



The use of propranolol as primary prophylaxis in preventing an index bleed in patients with liver cirrhosis: a retrospective cohort study

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Background: Oesophageal varices are common in patients with liver cirrhosis. A proportion of them develop variceal bleeding which leads to significant morbidity and mortality. Primary prophylaxis has been recommended to prevent variceal bleeding. Endoscopic variceal ligation (EVL) and non-selective beta blockers (NSBBs) are two commonly used modalities in primary prophylaxis. However, EVL requires repeated procedures whereas NSBBs are equally effective and cost less. Our objective was to evaluate the effectiveness of propranolol as primary prophylaxis to prevent an index bleed in a secondary referral centre in West Pahang, Malaysia.

Methods: We retrospectively evaluated all patients who underwent surveillance upper endoscopy for liver cirrhosis from 1st January 2015 to 31st December 2016 in Hospital Sultan Haji Ahmad Shah (HoSHAS), Pahang, Malaysia. Patient demography, Child-Pugh score, endoscopic findings, whether EVL was done, propranolol administration and presence of any index bleed in 2 years were recorded and analysed using SPSS version 20.

Results: Sixty-nine patients had surveillance upper endoscopy for liver cirrhosis. Seven patients died of other causes unrelated to varices. About half the patients had EVL performed. Fifty-four patients (87.1%) received propranolol prophylaxis, of which 44 (81.5%) did not develop an index bleed in 2 years.

Conclusions: NSBBs is an effective method of primary prophylaxis in preventing index bleed for patients with liver cirrhosis, either as a stand-alone therapy or in combination with EVL, especially in a resource-limited centre.

Keywords: Propranolol; primary prophylaxis; oesophageal varices; liver cirrhosis; non-selective beta blockers (NSBBs)

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Introduction

About half of patients with liver cirrhosis develop oesophageal varices, as a consequence of portal hypertension (1). Variceal bleeding accounts for about 70% of all upper gastrointestinal bleeds in patients with portal hypertension (2). This is not only life-threatening but burdens the healthcare system with repeated hospital admissions and multiple blood transfusions. Each event of bleeding carries 30% mortality rate (1,3). Furthermore,

there is a 70% risk of recurrent bleed within one year from the first episode of bleeding (4).

Portal hypertension occurs when there is an increase in the intrahepatic resistance, coupled with reduction in splanchnic and systemic vascular resistance (5). Patients with decompensated liver cirrhosis are at higher risk of developing variceal bleed. Studies show that Child-Pugh B and C liver cirrhotic patients are almost twice as likely to have variceal bleeds as compared to that of Child-Pugh A

patients (6). The risk of variceal bleed in these patients is between 5–15% per annum (7).

Primary prophylaxis has been recommended to prevent an index bleed in a patient with oesophageal varices. The aim is not just to identify and prevent index bleeds in high risk patient but also to improve their clinical course and outcomes (8). Many modalities have been used, namely pharmacological agents such as non-selective beta-blockers (NSBBs) and invasive procedures to reduce portal hypertension (e.g., transjugular intrahepatic shunts) and endoscopic variceal ligation (EVL).

Screening programmes in patients with liver cirrhosis are usually carried out using upper endoscopy. The period for repeat endoscopy is determined based on the endoscopy findings and whether the patient has compensated or decompensated liver cirrhosis. The American Association for the Study of Liver Diseases (AASLD) (1), the American Society of Gastrointestinal Endoscopy (ASGE) (9) and the British Society of Gastroenterology (10) have produced guidelines for primary prophylaxis.

Pharmacological therapy using NSBBs has been shown to reduce the incidence of an index bleed in patients with oesophageal varices. A meta-analysis comparing NSBBs versus placebo in preventing the first variceal bleed showed that patients who received NSBBs had lower rates of variceal bleeding (2). For secondary prophylaxis, NSBBs has the important advantage of being immediately effective, compared with endoscopic procedures that protect against recurrent bleeding after complete obliteration of varices (11). In Malaysia, propranolol has been recommended as the best available modality for primary prophylaxis and first choice treatment in secondary prophylaxis (12).

Whilst the benefit of medical prophylaxis has been proven in many studies, there have not been any local studies looking at the clinical outcome of NSBBs in Malaysia. Endoscopy services in Malaysia is only available in major tertiary hospitals, thus many patients, especially from the rural population, have to travel far to receive treatment. Thus, prophylaxis using NSBBs is a cheap and effective modality that can prevent index bleed and improve overall outcome. With that in mind, we aimed to evaluate the effectiveness of propranolol as primary prophylaxis to prevent an index bleed in a secondary referral centre in West Pahang, Malaysia.

Methods

This is a retrospective study of all patients who underwent

surveillance upper endoscopy for liver cirrhosis from 1st January 2015 to 31st December 2016 in Hospital Sultan Haji Ahmad Shah (HoSHAS), Temerloh, Pahang. The patient details were obtained from Fisicien medical records (an integrated hospital internet system).

Patients were selected for inclusion if, (I) they were ≥ 18 years old, (II) they underwent surveillance endoscopy for chronic liver disease, and (III) presence of oesophageal or gastric varices on endoscopy. As the study involved data collection from electronic medical records only, the need for informed consent was waived.

Analyses were performed using IBM SPSS Statistics Version 20. Categorical variables were expressed as frequencies and percentages. Continuous variables in normal distribution were summarised as mean and standard deviation (SD). A chi square test was performed to find association between usage of propranolol and index bleeding within 2 years after first endoscopy.

Results

A total of 69 patients underwent upper endoscopy in HoSHAS between 2015 and 2016. During the 2 years period, there were 7 deaths which were not related to gastrointestinal causes. Sixty-two patients were included in the final analysis. The demographic and clinical characteristics are shown in *Table 1*.

Almost half of the patients had EVL performed during their first endoscopy procedures. Decision to initiate propranolol as primary prophylaxis was left at the discretion of the surgeons. Our data showed that all large grade varices were given propranolol prophylaxis. In contrast, only 91.7% and 78.6% of the medium and small grade varices respectively, were prescribed with propranolol. Follow-up over 2 years revealed that 82.3% of all patients did not have variceal bleeding. In our cohort of patients, there was no statistically significant correlation between baseline Child-Pugh score and risk of future variceal bleed ($P=0.205$).

Further statistical analyses however did not show any significant association between use of propranolol and index bleed within 2 years (*Table 2*).

Discussion

Pahang is the largest state in the peninsula of Malaysia with a land area of 35,840 km², a population of 1,679,000, and one of the lowest population density at 46/km² (13). Hospital Sultan Haji Ahmad Shah (HoSHAS) is a secondary

Table 1 Clinical characteristics of all patients included in the study

Characteristics	All (N=62), N (%) or mean (SD)
Age, years	57.4 (9.8)
Gender, male	45 (72.6)
Race distribution	
Malay	44 (71)
Chinese	13 (21)
Indian	5 (8)
Child-Pugh score	
A	32 (51.6)
B	17 (27.4)
C	13 (21.0)
First endoscopy	
Variceal grade	
Small	28 (45.2)
Medium	24 (38.7)
Large	10 (16.1)
EVL done	
Yes	28 (45.2)
Propranolol prophylaxis	54 (87.1)
Index bleed in 2 years	11 (17.7)

referral centre and a 498-bedded hospital in West Pahang, which covers half of the districts in the state of Pahang. With mean household income of RM 5012 (USD 1232), below the national mean of RM 6958 (USD 1710), and poverty index up to 0.9% in some of its districts, most patients have to travel far and do not have the financial means for repeated appointments (13).

Although EVL proves to be an effective method to prevent an index bleed, the finances and travel make these visits burdensome. EVL requires patients to have repeated endoscopies every two weeks until eradication and subsequent endoscopies are scheduled at three and six months if no further varices are encountered (14). Propranolol is a relative cheap medication (a 40 mg tablet costs RM 0.11/<USD 0.03) that is widely available in the local health clinics and district hospitals. Besides being effective in reducing portal hypertension, the pathophysiology responsible for the formation of varices, it also is an effective method in primary prophylaxis to

prevent an index bleed.

The rate of variceal bleeding is 5–15% per year (15). In a meta-analysis by Poynard (16), 78% of patients who received NSBBs did not have a variceal bleed in 2 years. Similarly, 81.5% of our patients who received NSBBs did not develop an index bleed in 2 years. This shows that propranolol prophylaxis is effective in reducing the morbidity and mortality associated with variceal bleed in our cohort, although the association was not statistically significant. This finding is limited by the small sample size of the study.

Although many non-invasive methods have been studied, none has been recommended to replace endoscopic screening. The advantages of endoscopy include detailed assessment of red wale signs which put patients at higher risk of bleeding, grading of varices and it allows therapeutic measures like EVL if indicated. Endoscopic screening has reported a prevalence of oesophageal varices up to 30% in compensated liver cirrhosis and 60% in decompensated liver cirrhosis (8). In our setting, all patients who underwent surveillance upper endoscopy had oesophageal varices. Kim (17) reported a 25% incidence of gastric varices at screening endoscopy. In our patient population, none of them had gastric varices at the initial endoscopy.

Using endoscopic surveillance as primary prophylaxis, Jutabha (18) found that the prevalence of different sizes of varices were mainly large, followed by medium then small. Contrary to that, our data showed the reverse, with small varices being the majority, followed by medium and large. The grade of the varices may differ depending on the period between diagnosis of cirrhosis and endoscopy, and whether the liver cirrhosis is compensated or decompensated.

Both EVL and NSBB have been shown to be superior to no treatment in preventing an index bleed (19,20). There have been many debates on which modality is superior. EVL has been suggested to lower the risk of variceal haemorrhage (19). However, some argue that the procedure itself may put the patient at risk of bleeding. Furthermore, EVL is aimed at eradicating varices without actually treating the portal hypertension, which is responsible for the varices formation. On the other hand, NSBBs are cheap, have relatively low side effects and reduce the development of ascites and spontaneous bacterial peritonitis (21,22). There is no concrete evidence to suggest the addition of NSBB after an EVL is beneficial. There have been some suggestions of adding NSBB in high risk varices (23). The Baveno V consensus workshop recommends the choice of treatment should be according to the local setting, expertise

Table 2 Comparison of characteristics between patients who received propranolol and those who did not receive propranolol

Characteristics	Patients who received propranolol (N=54), N (%)	Patients who did not receive propranolol (N=8), N (%)	P value
Gender, male	39 (72.2)	6 (75.0)	1.000*
Child-Pugh score			1.000*
A	28 (51.9)	4 (50.0)	
B	15 (27.8)	2 (25.0)	
C	11 (20.4)	2 (25.0)	
First endoscopy			
Variceal grade			0.205*
Small	22 (40.7)	6 (75.0)	
Medium	22 (40.7)	2 (25.0)	
Large	10 (18.5)	0 (0)	
EVL done			0.063*
Yes	27 (50.0)	1 (12.5)	
Index bleed in 2 years	10 (18.5)	1 (12.5)	1.000*

and resources available, patients' choice and contra-indication (24).

In conclusion, NSBBs is an effective method of primary prophylaxis in preventing index bleed for patients with liver cirrhosis, either as a stand-alone therapy or in combination with EVL, especially in a resource-limited centre.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/dmr.2019.10.04>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in

2013). The ethics committee is Medical Research Ethics Committee (MREC) of Ministry of Health (MOH) Malaysia (MREC MOH No: NMRR-19-2469-50156). Informed consent was not required as the study is a retrospective cohort study from a patient database.

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