lipid metabolism progression in GalN-induced liver injury in rats by the increase of concentration of total cholesterol.

In sum, the data suggest that the hepatotherapeutic effect on liver injury is intensive to treat only liver meridian channel within the EA at LR3-TE4.

## V. Conclusion

The hepatoprotective effects of EA at LR3-TE4 on liver injury induced by GalN in rats are observed as follows.

1. On the hepatoprotective effect of EA at LR3-TE4, the  $\gamma$ -GTP, GOT, GPT, total cholesterol and triglyceride are significantly decreased in the Pre 10 group.
2. On the hepatoprotective effect of EA at LR3-TE4,  $\gamma$ -GTP, GOT, GPT, LDH, total bilirubin, total cholesterol and triglyceride are significantly decreased in the Pre 50 group,
3. On the hepatoprotective effect of EA at LR3-TE4,  $\gamma$ -GTP, GOT, LDH, total bilirubin and total cholesterol are significantly decreased in the Pre 100 group.

Based on the results, we have indicated that the electro-acupuncture may contribute to its preventive and hepatotherapeutic effect on the progression of GalN-induced liver injury in rats.

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