Transient Elastography Changes on Patient with Hepatic Cirhossis who were Treated by Simvastatin 20 Mg Compared to Simvastatin 10 mg

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Abstract

Background. Liver cirrhosis is a pathological condition that describes the end stage of liver fibrosis. Fibrosis is currently a two-way process. The process of returning from fibrosis now is a clinical reality. According to Abraldes *et al.* (2009), administration of simvastatin for one month will increase liver cell regeneration and improve endothelial dysfunction. Liver biopsy is still the gold standard for assessing liver cirrhosis, but this procedure is invasive and has the potential to cause life-threatening complications. Liver biopsy is complicated by sampling errors (reaching 30%) and different abilities between observers. Transient elastography (Fibro scan) is a non-invasive modality for diagnosing liver fibrosis that has high sensitivity and specificity.
Aim. The aim of the study was to discover the difference in effect, of simvastatin 20 mg compared to 10 mg for 3 months to improve liver stiffness in patients with liver cirrhosis.
Method. The study design used a double blind, randomized clinical trial. The subjects of the study consisted of a group given simvastatin 10 mg / day and the group given simvastatin 20 mg / day for 3 months. Routine medications for cirrhosis were still made according to the original dose. During the study, an initial and final transient elastography examination was carried out and monthly supervision of medication compliance and side effects. Data analysis for statistical tests was carried out by t-test, Mann Whitney test, fisher's-exact test, and ANOVA test.
Result. A total of 21 subjects underwent thorough research and transient elastography. The simvastatin 10 mg group (n = 12) experienced a decrease in liver stiffness, with a delta mean of liver stiffness of -4.97 + 7.09 (p <0.023) compared to the simvastatin 20 mg group (n = 9) with a heart stiffness of -4.09 + 10.06 (p= 0.982). Changed liver stiffness in the two groups were not statistically significant differences. Etiology and confounding drugs showed statistically no significant effect.
Conclusion. Both simvastatin 10 mg and 20 mg can reduce liver stiffness. The effect of the two doses of the drug in reducing liver stiffness was not statistically significant different.

Keywords: *cirrhosis of the liver, simvastatin, fibro scan, transient elastography*

Abstrak

Latar Belakang. *Sirosis hati adalah keadaan patologis yang menggambarkan stadium akhir fibrosis hati. Fibrosis saat ini merupakan proses dua arah. Proses pengembalian dari fibrosis saat ini adalah suatu realitas klinis. Menurut penelitian Abraldes et al. (2009), pemberian simvastatin selama satu bulan akan meningkatkan regenerasi sel hati dan memperbaiki disfungsi endotel. Biopsi hati masih menjadi baku emas untuk menilai sirosis hati, akan tetapi prosedur ini invasif dan berpotensi menimbulkan komplikasi yang mengancam nyawa. Biopsi hati dipersulit dengan kesalahan pengambilan sampel (mencapai 30%) dan beda kemampuan antar pengamat.*

Transient elastography (Fibroscan) *adalah modalitas non-invasif untuk mendiagnosis fibrosis hati yang memiliki sensitifitas dan spesifisitas yang tinggi.*
***Tujuan**. Mengetahui perbedaan pengaruh simvastatin 20 mg dibandingkan 10 mg selama 3 bulan terhadap perbaikan kekakuan hati penderita sirosis hati.*
Metode. Rancangan penelitian menggunakan uji klinis acak tersamar ganda. Subyek penelitian terdiri dari kelompok yang diberi simvastatin 10mg/hari dan kelompok yang diberi simvastatin 20mg/hari selama 3 bulan. Obat-obat rutin untuk sirosis tetap diberikan sesuai dengan dosis semula. Selama penelitian dilakukan pemeriksaan transient elastography awal dan akhir penelitian serta pengawasan setiap bulan terhadap kepatuhan makan obat dan efek samping. Analisis data untuk uji statistik dilakukan dengan uji-t, uji Mann Whitney*, uji* fisher's-exact*, dan uji anova.*
***Hasil**. Sebanyak 21 subyek menjalani penelitian dan transient elastography dengan tuntas. Kelompok simvastatin 10 mg (n=12) mengalami penurunan kekakuan hati, dengan rerata delta kekakuan hati -4, 97 ± 7, 09 (p<0,023) dibandingkan kelompok simvastatin 20 mg (n=9) dengan rerata delta kekakuan hati -4,09 ± 10,06 (p=0,982). Perubahan kekakuan hati pada kedua kelompok secara statistik tidak berbeda segnifikan. Analisis etiologi dan obat perancu menunjukkan hasil yang secara statistik tidak berpengaruh signifikan.*
***Kesimpulan.** Baik simvastatin 10 mg maupun 20 mg mampu menurunkan angka kekakuan hati. Pengaruh kedua dosis obat tersebut dalam menurunkan kekakuan hati secara statistik tidak berbeda signifikan.*

***Kata kunci:** sirosis hati, simvastatin, fibro scan, transient elastography*

Introduction

Liver cirrhosis is the 14th worldwide most common caused death in adult populations. Indonesia's prevalence of liver cirrhosis in 2007 ranged from 1-2.4%. The prevalence is (1.7%), it estimated that more than 7 million of Indonesian people have liver cirrhosis. Prevalence of liver cirrhosis in Dr. Sardjito General Hospital Yogyakarta were from 4.1% of patients admitted to the Internal Medicine Department during the 2004 period.[1]

Clinical symptoms of cirrhosis of the liver vary greatly. Compensate liver cirrhosis take several years to become decompensated, which characterized by the development of the following complications: jaundice, variceal bleeding, ascites and/or encephalopathy. Other complications occur mainly because of hyper dynamic portal and circulatory hypertension.[2] Patients with cirrhosis also need screening for hepatocellular carcinoma every 6 to 12 months.[3]

Parenchymal and non-parenchymal cells involved in the initiation and progression of liver fibrosis until cirrhosis.[4] Liver injury caused necrosis and/or cell apoptosis. Release of cell content and reactive oxygen species (ROS) will activate stellate cells and attract and activate tissue macrophages.[5] Exposure to inflammatory cytokines causes stellate cell changes to become active.[6] This activation was a very important event in the initiation and progression of liver fibrosis and contributes greatly to collagen deposition.[7]

Liver biopsy is important in identifying fibrosis and monitoring progression of liver disease.[8] Liver biopsy is still the gold standard for assessing liver cirrhosis, but this procedure is invasive and has the potential to cause life-threatening complications.[9] Currently transient elastography is a new non-invasive modality to diagnose liver fibrosis due to various etiologies. Transient elastography sensitivity when compared with liver biopsy in stage F≥ 1, F≥2, F≥ 3 and F≥ 4 respectively 83.7%; 87.5%; 93.7% and 96.2% (95% CI). Whereas the specificities are respectively 78.2%; 78.4%; 91.1% and 92.2% .[10]

At present, anti-fibrosis drugs continue to be produced. According to Abraldes et al. (2009) research, giving simvastatin for one month will increase liver cell regeneration and improve endothelial dysfunction in hepatic blood vessels in patients with cirrhosis so that it can decrease the effectiveness rate of fibrosis to reduce port pressure. [11] HMG-CoA-reductase inhibitor (Statins) are classified in drugs that inhibit liver cell migration / proliferation.[12]

Previous research is known to compare simvastatin 20 mg and placebo to assess cirrhotic patients with transient elastography. No studies have been found that compare the effect of giving simvastatin doses of 20 mg and 10 mg in patients with liver cirrhosis with Child Pugh A and B on the results of transient elastography.

Method

Double-blind randomized trial was used to investigate the effect of simvastatin 20 mg and simvastatin 10 mg for 3 months to improve liver stiffness in patients with liver cirrhosis. Selection of therapy for 3 months based on Abraldes et al. (2009) that simvastatin therapy for 1 month reduced portal hypertension and according to Kumar et al. (2014) statin therapy for at least 3 months can inhibit decompensation in liver cirrhosis.[11, 13]

The study was conducted at Dr. Sardjito General Hospital Yogyakarta in 2016. The study subjects underwent the first transient elastography examination and were given simvastatin 20 mg compared to the group given simvastatin 10 mg for 3 months and followed by clinical development and transient elastography evaluation.

Patients with liver cirrhosis were the target population of the study, while the affordable populations were adult patients who met the inclusion and exclusion criteria. There were two inclusion criteria. First, were patients who had erected child Pugh A & B cirrhosis based on clinical, laboratory, and liver ultrasonography, aged over 18 years who were treated at the gastroentero Hepatology polyclinic of Dr. Sardjito General Hospital Yogyakarta. Second, were agreed to participate in research by signing the consent sheet.

There were five exclusion criteria of the study. The first was subject with alcoholic fatty liver. The second were subjects with liver cirrhosis that progress to hepatocellular carcinoma (KHS). Third were subjects with liver cirrhosis with comorbid sepsis, chronic renal failure, chronic heart failure, acute stroke, acute complications diabetes mellitus (DM) namely diabetic ketoacidosis (KAD), coma hyperosmolar hyperglycemia and hypoglycemia and malignancies in addition to the liver. Fourth were subjects with liver cirrhosis who had experienced complications of hepatorenal syndrome and acute liver failure. Fifth, where subjects with obtaining simvastatin therapy before the study and the last were subjects with ascites and/or obesity.

The subjects were randomly divided into two groups. The first group had given simvastatin 20mg/day and the second group was given simvastatin 10mg/day, both treated in 3 months. Routine medications for cirrhosis were still given according to the original dosage. The subjects of the study were completed examination of history, physical examination, and laboratory examination. Then performed an ultrasound examination and transient elastography at the beginning and at the end of treatment.

Result

The study running for 6 months, from January to June 2018. The number of cases with liver cirrhosis who underwent outpatient care at the Gastroentero Hepatology clinic in Dr. Sardjito General Hospital and contact with researchers as many as 57 subjects. Subjects who met the inclusion criteria for the study were 51 subjects, but 9 subjects were excluded from 3 subjects because they received simvastatin therapy within the previous 2 months, 1 subjects were diagnosed with HCC (Hepatocellular carcinoma) and 5 subjects were not willing to take the study. Here the result was 42 subjects willing to conduct the study.

The study started with computerized system and interview, also physical examinations, and laboratory tests. Both groups were given simvastatin 10 mg or 20 mg for 3 months. Researcher and subjects were not aware of the intervention given because simvastatin 20 mg and 10 mg were given to the subjects used capsules of the same shape and color. A total of 42 research subjects underwent research for 3 months, and only 38 subjects

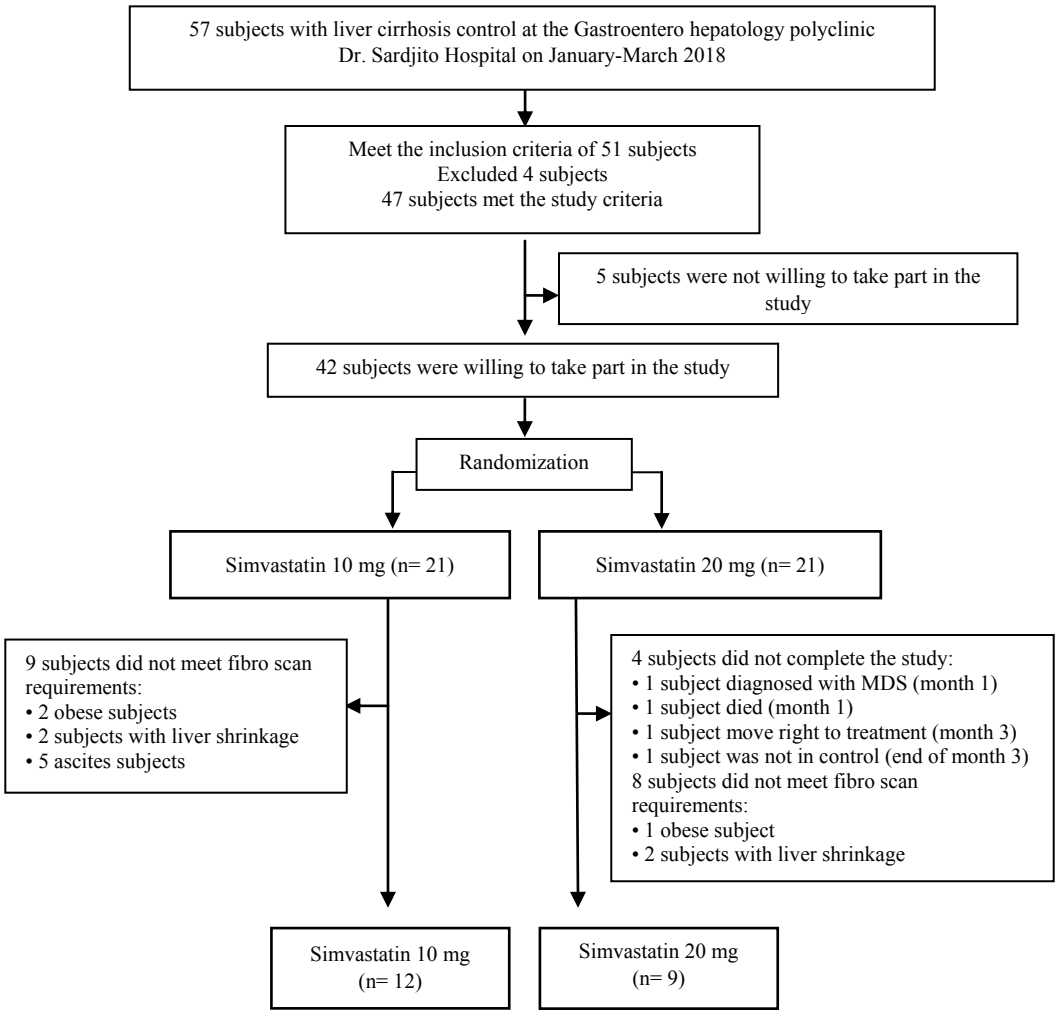

Figure 1. Flow of research

continued until the end of the study. A total 12 subjects in the simvastatin 10 mg group, and the simvastatin 20 mg group were 9 subjects for further analysis of the data.

The basic characteristics of the study subjects were difference changed in liver stiffness in subjects with liver cirrhosis treated with simvastatin 20 mg compared with 10 mg described in table 1.

There were 21 research subjects divided into two treatment groups. The simvastatin 10 mg group consisted of 12 subjects and the simvastatin 20 mg group as many as 9 subjects. In both groups, the average age in the simvastatin 10 mg group was 56 years while in the simvastatin group 20 mg was 60 years. The gender in the simvastatin 10 mg group was mostly male at 83.3% and in the simvastatin group 20 mg the majority were

Table 1. Basic Characteristics of Research Subjects

Characteristics	Simvastatin 10mg			Simvastatin 20mg			p
	n (12)	%	Mean ± SD/Median (min-max)	n (9)	%	Mean ± SD/Median (min-max)	
Age			56.17±6.25			60.78± 9.02	0.182[a]
Gender							
Male	10	83.3%		3	33.3%		0.032[b]
Female	2	16.7%		6	66.7%		
Education							
Uneducated	1	8.3%		0	0.0%		0.744[c]
Elementary School	3	25.0%		1	11.1%		
Junior High School	2	16.7%		2	22.2%		
Senior High School	4	33.3%		3	33.3%		
Diploma/Bachelor	2	16.7%		3	33.3%		
Occupation							
Housewife	0	0.0%		4	44.4%		0.095[c]
Civil servants	2	16.7%		1	11.1%		
Retired	1	8.3%		2	22.2%		
Private employees	1	8.3%		1	11.1%		
Entrepreneur	3	25.0%		0	0.0%		
Farmer	2	16.7%		1	11.1%		
Freelancer	3	25.0%		0	0.0%		
Etiology							
Hepatitis B	10	83.3%		6	66.7%		0.128[c]
Hepatitis C	0	0.0%		1	11.1%		
NAFLD	0	0.0%		2	22.2%		
Others	2	16.7%		9	0.0%		
Propranolol							
Yes	12	100%		9	100%		-
No	0	0.0%		0	0.0%		
Spironolactone							
Yes	10	83.3%		9	100%		0.486[b]
No	2	16.7%		0	0.0%		
Vitamin K							
Yes	3	25.0%		9	33.3%		1.000[b]
No	9	75.0%		6	66.7%		

Characteristics	Simvastatin 10mg			Simvastatin 20mg			p
	n (12)	%	Mean ± SD/Median (min-max)	n (9)	%	Mean ± SD/Median (min-max)	
Lamivudine							
Yes	4	33.3%		4	44.4%		0.673 [b]
No	8	66.7%		5	55.6%		
Telbivudine							
Yes	3	25.0%		1	11.1%		0.603 [b]
No	9	75.0%		8	88.9%		
Tenofovir							
Yes	1	8.3%		0	0.0%		1.000 [b]
No	11	91.7%		9	100%		
Sofosbuvir							
Yes	0	0.0%		0	0.0%		-
No	12	100%		9	100%		
Daclatasvir							
Yes	0	0.0%		0	0.0%		-
No	12	100%		9	100%		
Smoking							
Yes	8	66.7%		1	11.1%		0.024 [b]
No	4	33.3%		8	88.9%		
Nutritional Status							
Obesities	0	0.0%		0	0.0%		0.142[c]
Overweight	0	0.0%		1	11.1%		
Normal	1	8.3%		3	33.3%		
Underweight	11	91.7%		5	55.6%		
Early Child Pugh							
A	11	91.7%		8	88.9%		1.000[b]
B	1	8.3%		1	11.1%		
BMI			23.33±2.23			23.74±4.05	0.769[a]
Hb			11.27±3.33			12.13±1.71	0.486[a]
Early BUN			11.9(5.0-71.0)			11.5(8.0-20.3)	0.749[d]
Early CREA			1.05±21			0.99±.21	0.575[a]
Early CCT			68.07±16.97			58.05±15.79	0.184[a]
Early INR			1.34±.19			1.28±.14	0.394[a]
Early TBIL			1.11±.51			1.30±.38	0.370[a]
Early Alb			3.89±.57			3.68±.62	0.422[a]
Early MELD			11.25±2.22			10.89±1.83	0.696[a]

a = Independent T-Test, b = Fisher Exact Test, c = Chi-Square Test, d = Mann Whitney Test (significance p<0, 05), (-) = cannot be analyzed.

female as much as 66.7%. The education level of the research subjects in the simvastatin 10 mg group included Senior High School at 33.3%, Elementary School 25%, Junior High School 16.7%, Diploma / Bachelor 16.7%, while in the Simvastatin group 20 mg the level of education included Diploma or Bachelor 33.3 %, Senior High School 33.3%, Junior High School 22.2% and Elementary School 11.1%. Liver cirrhosis in the two majority groups were caused by Hepatitis B where in the simvastatin 10 mg group was 83.3% and in the Simvastatin 20 mg group was 66.7%. For routine medication in both groups used propranolol at 100%, in the simvastatin 10 mg group was 83.3% of patients used

spironolactone, while in the simvastatin group 20 mg was 100%. The used of vitamin K in the simvastatin 10 mg group was 25% and in the simvastatin 20 mg group was 33.3%. More used of antiviral drugs was found in the simvastatin 10 mg group, namely lamivudine, telbivudine, tenofovir, sofosbuvir, daclatasvir respectively 33.3%, 25%, 8.3%, while in the simvastatin 20 mg group respectively 44%, 11%, 0%. In both groups did not used of sofosbuvir and daclatasvir was obtained.

The nutritional status of the two groups were approximately the same as the average body mass index is 23.3 kg/m^2 and 23.7 kg/m^2. Child Pugh in the two majority groups was Child Pugh A, the Simvastatin 10 mg group was 91.7% and the Simvastatin 20 mg group was 88.9%. Overall, the characteristics of the sample are almost similar, except for gender and smoking habits. Both variables indicate a significant difference. In the simvastatin 10 mg group the number of men and women, respectively was 83.3% and 16.7%, while in the simvastatin 20 mg group the number of men and women respectively was 33.3% and 66.7% with p value 0.032. Smoking habits in the simvastatin 10 mg group were 66.7%, while in the simvastatin 20 mg group only 11.1% with p value 0.024.

In the simvastatin 10 mg group, the middle value of liver stiffness at the beginning of the study was 18.75 kPa, down to 15.45 kPa at the end of the study with p value 0.023, while simvastatin 20 mg at midpoint at 26.30 kPa dropped to 21.30 kPa with p-value 0.1.

Based on the table 2, changed liver stiffness in the simvastatin 10 mg group was statistically significant while in the simvastatin 20 mg group was not statistically significant. When we compared changes in liver stiffness between the simvastatin 10 mg group and the simvastatin 20 mg group, it did not differ statistically significant, this change can be seen in table 3 with p value of 0.982.

Table 3. Differences in Changes in Liver Stiffness

		Delta Liver Stiffness		p
		Mean	Deviation standard	
Group	Simvastatin 10mg	-4.97	7.09	0.982[a]
	Simvastatin 20mg	-4.89	10.06	

a = Independent T-Test (significance p<0.05)

After received simvastatin therapy for 12 weeks, an evaluation of the occurrence of side effects obtained from the history, physical examination, and investigation (Table 4).

In this study we obtained data on the side effects of used simvastatin in each treatment group. In the Simvastatin 10 mg group there were 5 out of 12 subjects (41.6%) experiencing side effects, whereas in the simvastatin 20 mg group 6 of 9 subjects (66.6%) experienced simvastatin side effects. It appears that in simvastatin 20 mg, the incidence of side effects was higher compared to simvastatin 10 mg (Table 4), but statistically the two groups were not significantly different.

Table 2. Early and Final Differences in Liver Stiffness.

Group	Liver Stiffness			Liver Stiffness			p
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Simvastatin 10mg	18.75	6.10	75.00	15.45	7.30	54.20	0.023[a]
Simvastatin 20mg	26.30	11.90	53.50	21.30	8.30	63.90	0.173[a]

a = Mann Whitney Test (significance p<0.05)

Table 4. Adverse Events of Simvastatin Therapy

Adverse Events	Simvastatin 10 mg		Simvastatin 20 mg		p
	n= 12	%	n=9	%	
Sleep disorder	1	8.3	0	0	1.000[a]
Pruritus	0	0.0	3	33.3	0.063[a]
Myalgia	1	8.3	1	11.1	1.000[a]
Arthralgia	0	0.0	1	11.1	0.429[a]
Paresthesia	1	8.3	2	22.2	0.553[a]
Headache	1	8.3	0	0.0	1.000[a]
Dizziness	0	0.0	1	11.1	0.429[a]
Atypical chest pain	1	8.3	0	0.0	1.000[a]
Abdominal pain	1	8.3	0	0.0	1.000[a]
Nausea	0	0.0	3	33.3	0.063[a]
Constipation	0	0.0	0	0.0	-
AST >3x upper limit	0	0.0	1	11.1	0.429[a]
ALT >3x upper limit	0	0.0	0	0.0	-
CK >3x upper limit	0	0.0	0	0.0	-

a = Fisher Exact Test (significance p<0.05), (-) cannot be analyzed

In this study the etiology of liver cirrhosis in both groups included Hepatitis B, hepatitis C, non-alcoholic fatty liver disease (NAFLD) and other unknown causes. Further analysis was carried out to see the etiological relationship of fibrosis with liver stiffness in the two treatment groups.

In table 5 it appears that changes in liver stiffness in patients with hepatitis B were not significantly different from non-hepatitis B patients, changes in liver stiffness in patients with hepatitis C did not differ significantly from non-hepatitis C patients and changes in liver stiffness in NAFLD were not significantly different from non-patients NAFLD.

The basic characteristics that showed significant differences were gender and smoking. After analysis in table 7, both men and women did not show a significant difference in liver stiffness decreased. Likewise, smoking habits in both treatment groups did not differ significantly.

Table 5. Etiological Analysis of Liver Fibrosis as Confounder

Etiology		Delta Liver Stiffness		p
		Mean	Deviation standard	
Hepatitis B	Yes	-4.87	7.62	0.947[a]
	No	-5.16	11.09	
Hepatitis C	Yes	-5.70	-	0.927[a]
	No	-4.90	8.47	
NAFLD	Yes	2.00	11.88	0.220[a]
	No	-5.67	7.87	
Others	Yes	-12.05	12.37	0.208[a]
	No	-4.19	7.81	

a = Independent T-Test (significance p<0.05), (-) = cannot be analyzed.

Table 6. Analysis of Routine Drugs as Confounding

		Difference in liver stiffness		p
		Mean	Standard Deviation	
Propanol	Yes	-4.93	8.25	-
	No	0	0	
Spironolactone	Yes	-4.90	8.62	0.556[a]
	No	-5.30	4.94	
Vitamin K	Yes	-11.70	9.56	0095[a]
	No	-2.23	6.09	
Antivirus	Yes	-3.78	7.83	0.677[a]
	No	-6.81	9.10	

A = Independent T-Test (significance p<0.05), (-) = cannot be analyzed.

Discussion

Liver fibrosis was a reversible wound healing response. The process of reaching the final stage of cirrhosis taken 20 to 40 years in patients with chronic liver injury the rate of development was influenced by both genetic and environmental factors.[14]

Based on research by Marron et al. (2014), in the liver there was a Kruppel-like factor 2-transcription factor (KLF2) increased in number during the progression of cirrhosis to reduce the development of

Table 7. Gender and Smoking Analysis as a Screw

		Difference in liver stiffness		p
		Mean	Standard Deviation	
Gender	Male	-2.55	6.23	0.092 [a]
	Female	-8.81	10.01	0.142 [a]
Smoking	Yes	-4.24	5.65	0.748 [a]
	No	-5.45	9.99	

a = Independent T-Test (significance p<0.05)

vascular dysfunction. An in vivo study showed that increased regulation of KLF2 could affect the liver cell phenotype and could improve liver fibrosis, endothelial dysfunction, and port hypertension in cirrhosis. In the study simvastatin was known to induce expression of KLF 2 when stellate cells were active.[15]

Abraldes' research in 2009 showed that giving simvastatin 20-40 mg for one month would improve liver cell regeneration and improve vascular endothelial dysfunction. A study of the administration of simvastatin 20 mg for 4 weeks to liver stiffness scores was carried out in Solo, Indonesia. In this study, there was a significant decrease in liver stiffness scores with a p value equal to 0.049.[16]

Whereas in this study showed an improvement in liver stiffness scores that were statistically significant with the treatment of simvastatin for 3 months at lower doses of 10 mg, p value = 0.023. Even so, if changes in liver stiffness compared between the two treatment groups results showed not significantly different.

Some conditions that affect the results of transient elastography include obesity, old age, ascites, and metabolic syndrome.[17] A total of 17 subjects were excluded due to obesity, ascites, and liver shrinkage. Liver stiffness could be affected by, among others: fasting status, increased transaminases, cardiac congestion, and extra hepatic cholestasis. The type and position of the probe and operator experience also influence the results of transient elastography.[18]

The significant difference between the two groups was probably due to differences in the number of samples where in the simvastatin 10 mg group the number of samples was greater than the simvastatin 20 mg group. The sample in the study may not be too large or too small because both have limitations that could influence the conclusions of the study. Samples that were too small and less able to predict a possibility.[19]

Some other things that caused different results included etiology and routine medications used by the research subjects. Patients with liver cholestasis, such as primary biliary cirrhosis and primary sclerotic cholangitis, appear to be had a higher liver stiffness than viral hepatitis. Some conditions that could lead to overestimation of liver fibrosis in transient elastography include: increased transaminases, extra hepatic cholestasis and congestion of the heart, non-fasting conditions and liver steatosis.[18] Liver stiffness seen with transient elastography in patients with chronic hepatitis B was similar to patients with hepatitis C at the same stage of fibrosis. Liver stiffness were also related to the severity of fibrosis in both hepatitis B and hepatitis C patients.[20]

In this study, after analysis of confounding factors for etiology and routine drugs used did not show a significant difference between the two treatment groups. Not only liver stiffness has the different results, but the frequency of simvastatin side effects in both groups also showed some differences even though it was not statistically significant.

The results of this study showed that the simvastatin 20 mg group has a greater frequency of side effects than in the simvastatin 10 mg group. This could be appeared because of the simvastatin 20 mg group was older with an average age of 60 years while in the simvastatin 10 mg group the average age of the subject is 56 years. A study conducted by the 2008 National Institute of Health in the United States mentioned several risk factors for undesirable events due to statins, one of which was elderly subjects.

A study with research subjects received simvastatin 80 mg with basic characteristics > 65 years of age was associated with an increased incidence of both definite myopathy and insipient myopathy with a relative risk of 2.2 (95% CI 1.4-3.4) and 2, 3 (95% CI 1.3-4.1). Among patients who received simvastatin 20-40 mg every day, the incidence of myopathy was typically around 1/10.000 patients/year. Old age also signifies fragility of mitochondria because DNA mutations occur with age.[21]

Evidence regarding matters affecting simvastatin side effects continues to develop towards the role of systemic factors were genetics, food intake, and estrogen use and bone density. Here, the mechanical factors, namely muscle weakness, obesity, and joint weakness.[21.22] Various other variables were overall health status, comorbidity, exercise habits, smoking, depression, poor personal mastery and low education. Apart from the presence of risk factors, an increase in the incidence of simvastatin side effects was also influenced by drug interactions.[23]

In this study, the subjects involved had routine medications, including propranolol, spironolactone, vitamin K and antivirals (lamivudine, telbivudine and tenofovir). Setoguchi et al. (2010) found no synergistic effect between the used of propranolol and statins in cases of myopathy. Chronic infection or inflammatory conditions such as cirrhosis of the liver were known to have increased CRP levels.[24] The used of beta blockers (metoprolol or propranolol) together with statins can significantly weaken the anti-inflammatory effect.[25] Statin interactions were also found in the used of spironolactone, where spironolactone could increase the level or effect of statins and increased the risk of muscle toxicity.[26] While the influence of statins on oral vitamin K has not been widely studied.

Studied of the side effects of statins have shown that increased creatinine kinase and liver enzymes were in line with increased statin doses and intensity of use. Most side effects of statins were dose dependent in some literature suggested "the lower the better". The FDA of United States that all statins should be given the lowest dose.[23]

Results from measurements of liver stiffness in 21 subjects divided into the simvastatin 10 mg group and simvastatin 20 mg showed a decrease in liver stiffness in 3 months of treatment. However, the decreased in liver stiffness that occurred in both treatment groups was not statistically significantly different. The used of simvastatin in chronic liver disease was a long-term used for a lifetime. In the results of this study and the financial considerations and FDA recommendations, simvastatin 10 mg could be a good therapeutic choice.

Conclusion

Both simvastatin 10 mg and 20 mg could reduce liver stiffness in patients with cirrhosis. The effect of the two doses of the drug in reducing liver stiffness was not statistically significant different.

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