Research Article

Safety Profile Assessment of Propranolol Prophylactic Pharmacotherapy for Portal Hypertension in Liver Cirrhosis Patients with Different Child Pugh Class

Anuja sasidharan[1*], Siby joseph[2] and Rajesh G[3]

[1]Department of pharmacy practice, Amrita school of pharmacy, Kerala, India.

[2]Department of pharmacy practice, St. Joseph College of pharmacy, cherthala, Kerala, India.

[3]Department of Gastroenterology, Amrita institute of medical sciences,

Amrita viswavidyapeetham University, AIMS cochin campus, Kerala, India.

ABSTRACT

Background: Propranolol has been established in numerous studies as cornerstone of primary and secondary prophylaxis of portal hypertension. Our study aimed to analyse dosage and safety profile of propranolol in different child Pugh classes of cirrhosis. **Methods:** A prospective observational study for one year was conducted in gastroenterology department of tertiary care hospital .Admitted patients with age ≥18 years and on propranolol for prophylaxis of portal hypertension was included after getting consent from patients or care givers. Patients discharged against medical advice were excluded. Patient's demographic details, pertinent laboratory investigations and treatment details were collected by reviewing treatment charts and direct interaction with patient /caregivers and healthcare providers. **Result:** Out of 202 patients studied, majority were in age group 49-58 years with male preponderance (89.6%). De-prescribing of propranolol required in 32 patients but Propranolol induced ADR occurred in 14 patients. Majority de-prescribing occurred in Child Pugh Class C (62.5%) followed by class B ((31.25%). Commonly observed reasons were breathing difficulty (37.5%) elevation of serum creatinine (28.12%), spontaneous bacterial peritonitis (21.88%), hypotension (6.25%) and refractory ascites (6.25%). Statistical significant association exists between De-prescribing and Child Pugh class C (p value=0.009).ADR based on WHO-SOC and Causality assessment by Naranjo ADR probability scale shown majority as respiratory thoracic and mediastinal disorders (85.71%), 12 as probable and 2 possible respectively. **Conclusion:** The study suggests that propranolol can be safely used in cirrhosis patients within a particular clinical window. Outside this window it causes deleterious effects. The risk/benefit ratio of therapy varies according to stages of cirrhosis, unfavourable in patients with most advanced stage.

Keywords: Portal hypertension, propranolol, De-prescribing.

INTRODUCTION

Cirrhosis and chronic liver failure are leading causes of morbidity and mortality with the majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis, or non-alcoholic fatty liver disease.[1] The severity of cirrhosis is important to assess because it serves as a predictor of patients survival, surgical outcomes and the risk of complications such as variceal bleeding. Assessment tool commonly used in cirrhosis patient includes Model for End stage liver disease (MELD), which has score ranging from 0-40, and the Child Pugh classification system. The Child Pugh score is used to group the patients into three categories 1) Class A score of less than 7 (Mild disease) 2) Class B score of 7-9(moderate disease), Class C score of 10-15 (severe disease).[2]

Cirrhosis often is an indolent disease; most patients remain asymptomatic until the occurrence of decompensation, characterized by ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, or variceal bleeding from portal hypertension.[1] Portal hypertension is the main cause of morbidity and mortality in patients with cirrhosis.[1,2] It is a common clinical

syndrome, which is hemodynamically defined by a pathological increase of the portal pressure gradient and by the formation of portal–systemic collaterals that shunt part of the portal blood flow to the systemic circulation bypassing the liver. Normal values of the portal pressure gradient are of 1–5 mm Hg.[3] When the portal pressure gradient (estimated by the hepatic venous pressure gradient or HVPG) increases to 10 mmHg or more, the cirrhotic patient is at risk of decompensation. Thus, an HVPG ≥10 mmHg defines the presence of clinically significant portal hypertension (CSPH).[4]

Portal hypertension, major complication of cirrhosis is responsible for complications such as massive gastrointestinal bleeding (oesophageal or gastric varices), ascites, hepatorenal syndrome, and hepatic encephalopathy.[5] Variceal bleeding is the most dreaded complication of portal hypertension. It may occur once the portal-systemic gradient increases above 12 mm Hg, occurs in 30% of patients with cirrhosis, and carries a 30-day mortality of 20%.[6]

Hepatic encephalopathy also referred as porto-systemic encephalopathy, is a syndrome of neuropsychiatric abnormality caused by acute or chronic hepatic insufficiency. It affects about 30-45% of patients with cirrhosis.[7] Agents used in treating hepatic encephalopathy include non-absorbable disaccharides (lactulose and lactitol) and antibiotics (rifaximin, neomycin and metronidazole), with lactulose and rifaximin being the most common.[2]

Because of the high mortality and morbidity of variceal bleeding, primary prevention of bleeding is a major goal in the management of portal hypertension, which in turn depends on the phase of portal hypertension at which the patient is situated.[6] The prevention of variceal bleeding is categorised into primary and secondary prophylaxis. For primary prophylaxis patients are classified as having highest risk of variceal bleeding when they are presented with medium/large varix, red wale marks on varix and Child Pugh class C. Patients with lowest risk of variceal bleeding include those with no varices where it is not recommended to give beta blockers prophylaxis. [2] In primary prophylaxis, patients with high risk small varices or large/medium varices should receive primary prophylaxis either with non selective beta blocker(NSBB) or with endoscopic band ligation if they are contraindicated to NSBB. For secondary prophylaxis the current recommendation is to receive a combination of NSBB and endoscopic variceal ligation.[8]

Non selective betablockers are more effective than selective beta blockers in preventing variceal bleeding because of their beta1 and beta2 antagonistic properties. Propranolol and nadalol with beta 1 and beta 2 antagonistic properties were the most commonly used NSBB for the prophylaxis of variceal bleeding .Carvedilol a NSBB with alfa 1 adrenergic blocking activity has a potent hypotensive effect which is superior to propranolol.[9]

The advantage of using NSBBs must be weighed against the risks associated with their chronic use.[10] NSBBs are contraindicated in patients with refractory asthma, severe COPD, advanced atrio-ventricular block, and severe arterial hypotension. The adverse effects associated with NSBBs such as bronchospasm, hypotension, light headedness ,fatigue, impotence and sleep disorders requires early recognition and discontinuation of the drug.[11] NSBB can be started only to the patient that can be properly followed in terms of blood pressure and frequent blood test (at least weekly during titration).Discontinuation of the therapy is needed if systolic blood pressure decreases below 95 mmHg, if the patient experiences orthostatic symptoms, or if there is an increase in creatinine. Septic episodes also requires discontinuation of NSBBs.[4]

METHODOLOGY

A prospective observational study was conducted in the gastroenterology department of a tertiary care teaching hospital, South India for a period of 1 year. Patients with age ≥18 years and on propranolol for the prophylactic treatment of Portal hypertension were included in the study after getting consent from the patient or care givers. Patients who got discharged against medical advice were excluded from the study. All patients who met inclusion criteria were intensively monitored from the first day of admission till discharge on a daily basis. Patient's demographic details, medical history, relevant laboratory investigations and treatment details were collected by reviewing medical charts, and by interviewing patient or care givers and direct interaction with health care providers. The data were transcribed into a specially designed data collection form. Adverse events were closely monitored and classified based on WHO –System Organ Classification. Causality assessments of ADR were carried out using Naranjo ADR probability scale.

RESULT

A total of 202 cases were selected as study sample. Majority of patients were in the age group of 49-58 years (32.17%).Mean age in the group was 55.93±11.23. There exists a male preponderance in the sample population (89.6%). Among the study population 67(33.17%) patients were alcoholic and 87(43.07%) were ex-alcoholic. Majority of the populace had history of cirrhosis (80.69%). The comorbid condition predominated in the subjects were diabetes mellitus in 108 patients (53.46%) followed by hypertension in 45 patients (22.27%).

The most common etiology found was alcohol in 146 patients (72.27%) followed by Cryptogenic in 36 patients (17.82%).

The demographic detail, comorbidities and etiology of cirrhosis in study population were assessed and the results are depicted in table 1.

Table 1: Demographic details, comorbidities and etiology of study subjects

Characteristics	No: of patients
Female sex	21
Male sex	181
Alcoholic status	
Alcoholic	67
Ex-alcoholic	87
Co-morbidities	
CLD	163
Diabetes Mellitus	108
Hypertension	45
COPD	6
Epilepsy	3
Etiology	
Alcohol	146(72.27)
Cryptogenic	36(17.82)
Hepatitis	13(6.44)
Hepatitis B	7
Hepatitis C	6
NASH	7(3.47)

The correlation of complications of cirrhosis with different Child Pugh Classes were illustrated in table 2. Complications esophageal varices (45.66%), fundal varices (42.86%), portal hypertensive gastropathy (45.33%), duodenopathy(48.39%) and upper gastrointestinal bleed(50%) were higher in Child Pugh class B with an average MELD Score of 15.64±3.44, 14.5±3.58, 15.68±3.65, 15.93±3.61 and 15.03±3.44 respectively. Statistical validation done by Pearson Chi-square test verifies statistical significant association of fundal varices (p=0.05) and upper gastrointestinal bleed (p<0.05) with Child Pugh class B. However ascites (55.66%), hepatic encephalopathy (72.09%), spontaneous bacterial peritonitis (78.57%), hepatorenal syndrome (82.35%), acute kidney injury (58.33%) and lower gastrointestinal bleed (66.67%) were higher in Child Pugh class C with mean MELD score 22.75±5.41, 22.71±6.56, 21.09±5.61, 25.21±6.15, 21.71±5.47 and 20.25±4.57 respectively. Statistical analysis shown significant association of ascites(p<0.001), hepatic encephalopathy (p<0.001), spontaneous bacterial peritonitis (p=0.006) and hepatorenal syndrome (p<0.001) with Child Pugh class C. Complication Gastric antral vascular ectasia were more in Child Pugh Class A(45.56%) (p value <0.05) having mean MELD score of 13±4.06.

Reasons for the upper gastrointestinal bleeding was assessed and demonstrated in Table 3. Out of 56 patients with bleeding, esophageal varices were the most commonly found etiology in 27 subjects (48.21%) followed by portal hypertensive gastropathy in 11 subjects (19.64%). Other reasons for bleeding observed were gastric variceal bleeding (16.07%), duodenal ulcer (3.57%), post EVL ulcer (8.93%), Glue injection ulcer (1.79%) and Gastric antral vascular ectasia (1.79%).

Majority of patients were prescribed propranolol for secondary prophylaxis (55.94%). Most commonly prescribed daily dose for both primary and secondary prophylaxis was 40mg in 75(84.26%) and 101 (89.38%) subjects respectively followed by 20mg in 24(11.88%) subjects (Table 4).

Table 5 illustrates the reasons for de-prescribing of propranolol in different Child Pugh Classes. Majority de-prescribing occurred in Child Pugh Class C (62.5%) followed by class B ((31.25%). Most commonly observed reasons for de-prescribing were breathing problem (37.5%) followed by elevation of serum creatinine (28.12%). Other reasons include spontaneous bacterial peritonitis (21.88%), hypotension(6.25%) and refractory ascites(6.25%). Statistical analysis show significant association between De-prescribing and Child Pugh class C (p value=0.009).

Distribution of adverse drug reaction based on WHO-System Organ Classification of adverse events were tabulated in table 6. Majority of adverse events were in the category respiratory thoracic and mediastinal disorders (85.71%) and the rest were in cardiac disorders category (14.29%).

Table 7 represents the causality assessment of adverse drug reaction based on Naranjo ADR probability scale. Out of 14 ADR observed 12(85.71%) were probable and 2(14.29%) were possible.

Table 8 summarizes the duration of propranolol treatment. Out of 202 subjects majority of patients were on propranolol for more than 1 years (51.98%). And propranolol induced side effects were also more in this group.

Table 2: Correlation of complications with different Child Pugh Classes

Complications	#	CPS A (n=35)	Mean MELD score	CPS B (n=88)	Mean MELD score	CPS C (n=79)	Mean MELD score
EV* grade1	71	11 (15.49%)	11.64± 3.11	32 (45.07%)	16.81± 2.91	28 (39.44%)	22.71± 4.34
EV* grade2	85	15 (17.65%)	10.53± 2.26	40 (47.06%)	14.4± 3.27	30 (35.29%)	21.7± 5.56
EV* grade3	14	3 (21.43%)	9.67± 1.15	7 (50%)	17.43± 4.39	4 (28.57%)	22± 8.25
EV* grade4	3	0	0	0	0	3 (100%)	18
FV*	28	9 (32.14%)	10.67± 1.41	12 (42.86%)	14.5± 3.58	7 (25%)	20.43± 4.79
PHG*	150	24 (16%)	11.08± 2.30	68 (45.33%)	15.68± 3.65	58 (38.67%)	22.22± 4.63
Duodenopathy	31	5 (16.13%)	12.6± 3.78	15 (48.39%)	15.93± 3.61	11 (35.48%)	22.45± 3.29
HRS*	17	0	0	3 (17.65%)	16.33± 2.08	14 (82.35%)	25.21± 6.15
SBP*	14	0	0	3 (21.43%)	14.67± 7.37	11 (78.57%)	21.09± 5.61
AKI*	12	0	0	5 (41.67%)	19± 1.73	7 (58.33%)	21.71± 5.47
GAVE*	11	5 (45.56%)	13± 4.06	3 (27.27%)	16.33± 4.93	3 (27.27%)	24.67± 5.03
Ascites	106	2 (1.89%)	10.5± 2.12	45 (42.45%)	15.11± 2.85	59 (55.66%)	22.75± 5.41
HE*	43	1 (2.33%)	11	11 (25.58%)	15.09± 2.12	31 (72.09%)	22.71± 6.56
UGI bleed*	56	18 (32.14%)	10.89± 2.87	28 (50%)	15.03± 3.44	10 (17.86%)	21.8± 5.43
LGI bleed*	6	0	0	2 (33.33%)	17	4 (66.67%)	20.25± 4.57

#*- No: of patients, EV*- Esophageal varices, FV*- Fundal varices, PHG*- Portal hypertensive gastropathy, HRS*- Hepatorenal syndrome, SBP*- Spontaneous bacterial peritonitis, AKI*Acute kidney injury, GAVE*- Gastric antral vascular ectasia, HE*- Hepatic encephalopathy, UGI bleed*-Upper gastrointestinal bleed, LGI-bleed*-Lower gastrointestinal bleed

Table 3: Reasons for the upper gastrointestinal bleeding in the study population

Reasons	No: of subjects
Grade 2 esophageal varices	21
Grade 3 esophageal varices	6
Severe Portal hypertensive gastropathy	11
Gastric variceal bleeding	9
Duodenal ulcer	2
Post EVL ulcer	5
Glue injection ulcer	1
Gastric Antral Vascular Ectasia	1
Total	56

Table 4: The dosage profile of propranolol for the prophylactic treatment of portal hypertension in the study subjects

Prophylactic treatment	No: of subjects	Dose /day of the drug			
		10mg	20mg	40mg	80mg
Primary prophylaxis	89	1	12	75	1
Secondary prophylaxis	113	0	12	101	0

Table 5: Reasons for de-prescribing of propranolol in different Child Pugh Classes

Reasons for De-Prescribing	No. of subjects	Different Child Pugh Classes		
		A	B	C
Breathing difficulty	12	2	6	4
High serum creatinine	9	0	2	7
Spontaneous bacterial peritonitis	7	0	1	6
Hypotension	2	0	0	2
Refractory ascites	2	0	1	1

Table 6: Distribution of ADR based on WHO-System Organ Classification of adverse events

SOC-ID	SOC-Criteria	No(%) of ADRs(n=14)
13	Respiratory thoracic and mediastinal disorders	12(85.71%)
11	Cardiac disorders	2(14.29%)

Table 7: Causality assessment of ADR based on Naranjo ADR probability scale

ADR probability	No: of ADR in study population (n=14)
Definite	0
Probable	12
Possible	2
Doubtful	0

Table 8: Duration of propranolol treatment

Duration	<3months (n=25)	3-6months (n=23)	6-9months (n=29)	9-12 months (n=20)	>1 year n=(105)
No: of patients	24	23	25	19	97
No: of patients with propranolol induced side effects	1	0	4	1	8

DISCUSSION

The demographic assessment of 202 patients enrolled in the study revealed that aged population (49-58 years) were more affected by cirrhosis and there was a marked male predominance which could be possibly explained by the greater presence of alcoholism among them. A study conducted by **R maskey et al**[12] to assess the clinical profile of patients with cirrhosis in a tertiary care teaching hospital showed a result comparable with age and gender distribution as that of our patients

In our study, alcohol related cirrhosis (72.27%) was found to be the most common etiology followed by Cryptogenic etiology, Hepatitis and NASH. A study conducted by **Patricia Lofego Goncalves et al**[13] in Brazil also reported alcoholism as the main reason for cirrhosis. In contrast, a study conducted in the hepatology department of tertiary care centre South India by **Ashish Goel et al**[14] reported that Cryptogenic etiology was the most commonest cause identified followed by alcohol or hepatitis B.

Among the study population majority of patients were coming under Child Pugh class B (43.56%) followed by class C (39.11%). Only 17.33% were found in Child Pugh class A. This observation

slightly varies from the prospective study conducted by **Marchesini G, Bianchi G**[15] et al which shown 38% of patients each in both class B and A and 24% in Child Pugh class C. The slighter change in proportion in different classes in our study may be due to variation in selection of subjects. Those patients who are on propranolol for the prophylactic treatment of portal hypertension were included in the study and lesser proportion were found in Child Pugh class A as risk benefit ratio was more in this class.

Cirrhosis patients are at a risk of developing complication that can negativety affect their survival. The incidence of complications increases with the severity of the diseases. But a significant percentage of Child Pugh class B patients had cirrhosis complications. In the study esophageal varices one of the main complication of portal hypertension were mostly seen in Child Pugh class B (45.66%).Similar results were obtained in an Endoscopic screening study for varices in cirrhosis patients conducted by **Kovalak M et al**[16], and concluded that the presence of varices was higher in Child Pugh Class B/C compared to Child Pugh class A patients.

The presence of Portal hypertensive gastropathy was associated with severity of liver disease and commonly occurred in patients with varices. **Merli M et al**[17] under taken a study to determine natural history of portal hypertensive gastropathy in cirrhosis patients with portal hypertension. They found that the presence of esophageal varices and Child Pugh B/C at enrollment was predictive of the incidence of portal hypertensive gastropathy. Our study results are similar to this study.

According to the **AASLD guidelines**[18], approximately 50% of the patients with cirrhosis will develop ascites during 10 year follow up. Our study accounts for 52.47% of study population with ascites. Majority (55.66%) were in Child Pugh class C (p<0.001). Other main complication of cirrhosis is hepatic encephalopathy which occurred in 43 patients (21.29%) and majority of them were in Child Pugh class C (72.09%) (p<0.001).

In this study out of 106 patients with ascites, only 14 developed SBP and majority were in Child Pugh class C (78.57%)(p=0.006). The studies conducted by **Syed VA et al**[19]**and Kavita Paul**[20] et al on the Spontaneous bacterial peritonitis in cirrhosis patients with ascites reported that occurrence of SBP is 24.69% and 20.4% and majority were in the Child Pugh class C 85% and 70% respectively. The prevalence depends on the severity of the liver dysfunction, being higher in advanced cirrhosis. The reason for the lower incidence of SBP in our study while comparing with other studies is that the most patients with severe liver disease were not on study drug.

A prospective study under taken by **Daniela et al**[21] reported gastrointestinal bleeding in 55% cirrhosis patients and majority (57.89%)were in Child Pugh class B with p value <0.05 . In our current study 27.72% cirrhosis patients had upper gastrointestinal bleeding in which 50% were in class B.

The reasons for the upper Gastrointestinal bleeding were analyzed and came in to a conclusion that majority of bleeding were due to the esophageal varices (48.21%) followed by severe portal hypertensive gastropathy (19.64%). **Anca alexander romcea**[22] et al conducted a study to evaluate the etiology of upper gastrointestinal bleed in patients with cirrhosis. Their observation was upper GI bleed occurred in 73% due to variceal bleeding and rest 27% due to non variceal digestive hemmorhage. A similar study conducted by **Svoboda et al**[23]**, Olajide O Odelowo et al**[24] also pointed esophageal varices as the major bleeding reason 57.7%, 50%, respectively.

While analyzing the daily dose of the propranolol majority of the patients were having 40mg (87.12%) dose followed by 20mg (11.8%). Most commonly prescribed dose was 20 mg twice daily. A study on the pharmacology of propranolol in cirrhosis patients by **MJ PArther**[25] et al highlights the importance of initiating treatment with a lower dose because of the abnormal pharmacokinetics and excessive effects of the drug according to the severity of liver diseases.

De-prescribing of propranolol in different Child Pugh classes due to various reasons were also analyzed in our study. Majority of de-prescribing occurred in Child Pugh class C (62.5%) (p =0.009) when compared to B (31.25%) mainly due to the safety issues occurred by NSBBs in advanced stage of cirrhosis. The adverse effects like breathing difficulty and hypotension accounted for 37.5% and 6.25% of de-prescribing respectively. The remaining de-prescribing occurred due to the Spontaneous bacterial peritonitis (21.88%), high serum creatinine (28.12%) and refractory ascites (6.25%).

Mattias Mandorfer et al[26] investigated a retrospective study assessing the safety of

NSBBs in patients with SBP. Their observation was higher proportion of patients with SBP on NSBBs had increased risk of development of hepatorenal syndrome(24%) and acute kidney injury(20%) compared to those with out on NSBBs. **Thomas Serte et al**[27] conducted a study to evaluate the negative effect of non-selective beta blocker in patients with refractory ascites. They concluded that non-selective beta blockers are associated with poor survival in patients with refractory ascites. Both the studies are supporting the necessity for the de-prescribing of propranolol in patients with SBP, HRS and refractory ascites.

Adverse drug reaction of the drug propranolol were assessed and categorized based on the WHO-System Organ Classification. Majority of the adverse drug reactions were in respiratory disorders (85.71%) and rest were in cardiac disorders (14.29%). The causality assessment of adverse drug reaction based on the Naranjo probability scale illustrated that out of 14 ADR found 12 were probable and 2 in the possible category.

A study carried out by **Jean –Pierre et al**[28] determined the incidence of the adverse effects in patients treated with propranolol and reported that out of 17% patients with ADR, 11% required withdrawal of the drug. In our study side effects occurred in 7% of patients and led to the stopping of propranolol.

CONCLUSION

Even though propranolol has been established in numerous studies as cornerstone of primary and secondary prevention of portal hypertension and variceal haemorrhage it can be safely used in a particular clinical window only. The beneficial window of propranolol opened by the first appearance of esophageal varices at the risk of bleeding and would be closed by the development of refractory ascites or other severe complications like spontaneous bacterial peritonitis (SBP) / Hepatic renal syndrome (HRS)– the clinical hall mark of advanced liver diseases . The average daily dosage of Propranolol prescribed in our center for this indication was found to be 40mg.

REFERENCES

1. Heidelbaugh JJ and Bruderly M. Cirrhosis and Chronic Liver Failure: Part1.Diagnosis and evaluation. American Family Physician. 2006; 74: 756-62.
2. Mohammad RA. Gastroenterology and Nutrition. Complication of Chronic Liver Disease; PSAP. VII: 91-103.
3. Bosch J, Berzigotti A, Garcia-Pagan JC and Abraldes JG. The management of portal hypertension: Rational basis, available treatments and future options. J Hepatol. 2008; 48: S68–S92.
4. Abraldes JG and Tandon P. The Use of Beta-Blockers in Advanced Cirrhosis—Where Do We Stand?. Curr Hepatology Rep. 2015; 14: 46-52.
5. Samonakis DN, Triantos CK, Thalheimer U, Patch DW and Burroughs AK. Management of portal hypertension. Postgrad Med J. 2004; 80: 634– 41.
6. Wright AS and Rikkers LF. Current Management of Portal Hypertension. J Gastrointest surg. 2005; 9: 992-1005.
7. Bleibel W and Al-Osaimi AMS. Hepatic Encephalopathy. The Saudi Journal of Gastroenterology. 2012; 18: 301-9.
8. Giannelli V, Lattanzi B, Thalheimer U and Merlia M. Beta-blockers in liver cirrhosis. Annals of Gastroenterology. 2014; 27: 20-26.
9. Banares R, Moitinho E, Matilla A et al. Randomized comparison of Long-Term Carvedilol and Propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatology. 2002; 36: 1367-73.
10. Wong F and Salerno F. Beta-Blockers in Cirrhosis: Friend and Foe?. Hepatology. 2010; 52: 811-13.
11. Douglas A. Simonetto, Vijay H. Shah, MD and Patrick S. Kamath. Primary Prophylaxis of Variceal Bleeding. Clin Liver Dis. 2014. 18 : 335–345.
12. Maskey R, Karki P, Ahmed SV and Manandhar DN. Clinical profile of patients with cirrhosis of liver in a tertiary care hospital, Dharan, Nepal. Nepal Med Coll J. 2011; 13: 115-8.
13. Goncalves PL, da Penha Zago-Gomes M, Marques CC, Mendonca AT, Goncalves CS and Pereira FEL. Etiology of liver cirrhosis in Brazil: chronic alcoholism and hepatitis viruses in liver cirrhosis diagnosed in the state of Espirito Santo. Clinics. 2013; 68: 291-5.
14. Goel A, Madhu K, Zachariah U et al. A study of aetiology of portal hypertension in adults (including the elderly) at a

tertiary centre in southern India. Indian J of Med Res. 2013; 137(5): 922-27.
15. Marchesini G, Bianchi G, Amodio P et al. Factors associated with poor health–related quality of life of patients with cirrhosis. Gastroenterology. 2001; 120: 170-8.
16. Kovalak M, Lake J, Mattrk N, Eisen G, Liebermann D and Zaman A. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic data base. Gastrointest Endosc. 2007; 65: 82-8.
17. Merli M, Nicolini G, Angeloni S, Gentili F, Attili AF and Riggio O. The natural history of portal hypertensive gastropathy in patients with liver cirrhosis and mild portal hypertension. Am J Gastroenterol. 2004; 99: 1959-65.
18. Garcia-Tsao G, Sanyal AJ, Grace ND and Carey W. The Practice Guidelines Committee of the American Association for the Study of Liver Diseases, the Practice Parameters Committee of the American College of Gastroenterology. Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis. AASLD practice guidelines. Hepatology. 2007; 46: 922-38.
19. Syed VA, Ansari JA, Karki P, Reqmi M and Khanal B. Spontaneous bacterial peritonitis in cirrhotic ascites :a prospective study in a tertiary care hospital, Nepal. Kathmandu Univ Med J. 2007; 5: 48-59.
20. Paul K, Kaur J and Kazal HL. To study the incidence, predictive factors and clinical outcome of spontaneous bacterial peritonitis in patients of cirrhosis with ascites. J Clin Diagn Res. 2015; 9: OC09-OC12.
21. Benedeto –Stojanov D, Nagorni A, Bjelakovic G, Milanovic J and Stojanov D. Predictive factors of bleeding from esophageal varices in patients with liver cirrhosis and portal hypetension. Medicine and Biology. 2006; 13: 164-7.
22. Romcea AA, Tantau M, Seicean A and Pascu O. The etiology of upper gastrointestinal bleeding in cirrhotic patients. Clujul Medical. 2013; 86: 21-23.
23. Svoboda P, Konecny M, Martinek A, Hrabovsky V, Prochazka V and Ehrmann J. Acute upper gastrointestinal bleeding in liver cirrhosis patients.Biomed pap Med Fac Univ Palacky Olomouc Czech Repub. 2012; 156: 266-70.
24. Odelowo OO, Smoot DT and Kim K. Upper gastrointestinal bleeding in patients with liver cirrhosis. J Natl Med Assoc. 2002; 94: 712-15.
25. Arther MJP, Tanner AR, Patel C, Wright R, Renwick AG and George CF. Pharmacology of propranolol in patients with cirrhosis and portal hypertension. Gut. 1985; 26: 14-19.
26. Mondorfer M, Bota S, Schwabl P et al. Nonselective Beta blockers increase the risk for Hepatorenal Syndrome and Death in Patients with Cirrhosis and Spontaneous bacterial peritonitis. Gastroenterology. 2014; 146: 1680-90.
27. Serste T, Melot C, Francoz C et al. Deleterious effects of Beta-blockers on survival in patients with cirrhosis and Refractory ascites. Hepatology. 2010; 53: 1071-22.
28. Pascal JP and Cales P. Propanolol in the primary prevention of upper gastrointestinal haemorrhage in patients with cirrhosis of the liver and esophageal varices. N Engl J Med. 1987; 37: 856-61.