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RESEARCH ARTICLE

Effect of Glycyrrhizin on Liver Function Improvement in Covid-19 Patients at Dr. M. Djamil General Hospital Padang

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Abstract

Background: Many of COVID-19 patients have an impaired liver function. Glycyrrhizin is a common ingredient in the Chinese herb licorice that has been used for liver disease treatment. The aim is to examine the effect of glycyrrhizin on the improvement of liver function in COVID-19 patients.

Methods: This was a nested cohort study, conducted on patients in Dr. M. Djamil General Hospital, Padang, West Sumatra, Indonesia from May 2021 until October 2021. All COVID-19 with impaired liver function and treated with glycyrrhizin in this hospital with were eligible to participate in the study. COVID-19 was confirmed by reverse transcription polymerase chain reaction (RT-PCR) swab. Liver function test was assessed on 0^{th}, 4^{th} and 7^{th} days of glycyrrhizin administration including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, indirect bilirubin, direct bilirubin, albumin, and globulin serum. Data entry and analysis were conducted using IBM SPSS ver. 26.

Results: This study involved 30 patients. The average age was 54,5 (16,46) years with 22 (73,3%) was male. There was significant improvement of AST, ALT, and total bilirubin ($p < 0,001$) without significant improvement of albumin and globulin serum ($p = 0,016$ and $<0,001$) after 7 days of glycyrrhizin administration.

Conclusion: Glycyrrhizin administration for 7 days improved AST, ALT and total bilirubin serum level in COVID-19 patients. Suggesting that glycyrrhizin administration will be more beneficial if given for 7 days than 4 days.

Keywords: COVID-19; Glycyrrhizin; Impaired Liver Dysfunction

Introduction

In December 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, China, known as coronavirus disease-2019 (COVID-19) [1-3]. Infection with the SARS-CoV-2 virus is asymptomatic mainly or mild symptoms, and need to be studied [4]. Most people about 80% recover without needing special treatment, but some people who have co-morbidities could be causing severe symptoms [5]. Severe cases present bilateral interstitial pneumonia and severe inflammation [1-2,6]. Hyperactive inflammatory state localized in lung tissue and all tissues of the body are causing multi-organ dysfunction and risk of thrombosis [6-8].

It is reported that up to 60% of SARS patients have an impaired liver function. A recent epidemiological study showed that 43 cases of COVID-19 had varying degrees of liver function abnormalities and higher ALT or AST serum level, and 1 of 99 COVID-19 patients had serious liver damage [9-10]. The impaired liver function in COVID-19 patients were mainly manifested as an abnormal level of ALT or AST, with a slight increase in bilirubin levels [9]. Wahid et al reported control group of COVID-19 patients had a higher ALT or AST serum level [11]. Cai et al reported 44 of 298 patients (14.8%) had liver injury, and those with severe liver injury (36.2%) were more prone to these elevations than patients with mild liver injury (9.6%) [12].

Glycyrrhizin acid, also called glycyrrhizin, a common ingredient in the Chinese herb licorice, has been used for liver disease treatment (including viral hepatitis) and specific inflammatory disorders of the skin (such as atopic dermatitis) [13]. Glycyrrhizin has an antiviral effect against different viruses, including SARS-related coronaviruses. Based on its characteristics, glycyrrhizin is considered as one promising novel drug candidate to fight SARS-CoV-2 as a single therapy or combined with other drugs [14-15].

This study aimed to examine the effect of glycyrrhizin on the improvement of liver function in COVID-19 patients.

Methods

Study Design

This study was an analytic observational study with a nested cohort approach. The research was conducted in Dr. M. Djamil General Hospital, Padang, West Sumatra, Indonesia, from May 2021 until October 2021. The sampling used random sampling method. Inclusion criteria were COVID-19 patients confirmed with positive PCR result from throat swab patients and had an impaired liver functions. The liver functions examined in this study were AST, ALT, indirect bilirubin, direct bilirubin, albumin, and globulin serum. Liver function was assessed on 0^{th}, 4^{th}, and 7^{th} days of glycyrrhizin administration.

Study Setting

West Sumatra is a province of Indonesia. It is located on the west coast of the island of Sumatra and includes Mentawai Island off that coast. The province is subdivided into twelve regencies and seven cities. Each regency and city in West Sumatra had one referral district hospital and an integrated referral system to refer patients to West Sumatra Province Referral Hospital located at Padang. Padang is the capital and largest city of the Indonesian province of West Sumatra. In the center of the city, there is a provincial referral hospital and the largest health care facility that handles referral COVID-19 patients from districts and cities, namely the Dr. M. Djamil General Hospital. This hospital has a capacity of 800 beds and serves as a educational and research hospital in West Sumatra.

Treatment Protocol

The main drug of choice for the treatment of this study patients was an injection of Glycyrrhizin acid through the Intravenous route. The medication was administered over a seven-day period starting from the date of admission up to the seventh day. The treatment is discontinued after seven days.

Ethics Review

We obtained ethical approval for this study from the Dr. M Djamil General Hospital Research Ethics Committee at Andalas University in Padang which waivered the requirement to obtain individual informed consent from patients whose medical records we analyzed since these data were healthcare facility-specific aggregated patient records.

Statistical Analysis

Ethical approval was granted by Dr. M Djamil Hospital Research Ethics Committee. Continuous variables were expressed as the appropriate means and standard deviations or median and ranges. Categorical variables were summarized as the counts and percentages in each category. Paired T-test or Wilcoxon test was used to examine the difference of liver function tests during follow up. P <0,05 was recognized as statistically significant. All these statistical calculations were performed using SPSS 26.0 software (SPSS Inc, Chicago, USA).

Results

This study involved 30 patients. The average age was 54,5 (16,46) years with 22 (73,3%) was male with characteristic presented in Table 1.

Variable	n (%)	p
Age (years)	54.5 (16.46)	<0.001
<30	3 (10)	
30 – 40	3 (10)	
40 – 50	2 (6.67)	
50 – 60	9 (30)	
>60	13 (43.33)	
Sex		
Male	22 (73.3)	
Female	8 (26.7)	

Table 1: Characteristics of patients

Variable	Median (min – max)					
	Day 1	Day 4	Day 7	p Day 1 - 4	p Day 4 - 7	p Day 1 - 7
AST(u/l)	104.5 (80-801)	62.5 (24-297)	40.5 (16-264)	<0.001	<0.001	<0.001
ALT (u/l)	121.5 (81-893)	121 (28-447)	65.5 (15-217)	0.002	<0.001	<0.001
Bil Indirect (mg/dl)	0.4 (0.2-3.2)	0.3 (0.2-2.7)	0.45 (0.1-2.1)	0.065	<0.001	<0.001
Bil Direct (mg/dl)	0.3 (0-8.4)	0.3 (0.1-8.7)	0.2 (0-8.1)	0.114	0.038	<0.001
Bilirubin total (mg/dl)	0.7 (0.3-11.2)	0.6 (0.3-11.2)	0.5 (0.2-10.2)	0.054	<0.001	<0.001
Albumin (g/dl)	3.5 (2.2-5)	3.15 (2.4-4.5)	3.1 (2.4-4.3)	0.002	0.556	0.016
Globulin (g/dl)	3.2 (2-4.4)	3.0 (1.9-4.2)	2.9 (1.6-4.4)	0.008	0.057	<0.001

Table 2: Liver functions follow-ups during administration of Glycyrrhizin

Level of AST serum at the beginning of glycyrrhizin administration was 104.5 (80-801) U/l which decreased on 4th day to 62.5 (24-297) U/l, p<0.001 and decreased again on 7th day to 40.5 (16-264) U/1, p<0.001. Level of ALT serum also decreased on 4th day from 121.5 (81-893) U/l to 121 (28-447) U/l, p = 0.002 and decreased again on 7th day to 65.5 (15-217) U/l, p<0.001 (Table 2). These findings suggest that glycyrrhizin administration will be more beneficial if given for 7 days than 4 days.

Level of indirect bilirubin serum did not change significantly on 4th day from 0.4 (0.2-3.2) mg/dl to 0.3 (0.2-2.7) mg/dl, p = 0.065 and experienced a significant increase on 7th day to 0.45 (0.1-2.1) mg/dl, p = 0.001. From the beginning of glycyrrhizin administration until 7th day, there was a significant increase in indirect bilirubin (p<0.001). These findings suggest awareness of increased of indirect bilirubin serum from 4th to 7th days administration of glycyrrhizin.

Level of direct bilirubin serum did not change significantly on 4th day from 0.3 (0-8.4) mg/dI to 0.3 (0.1- 8.7) mg/dl, p = 0.114 but decreased significantly at 7th day to 0.2 (0-8.1) mg/dl. p = 0.038. From the initial administration of glycyrrhizin until 7th day, there was a significant decrease of indirect bilirubin level (p <0.001).

Level of total bilirubin serum did not change significantly on 4th day from 0.7 (0.3-11.2) mg/dI to 0.6 (0.3- 11.2) mg/dl, p = 0.054 but decreased significantly at 7th day to 0.5 (0.2-10.2) mg/dl. p <0,001. From the initial administration of glycyrrhizin until 7th day, there was a significant decrease of total bilirubin level (p <0.001).

Level of albumin serum decreased on 4th day of glycyrrhizin administration from 3.5 (2.2-5) g/dl to 3.15 (2.4-4.5) g/dl, p = 0.002. There was no decrease in serum albumin levels between 4th to 7th of glycyrrhizin administration with 3.1 (0.4-4.3) g/dl, p = 0.556. There was a significant decrease level of albumin serum from the initial until 7th day administration of glycyrrhizin (p = 0.016).

Level of globulin serum decreased on 4th day of glycyrrhizin administration from 3.2 (2 – 4.4) g/dl to 3.0 (1.9 - 4.2) g/dl, p = 0.008. There was no significant decrease between 4th to 7th days of glycyrrhizin administration (p = 0.057). There was a significant decrease level of globulin serum from the initial until 7th days administration of glycyrrhizin (p = 0.001).

Discussion

Liver damage is one of serious complications found in several COVID-19 patients marked by elevated liver transaminases or elevated bilirubin. The incidence of elevated liver transaminases is about 2.5% to 76.3% in COVID-19 patients. Elevated bilirubin level also found in 35% of cases. Recent investigation has proved that SARS-CoV-2 infection directly impaired liver function by cytotoxicity due to replication of the virus. The expression of ACE2 as a receptor of Spike-I Glycoprotein of COVID-19 was increased in cholangiocytes (59.7% of cells) and in hepatocytes (2.6% of cells). Another study showed that the renin-angiotensin system and peroxisome proliferator-activated receptor signaling pathway potentially enhance the infection. Some antiviral agents, antibiotics, antipyretics or steroids used in the treatment of COVID-19 might also impaired the liver function [10-13].

Liver cells expressing SARS-CoV protein were found in the deceased SARS patients. This indicated the possibility of direct viral infection of liver cells. In addition, autopsy results in patients with SARS showed many mitotic liver cells, hepatocyte balloon degeneration, mild inflammation. Moderate lymphocyte infiltration, steatosis, and central lobular necrosis, accompanied by apparent apoptosis [9]. By comparing cases of liver injury caused by SARS-CoV and MERS-CoV, Xu et al pointed out that highly pathogenic human coronavirus infection can directly lead to liver injury, or it may to be caused by an immunopathological reaction caused by an excessive inflammatory response [14].

According to the Chinese Pharmaceutical Association, COVID-19 patients with significant liver damage should be treated with hepatoprotective, anti-inflammatory, and jaundice reducing agents such as polyene phosphatidvl choline, glycyrrhizin acid, bicyclol, and vitamin E. The treatment in critically ill patients should be chosen according to liver function injury and may include 1-2 kinds of drugs to avoid aggravating liver burden and interactions between drugs [15].

In general, experience in preventing and treating liver damage in patients in previous outbreaks caused by SARS-CoV may be a reference for treating COVID-19 patients with liver injury risk. The liver injury causes should be founded. Close monitoring of ALT, AST, total bilirubin, direct bilirubin, and albumin is needed [7,16]. Acute liver failure should be monitored intensively. Symptomatic and supportive treatment must conduct, and hypoproteinemia should be managed. In drug-induced liver injury, in addition to conventional anti-inflammatory liver protection treatment, consideration should be given to changing the dosage or reducing the number of suspected drugs, and the degree of liver damage should be assessed, followed by an adjustment of the treatment plan. Patients with severe liver damage caused by COVID-19 should be treated with hepatoprotective and anti-inflammatory agents [7].

There are some clinical trials using compound glycyrrhizin acid injection. Case control between chronic hepatitis C patient showed that the proportion of patients with ALT reduction ≥50% after 12 weeks was significantly higher with 5x/week glycyrrhizin (28.7%, p <0.0001) and 3x/week glycyrrhizin (29.0%, p <0.0001) compared with placebo (7.0%) [17]. Another case control on chronic severe hepatitis disease explain the effect of glycyrrhizin acid. Compared with control group the Total Bilirubin. ALT, and AST were significantly ameliorated in treatment group ($p < 0.01$). These supports the findings in this study that Level of AST serum was decreased from 104.5 to 62.5 U/l (on 4^{th} day: $p <0.001$) then to 40.5 U/l (on 7^{th} day; $p <0.001$). Level of ALT serum also decreased from 121.5 U/1 to 121 U/l (on 4^{th} day; $p = 0.002$) then to 65.5 U/l (on 7^{th} day; $p<0.001$). On direct bilirubin level, from the initial administration of glycyrrhizin until 7^{th} day, there was a significant decrease of direct bilirubin level ($p = 0.001$). However, the effect of glycyrrhizin acid on indirect bilirubin, albumin and globulin did not give representative results (Table 2).

Research about glycyrrhizin acid in liver disease is predominantly focused on anti-inflammatory and anti-apoptotic effects via suppression of TNF-α and caspase-3. These are used to explain the hepatoprotective effect of glycyrrhizin acid. Glycyrrhizin acid significantly inhibits the release of cytochrome C from mitochondria into the cytoplasm. The anti-inflammatory activity of GA may rely on myeloperoxidase activity, and translocation of nuclear factor-kB (NF-kB) into the nuclei. Upregulation on the expression of proliferating cell nuclear antigen might be able to promote regeneration of liver injury. These are the way of glycyrrhizin acid can improve the liver function [18-19].

Recently, Chen et al reported that glycyrrhizin acid derivatives might also have antiviral activity against SARS-CoV-2 [20]. Glycyrrhizin was the preferred anti-inflammatory drug to protect against liver disease and has been used in clinical practice for many years. Glycyrrhizin is well-established oriental phytomedicine used for a long time to treat hepatic disorders. The production of the drug is securitized and drug products of good quality can be found casily [21].

Conclusion

Glycyrrhizin administration for 7 days improved AST, ALT and total bilirubin serum level in COVID-19 patients. Suggesting that glycyrrhizin administration will be more beneficial if given for 7 days than 4 days.

Declarations

Ethics approval and consent to participate

Dr. M Djamil General Hospital Research Ethics Committee at Andalas University in Padang granted ethical clearance for conducting this study.

Availability of data and materials

The datasets generated and analyzed during the current study are not for public access due to patient confidentiality. This study used an aggregated dataset protected by the Dr. M Djamil General Hospital Research Ethics Committee at Andalas University in Padang to protect patient identities.

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