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Assessment of clinical practice of secondary prophylaxis for varceal bleeding and prevalence of recurrence, among adult patients in Tikur-Anbesa Specialized Hospital, in Addis Ababa, Ethiopia, 2020.

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AVB	Acute Varceal Bleeding
EBL	Endoscopic Band Ligation
EGD	Esophago Gastric Deodunoscopy
EGV	Esophageal Gastric Bleeding
HVPG	Hepatic Venous Pressure Gradient
MRN	Medical Registration Number
NSBB	Non Selective Beta Blocker
RCT	Randomized Control Trials
TASH	Tikur Anbesa Specialized Hospital
TIPS	Trans jugular Intrahepatic Porto systemic Shunt

Abstract

Background: - Variceal bleeding refers to bleeding due to rupture of varix which is usually found in the esophagus or stomach. Recurrent variceal bleeding is a bleeding episode that occurs after 5th day of initial episode. The approaches to patients who have had first variceal bleeding is controlling the acute bleeding and prevent further re-bleeding. To prevent re-bleeding and mortality, secondary prophylaxis is indicated for all patients. This usually requires repeated variceal band ligation until varices are obliterated and/or nonselective Beta blocker. Failure to apply guideline based clinical practice of secondary prophylaxis will predispose to increased risk of recurrent variceal bleeding, hospitalization and mortality. There is no published data regarding clinical practice of secondary prophylaxis for variceal bleeding and prevalence of recurrence in Ethiopian context.

Objective: - To assess the clinical practice of secondary prophylaxis for variceal bleeding and prevalence of recurrence among adult patients in Tikur Anbesa Specialized Hospital, in Addis Ababa, Ethiopia, 2015-2019.

Methods: - A hospital based cross-sectional study was conducted on 140 adults who had endoscopically confirmed variceal bleeding during 2015-2019. Retrospective data from hospital records including socio-demographic characteristics, clinical and laboratory data and endoscopic results of the patients were collected. EpiData version 4.4.2.1 software was used for data entry and STATA15.1 for analysis. Descriptive data were presented as mean, percentage and standard deviations.

Result: - Propranolol was the main medical treatment given as secondary prophylaxis. Propranolol (96.4%), EVL & propranolol (2.9%), and carvidelol (0.7%) were started before or at discharge. Of these patients 9.4%, 11.5%, 20.2% and 28.6% achieved the guide line recommended target heart rate at 2-6 week, 6 week-3 month, 3 month-6 month, and 6 month- 1 year respectively on follow up. More than 70% of the patients' heart rate is not in the target rate in each follow up. 61.2%, 65.8%, 53.6%, 69% patients had their dose of propranolol adjusted at each consecutive follow up. Significant proportion of patients, 38.8%, 34.2%, 46.4%, & 31% were not provided with the appropriate dose adjustment. Of the patients who were on follow up 11.5% had experienced recurrence of variceal bleeding.

Conclusion and recommendation:-There was a significant gap in clinical practice of guideline recommended secondary prophylaxis for the prevention of variceal rebleeding in patients on follow up in TASH during the study period. There was lack of continuous supply of EVL bands in the country and appropriate escalation of the dose of propranolol was not implemented as per guideline recommendations in significant proportion of patient. Physicians should follow the appropriate evidence based guidelines in the management of variceal bleeding and prevention of rebleeding. Furthermore the hospital should avail necessary supplies like EVL which are vital for endoscopic intervention to control acute bleeding and for prevention of rebleeding.

1. Introduction

1.1. Background

Varices are vascular connection between the portal venous system and systemic circulation. Variceal bleeding refers to bleeding from rupture of varix which is usually found in the esophagus or stomach. It is characterized by hematemesis, melena or both. Rarely it can present as hematochezia (1).

Esophageal & Gastric varices are developed as a complication of clinically significant portal hypertension. The major causes of portal hypertension which account for over 95% of cases are an intra-hepatic condition which leads to cirrhosis, like chronic alcoholic liver disease, chronic viral hepatitis, advanced stage of Schistosomiasis. It can be caused by portal vein thrombosis, splenic vein thrombosis, Massive splenomegaly (Banti's syndrome), Buddi chiary syndrome & Right side heart failure (2).

Recurrent variceal bleeding is a bleeding episode that occurs after 5^{th} day of initial episode, an interval that defines the acute bleeding episode. There is a higher risk of re-bleeding between 5^{th} day and 6weeks of first episode (1, 3).

Treatment of gastro-esophageal varix in general encompasses two main categories: primary prophylaxis and secondary prophylaxis (2). The approach to patients who have had first variceal bleeding is controlling the acute bleeding, which can be life-threatening and preventing further re-bleeding. Treatment of acute active bleeding involves hemodynamic stabilization, prophylactic antibiotics, vaso-constricting agents & endoscopic intervention. Endoscopic intervention is used as first-line treatment to control bleeding acutely. Variceal band ligation is used to control acute bleeding in over 90% of cases and should be repeated until obliteration of all varices is accomplished. Sometimes variceal injection therapy used as initial therapy, particularly when bleeding is vigorous (2).

Once patients have had an acute bleed and have been managed successfully, attention should be paid to preventing recurrent bleeding. This usually requires repeated variceal band ligation until varices are obliterated and non-selective Beta blocker (NSBB) (2, 4).

A slow NSBB dose titration is recommended in order to assess and improve tolerance and reduce dose-dependent side effects of NSBBs. Guidelines recommend titrating NSBBs until the highest tolerated dose or target heart rate of 55–60 bpm achieved (5,6,7).

1.2. Statement of the problem

Among the major causes of cirrhosis-related morbidity and mortality is the development of variceal hemorrhage, a direct consequence of portal hypertension (8). Active variceal hemorrhage accounts for approximately one-third of all deaths related to cirrhosis (9).

Variceal hemorrhage is an immediate life-threatening event. The incidence in patients with portal hypertension is 30–50% and, in those that do bleed a 20–30% mortality rate associated with each episode of bleeding (10).

The outcome of acute variceal bleeding depends upon the control of active bleeding and prevention of the major complications associated with bleeding and its treatment. Approximately 70 percent of all untreated patients with variceal bleeding will die within the first year. The causes of death include recurrent variceal hemorrhage, liver failure, hepatic encephalopathy, and progressive ascites and infections. Survivors of an episode of active bleeding have a 30% to 40% risk of recurrent hemorrhage with in the first 6 week, and a 60% risk within one year (11, 12).

There are three primary goals of management during the active bleeding episode: hemodynamic resuscitation, control of bleeding and prevention and treatment of complications (2, 13).

To prevent re-bleeding and mortality, secondary prophylaxis is indicated for all patients with variceal bleeding. The recommendations by American Association for the Study of Liver Diseases (AASLD) include non-selective beta blockers, endoscopic variceal ligation, Transjugular Intrahepatic Portosystemic Shunts (TIPS) and liver transplantation (13). Combination of nonselective beta blockers plus endoscopic variceal ligation is the best option for secondary prophylaxis of variceal hemorrhage (2, 13). The consequence of failure to apply guideline based clinical practice will predispose to increased risk of recurrent variceal bleeding, hospitalization and mortality (2, 13).

There is no published data regarding clinical practice of secondary prophylaxis for variceal bleeding and prevalence of recurrent variceal bleeding in Ethiopian context. Hence, this aimed to assess the clinical practice of secondary prop]hylaxis for variceal bleeding and the prevalence of recurrent variceal bleeding among adult patients in Tikur Anbessa Specialized Hospital (TASH), Addis Ababa University, Addis Ababa, Ethiopia.

1.3. Significance of the study

The findings of this study could be used as a base line to understand the clinical practice of secondary prophylaxis for variceal bleeding and the recurrence rate. The findings of this study also show current status of the clinical practice on secondary prophylaxis in TASH, Addis Ababa, Ethiopia.

2. Literature review

2.1. Variceal hemorrhage

Varices are vascular connection between the portal venous system and systemic circulation caused by portal hypertension. Portal hypertension is defined as the elevation of the hepatic venous pressure gradient (HVPG) to >5 mmHg. Portal hypertension is caused by a combination of two simultaneously occurring hemodynamic processes: (1) increased intrahepatic resistance to the passage of blood flow through the liver due to cirrhosis and regenerative nodules, and (2) increased splanchnic blood flow secondary to vasodilatation within the splanchnic vascular bed. Variceal hemorrhage is one of the major consequences of portal hypertension (2).

2.2. Epidemiology of variceal bleeding

Variceal hemorrhage occurs at a yearly rate of 5% to 15% among patients with cirrhosis or portal hypertension. Variceal bleeding accounts for 10–30% of all cases of upper gastrointestinal bleeding. Although varices may form in any location along the gastrointestinal tract, it most often develops within the distal few centimeters of the esophagus. Gastro-esophageal varices are present in approximately 50% of patients with cirrhosis (14). There is a good correlation with the severity of liver diseases; while only 40% of child A patients have varices, it is seen in 85% of child C patients. Gastric varices are less prevalent, occurring in 5% to 33% of patients with portal hypertension (14, 15).

In the United States, the percentage of variceal bleeding varies from 5-30% of the total cases of upper GI (Gastro Intestinal) bleeding in different areas (16).

In cross sectional hospital based study done in Ghana among 149 subjects with liver cirrhosis from 2015 to 2016, 82.2% of them had large varices and 17.8% had small varices (17).

Approximately 30% of patients with esophageal varices will bleed within the first year after diagnosis (15).

A retrospective descriptive cohort study of cirrhotic patients with acute varceal bleeding who were admitted to King Abdul Aziz University Hospital in Saudi between January 2005 and

December 2009, re-bleeding prevalence was 9.6% during the same admission and 44% after discharge (18).

Researches conducted in different setting shows that Shistosomiasis is one of a major causes of variceal bleeding in developing countries (19-21). In a prospective cohort study in Tanzania, nearly 60% of patients presenting with hematemesis due to varceal bleeding had evidence of active Schistosomiasis (19).

In Egypt Portal hypertension and its consequences due to Shistosomiasis are a common health problem. In addition bleeding varices is considered to be the most lethal squeal (20).

In Sub Saharan Africa, about 0.2 million deaths are attributed to chronic S. Mansoni every year, which is mainly due to varices. Death occurs in up to 29% of those who present late with bleeding varices even with the best available in-hospital care (21).

2.3. Consequences of variceal bleeding

The mortality rate of each episode of bleeding may range from < 10% in well compensated cirrhotic patients with Child–Pugh grade A to > 70% in those in the advanced Child–Pugh C cirrhotic stage (15).

The risk of re-bleeding is high, reaching 60% within 1 year. Patients with a hepatic venous pressure gradient > 20 mmHg within 24 h of variceal hemorrhage, in comparison with those with lower pressure, are at higher risk for recurrent bleeding within the first week of admission, or of failure to control bleeding (83% vs. 29%) and have a higher 1-year mortality rate (64% vs. 20%) (15)

In Ghana, Death from esophageal bleeding is the leading cause of death from acute upper gastro-intestinal bleeding rose from 46% in 2010 to 76% in 2013. Outcomes following acute upper gastro-intestinal bleeding were dismal with 38% of fatalities occurring within the first 24 hours (22).

2.4. Management of variceal bleeding

Variceal bleeding is a medical emergency requiring a coordinated multidisciplinary-team approach. A systematic review of 12 studies found that a reduction of the hepatic venous pressure gradient to less than or equal to 12 mmHg was associated with a significant reduction in the risk of variceal bleeding and mortality (23).

The treatment of variceal bleeding started prior to episode of active bleeding events as primary prophylaxis, and continued as secondary prophylaxis for prevention of re bleeding (2, 24).

2.4.1. Primary prophylaxis

Primary prophylaxis aims to prevent Variceal bleeding in patients with varices who didn't have a history of bleeding. It is indicated in cirrhotic patients based on variceal size and the presence of other risk factors for bleeding. The strategies that have being effective in the primary prophylaxis in cirrhotic patients were NSBB (propranolol, nadolol or carvedilol) are mostly used and endoscopic therapy, especially band ligation (BL) (2, 24).

2.4.2. General principles of management for active bleeding

There are three primary goals of management during the active bleeding episode: hemodynamic resuscitation, control of bleeding and prevention and treatment of complications (13, 25, 26).

Hemodynamic resuscitation: - Restoration of the intravascular volume should be aggressively managed with large bore peripheral intravenous lines or a central line. Blood loss should be replaced by packed cells, and clotting factors should be replaced as needed. In extreme settings, correction of the coagulopathy may be necessary (25).

Control of active bleeding: - The major treatment options in order to control acute active variceal bleeding are medical and endoscopic intervention. Medical treatment involves initiation of vasopressors (terlipressin, somatostatin, and their analogs octeiortide). Rarely it may require transjugular intrahepatic portosystemic shunt placement, and surgical intervention (13).

Prevention and management of complications: - Complications related to bleeding and to the treatment of bleeding contribute substantially to mortality from active hemorrhage. While

hemostasis is almost invariably achieved, many patients succumb to the complications that develop following admission. Thus, prevention, monitoring, and treatment are critically important. The principal complications that cause death are aspiration pneumonia, sepsis, acute-on-chronic liver failure, hepatic encephalopathy, and renal failure (26, 27).

2.4.3. Secondary prophylaxis

Patients who had a first bleeding have risk of re-bleeding and high mortality. Thus, it is mandatory that all patients who presented with acute bleeding and treated with pharmacological and endoscopic treatment should also get secondary prophylaxis. NSBB and endoscopic therapy are options for secondary prophylaxis (2, 4, 13).

NSBB are effective in preventing re-bleeding (decreasing of risk by 40-45%) and it improves long-term outcomes (increasing overall survival in 5% in two years). It should be initiated after 5^{th} day post-hemorrhage and kept continuously since its interruption can cause rebound increase of portal pressure and predispose to re-bleeding (24).

Regarding endoscopic therapy, EBL (endoscopic band ligation) is better than sclerotherapy to prevent re bleeding and increase survival. A meta-analysis showed reduction of risk of re-bleeding in 48% and mortality in 23% in patients who underwent secondary prophylaxis with EBL when compared to those who underwent sclerotherapy (24, 28).

Randomized clinical trials comparing pharmacological therapy and EBL demonstrated conflicting results that did not demonstrate clear superiority of any of them alone. The combination of pharmacological therapy (NSBB) with endoscopic therapy (EBL) has better results in secondary prophylaxis. The early administration of NSBB can reduce the risk of bleeding until the patient undergoes endoscopic therapy. Randomized clinical trials demonstrated better results on re-bleeding control in patients who received combined therapy than the group of patients that received only EBL (11-14% vs 27-38%) (29).

A recent meta-analysis of five studies involving 476 patients comparing EBL alone or in combination with NSBBs also showed a reduced risk of re-bleeding with combination therapy and lower mortality (30). An analysis of a further four RCTs involving 409 patients where pharmacological therapy was used alone or in combination with EBL showed variceal bleeding

rates decreased with combination therapy (4, 30). This shows that adding pharmacological treatment to EBL significantly reduces the risk of further variceal bleeding and the approach of choice for secondary prophylaxis. The American Association for the Study of Liver Diseases (AASLD) issued guidelines for the prevention of variceal recurrent bleeding (13).

The AASLD recommends:-

- Patients with cirrhosis who survive an episode of active variceal hemorrhage should receive therapy to prevent recurrence of variceal hemorrhage (secondary prophylaxis).
- Combination of nonselective beta blockers plus endoscopic variceal ligation is the best option for secondary prophylaxis of variceal hemorrhage.
- The nonselective beta blocker should be adjusted to the maximal tolerated dose. Endoscopic variceal ligation should be repeated every 1 to 2 weeks until obliteration, with the first surveillance Esophago gastric deodunoscopy (EGD) performed 1 to 3 months after obliteration and then every 6 to 12 months to check for variceal recurrence.
- Transjugular intrahepatic portosystemic shunts should be considered in patients who have Child A or B cirrhosis and experience recurrent variceal hemorrhage despite combination pharmacologic and endoscopic therapy. In centers where the expertise is available, surgical shunts can be considered in Child A patients.
- Patients who are otherwise transplant candidates should be referred to a transplant center.

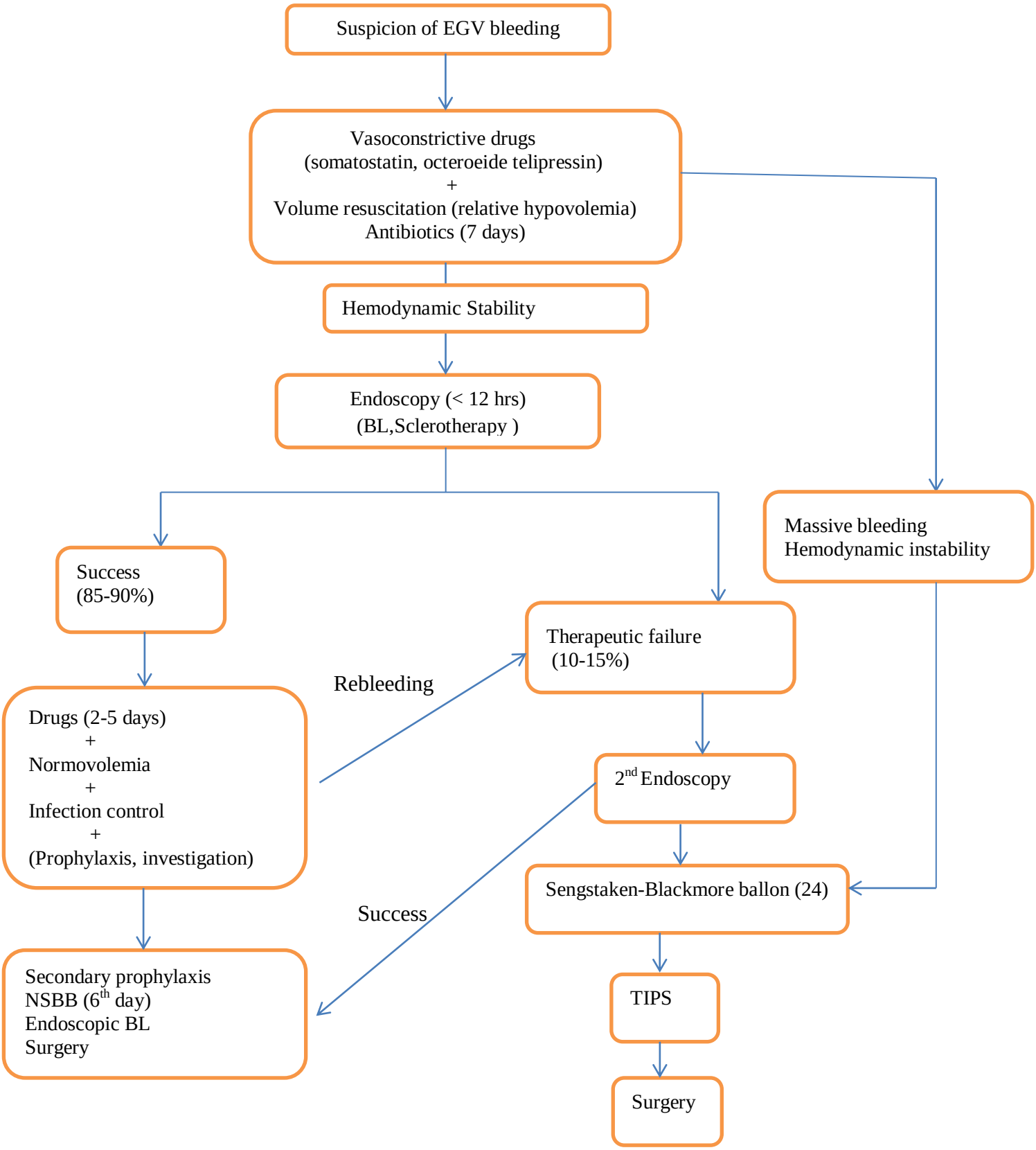

Figure 1: Flowchart of management of acute variceal hemorrhage (24)

3. Objectives

3.1. General objective

The general objective of this study was to assess the clinical practice of secondary prophylaxis of variceal bleeding and prevalence of recurrence among adult patients treated during 2015-2019 in Tikur Anbesa Specialized Hospital, in Addis Ababa, Ethiopia.

3.2. Specific objectives

The specific objectives of the study include:-

- To assess the clinical practice of secondary prophylaxis of variceal bleeding among adult patients in Tikur Anbesa Specialized Hospital, in Addis Ababa, Ethiopia, during 2015-2019.
- To determine the prevalence of recurrent variceal bleeding among adult patients in Tikur Anbesa Specialized Hospital, in Addis Ababa, Ethiopia, during 2015-2019.

4. Methods and materials

4.1. Study area and study period

The study was conducted in Tikur Anbesa Specialized Hospital (TASH). It is the largest referral tertiary university hospital in the country with 800 beds. It is the main teaching hospital for both undergraduate and postgraduate training of most disciplines in medical science in the country. Gastro- intestinal unit is one of sub-specialty unit under department of internal medicine which involves in various activities including services for patients with upper gastrointestinal bleeding. The study was conducted in those patients who had been on follow up for variceal UGIB during 2015-2019.

4.2. Study design

We employed a hospital based cross-sectional retrospective study design.

4.3. Population

4.3.1. Source population

The source population for this study was all patients greater than 18 years of age and has endoscopically confirmed variceal bleeding attending at TASH during study period.

4.3.2. Study population

The study population for this study was selected patients greater than 18 years of age and has endoscopically confirmed variceal bleeding attending at TASH during study period.

4.3.3. Inclusion criteria

All adult patients who had endoscopically confirmed variceal bleeding and started secondary prophylaxis during the study period was included in the study.

4.3.4. Exclusion criteria

- Patient records with incomplete information,
- Those patient who didn’t have at least three month follow up after initial bleeding,

- Patient who had varices with no evidence of active or stigmata of recent bleeding but endoscopically confirmed bleeding from other causes (ulcer, gastropathy e.t.c)

4.4. Sample size determination

All patients with endoscopically confirmed variceal bleeding who had been attending TASH from 2015-2019 were included in this study. 600 patients' MRN (medical registration number) was retrieved from endoscopy procedure documentation which was done during the study period. From these patients only 140 patients fulfill the inclusion criteria of this study and were included in this study.

4.5. Sampling procedure

First we extracted all patients' MRN from endoscopy procedure documentation with endoscopically confirmed variceal bleeding during 2015- 2019. We have got 600 patients' MRN from chart room & i-CARE. All 600 patient charts were evaluated for the inclusion criteria and those eligible for the study were included. From 600 patients only 140 patients were eligible for the study based on the inclusion criteria. Patient records (charts) lacking important study variables were also excluded. (Figure 2)

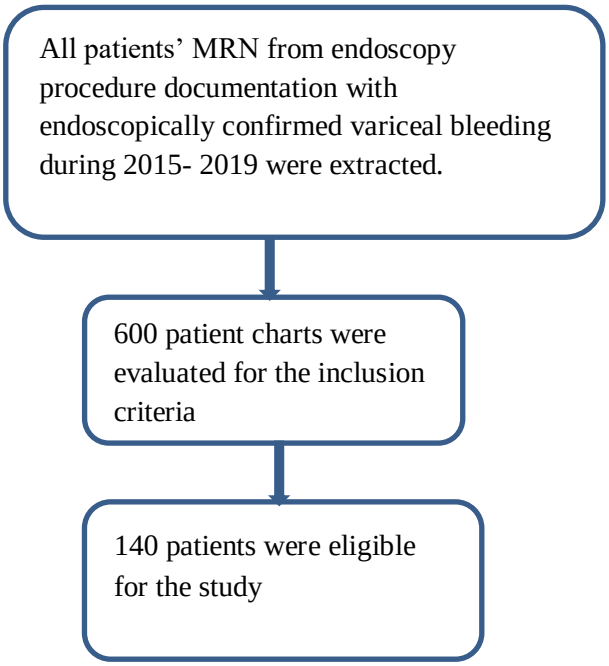

Figure 2: Sampling procedure of the study in TASH, 2020

4.6. Study variables

- Socio-demographic characteristics (age, gender, region)
- Heart rate (periperal pulse rate) at initation of beta blockers and during follow up
- Recurrent varceal bleeding
- Endoscopic findings (Type of varices, EV grade)
- Laboratory and clinical characteristics (BP, serum Creatinine, Na and Ascites)

4.7. Data collection tools and procedures

English version questionnaire which was constructed by the principal investigator and pretested questionnaire, adapted from different literatures was used. Data: - socio-demographic characteristics, clinical, laboratory and endoscopic results of the patients from hospital record and electronic database were collected.

Charts MRN (Medical Registration Number) was taken from endoscopic procedure record in GI (Gastro Intestinal) endoscopy unit. It was given to chart room staffs to get patient charts. Finally the required data was retrieved by the principal investigator.

4.8. Data quality management

Pretest was done on 15 (10.7%) patients and modifications on the questionnaire were done accordingly. Completeness and consistency of the records of cards were checked and those cards with incomplete data were excluded. Data were coded using non overlapping codes and entered using EpiData version 4.4.2.1. Data cleaning and completeness was checked using STATA version 15.1.

4.9. Data analysis

All statistical analysis was performed using STATA version 15.1. Numerical variables were presented as mean (SD). Categorical variables were expressed as percentage. Cross tabulation was done to see the relationship between variables.

4.10. Ethical consideration

Ethical clearance was obtained from research ethics committee of Addis Ababa University, College of health sciences department of internal medicine. Since this is a retrospective study with no direct impact on care of individual patients, consent was not taken. Confidentialities of the information gathered were assured via avoiding the name and address of the patients from the questionnaire.

4.11. Dissemination of results

The final report of the study will be submitted to Addis Ababa University, College of Health Sciences, School of Medicine, department of internal medicine. The study also will be compiled, reviewed and will be submitted for publication in reputable peer reviewed journal.

5. Results

5.1. Socio-demographic characteristics

A total of 140 patients were included in this study. The socio-demographic characteristics of the study patients are presented in Table 1. In this study, males accounted for 106(75.7%) of the total study patients. The age distribution showed that 74(52.9%) are in the age range of 18-29 years and only 13.6% are above the age of 50.

Table 1: Socio-demographic characteristics of patients with variceal bleeding during the study period 2015-2019, in TASH, Addis Ababa, Ethiopia

Variables	**Frequency**	**Percent**
Sex		
Male	106	75.7
Female	34	24.3
Age (years)		
18-29	74	52. 9
30-39	32	22. 9
40-49	15	10.7
50-59	12	8.6
>60	7	5
Region (Address)		
Addis Ababa	41	29.3
Amhara	27	19.3
Oromia	47	33.6
SNNPRS	15	10.7
Tigray	1	0.7
Others	9	6.4

5.2. Causes of varices

Figure 3 shows the commonest causes of variceal bleeding in TASH among patients treated during the study period of 2015-2019. The three most common causes are Schistosomiasis (41.4%) followed by HBV (20.7%) and portal vein thrombosis (10%).

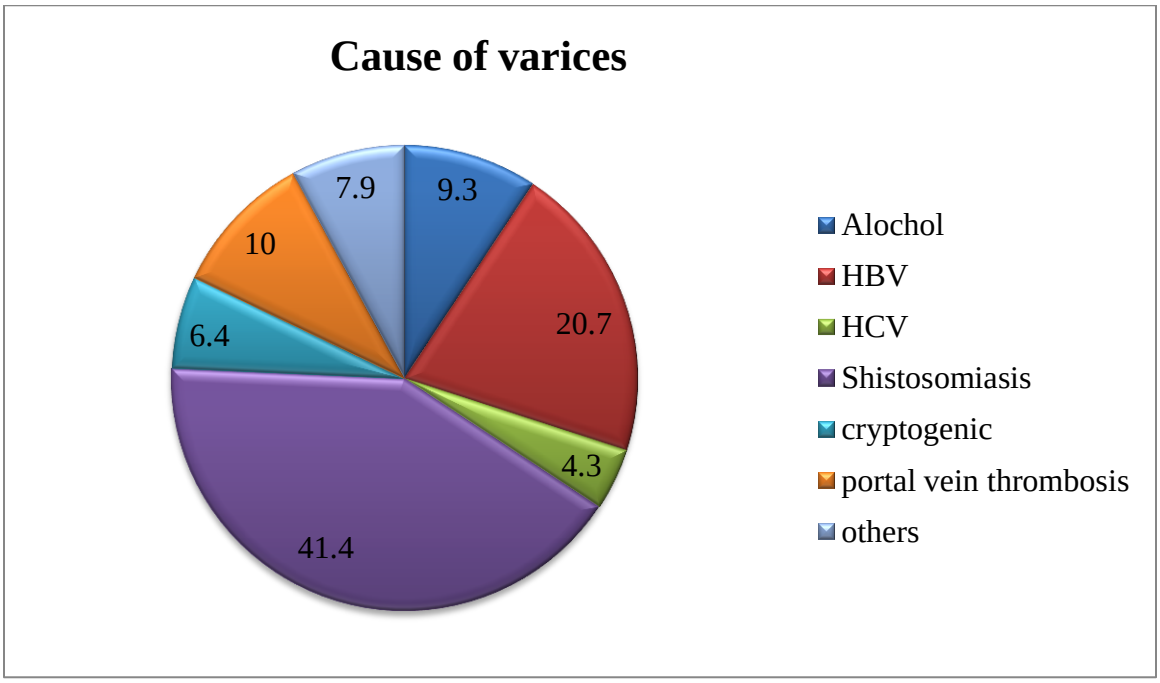

Figure 3: Causes of variceal bleeding in TASH, Addis Ababa, Ethiopia, 2020 (N=140)

5.3 Endoscopic findings and interventions

Among patients treated for variceal bleeding in TASH, Addis Ababa during the study period, 113 (80.7%) had esophageal varices while 23 (16.4%) had Esophageal and gastric (GOV1 or GOV2) varices. 104 (76.5%) of the patients had grade 3 (large) varices. The most commonly utilized endoscopic intervention was esophageal band ligation (EVL) in 44/46 (95.6%) cases, in which 3-5 bands were successfully applied in the first session in majority 23/35 (65.6%) of treated patents.(Table 2)

Table 2: Endoscopic findings among patients treated for variceal bleeding in TASH, Addis Ababa, 2020

Endoscopic findings	**Frequency**	**Percent**
Type (location) of varices		
Esophageal	113	80.7
Gastroesophageal (GOV 1 or 2)	3	2.1
Gastric (Isolated IGV)	1	0.7
Esophageal and GOV 1 or 2	23	16.4
Variceal grade n=136		
G1	3	2.2
G2	29	21.3
G3	104	76.5
Endoscopic intervention at first endoscopy (first presentation) N=140		
Yes	46	32. 9
No	94	67.1
Type of Endoscopic intervention at first endoscopy (first presentation) N=46		
EVL	44	95.6
EVL and sclerotherapy	2	4.4
Number of successful EV bands applied per session (n=35)		
0-2	1	2. 9
3-5	23	65.7
6-8	11	31.4

Prophylactic antibiotics were given to 30 (21.4%) of the patients following the first bleeding using ceftriaxone in 27/30 (90%) and ciprofloxacin in the remaining 3(10%) of treated patients.

5.4 Type of secondary prophylaxis

Figure 4 shows the type of secondary prophylaxis given for patients presenting with variceal bleeding in TASH. The commonest secondary prophylaxis given for the patients was propranolol (96.4%).

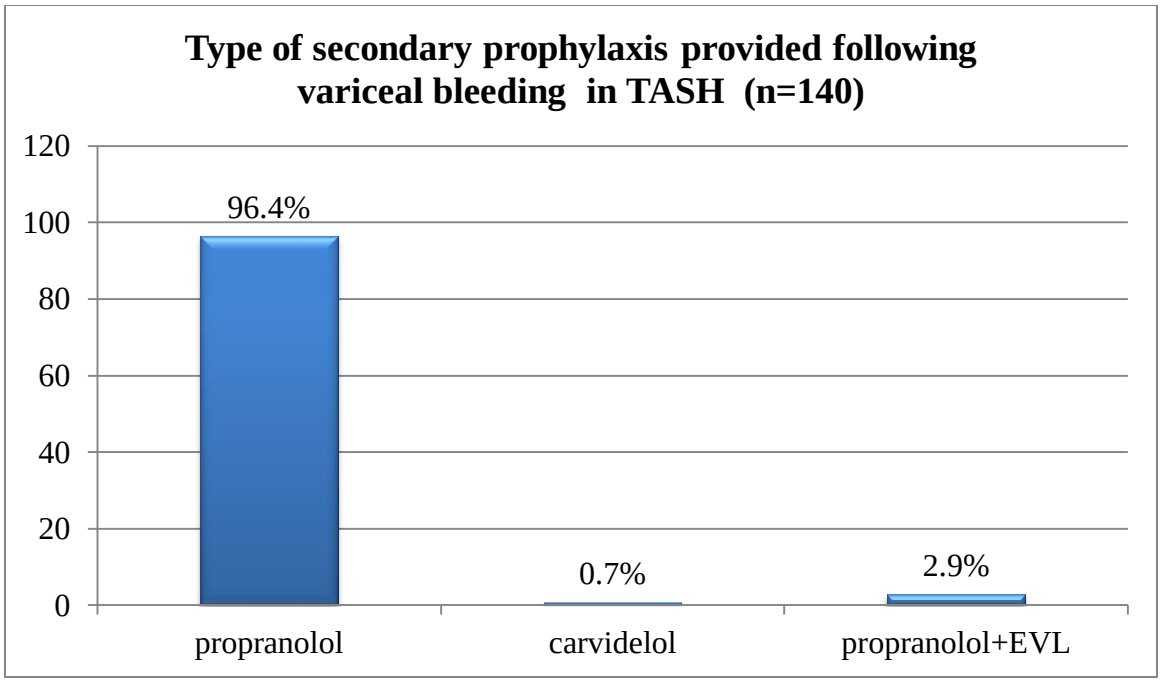

Figure 4: Type of secondary prophylaxis given for patients presenting with variceal bleeding in TASH, Addis Ababa, 2020.

5.5 Heart rate (Pulse rate) during follow up

Among the patients included in this study pulse rate was documented for 107, 117, 113, 109 &, 70 at discharge, 2-6 week, 6 week-3 month, 3-6 month & 6-12 month respectively.

Among the patients seen at follow up 9.4%, 11.5%, 20.2% and 28.6% had achieved heart rate target (55-60 beats per minute) during their follow up of 2-6 week, 6 week-3 month, 3 month-6 month, and 6 month- 1 year respectively, while about 23% had pulse rate of >80 beats per minute at 6 month- year.(Figure 5)

Pattern of pulse rate of patients on beta blockers as secondary prophylaxis following first variceal bleeding on follow up in TASH during the study period.

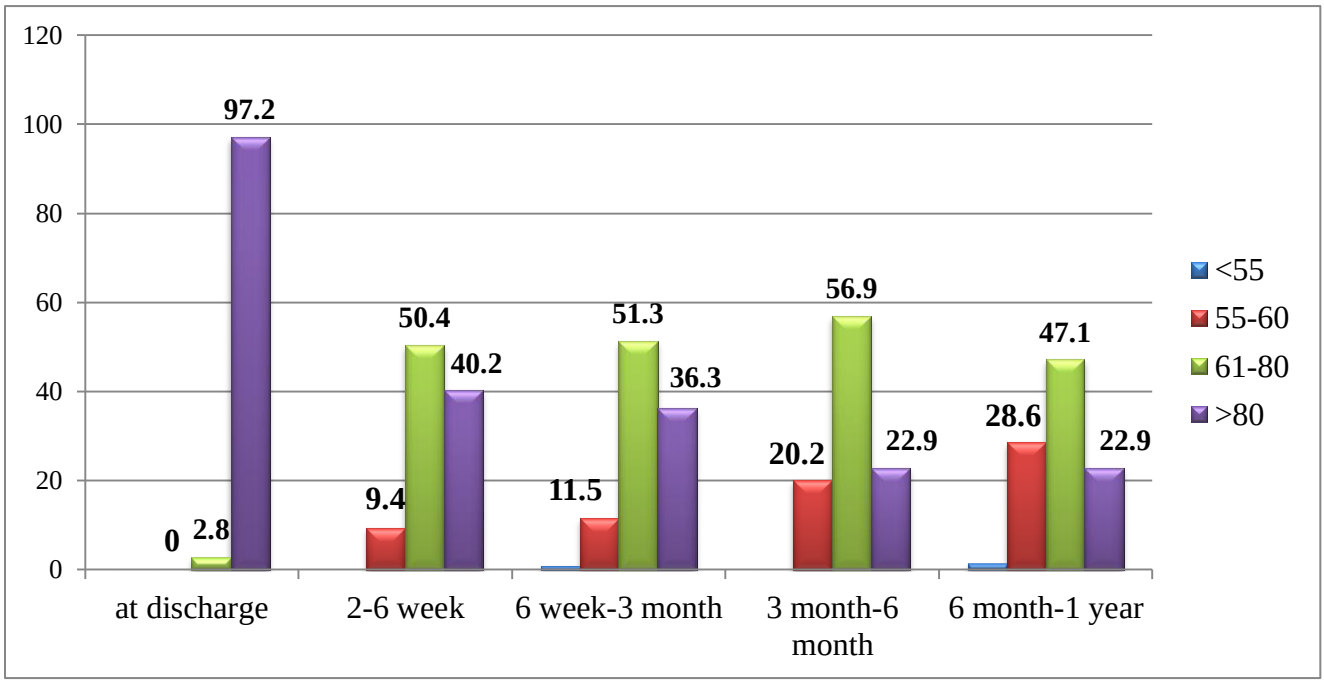

Figure 5: Pattern of heart rate of patient on secondary prophylaxis during a period of one year follows up after treatment for variceal bleeding in TASH, Addis Ababa, 2020.

5.6 Summary of laboratory and clinical findings during the follow up

The laboratory and clinical characteristics of the patients during each follow up presented in table 3 and table 4. The mean values of both clinical and laboratory characteristics are in the normal range and more than half of the patients had no ascites in each follow up.

Table 3: Clinical and laboratory characteristics of the patients on follow up after treatment for variceal bleeding in TASH, Addis Ababa, 2020.

Clinical and laboratory characteristics	**Follow up**				
	At discharge	**2-6 week**	**6week-3 month**	**3 month-6 month**	**6 month 1 year**
Systolic BP	113.6±13.4	108.7±14.2	109.1±15.1	108.8±10.1	106.8±8.9
Diastolic BP	69.6±8.3	71.5±8.9	70±9	69.4±8	70.5±7.5
Hemoglobin	9.7±1. 9	10.6±2.5	11.5±2.8	11.8±2.2	12.2± 2.6
Creatinine	0.99± 0 .21	0. 96±0.17	1.04± 0.27	0.94±0.2	1± .2
Na	135.6±5.1	133.1± 2.1	136.2±5.63	134.6±4. 9	136.3 ±3.3

Table 4: Frequency of Ascites in patients on follow up after treatment for variceal bleeding in TASH, in Addis Ababa, 2020

Follow up period	**Ascites documented**	
	Yes **N (%)**	**No** **N (%)**
At discharge (n=105)	39 (37.1)	66(62. 9)
2-6 week (n=119)	38(31. 9)	81(68.1)
6week-3 month (n=106)	18(17)	88(83)
3 month-6 month (n=101)	21(20.8)	80(79.2)
6 month 1 year (n=60)	8(13.3)	52(86.7)

5.7 Clinical practice of adjusting the dose of propranolol to achieve the recommended target heart during follow up visits.

Table 5 shows the clinical practice in adjusting the dose of propranolol with respect to heart rate to achieve recommended target during each follow up.

Table 5: Proportion of patients on follow up for whom the dose of propranolol was adjusted based on their heart rate during a period of one year follow up after initial bleeding in TASH, Addis Ababa. 2020.

Follow up Period (number of patients seen on FU)	**Dose of propranolol adjusted appropriately?**							
	Yes N (%)				**No N (%)**			
	<55 bpm	**55-60 bpm**	**61-80 bpm**	**>80 bpm**	**<55 bpm**	**55-60 bpm**	**61-80 Bpm**	**>80 bpm**
2-6 weeks (n=116)	-	11(100)	30/(50.9)	30(65.2)	-	0	29(49.2)	16(34.8)
6week-3 month(n=111)	1(100)	12(100)	30(51.7)	30(75)	0	0	28(48.3)	10 (25)
3-6 month(108)	-	19 (86.4)	25(40.3)	15(62.5)	-	3(13.6)	37(59.7)	9 (37.5)
6 month 1 year (n=70)	1(100)	20(100)	14(42.4)	14(87.5)	0	0	19 (57.6)	2(12.5)

5.8 Trend of adjustment of propranolol during one year follow-up

Figure 6 shows whether the dose of propranolol adjusted during each follow up. More than one third of patients didn't receive appropriate dose in each follow up.

Among 116 patients who were seen between 2-6 weeks, the dose of propranolol was adjusted for 71/116 (61.2%) of patients while appropriate dose adjustment was not done for 45 (38.8%) patients according to their heart rate level.

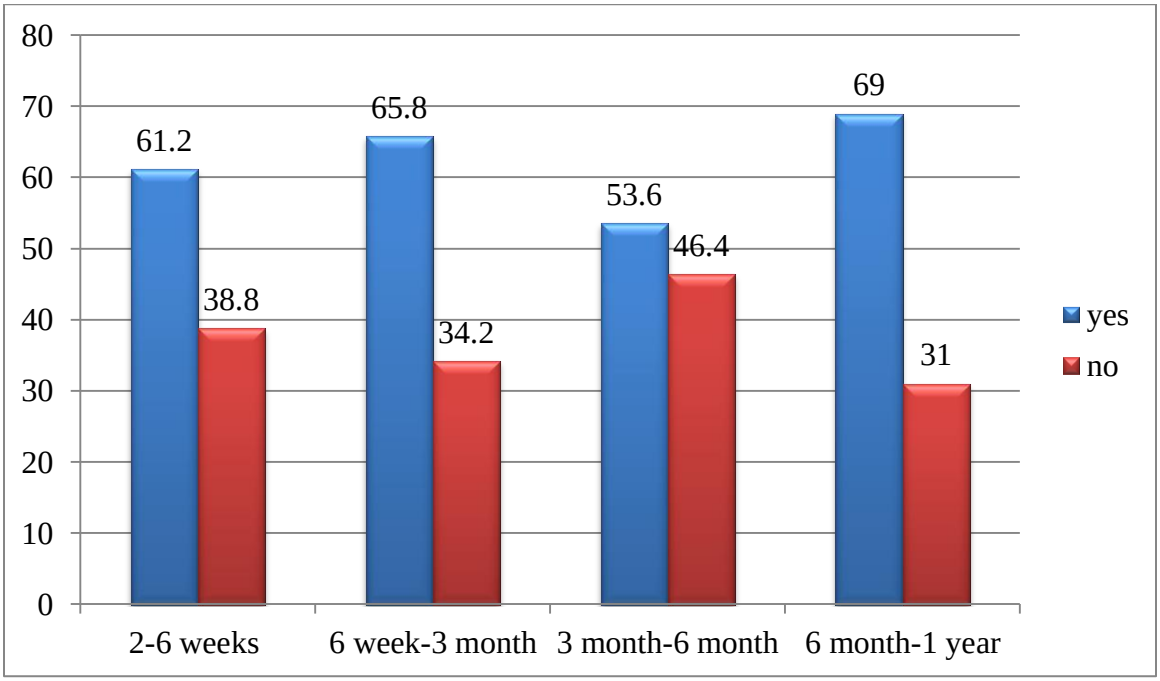

Figure 6: Trend of adjustment of the dose propranolol during one year follow-up for patient treated for variceal bleeding in TASH, Addis Ababa, 2020.

5.9 Recurrence of variceal bleeding

Of the total 140 patients included in the study 16 (11.5%) had variceal re-bleeding upon one year period of follow up (figure 7). All recurrence bleedings were diagnosed by endoscopy. From those who re-bled during one year follow up 11/16 (68.8%) recurrent bleeding occurred after 6 weeks of initial bleeding.

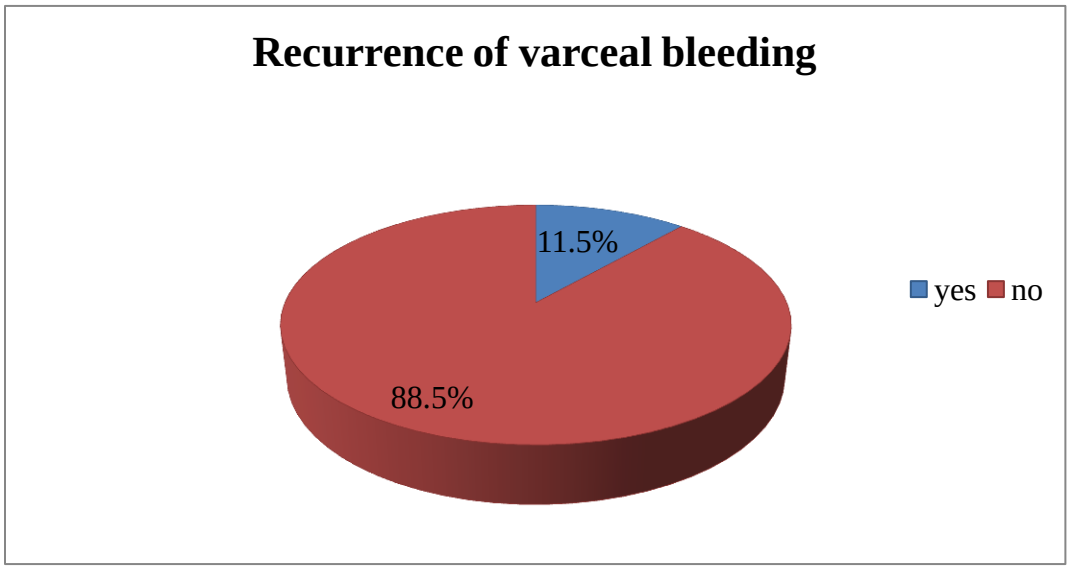

Figure 7: Documented recurrence of variceal bleeding during one year follow up in TASH, Addis Ababa, 2020.

5.10. Dose adjustment of propranolol after rebleeding.

Figure 8 shows dose adjustment of propranolol after re bleeding. Of those patients who re-bleed 43.8% of patients received same dose of propranolol (re-filled.)

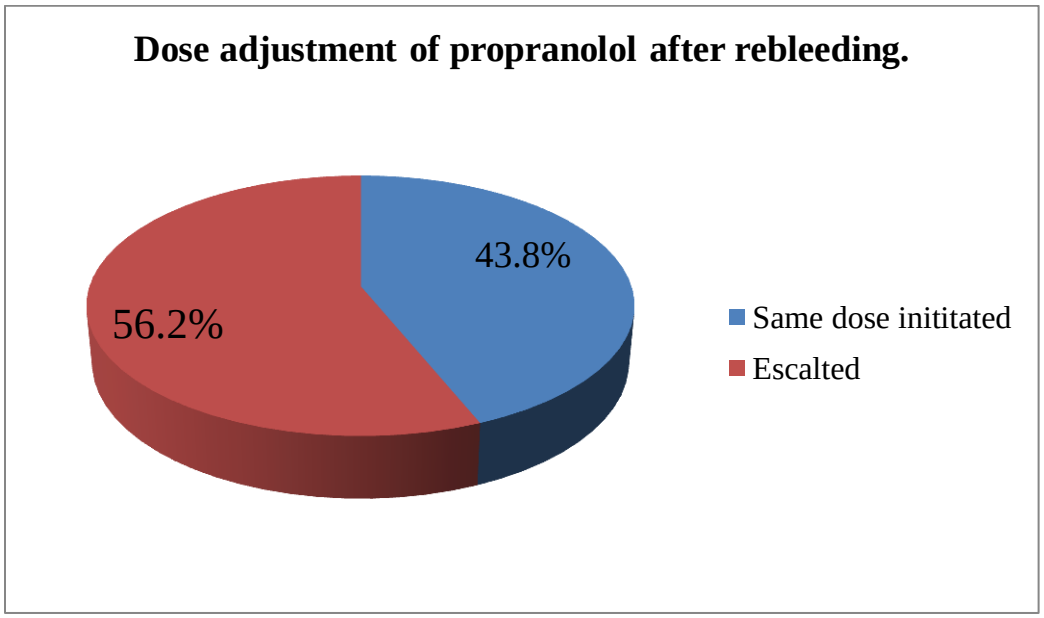

Figure 8: Dose adjustment of propranolol after rebleeding in TASH, Addis Ababa, 2020.

6. Discussion

This study was conducted with the main aim of assessing the clinical practice of secondary prophylaxis for variceal bleeding and the recurrence rate in TASH. More than 75% of patients treated for variceal bleeding during the study period were male and are younger than 40 years of age. By far the most common etiology of portal hypertension among our patients was Schistosomiasis (41%) and the majority of patients had relatively good renal function, sodium level, and vital signs. Ascites was documented in 37%, 32%, 17%, 21%, &13% at discharge, 2-6 week, 6 week-3 month, 3-6 month, & 6-12 month respectively.

EVL was the main intervention for acute variceal bleeding as well as initial sessions of secondary prophylaxis (2) but according to our study it was provided for only 33% of patients presented with variceal bleeding. Most likely possible reason as documented in the endoscopy report is unavailability of band in the hospital.

Patients who had first variceal bleeding will have subsequent risk of re-bleeding and high mortality unless appropriate secondary prophylaxis is started (2, 4). Thus, it is mandatory that all patients who presented with acute bleeding and treated with pharmacological and endoscopic treatment should also get secondary prophylaxis (2, 4). Combination of NSBBs and endoscopic band ligation are the recommended standard of therapy for secondary prophylaxis (4). In our study only 2.9% of patients get the standard secondary prophylaxis. In areas where endoscopic therapy is not feasible, NSBBs are the main management modalities (8).

In our study propranolol was the main medical treatment given as secondary prophylaxis. Propranolol in 96.4%, EVL & propranolol (2.9%), and carvidelol (0.7%) were started before or at discharge for secondary prophylaxis. Of these patients 9.5%, 11.5%, 20.2% and 28.6% achieved the guide line recommended target heart rate at 2-6 week, 6 week-3 month, 3 month-6 month, and 6 month- 1 year respectively on follow up. 61.2%, 65.8%, 53.6%, 69% patients had their dose of propranolol adjusted at each consecutive follow up. Despite which they could not achieve the desired target pulse rate. Possible contributing factors can be compliance, side effects, availability of drugs on market, & suboptimal dose escalation.

Guidelines recommend titrating NSBBs until the highest tolerated dose or target heart rate of 55–60 bpm achieved (6.7). Significant proportion of patients, 38.8%, 34.2%, 46.4%, & 31% were

not provided with the appropriate dose adjustment by treating physician even though the documented heart rate is well above the target in each follow up. When we evaluate the mean BP, serum Creatinine, serum Sodium and presence of ascites that may influence the decision to escalate dose of beta blocker, majority of the patients have normal ranges of these parameters despite these the same dose of propranolol was refilled irrespective of the heart rate level. Hence, there was a clear gap in strictly following the international guideline recommendations in relation to secondary prophylaxis (2.4).

One of consequence of varceal bleeding is recurrent bleeding. The risk of re-bleeding is high, reaching 60 % within 1 year in patients who do not receive treatment (15, 31, 32). Similarly the risk of re-bleeding also high in patients with large varices (33) and in those not achieved target heart rate.

In this study, the proportion of patients' who achieved the recommended target heart rate was increasing in each follow up. But only less than 30% of patients were in the target rate in each follow up. This implies more than 70% of the patients heart rate is not in the target rate so they are at risk of re-bleeding. Majority of the patients had grade 3 (large) varices with high risk for rebleeding.

Of the patients who were on follow up 11.5% had experienced recurrence of variceal bleeding. The prevalence is low compared to the studies conducted in other countries. In Saudi Arabia in patients admitted to King Abdul Aziz University Hospital, re-bleeding prevalence was 44% after discharge (14). In addition 20.8% patients had recurrent bleeding within 6 week in Shandong hospital in china (33). The discrepancy may be due to several factors. First there were many lost to follow up patients in our study. More than 50% had lost to follow up during 6 month to1 year. Second possible reason may be patients who had minimal re-bleeding after index bleeding may not come to clinical attention. Third most of patients diagnosed to have index variceal bleeding with endoscopy was after weeks of bleeding history. Fourth among patients confirmed to have endoscopic variceal bleeding in our setting, only 23.3% (140/600) of them are involved in the study.

In this study, the majority of rebleeding occurred after 6 week of index bleeding. This gives adequate time for implementing all the proven methods for secondary prophylaxis. Though there

was clear shortage of supply for EVL bands for eradication of varices, proper adjustment of dose of propranolol at appropriate time could save many patients.

Multiple studies have confirmed that providing prophylactic antibiotics to acute variceal bleeding patients decreases both the risk of recurrent bleeding as well as the overall mortality rate (31). Therefore, antibiotics prophylaxis has been an indispensable component of the management of acute variceal hemorrhage. Because antibiotics are generally well tolerated, they should have been provided to the majority of our study patients. Unfortunately, only 21.4% of the eligible patients received an appropriate course of prophylactic antibiotics.

7. Strength and Limitation of the Study

7.1. Strength of the Study

The study evaluated real life clinical practice with an important implication on morbidity and mortality and identified a clear practice gap that can easily be addressed by increasing awareness about the identified gaps and promoting on practicing guideline recommendations. Second we have tried to see one year follow up.

7.2. Limitation of the study

The findings of our study should be interpreted in light of some study limitations. First being the data is secondary, it is subject to some limitation like incomplete records and missing data especially in majority of patients' laboratory results were not recorded. Second almost half of patients lost to follow up during the last follow up which may affect the result and interpretation of the study.

8. Conclusion and recommendation

8.1 Conclusion

There was a significant gap in clinical practice of guideline recommended secondary prophylaxis for the prevention of variceal rebleeding in patients on follow up in TASH during the study period. There was lack of continuous supply of EVL bands in the country and appropriate escalation of the dose of propranolol was not implemented as per guideline recommendations in significant proportion of patient.

8.2 Recommendation

For Clinicians & Hospital

- Physicians should be aware of the existing gap and follow the appropriate evidence based guidelines in the management of variceal bleeding and prevention of rebleeding.
- The hospital should avail necessary supplies like EVL which are vital for endoscopic intervention to control acute bleeding and for prevention of rebleeding.
- Patients should be well educated on the importance of compliance to their treatment and follow up.

For Researchers

- Explore the potential reasons for the observed gap in clinical practice for secondary prophylaxis.
- A study based on primary data is needed.

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Annex: Questionnaire

Questionnaire number _____

Card number _____

Part one: - Back ground information

No	Question	Record	Skip
101	Age in completed yrs ?	…….years old	
102	Gender	Female ……..……..……..… 1 Male……..…….2	
103	Region (Address)	Addis ababa…….1 Oromiya ……2 Amhara.....3 Tigray ……..4 SNNPR…….5 Other ……6	

Part two:- Causes of Varices and endoscopic findings

No	Question	Response	Skip
201	Etiology of the portal hypertension	Alcohol …….……1 HBV……..……2 HCV……..…….3 Schistosomiasis…….….4 Cryptogenc……..…5 Portal vein thrombosis……...6 Others (specify)……	
202	Type of varices (location)	Esophageal ……..1 Gastroesophageal (GOV 1 or 2).....2 Gastric (Isolated IGV) 3	

		Esophageal and GOV 1 or 2……4	
203	Endoscopic Varceal grade	G1……..1 G2…….2 G3…….3	
204	Endoscopic intervention done at first bleeding	Yes ----------1 No ----------2	If no go to ques no 207
205	If yes what was done	EVL……..1 EVL+ Schlerotherapy……2	If it is EVL got to ques no 206
206	Number of successful EV band ligations applied per session	0-2 ……1 3-5……2 6-8…….3	
207	The reason why endoscopy was not done		
208	Prophylactic antibiotics	Yes ……1 No …….2	If no go to 210
209	Type of antibiotics given	Ceftriaxone…….1 Ciprofloxacin……..2 Other (Specify)……3	
210	What secondary prophylaxis was given	Propranolol…….1 Carvidelol.....2 EVL…….3 EVL+ propranolol……4	
211	Number of prophylactic EVL sessions for obliteration of varices during the year	0-2 ……1 3-5……2 6-8…….3	

Part three: - Heart rate during follow up

No	Question	Response	Skip
301	At discharge	<55……1 55-60 ……2 61-80……..3 >80……..4	
302	Dose of propanol given at discharge		
303	HR b/n 2 weeks-6 weeks	<55……1 55-60 ……2 61-80……..3 >80……..4	
304	Dose of propanol given b/n 2 weeks - 6 weeks		
305	Was the dose appropriately escalated/deescalated b/n 2 weeks-6 weeks	Yes ……1 No ……..2	
306	Heart Rate b/n 6wks-3 month	<55……1 55-60 ……2 61-80……..3 >80……..4	
307	Dose of propranolol given b/n 6wks-3 month		
308	Was the dose appropriately escalated/deescalated b/n 6 weeks-3month	Yes ……1 No ……..2	
309	HR b/n 3-6 month	<55……1 55-60 ……2 61-80……..3 >80……..4	
310	Dose of propranolol given b/n 3-6		

	month		
311	Was the dose appropriately escalated/deescalated b/n3-6 month	Yes …….1 No …….2	
312	HR b/n 6 month-1 year	<55…….1 55-60 …….2 61-80……..3 >80……..4	
313	Dose of propranolol given b/n 6 month-1 year		
314	Was the dose appropriately escalated/deescalated b/n 6 month-1 year	Yes …….1 No …….2	

Part four: - Recurrent Varceal bleeding

No	**Question**	**Response**	**Skip**
401	Recurrence of varceal bleeding	Yes ……1 No ……..2	
402	Recurrence diagnosed(Confirmed) by	Endoscopic finding ……1 Melena or hematemesis or both ……2	
403	Time of recurrence of varceal bleeding	Within 2 weeks.....1 Within two to six weeks ……2 After six weeks ……3	
404	Endoscopic intervention done during rebreeding	Yes ……1 No …….2	
405	If no for question no 404 specify the reason		

405	Type of endoscopic intervention done during recurrence	EVL……..1 Sclerotherapy……2 Others……3	
406	Dose of Propranolol after re bleeding	Re initiated with the same dose ……1 Escalated ……..……2 Discontinued ……..……3	

Part five: - Clinical and laboratory results during the follow up

No	**Question**	**Response**				
		BP		**Creatinine**	**Na**	**Ascites (present/absent)**
		SBP	**DBP**			
501	At discharge					
502	b/n 2 weeks-6 weeks					
503	b/n 6 weeks -3 month					
504	b/n 3-6 month					
505	b/n 6 month-1 year					