

THE EFFECT OF COMBINATION OF LACTULOSE THERAPY IN LIVER CIRRHOSIS HANDLING WITH COMPLICATIONS IN Dr. SARDJITO YOGYAKARTA

Chynthia Pradiftha Sari*, Dewi Ardy Murdiati, Ndaru Setyaningrum

Pharmacy Department, Faculty of Mathematics and Natural Sciences, Indonesian Islamic University, Yogyakarta, Indonesia

Abstract. Liver cirrhosis is a liver structure that results in the liver not being able to work with the 14th death rank in the world. Treatment of liver cirrhosis is intended for the treatment of complications, comorbidities and limited therapeutic efficacy data after treatment is given. The purpose of this study was to determine the patients, and the efficacy of lactulose combination therapy in liver cirrhosis complications in the inpatient installation of Dr. Sardjito Yogyakarta. Method: the study was conducted observationally with a case-series design. Observation and truth of prospective data were obtained from inpatient status during June-September 2016, the number of 28 patients in the study, 4 other patients were excluded. The results of most liver cirrhosis patients during the study were men (71.43%), 46-55 (28.57%), risk factors for hepatitis B (50%), complications of hepatic encephalopathy (33.33%), disease gastrointestinal group (25.23%), child-pugh C criteria (32.14%), decreased albumin (16.87%). Efficacy of lactulose therapy in hepatic complications improved encephalopathy 71.43%; propranolol and lactulose in esophageal varices improved 100% bleeding defects; spironolactone, furosemide, and albumin in ascites improve 66.67%; propranolol in portal hypertension is 100% cured; lactulose, LOLA, and vitamin K in hepatic encephalopathy repair 100% esophageal varices; propranolol and lactulose in esophageal varices and portal hypertension improve 100%. Conclusion: The combination of Lactulose with propranolol provides 100% efficacy in variations in esophageal vaccine and portal esophageal portal hypertension. The combination of lactulose, LOLA, vitamin K has 100% efficacy in repairing esophageal varices. The combination of Lactulose and propranolol has a 100% efficacy on the portal of esophageal varices and hypertension.

Keywords: Lactulose, Liver Cirrhosis, combination therapy, efficacy

1. Introduction

Liver cirrhosis is a chronic and irreversible disease with significant morbidity and mortality. The most common causes of liver cirrhosis in some western countries are alcoholics, whereas in Indonesia there are hepatitis B and C virus infections [1]. The results of research in Indonesia said the

hepatitis B virus causes cirrhosis of 40-50%, hepatitis C virus 30-40%, 10-20% of the causes are unknown and includes a group of viruses not B and C [2]. WHO data in 2011, shows cirrhosis, the cause of 14 deaths in the world with 738,000 patients dying. DIY health profile data in 2008, placed cirrhosis in the top 10 causes of death with a prevalence of 1.87% at the ninth rank [3].

*Corresponding author: pradiftha@uii.ac.id

The high prevalence of cirrhosis can be affected by complications of hepatic encephalopathy, septic shock and an increase in Child-Pugh and MELD (Model for End-Stage Liver Disease) scores in the majority of patients [4]. The mortality rate due to complications in cirrhosis patients needs to be suppressed by paying attention to the right choice of therapy with regard to the type of complications.

The therapeutic options that are widely used in patients with hepatic cirrhosis vary, including a combination of LOLA (L-ornithine L-aspartate), Lactulosa, vitamin K (83.33%) in conditions of complications [5]. Complications of hepatic encephalopathy (EH) are widely treated with erythromycin and lactulose, lactulose greatly reduces neurological abnormalities in EH patients [6].

Lactulose treatment in cirrhosis patients today at Dr. Sardjito is quite numerous and has never been monitored for the therapeutic results of the expected therapeutic efficacy. This study was conducted to determine patient characteristics, and assess the efficacy of lactulose combination therapy in cirrhosis of the liver complications in the inpatient installation of Dr. Sardjito Yogyakarta.

2. Methodology

The research is an observational descriptive with a case-series design and has fulfilled the results of the ethics committee test from the Faculty of Medicine UGM. Data was taken prospectively from June to September 2016 at the inpatient installation of the Central General Hospital (RSUP) Dr. Sardjito Yogyakarta is 28 patients, in the form of therapeutic characteristics and efficacy. The inclusion criteria studied included, complicated liver cirrhosis patients (ascites, esophageal varices, spontaneous bacterial peritonitis (PBS), hepatic encephalopathy, portal hypertension and hepatorenal syndrome) who received treatment therapy during hospitalization, had complete medical

records, including names, gender, age, diagnosis, history of disease, complaints, comorbidities, laboratory data and risk factors for liver cirrhosis, and are willing to be involved in the study.

Patient characteristics, measured by looking at medical records and conducting a complete list of patient data including age, risk factors, complications, comorbidities, child-pugh criteria, laboratory results. The efficacy assessment of therapy was measured by observing the parameters of treatment success in each complication, namely, a) ascites: daily weight loss, decreased abdominal circumference, tightness and tightness of the abdominal surface, b) varicose bleeding: monitoring of recurrent bleeding, vomiting bleeding, bloody defecation, c) Spontaneous Bacterial Peritonitis: fever, abdominal pain, vomiting, diarrhea, impaired consciousness, anorexia, malaise, fatigue. d) Hepatic encephalopathy: sleep rhythm disturbances, changes in mental status / personality, anxiety, coma. e) Hepatorenal syndrome: urine volume. Data were analyzed descriptively with the aim of describing, describing and processing data collection observations in the form of percentages.

3. Results and discussion

This study aims to determine the characteristics of patients, including gender, age, risk factors, complications, comorbidities, Child-Pugh criteria, and laboratory features. Distribution of these characteristics is shown in table 1.

Liver cirrhosis is experienced by many men (71.43%), the highest risk of hepatic cirrhosis in men is the incidence of hepatitis B [7], the habit of frequently consuming alcohol for a long time, sleeping late, hard-working, and drinking habits energy enhancer [4]. In this study, data on patient complaints as large include: insomnia, anxiety, nausea, vomiting, weakness, speech digress, and decreased awareness. Based on these complaints, there is a sign of hepatic encephalopathy (33.33%)

*Corresponding author: pradiftha@uii.ac.id

even though the diagnosis cannot be established. Hepatic encephalopathy can occur due to severe liver disease, both acute and chronic marked behavioral disorders, neurological symptoms, asthma, various degrees of disturbance of consciousness to coma [8].

Table 1. Characteristics of Liver Cirrhosis Patients hospitalized at Dr. Sardjito Yogyakarta

Characteristics	Category	N	%
Sex	Male	20	71.43
	Female	8	28.57
Age (years old)	17-25	1	3.57
	26-35	1	3.57
	36-45	5	17.86
	46-55	8	28.57
	56-65	6	21.43
	> 65	7	25
	Risk Factor	Hepatitis B	14
Hepatitis C		1	3.57
Hepatitis autoimmune		1	3.57
Alcohol		2	7.14
Hepatitis B & alcohol		2	7.14
Unknown		8	28.57
Complication	Hepatic Encephalopathy	12	33.33
	Esophageal Varices	8	22.22
	Ascites	4	11.11
	Portal Hypertension	4	11.11
	Hepatorenal Syndrome	3	8.33
	Spontaneous Bacterial Peritonitis	1	2.78
	Without complication	4	11.11
	<i>Child-Pugh criteria</i>	<i>Child-Pugh A</i>	5
<i>Child-Pugh B</i>		7	25
<i>Child-Pugh C</i>		9	32.14
Unknown		7	25
Laboratory Representation	Increase		
	Total Bilirubin	13	7.83
	<i>Direct</i> Bilirubin	17	10.24
	SGOT	17	10.24
	SGPT	13	7.83
	Prothrombin mass	21	12.65
	Decrease		
	Hemoglobin	27	16.27
	Albumin	28	16.87
	Sodium	14	8.43
Thrombocyte	16	9.64	

*Corresponding author: pradiftha@uii.ac.id

Child-Pugh criteria describes a poor prognosis for patients with liver cirrhosis, the higher the Child-Pugh score, the worse the patient's prognosis [9]. The majority of patients hospitalized at Sardjito General Hospital who died had a higher Child-Pugh score compared to survivors. Laboratory results show an increase and decrease in albumin (16.87%). The results of this study are in line with the research of Patasik et al. (2015), laboratory features in patients with cirrhosis of the liver who experience albumin abnormalities (16%) [10]. Hypoalbuminemia occurs in cirrhosis patients because the function of the liver to form albumin is disrupted, with a decrease in the supply of inadequate amino acids from the protein, thereby disrupting the synthesis of albumin and other proteins by the liver.

Complications experienced by liver cirrhosis patients affect the therapy given. If the patient gets the right therapy and according to complications, it will give good therapeutic results for the patient. Complications in cirrhotic patients in the study were mostly treated with lactulose. The following details of cirrhosis treatment therapy are presented in the table.

Cases number 5, 13, 14 received Lactulose therapy. Lactulose is used as the first line in the management of cirrhosis patients with HE because it can inhibit the production and absorption of ammonia in the intestine, and increase its elimination through feces. The efficacy and safety of lactulose in the prevention of encephalopathy has been demonstrated in various studies [8]. The efficacy of lactulose is shown by the improvement of the patient's clinical condition, in the form of improvement in sleep rhythm, improvement in mental status, reduction in anxiety and increased awareness [11].

Table 2. Treatment efficacy profiles in Hepatic Complications of Encephalopathy

Case	Therapy	Dose/ Frekuensi	Durasi (day)	L O S	Efficacy Parameters				Data Lab		Out come
					Bleeding ↓	Hem atem esis ↓	melen a↓	Awa renes s↑	Bil tot al	Bil direc t	
10	Propranolol	10 cc/12 h	5	6	✓	✓	✓	✓	↑	↑	Good
	Laktulosa	15 cc/12 h	5								
	Vitamin K	1 amp/8 h	5								
11	Propranolol	10 cc/12 h	7	8	✓	✓	✓	✓	↓	↓	Good
	Laktulosa	15 cc/12 h	6								
	Somatostatin	250 mcg/day	6								
	Vitamin K	1 amp/8 h	6								
19	Propranolol	10 mg/8 h	6	8	✓	✓	✓	✓	↑	↑	Good
	Laktulosa	15 cc/8 h	7								
28	Propranolol	10 mg/12 h	3	14	✓	✓	✓	✓	↑	↑	Good
	Laktulosa	10 cc/8 h	13								
	Vitamin K	1 amp/8 h	13								

Ket :
(✓) = Yes, (-) = No, (↑) = Increases, (↓) = Decreases,
(n) = Normal, LOLA = (L-ornithine L-aspartate)

Case no. 7 and 9, the patient did not experience improvement and was declared dead due to hepatic encephalopathy. Lactulose therapy is 15 cc / 24 hours and LOLA 1 sachet / 8 hours is given from the first day of hospitalization, according to the study of Jorge Luis et al. (2006), a dose of 1 sachet 3 times a day or 9 grams / day can significantly reduce serum ammonia levels and can improve mental status parameters, NCT (Number Connection Test), asterixis score, and EEG activity in the group receiving LOLA [11] but does not improve overall complications. Case No. 7, 18, 19, the patient experienced improvement in parameters with LOLA combination lactulose therapy. RCT research shows that LOLA 20 g / day intravenously can improve ammonia levels and HE [12]. LOLA directly limits hepatocyte damage through mechanisms that involve increased glutamine, GSH antioxidants and L-arginine / NO systems [13]. A meta-analysis study shows the benefits of LOLA in overt patients and a minimum of HE in improving HE with decrease serum ammonia concentration [14]. Another study by HU Xiaowu (2010), of 68 cirrhosis patients with HE, the mortality rate in 28 patients with LOLA therapy was 25%, 23 patients with LOLA and lactulose combination therapy were 21.7%. This means that LOLA combined with lactulose in the treatment of HE patients is effective in reducing mortality [15].

Table 3. Profile of therapeutic efficacy on Esophageal Varices Complications

Esophageal Varices Complications and Portal Hypertension												
Case	Therapy	Dose/ Frequency	Duration (day)	LOS	Efficacy Parameters			Data Lab			Outcome	
					Bleeding	Hematemesis	melena	Hb	Na	ALT/AST		PTT
2	Propranolol	10 mg/8 h	3	9	✓	✓	✓	↓	n	↑	↑	Good
	Somatostatin	250 mcg/h	3									
	Vitamin K	10 mg/8 h	7									
11	Lactulosa	15 cc/12 h	9	9	✓	✓	✓	↓	n	↑	↑	Good
	Propranolol	10 cc/12 h	7									
	Lactulosa	15 cc/12 h	6									
19	Somatostatin	250 mcg/h	8	8	✓	✓	✓	↑	n	↑	↑	Good
	Propranolol	20 mg/12 h	8									
	Lactulosa	10 cc/24 h	7									

Ket :
 (✓) = Yes, (-) = No, (↑) = Increases, (↓) = Decreases,
 (n) = Normal, LOLA = (L-ornithine L-aspartate)

Table 3 shows that the therapy received by patients with esophageal varices complicates maximum efficacy by improving the parameters and condition of the patient. The most combination therapy is propranolol + lactulose + vitamin K (50%). A meta-analysis study, of 11 trials involving 1,189 patients evaluating non-selective β blockers (propranolol, nadolol) versus placebo in preventing varicose veins showed, the risk of bleeding was reduced with nonselective β blockers. Lower mortality in the β blocker group compared to the control group and this difference has been shown to be statistically significant. Nonselective β Blockers (propranolol, nadolol) can also reduce portal pressure by reducing cardiac output and producing splanchnic vasoconstriction, thereby reducing portal blood flow [16]

Table 4. Profile of therapeutic efficacy in ascites complications

No. Pasien	Terapi	Dosis dan Frekuensi	Lama Pemberian	Lama Rawat Inap	Parameter		Data Laboratorium			Status
					Penurunan BB	Penurunan Lingkar Perut	Penurunan Seseak & Tegang Perut	Alb	Na	
1	Spirolonaktone	50 mg/12 jam	13 hari	13 hari	✓	✓	✓	↓	↓	Memb.
	Furosemid	1 amp/12 jam 1 tab/24 jam	1 hari 12 hari							
6	Spirolonaktone	50 mg/12 jam	4 hari	4 hari	-	-	-	↓	n	Mening
	Furosemid	1 amp/12 jam	4 hari							
23	Albumin	100 ml/hari	1 hari	9 hari	✓	✓	✓	↓	n	Memb.

Ket :
 (✓) = Yes, (-) = No, (↑) = Increases, (↓) = Decreases,
 (n) = Normal

In the case of complications of ascites, lactulose is not given to patients, because the goal of therapy is to balance sodium and kidney retention, namely by reducing sodium intake in food and increasing sodium excretion by the kidneys with diuretic treatment [17]. Patients with complications

*Corresponding author: pradiftha@uii.ac.id

of ascites 66.67% gave a response in the form of improvement of the condition during hospitalization with the most widely used therapies were spironolactone, furosemide, and albumin.

Table 5. Profile of therapeutic efficacy on Hepatic Complications of Encephalopathy and Esophageal Varices

No. Pasien	Terapi	Dosis dan Frekuensi	Lama Pemberian	Lama Rawat Inap	Parameter						Data Laboratorium			Status		
					Perbaikan Ritme Tidar	Perbaikan Status Mental	Pengurangan Gatal	Peningkatan Kesadaran	Penurunan BB	Penurunan Lingkar Perut	Penurunan Seseak & Tegang Perut	Na	Alb		BB total	BB direct
26	Laktulosa	15 cc/8 jam	6 hari	13 hari	✓	✓	✓	✓	✓	✓	✓	✓	↓	↓	n	Memb.
	LOLA	1 sac/8 jam	8 hari													
	Vitamin K	1 amp/8 jam	13 hari													

Ket :
 (✓) = Yes, (-) = No, (↑) = Increases, (↓) = Decreases,
 (n) = Normal

HE case complications of esophageal varices with lactulose therapy and LOLA aim to inhibit the production and absorption of ammonia in the intestine, and increase drug elimination through feces. The use of vitamin K on the first to the 13th day aims to stop bleeding from esophageal varices [18].

Table 6. Profile of therapeutic efficacy in Hepatic Complications of Encephalopathy and Ascites

No. Pasien	Terapi	Dosis dan Frekuensi	Lama Pemberian	Lama Rawat Inap	Parameter						Data Laboratorium			Status		
					Perbaikan Ritme Tidar	Perbaikan Status Mental	Pengurangan Gatal	Peningkatan Kesadaran	Penurunan BB	Penurunan Lingkar Perut	Penurunan Seseak & Tegang Perut	Na	Alb		BB total	BB direct
22	Laktulosa	15 cc/8 jam	5 hari	6 hari	-	-	-	-	-	-	-	-	↓	↓	n	Meninggal
	LOLA	1 sac/8 jam	5 hari													
	Spirolonaktone	50 mg/12 jam	5 hari													
	Furosemid	1 amp/24 jam	5 hari													

Ket :
 (✓) = Yes, (-) = No, (↑) = Increases, (↓) = Decreases,
 (n) = Normal

Cases of HE complications and ascites do not show lactulose has efficacy against repairing complications. Day 5 treatment of patients experienced repeated blood vomiting averaging 1 cup. On day 6, the pulse is weak, the patient has a coma, spontaneous breathing stops. The patient was declared dead due to hepatic complications of encephalopathy.

Table 7. Profile of therapeutic efficacy in Hepatic Complications of Encephalopathy and Hepatorenal Syndrome

No. Pasien	Terapi	Dosis dan Frekuensi	Lama Pemberian	Lama Rawat Inap	Parameter						Data Laboratorium			Status		
					Perbaikan Ritme Tidar	Perbaikan Status Mental	Pengurangan Gatal	Peningkatan Kesadaran	Peningkatan Volume Urine	Na	Alb	BB total	BB direct		Kreatinin	
3	Laktulosa	30 ml/8 jam	7 hari	7 hari	-	-	-	-	-	-	-	-	↑	↑	Meninggal	
	Albumin	100 ml/hari	1 hari													
12	Laktulosa	15 cc/12 jam	8 hari	6 hari	-	-	-	-	-	-	-	-	↑	↑	↑	Meninggal
	Albumin	100 ml/hari	4 hari													
16	Laktulosa	15 cc/8 jam	8 hari	8 hari	-	-	-	-	-	-	-	-	↓	↓	↑	Meninggal
	Albumin	100 ml/hari	3 hari													

Ket :
 (✓) = Yes, (-) = No, (↑) = Increases, (↓) = Decreases,
 (n) = Normal

Complications of hepatorenal syndrome are supported by complaints of patients who claim to urinate rarely and little. Recommendations for the 2012 American Association for the Study of Liver Diseases (AASLD), albumin infusion has been shown in a randomized study to prevent HRS and improve survival in SBP [19].

Table 8. Profile of therapeutic efficacy on Esophageal Varices Complications and Portal Hypertension

No. Pasien	Terapi	Dosis dan Frekuensi pemberian	Lama pemberian	Lama Rawat Inap	Parameter			Data Laboratorium							Status
					Penurunan Perdarahan Berulang	Penurunan Muntah Darah	Penurunan Berat Darah	Hb	Na	SGOT	SGPT	PPT	TD		
2	Propranolol	10 mg/8 jam	3 hari	9 hari	✓	✓	✓	↓	n	↑	↑	↑	n	Membaik	
	Somatostatin	250 mcg/jam	3 hari												
	Laktulosa	15 cc/12 jam	7 hari												
4	Vitamin K	10 mg/8 jam	9 hari	9 hari	✓	✓	✓	↓	n	↑	↑	↑	n	Membaik	
	Propranolol	10 mg/8 jam	7 hari												
	Somatostatin	250 mcg/jam	6 hari												
21	Propranolol	20 mg/12 jam	8 hari	8 hari	✓	✓	✓	↑	n	n	n	↑	n	Membaik	
	Laktulosa	10 cc/24 jam	7 hari												

Ket :
 (✓) = Yes, (-) = No, (↑) = Increases, (↓) = Decreases,
 (n) = Normal

Based on Table 8, therapy in 3 cirrhotic patients with complications of esophageal varices and portal hypertension provides 100% efficacy with propranolol and lactulose therapy. Propranolol is safe and effective for reducing portal pressure in cirrhosis patients, according to the complaints of patients at the hospital where the study [20]. Somatostatin is given in empirical doses as an effort to reduce portal pressure quickly, thereby reducing the risk or stopping the patient's bleeding. This study has limitations, the efficacy is monitored based on the parameters of clinical condition improvement, and there is no monitoring related to drug interactions and side effects so that further research is needed with other parameters. The results of the study can only be applied to research locations due to the limited number of samples involved.

4. Conclusion

The combination of Lactulose with propranolol provides 100% efficacy in variations in esophageal vaccine and portal esophageal portal hypertension. The combination of lactulose, LOLA, vitamin K has 100% efficacy in repairing esophageal

varices. The combination of Lactulose and propranolol has a 100% efficacy on the portal of esophageal varices and hypertension

References

- [1] J. Sease, E. Timm and J. Stragand, "Cirrhosis and Portal Hypertension. In: Dipro. Pharmacotherapy A Pathophysiologic Approach," 8th Edition. USA: McGraw Hill Companies Inc. Section 5 Chapter 21, 2011.
- [2] Anonim, "Profil kesehatan provinsi DIY 2008," Dinas Kesehatan Provinsi DIY, Yogyakarta, 2009.
- [3] Karina, "Faktor Risiko Kematian Penderita Sirosis Hati Di RSUP Dr. Kariadi Semarang Tahun 2002-2006 [skripsi]," Semarang, 2007.
- [4] L. Fitriyani, "Kesesuaian Pemilihan Obat pada Pasien Sirosis Hepatik di RSUP Dr. Sardjito Yogyakarta Tahun 2008 [skripsi]," Universitas Islam Indonesia, Yogyakarta., 2010.
- [5] M. Charles Trey and W. V. McDe, "Lactulose Treatment of Hepatic Encephalopathy in Outpatients," JAMA, 2018.
- [6] J. Boursier, E. Cesbron, A. Tropet and C. Pilette, "Comparison and Improvement of MELD and Child-Pugh Score Accuracies for the Prediction of 6-month Mortality in Cirrhotic Patients.," *J Clin Gastroenterol*, vol. 43, p. 580–585, 2009.
- [7] H. Vilstrup, P. Amodio, J. Bajaj and J. Cordoba, "Hepatic Encephalopathy in Chronic Liver Disease," *Practice Guideline by AASLD and EASL-Hepatology*, 2014.
- [8] Y. Z. Patasik, B. J. Waleleng and F. Wantania, "2015 PROFIL PASIEN SIROSIS HATI YANG DIRAWAT INAP DI RSUP PROF. DR. R. D. KANDOU MANADO PERIODE AGUSTUS 2012 –AGUSTUS 2014," *Jurnal e-Clinic (eCl)*, vol. 3, no. 1, Januari-April 2015.
- [9] J. Poo , L. Gongora and F. Avila, "Efficacy of Oral L-Ornithinr-L-Aspartate in Cirrhotic Patients with Hyperammonemic Hepatic Encephalopathy, Result of Randomized, Lactulose-Controlled Study," *Annals of*

*Corresponding author: pradiftha@uui.ac.id

- Hepatology J.*, vol. 5, no. 4, pp. 281-288, 2006.
- [10] Perhimpunan Peneliti Hati Indonesia, Panduan Praktik Klinik Penatalaksanaan Ensefalopati Hepatik di Indonesia, Jakarta, 2014, pp. 1-28.
- [11] R. F. Butterworth and K. Gruengreiff, "L-Ornithine L-Aspartate (LOLA) for the Treatment of Hepatic Encephalopathy in Cirrhosis: Evidence for Novel Hepatoprotective Mechanisms," *Journal of Liver and Clinical Research*, vol. 5, no. 1, p. 1044, Februari 2018.
- [12] Q. Jiang, X.-H. Jiang and M.-H. Zheng, "L-Ornithine-L-aspartate in the management of hepatic encephalopathy: A meta-analysis," *Journal of Gastroenterology and Hepatology*, Vols. 24(1):9-14, 2008.
- [13] H. Xiao-wu, "Effect of L-ornithine-L-aspartate combined with lactulose in the treatment of patients with hepatic encephalopathy after hepatic cirrhosis.," *Anhui Medical and Pharmaceutical Journal*, 2010.
- [14] G. Garcia-Tsao, A. Sanyal, Grace ND and W. Carey, "Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis," *Hepatology Journal*, vol. 46(3), pp. 922-938, 2007.
- [15] B. Runyon, "Management of Adult Patients with Ascites Due to Cirrhosis : Update 2012 AASLD Practice Guideline," *Hepatology*, 2013.
- [16] T. Chen, G. Lo, K. Lai and W. Lin, "Single daily amikacin versus cefotaxime in the short-course treatment of spontaneous bacterial peritonitis in cirrhotics.," *World J Gastroenterol*, vol. 11 (43), pp. 6823-6827, 2005.
- [17] R. W. Triningtyas, C. P. Sari and N. Setyaningrum, "EVALUASI TERAPI PADA PASIEN HEPATITIS B DI RSUP Dr.SARDJITO YOGYAKARTA," *Jurnal Ilmiah Farmasi*, pp. 29-34, 2017.
- [18] K. T. Suk, M. Y. Kim, D. H. Park and K. Ho, "Effect of Propranolol on Portal Pressure and Systemic Hemodynamics in Patients with Liver Cirrhosis and Portal Hypertension: A Prospective Study," *Jurnal Gut and Liver*, vol. 1, no. 2, pp. 159-164, 2007.
- [19] S. Nurdjanah, Buku Ajar Ilmu Penyakit Dalam, Jakarta: Pusat Penerbitan Departemen Penyakit Dalam Fakultas Kedokteran Universitas Indonesia, 2009, pp. 668-673.
- [20] G. Garcia-Tsao MD and A. J. Sanyal, "Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis," *The American Journal of Gastroenterology*, vol. 102, p. 2086–2102, 2007.