Al-Azhar International Medical Journal

Volume 4 | Issue 10 Article 4

2023
Section: General Medicine

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How to Cite This Article

Mohamed, Anwar Abdelaleem; Mahmoud, Amal Mohamed Mohamed; Eljaky, Mohamed Ashraf; Aly, Rasha Abdelhafiz; and Rady, Mohamed Akl (2023) "Impact and outcome of primary prophylaxis of variceal bleeding among Egyptian hepatocellular carcinoma patients with portal vein thrombosis treated with Sorafenib," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 10, Article 4.
DOI: https://doi.org/10.58675/2682-339X.1971

ORIGINAL ARTICLE

Impact and Outcome of Primary Prophylaxis of Variceal Bleeding Among Egyptian Hepatocellular Carcinoma Patients With Portal Vein Thrombosis Treated With Sorafenib

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Abstract

Background: **Patients with cirrhosis and hepatocellular carcinoma (HCC) experience portal hypertension, causing esophageal varices (OV). Some HCC patients taking Sorafenib experience bleeding, while others ignore this effect and believe that sorafenib might minimize bleeding. A comparison was made between carvedilol therapy and primary preventive band ligations in HCC patients with a large, risky OV and portal vein thrombosis (PVT) taking sorafenib. The survival of these patients is also analyzed.**

Methods: **Study enrolled 120 HCC patients with PVT and large OV. They were divided into four groups: 1) Sorafenib with prophylactic band ligation, 2) Sorafenib with prophylactic carvedilol, 3) prophylactic band ligation, and 4) prophylactic carvedilol. For six months, they were followed. Primary outcomes included changes in variceal size, variceal bleeding frequency, and survival rate.**

Results: **Baseline characteristics were not significantly different between the four groups. After preventive band ligation with or without sorafenib, variceal size declined significantly [27 (90%), 16 (53.3%), respectively; $P < 0.001$]. Among the four groups, variceal bleeding occurred only in [6 (20%), 5 (16.7%), 9 (30%), 4 (13.3%); $P = 0.41$]. Moreover, there was a significant difference in overall survival rates across the four groups [$P = 0.001$] with sorafenib groups having the highest survival. Whether sorafenib was used or not, the primary adverse event, a postbanding ulcer, did not significantly differ between groups I and III.**

Conclusion: **In HCC patients with malignant PVT treated with sorafenib, prophylactic band ligation or beta-blockers had no effect on mortality or bleeding. Sorafenib-treated patients have the longest survival rates.**

Keywords: Hepatocellular carcinoma, Esophageal varices, Portal hypertension, Portal vein thrombosis, Sorafenib

1. Introduction

The second-leading factor in mortality from cancer Hepatocellular carcinoma (HCC)[1] is the fifth most prevalent cancer in men and the seventh most prevalent in women worldwide.[2] Patients with hepatic cirrhosis who also have HCC are more likely to have portal hypertension. Aggressive portal vein thrombosis causes portal hypertension and a consequent decline in liver function.[3] Elevated portal pressure and potentially catastrophic esophageal and gastrointestinal haemorrhage arise from thrombotic blockage of the portal vein.[4]

For clinically compensated patients with advanced hepatocellular carcinoma, Sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, is the optimal treatment as it significantly increases survival rates.[5,6] Sorafenib has also led to a decrease in portal hypertension

Accepted 25 May 2023.
Available online 7 November 2023

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https://doi.org/10.58675/2682-339X.1971

associated with cirrhosis, a common companion of HCC, as a result of an inhibition of Porto collateral vascularization, in light of its anti-angiogenetic activity.[7] This was implied in three minor clinical reports that showed Porto collateral alterations in cirrhotic patients with advanced HCC receiving Sorafenib treatment.[4,8]

However, Sorafenib causes deadly bleeding in some individuals[9] while others dismiss its impact and come to the conclusion that Sorafenib may lessen bleeding.[10] This study compares the effectiveness and safety of primary prophylactic band ligations versus prophylactic beta-blockers (carvedilol) therapy in HCC patients with large, risky esophageal varices and portal vein thrombosis who are receiving Sorafenib. We also aim to determine the survival rates of these patients.

2. Patients and methods

In this retrospective and prospective study, 120 HCC patients who had malignant portal vein thrombosis (PVT) and large OV and in stage C according to BCLC staging system for HCC were studied. They received either primary preventive band ligations or beta-blockers (carvedilol 6.25 mg twice daily) (whether or not they were taking Sorafenib. They were categorized into 4 groups, for each group 30 patients were included. Patients were treated as follow: group (1) with prophylactic band ligation combined with Sorafenib; group (2) with prophylactic beta-blockers (carvedilol 6.25 twice daily) combined with Sorafenib; group (3) with prophylactic band ligation; group (4) with prophylactic beta-blockers (carvedilol 6.25 twice daily). Those HCC patients who did not received Sorafenib were selected from medical records of HCC clinic in our National Liver Institute, Menoufia University when Sorafenib was not available for treatment. Also, those who were eligible for prophylactic band ligation were intolerant to drug therapy. These patients were selected from HCC clinic of the National Liver Institute, Menoufia University, Egypt.

The excluded HCC patients are those with: (1) Previous episodes of hematemesis or melena; (2) Patients with decompensated cirrhosis; (3) Patients with advanced comorbid conditions; (4) Deaths that occurred during follow-up but were not caused by liver disease; (5) Contraindications to sorafenib treatment, such as acute elevations of transaminases; (6) Patients with decompensated HCC; (7) Patients who had previously received systemic chemotherapy.

These HCC were diagnosed according to the American Association for the Study of Liver Diseases 2010 (hepatic focal lesion with computed tomography (CT) or MRI criteria of HCC wash in arterial phase and washout in Porto venous-delayed phases).[11] The size of OV were graded into small and large varices during upper GI endoscopy according to the Japanese Research Society for Portal Hypertension classification (2) as follows: 1- Straight (F1) 2- Enlarged, tortuous (F2) 3-Very large varices (F3).[12] Those who had OV grade F1 were considered small OV and those with grade F2 or F3 varices were considered large varices. Those with grade F2 or F3 varices were included in our study.

All of the patients who were included underwent a thorough clinical examination, a full history taking, and such investigations as:

(1) Laboratory tests: International normalized ratio (INR); liver enzymes and liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin total and direct, serum albumin], complete blood count (CBC), Hepatitis C virus (HCV) Ab, HBsAg, and alpha fetoprotein (AFP).
(2) Abdominal ultrasound and triphasic spiral CT/dynamic MRI scan on the abdomen.
(3) Endoscopy of the upper gastrointestinal tract at the start of the study and three weeks after and those with large OV were chosen to be a part of our research. Prophylactic band ligation was done for group I and group III.

These patients were followed-up for 6 months during which the survival and any complications were reported. Every patient who was a part of the study gave their informed consent. Menoufia University's National Liver Institute's ethical committee gave its approval.

2.1. Statistical analysis

The SPSS (Statistical Package for Social Science) program was used to gather data and enter it into the computer for statistical analysis (version 20; Inc., Chicago. IL). Qualitative data was expressed as frequency and percent, whereas quantitative data was displayed as mean, SD, and range. The Mann Whitney test was used when the quantitative data was not normally distributed, and the student *t*-test was used to compare the mean and standard deviation of two sets of normally distributed quantitative data. The χ^2 test was used to assess the relationship between qualitative variables. When paired quantitative data are normally distributed, the paired *t*-test is used to compare the mean and standard deviation; when the data are not normally distributed, the Wilcoxon test is employed. A scalar response and

one or more explanatory factors, commonly known as dependent and independent variables, are modeled using multiple linear regression. To find the cutoff value with the maximum sensitivity and specificity, the ROC (Receiver Operating Characteristic) curve was created. *P* greater than 0.05 is insignificant, *P* less than 0.05 is significant (*), and P less than or equal to 0.001 is highly significant (**).

3. Results

In this trial, there were 120 HCC patients with large risky esophageal varices and thrombosis of the portal vein, 60 of whom were given Sorafenib (groups I and II). Table 1 showed summary of demographic data, laboratory test, viral serology, and radiological characteristics of hepatic focal lesion of studies groups. Regarding the baseline demographic information of the study groups, there were no significant differences. More than 25% of each group were diabetic mellitus (DM). Furthermore, DM was present in 9 out of 30 (30%) in group I, 8 out of 30 (26.7%) in group II, 13 out of 30 (43.8%) in group III, and 8 out of 30 (26.7%) in group IV. Most of our patients (more than 90%) were infected with HCV. There was no significant difference between the study groups in terms of alpha fetoprotein ($P > 0.05$). Additionally, there was no discernible variation in the location of the lesion across the four groups ($P = 0.37$).

Table 2 displays the variation in variceal size among the study groups after one session of banding ligation. After one session of prophylactic banding, there was a reduction in variceal size in HCC patients in groups I and III as compared to the other two groups, group II (with Sorafenib) and IV (without Sorafenib), who were treated with beta blockers. Furthermore, in group I, there were 27 out of 30 patients (90%) with small varices, compared to 16 out of 30 patients (53.3%) in group III. Also, the decrease in variceal size was markedly clear in group I than other groups. Variceal bleeding was less evident in group II and IV (treated with beta-blockers) than group I and III (treated with band ligation), but there was no statistical difference. Between groups I and III, there was no discernible difference in the frequency of postbanding ulcers ($P = 1.0$) as 5 out of 30 (16.7%) in each of group I and III declared postbanding ulcer.

Table 3 displays the mortality and reasons of death for the groups under study within a 6-month period. Survival rates in groups I and II were (76.7% and 80%, respectively), but they were (16.7% and 20%, respectively) in groups III and IV.

Table 4 displays the overall survival analysis for the patients that were examined. The 4 study groups showed a significant difference, with group I having the highest survival (mean = 22.97 weeks) and group III having the lowest survival (mean = 14.77 weeks).

Fig. 1 depicts a Kaplan-Meyer graph showing the survival of the various research groups. It demonstrates a survival advantage for HCC patients receiving sorafenib treatment (groups I and II) over those not receiving sorafenib treatment (groups III and IV).

4. Discussion

In Egypt, HCC is the second most common form of cancer, behind breast cancer in women and bladder cancer in men Elqatary and colleagues,[13] and it is the second leading cause of death globally Vogel and colleagues.[14] HCV, the most significant risk factor for developing liver cancer, including HCC in Egypt, is thought to be the cause of the rise in incidence and its complications Rashed and colleagues.[15] In Egypt, the relation between HCV and HCC is an important research area. Firstly, Egypt has a high recorded HCV transmission rate, with around 416 000 new infections each year Kamdeel and colleagues.[16] Secondly, there is known to be a relationship between HCV and HCC development. Many hospital-based studies in Egypt reported increasing incidence of HCC due to increasing incidence and complications of HCV Abd-Elsalam and colleagues, Ziada and colleagues.[17,18]

A wide range of manifestations are possible for HCC that develops in the context of liver cirrhosis. One of the terrifying side effects of HCC is thought to be the involvement of the portal vein (PV). PVT occurs in about 16–30% of HCC patients Kudo and colleagues.[19]

Although Sorafenib had an OS benefit of around 3 months in patients who had unresectable HCC, indicating modest advantages, it was approved as a systemic therapy Khan and colleagues.[20]

Patients who have a blocked portal vein frequently get variceal bleeding. So, prevention is crucial. Primary prophylaxis of variceal haemorrhage in adults has become the accepted standard of care as a result of multiple randomised clinical trials confirming the effectiveness of nonselective beta-blockers and endoscopic variceal ligation in reducing the incidence of variceal haemorrhage Gana and colleagues.[21]

In this study, sorafenib-treated HCC patients with large, risky esophageal varices and portal vein thrombosis were compared with the effects and side effects of primary preventive band ligations versus beta-blockers (carvidelol).

The mean age of the patients included in the current study was 59.78 ± 7.39 years, which is consistent with a recent study that found that patients with

Table 1. The baseline characteristics of the patients that were included.

	Group I $N = 30$	Group II $N = 30$	Group III $N = 30$	Group IV $N = 30$	P value
Age (years)					
M±SD	57.53 ± 6.29	61.50 ± 8.22	60.20 ± 7.85	59.90 ± 7.21	0.42[a]
Range	42–71	45–77	43–79	43–72	
Sex					
Male, *N* (%)	24 (80%)	26 (86.3%)	25 (83.3%)	24 (80%)	0.89[b]
Female, *N* (%)	6 (20%)	4 (13.7%)	5 (16.7%)	6 (20%)	
HTN					
Positive, *N* (%)	10 (33.3%)	14 (46.7%)	9 (30%)	13 (43.3%)	0.49[b]
Negative, *N* (%)	20 (66.7%)	16 (53.3%)	21 (70%)	17 (56.7%)	
DM					
Positive, *N* (%)	9 (30%)	8 (26.7%)	13 (43.3%)	8 (26.7%)	0.45[b]
Negative, *N* (%)	21 (70%)	22 (73.3%)	17 (56.7%)	22 (73.3%)	
Total bilirubin (mg/dl)					
M±SD	0.96 ± 0.39	1.09 ± 0.39	1.50 ± 0.84	1.42 ± 0.66	0.05^1 0.002^2 0.001^3 0.13^4 0.05^5 0.95^6
Range	0.6–1.9	0.3–2.0	0.45–3.6	0.45–3.0	
Direct bilirubin (mg/dl)					
M±SD	0.41 ± 0.23	0.44 ± 0.24	0.74 ± 0.60	0.66 ± 0.42	0.63^1 0.01^2 0.007^3 0.05^4 0.03^5 0.91^6
Range	0.09–1.0	0.1–1.03	0.17–2.7	0.17–2	
ALT (U/L)					
M±SD	26.77 ± 20.17	28.77 ± 24.30	43.57 ± 26.65	30.93 ± 13.97	0.33^1 $< 0.001^2$ 0.02^3 0.003^4 0.10^5 0.07^6
Range	7–98	10–144	12–119	10–73	
Albumin (g/dl)					
M±SD	3.72 ± 0.56	3.66 ± 0.45	3.46 ± 0.41	3.57 ± 0.52	0.67^1 0.05^2 0.30^3 0.08^4 0.5^5 0.39^6
Range	2.4–4.8	2.8–4.8	2.8–4.2	2.7–4.6	
INR					
M±SD	1.25 ± 0.13	1.25 ± 0.13	1.25 ± 0.18	1.18 ± 0.12	0.98^1 0.85^2 0.03^3 0.86^4 0.03^5 0.05^6
Range	1–1.5	1–1.5	1–1.65	1–1.5	
Viral serology					
Anti-HCV Ab positive, *N* (%)	29 (96.7%)	29 (96.7%)	25 (83.3%)	28 (93.3%)	
HBs-Ag positive, *N* (%)	0	0	0	0	0.16[b]
Others (non-C, non-B), *N* (%)	1 (3.3%)	1 (3.3%)	5 (16.7%)	2 (6.7%)	
Alpha feto protein (ng/ml)					
M±SD	1518.7 ± 3432.2	5287.9 ± 11269.4	2700.0 ± 11351.3	3570.6 ± 6766.8	0.341^1 0.872^2 0.723^3 0.564^4 0.92^5 0.9^6
Range	2.15–14542	4–44000	4.2–62720	4.19–28208	
Radiological characteristics of hepatic focal lesion					
Right, *N* (%)	9 (30.0%)	8 (26.7%)	15 (50.0%)	13 (43.3%)	
Left, *N* (%)	7 (23.3%)	6 (20.0%)	3 (10.0%)	5 (16.7%)	
Bilobar, *N* (%)	6 (20.0%)	11 (36.7%)	7 (23.3%)	8 (26.7%)	0.37[b]
Large infiltrative, *N* (%)	2 (6.7%)	3 (10.0%)	4 (13.3%)	1 (3.3%)	
Ill defined, *N* (%)	6 (20.0%)	2 (6.7%)	1 (3.3%)	3 (10.0%)	

Abbreviations: Ab, anti-body; ALT, alanine aminotransferase; DM, diabetes mellites; HBs-Ag, hepatitis B surface antigen; HCV, hepatitis C virus; HTN, hypertension; INR, international normalized ratio; M, mean; N, number; SD, standard deviation.
1 = comparing group I and group II, 2 = Comparing group I and group III.
3 = comparing group I and group IV, 4 = Comparing group II and group III.
5 = Comparing group II and group IV, 6 = Comparing group III and group IV.
[a] Test of ANOVA.
[b] Chi squared test, Mann Whitney test.

HCC who had portal vein thrombosis had a mean age of 52.40 ± 5.96 years Ashmawy and colleagues.[22] About 82.5% of the patients in the current study were males, which is similar to a prior study that included 200 patients with portal vein thrombosis in HCC patients and also revealed a male predominance Zhang and colleagues.[23] Male predominance of HCC may be explained by variations in risk factor exposure, sex hormone exposure, and other X-linked genetic variables Ramadan and colleagues.[24]

Esophageal varices in group I and group III who underwent variceal band ligation in the current study

Table 2. Variceal size changes before and after one session of banding ligation, postbanding ulcer, variceal bleeding within 6 months of treatment.

Upper endoscopy	Group I $N = 30$	Group II $N = 30$	Group III $N = 30$	Group IV $N = 30$	P value
Esophageal varices (pretreatment)					
Large, N (%)	30 (100%)	30 (100%)	30 (100%)	30 (100%)	–
Esophageal varices (posttreatment)					
Large, N (%)	2 (6.7%)	30 (100%)	8 (26.7%)	30 (100%)	<0.001[a]
Small, N (%)	27 (90.0%)	0 (0.0%)	16 (53.3%)	0 (0.0%)	
No, N (%)	1 (3.3%)	0 (0.0%)	6 (20.0%)	0 (0.0%)	
	52.0[b]	-[b]	34.74[b]	-[b]	
	<0.001[b]	-[b]	<0.001[b]	-[b]	
Variceal bleeding					
Yes, N (%)	6 (20.0%)	5 (16.7%)	9 (30.0%)	4 (13.3%)	0.41
No, N (%)	24 (80.0%)	25 (83.3%)	21 (70.0%)	26 (86.7%)	
Post-banding ulcer					
Yes, N (%)	5 (16.7%)	–	5 (16.7%)	–	1.0[$]
NO, N (%)	25 (83.3%)	–	25 (83.3%)	–	

Chi squared test, [$]Fisher's Exact test.
Abbreviations: N, number.
[a] comparison between the four studied groups.
[b] comparison between pre and post results in each group.

Table 3. Mortality and causes of death within 6 months of treatment.

	Group I $N = 30$	Group II $N = 30$	Group III $N = 30$	Group IV $N = 30$	P value
Mortality					
Survived, N (%)	23 (76.7%)	24 (80.0%)	5 (16.7%)	6 (20.0%)	<0.001
Died, N (%)	7 (23.3%)	6 (20.0%)	25 (83.3%)	24 (80.0%)	
Cause of death					
Bleeding related mortality, N (%)	2 (6.7%)	0	5 (16.7%)	1 (3.3%)	0.48
HE, N (%)	2 (6.75)	2 (6.7%)	9 (30.0%)	10 (33.3%)	
ESLD (complication other than bleeding related mortality and HE), N (%)	3 (10.0%)	4 (13.3%)	11 (36.7%)	13 (43.3%)	

Chi squared test.
Abbreviations: ESLD, end stage liver disease; HE, hepatic encephalopathy; N, number.

significantly shrank after treatment. This illustrates the impact of preventative band ligation with or without sorafenib on the size of esophageal varices. As a result, 27 out of 30 (90%) of patients in group I had small esophageal varices after one session of banding, whereas 1 out of 30 (3.3%) were varice-free. After three weeks, in group III, 16 out of 30 (53.3%) of participants had small esophageal varices, while 6 out of 30 (20%) had none. Additionally, we found that group I treated with sorafenib with band ligation had a significantly smaller variceal size than group III treated with band ligation without sorafenib in the current study. The impact of sorafenib on the portal and systemic hemodynamics in seven patients with cirrhosis and hepatocellular cancer was originally evaluated by Coriat and colleagues Two of them had

Table 4. Overall Survival analysis among the studied cases.

	Mean (weeks)				Median (weeks)			
				95% CI				95% CI
Groups	Estimate	SE	Lower Bound	Upper Bound	Estimate	SE	Lower Bound	Upper Bound
Group 1			22.29	23.65	Not reached			
Group 2	22.87	0.52	21.84	23.89	Not reached			
Group 3	14.77	0.95	12.90	16.64	12.0	0.84	10.35	13.65
Group 4	15.63	0.90	13.87	17.40	14.0	0.91	12.23	15.77
Overall	19.06	0.51	18.07	20.05	Not reached			
Log rank	59.58							
P value	<0.001							

Abbreviations: CI, confidence interval; SE, standard error.

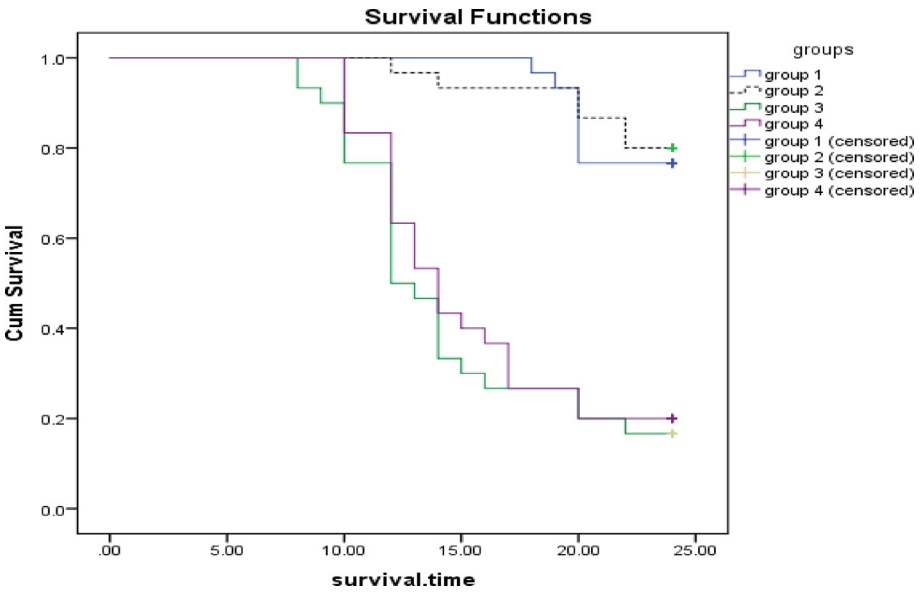

Fig. 1. Kaplan-Meyer graph for survival of different studied groups.

Child-Turcotte-Pugh (CTP) class B, while five of them had CTP class A. 400 mg of sorafenib was given twice daily for one month. At least a 36% reduction in portal blood flow was observed Coriat and colleagues.[25] Our findings demonstrated that prophylactic beta blockers had no impact on the size of esophageal varices, whether they were treated with sorafenib or not. This is comparable with an earlier meta-analysis, which revealed that nonselective betablockers did not work to stop varices from enlarging in cirrhotic patients Kumar and colleagues.[26]

These findings also showed that band ligation could shrink varices while having no impact on bleeding. The authors contend that the severity of liver disease and size of esophageal varices, rather than changes in coagulation test results, are associated with upper gastrointestinal bleeding after endoscopic variceal ligation. A previous study found that changes in coagulation test results are common in advanced liver disease, and it can be hypothesized that endoscopic variceal ligation related bleeding in cirrhosis patients may be attributable to these coagulation disturbances, portal hypertension, and CTP Drolz and colleagues.[27]

In the current study, there was no difference in variceal bleeding across the 4 examined groups within 6 months, demonstrating the effectiveness of beta blockers and variceal bandligation in avoiding variceal bleeding. In comparison with a placebo, nonselective betablockers and variceal band ligation have been shown to be much more effective at preventing variceal bleeding. Betablockers and variceal band ligation, however, produced inconsistent results when they were evaluated side by side in clinical trials. A previous study contrasting variceal band ligation with betablockers found no discernible difference between the two therapies Drastich and colleagues,[28] while one experiment found that individuals receiving variceal band ligation had much lower rates of bleeding and mortality than those receiving propranolol Jensen and colleagues.[29] According to a prior study, carvedilol had a better success rate than propranolol and fewer adverse effects, which did not require treatment interruption Abd ElRahim and colleagues.[30] Additionally, prior research suggested that carvedilol is a good drug that effectively prevents variceal bleeding by lowering portal pressure Kalambokis and colleagues.[31] Similar to our findings, a previous trial on cirrhosis patients with esophageal varices revealed no evidence of a difference in the incidence of the first bleeding episode, bleeding-related death, or all-cause mortality between carvedilol and variceal band ligation de Mattos and colleagues.[32]

The current study's findings on survival revealed that 23 out of 30 (76.7%) in group I and 24 out of 30 (80%) in group II (those receiving Sorafenib treatment) had significantly greater survival rates than groups III and IV (not treated with Sorafenib) within 6 months follow-up. The two renowned phase III clinical studies, SHARP and Oriental, have found that the use of sorafenib in patients with advanced stage HCC can increase overall survival by 44% and 47%, decrease time to progression by 74% and 73%, and reduce mortality risk by 31% and 32%, respectively

Cheng and colleagues, Llovet and colleagues.[6,33] Also, It was demonstrated that Sorafenib in many research studies had antifibrotic properties by different modalities by hepatic stellate cells inactivation or induction of their apoaptosis, supression of epigenetic alterations involved in the liver fibrosis Ma and colleagues, Chen and colleagues, Yuan and colleagues.[7,34,35]

Complications such as end-stage liver disease, bleeding-related mortality, and hepatic encephalopathy were much less common in groups I and II (those receiving sorafenib treatment) than in groups III and IV (not treated with Sorafenib), according to the results of the current study. Sorafenib can compromise hepatic function by decreasing portal blood flow, as Sorafenib induces significant vasoconstriction of the portal venous area and significantly reduced portal venous flow, according to Doppler ultrasonography in patients with unresectable HCC Hidaka and colleagues.[4] The high increased survival under treatment with Sorafenib may be because that Sorafenib is a small molecular inhibitor of several tyrosine protein (VEGFR and platelet-derived growth factor receptor) and Raf kinases (more avidly C-Raf than B-Raf). Sorafenib also inhibits some intracellular serine/threonine kinases Lencioni and colleagues, Raoul and colleagues.[36,37]

Although, increased survival in groups I and II than groups III and IV, the causes of mortality were not changed significantly among the studies groups.

4.1. Conclusion

Based on the data from our investigation, we came to the following conclusions: (a) Band ligation or beta-blockers were equivocal in primary prophylaxis of variceal bleeding in HCC patients with malignant PVT and large OV treated with Sorafenib. (b) There were shrinkage of OV treated with banding than beta-blockers and was efficacious in those treated with Sorafenib. (c) The advantage of the doubling use of beta-blockers or band ligation in primary prophylaxis of OV bleeding plus treatment with Sorafenib in ameliorating survival in HCC patients with large OV and PVT was unnegligable. While choosing and treating HCC patients with large, risky OV and PVT, these research findings had to be taken into consideration.

Authors' contribution

A A M: Study conception, design, data acquisition, analysis, interpretation, and drafting; A M M M: Study conception, design, data acquisition, analysis, interpretation, and drafting; M A e: Reviewing it critically for significant intellectual content; R A A: Data acquisition, analysis, interpretation; M A R: Reviewing it critically for significant intellectual content.

Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

Acknowledgements

None.

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