



Efficacy of Octreotide Versus Terlipressin along with Endoscopic Variceal Ligation (EVL) in Preventing Re-bleeding and Mortality in Acute Bleeding Esophageal Varices in Cirrhosis: A Randomized Prospective Study

Sunayana Lomte¹, Sourya Acharya^{2*} and Vijendra Kirnake²

¹Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha. India.

²Department of Gastroenterology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha. India.

Authors' contributions

This work was carried out in collaboration among all authors. Author SL designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SA and VK managed the analyses of the study. Author VK managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i32B31748

Editor(s):

(1) Dr. Barkat Ali Khan, Gomal University, Pakistan.

Reviewers:

(1) Hasta Handayani Idrus, Universitas Muslim Indonesia, Indonesia.

(2) Sunny, Chi Lik Au, Tung Wah Eastern Hospital, China.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/68601>

Study Protocol

Received 25 March 2021

Accepted 31 May 2021

Published 22 June 2021

ABSTRACT

Background: Octreotide and terlipressin are two pharmacologic drugs used as an adjuvant therapy in the treatment of acute esophageal variceal bleeding. Large enough clinical trial data is not available, in comparing the efficacy of octreotide versus terlipressin as an adjunct to EVL for control of variceal bleed. Still, there is a scarcity of data on which is the better efficient drug amongst terlipressin and octreotide to control 5 days rebleeding.

Aim: To compare efficacy of octreotide versus terlipressin in preventing the 6 weeks mortality (primary outcome) and 5 days rebleeding (secondary outcome) in cases of acute esophageal variceal bleeding.

*Corresponding author: E-mail: souryaacharya74@gmail.com;

Method: All the patients of cirrhosis of liver presenting with upper gastrointestinal bleeding admitted in the Medicine Intensive Care Unit(MICU) at Acharya Vinoba Bhave Rural Hospital (AVBRH) will be enrolled. In this Randomized Prospective study ,patients presenting with acute esophageal variceal bleed, after diagnostic endoscopy during a period of one year (august 2020 to july 2021) will be randomised into two group by simple randomisation with chits: Group A will receive Terlipressin while Group B will receive Octreotide for 5 days combined with esophageal variceal ligation. These two groups will be compared in terms of hemodynamic effects, child pugh score, MELD (Model for End stage Liver Disease) score to predict 6 weeks mortality as primary outcome and 5 day treatment failure as secondary outcome according to Bavino VI consensus statement.

Expected results: From our study we are anticipating that both octreotide and terlipressin will be equally efficacious in controlling the EVB when given along with EVL therapy and also there will be no difference in both the drugs in preventing 6 weeks mortality and 5 days rebleeding.

Conclusion: There will be no significant difference between Terlipressin and Octreotide in preventing 6 week mortality and 5 day rebleeding in bleeding esophageal varices when given along with EVL therapy.

Keywords: Esophageal Variceal Ligation (EVL); Esophageal Variceal Bleed (EVB); octreotide; terlipressin.

1. INTRODUCTION

In cases of cirrhosis of liver with portal hypertension, acute variceal bleed presents as a life threatening complication .Esophageal varices are seen in 30% of cases who have compensated cirrhosis and in about 60% of cases who have decompensated cirrhosis [1]. EVB is seen in 10-20% of cases of cirrhosis of liver yearly and commonly in patients with bigger varices [2].

In cases of cirrhosis of liver causes of upper GI bleed are divided into two groups: bleeding due to portal hypertension and bleeding due to non portal hypertension. The gastroesophageal varices and portal hypertensive gastropathy are included in the bleeding due to portal hypertension and peptic ulcer, erosive gastritis, reflux esophagitis, Mallory–Weiss syndrome, tumors are included in the bleeding due to non-portal hypertensive factors [3].

In cases of liver cirrhosis without varices the rate of occurring new varices is 5-10% annually [4]. After the development of varices it gets larger in size and ruptures to bleed and it consists mortality rate of 7%-15%.Deranged liver function, red wale signs, size of the varix ,these are the factors responsible for the variceal bleeding. As esophageal bleed is the complication of portal hypertension in cases of cirrhosis of liver comprises greater than two-thirds of all the bleeding events. So that every subject with cirrhosis of liver and GI bleed must be managed as having esophageal variceal bleeding till

definite diagnosis is confirmed by endoscopic approach [4].

Actual therapy modalities are able to suppress bleed in greater than 80% of cases. In the rest of the 20% of the cases, either there is difficulty in suppression of bleed or the recurrence of bleed in the first 6 weeks following early bleeding event, with the greater possibility of bleeding in the first 5 days can happen [4-7]. Following 6 weeks after the first event of bleed,the chances of bleeding are similar to those at the time of commencement of bleed. The first 5 days rebleeding is related to increase in mortality and was analysed in many studies as a primary outcome stated as 5 days therapy failure [4,8].

EVB is a critical condition which can lead to high mortality in spite of proper treatment. An endoscopic approach with drug therapy is able to suppress the bleed in almost 70-80% cases of variceal bleed [9]. The recommended preferred procedure for variceal bleeding till now is endoscopic variceal ligation (EVL).The drug therapy is the recommended modality when used with the EVL for the management of variceal bleed. Till now, Octreotide and terlipressin are the two preferred drugs for the management of variceal bleeding. These vasoactive drugs should be started immediately whenever variceal bleed is suspected because 25% of subjects die very early during continous bleeding.If vasoactive drugs are given before endoscopy it provides better endoscopic view for accurate diagnosis. The effects of octreotide and terlipressin have

been affirmed equal to the endoscopic approach as stated in other randomized studies [4,10,11].

In cirrhotic patients continuous intravenous octreotide therapy has been suggested to control the bleeding from oesophageal varices as it is able to decrease portal pressure and splanchnic circulation. In EVB octreotide is safe enough [12,13]. Terlipressin, through its splanchnic vasoconstricting activity reduces portal hypertension [14]. Terlipressin has no plasminogen activating activity so there is least possibility of aggravation of coronary ischemia [15].

In patients with acute EVB, a study has shown that drug therapy with EVL gives better results in attaining hemostasis than EVL without drug therapy [16]. In a meta analysis it was found that drug therapy in combination with endoscopic approach was much more beneficial in attaining early control of esophageal variceal bleed and 5 days of hemostasis [17]. However there have not been extensive studies comparing terlipressin and octreotide along with EVL.

In the management of variceal bleed till now there is no sufficient data available which is comparing efficacy of octreotide versus terlipressin as an adjunct to EVL [18]. Thus we planned a randomized prospective study to compare the efficacy of octreotide and terlipressin in combination with EVL in patients of cirrhosis of liver with EVB.

2. MATERIALS AND METHODS

2.1 Study Population

All the cases of cirrhosis of liver with upper gastrointestinal bleeding admitted in Medicine Intensive Care Unit (MICU) at Acharya Vinoba Bhave Rural Hospital (AVBRH) will be enrolled in the study.

In this Randomised Prospective study, cases of acute esophageal variceal bleed, after diagnostic endoscopy during a period of one year (August 2020 to July 2021) will be included.

2.2 Inclusion Criteria

All the subjects with liver cirrhosis having esophageal varices diagnosed on endoscopy presenting with acute variceal bleed of both genders having age > 18 years who will come to medicine ICU of AVBRH Sawangi (Meghe) Wardha will be included in the study.

2.3 Exclusion Criteria

2.3.1 Following patients will be excluded from study

Patients with non-variceal bleeding or gastric variceal/ portal hypertensive gastropathy associated bleeding detected by endoscopy.

Cases with prior history IHD.
Patient not willing to participate in the study.

2.3.2 Randomization

After diagnostic endoscopy, Patients with esophageal variceal bleed will be divided into two groups by simple randomization with chits: Group A will receive Terlipressin 2mg IV initially and 1 mg IV 6 hourly for 5 days while Group B will receive Octreotide 25µg/hour IV continuous infusion for 5 days combined with esophageal variceal ligation.

2.4 Assessment Criteria

The selected cases will receive monitoring of the non-invasive cardiac and hemodynamic parameters which includes heart rate, cardiac rhythm, blood pressure, and O₂ saturation and will be registered in the patients chart hourly by nurse as per the routine protocol of the intensive care unit of the hospital.

Hemoglobin (Hb) will be assessed 6 hourly for first 48 hours and then 12 hourly upto patient gets discharge. Serum creatinine and liver function test will be assessed 12 hourly. Blood transfusion will be done for maintenance of HB above 8gm/dl. Transfusion of platelets and Fresh frozen plasma will be advised as per the requirement. All the cases will receive supportive therapy with IV fluids, prophylactic antibiotics (inj. Ceftriaxone), blood sugar monitoring.

The selected patients will receive continuous monitoring of hematemesis, blood in nasogastric aspirate, melena as these variables are found to predict control of bleeding in other studies [18,19]. Endoscopic variceal band ligation will be done in 24 hours of admission.

Bavino consensus workshops has explained the risk factors, diagnostic assessment, complication and proper management protocol of portal hypertension and established new definitions of key events in portal hypertension and variceal bleeding in cirrhosis of liver. It also has described

recommendations for the planning of clinical trials. The Bavino VI consensus workshop was revised in 2015 which entitled as Stratifying risk and individualizing care for portal hypertension. The aim of this consensus workshop was to produce awareness for the application of invasive and non-invasive methods for the screening of gastroesophageal varices and portal hypertension, management of the acute bleeding episodes, prevention of rebleeding in cases of cirrhosis of liver [20].

The latest Bavino VI consensus statement has revised the definition of Bavino V and proposed key events related to bleeding episodes as:

- Six weeks mortality after initial standard control (drugs plus EVL) of esophageal variceal bleeding should be primary endpoint of therapy related studies for acute variceal bleeding.
- According to Baveno VI criteria: Secondary endpoints are - 5 day treatment failure, requirement of blood transfusions, ICU stay.
- Blood transfusion should be done to maintain HB level between 7-8gm/dl.
- Child Pugh class variables /score , Updated MELD score, are the variables consistently predicts six weeks mortality and 5 day rebleeding.
- Whenever there is suspicion of variceal bleeding, vasoactive drugs (octreotide, terlipressin) should be started before endoscopy. These vasoactive drugs should be given in combination with the endoscopic band ligation for up to five days.

Primary end points: In our study 6 weeks mortality is the primary outcome.

Secondary end point: 5 days treatment failure is the secondary outcome.

Child-Pugh class variables/score, the updated MELD score will be the variables included in this study to predict six weeks mortality and 5 days rebleeding as per Baveno VI consensus statement [20].

Child Pugh score: Child Pugh score is assessed by variables such as encephalopathy, ascites, bilirubin, albumin, PT-INR. According to the score, there are 3 stages which explains severity of liver disease and mortality risk.

Child Pugh class A- 5-6 points suggests Mild form of disease and low mortality risk

Child Pugh class B-7-9 points suggests Moderate form of disease and moderate mortality risk

Child Pugh class C-10-15 points suggests Severe form of disease and highest mortality risk

Updated MELD score: Updated MELD score assessed by formula :

$$\text{MELD score} = 3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$$

If MELD score is more than 18 in first 24 hours ,its highly suggestive of increased risk of 6 weeks mortality and 5 days rebleeding [21].

The two groups in this study, group A (receiving terlipressin) and group B (receiving octreotide) along with EVL will be compared in terms of hemodynamic effects, Childs Pughs score /variables, Updated MELD score/Variables which predicts 6 weeks mortality and 5 days treatment failure. The outcome will be recorded in terms of control of bleeding, re-bleeding within 5 days of treatment and mortality at 6 weeks.

Biochemical investigations: Hemoglobin level will be estimated by Coulter method, liver function test, serum albumin and serum creatinine will be estimated by Vitros 5600 method, PT-INR will be estimated by semiautomatic CL analyser.

Study sample: Sample size formula with desired error of margin

$$N = \frac{Z\alpha/2^2 * p * (1-p)}{D^2}$$

Where $Z\alpha/2$ is the level of significance at 5% i.e. 95% confidence interval =1.96

P= Prevalence of liver cirrhosis in Indian population = 5%=0.05

D= Desired error of margin = 6% = 0.06

$$N = \frac{1.96^2 * 0.05 * (1-0.05)}{(0.06)^2} = 50.68$$

N=51 patients are needed in the study.

In this study, we will have to collect data for at least 60 patients with upper GI bleed. Sixty patients will be divided into Group A (30) and Group B (30) patients each.

3. DATA ANALYSIS

An analysis of patients will be carried out according to the protocol and intention to treat analysis. Distribution of frequency will be analysed on the basis of mean \pm 1s.d. mainly for quantitative variables. In Univariate analysis, with the help of χ^2 test or Fishers exact test the categorical variables will be compared in the groups. The comparison of the means in the two treatment groups for continuous variable will be done by using the independent sample t test. The recognition of components which are related to prolonged hospital stay hours will be analysed by using Cox regression analysis.

4. EXPECTED RESULTS

From our study we are anticipating that both octreotide and terlipressin will be equally efficacious in controlling the EVB when given along with EVL therapy and also there will be no difference in both the drugs in preventing 6 weeks mortality and 5 days rebleeding.

5. DISCUSSION

This study will highlight the head to head comparison between octreotide and terlipressin when used with EVL in bleeding esophageal varices in preventing 6 weeks mortality as primary endpoint as per Bavino VI Consensus statement.

This study will also individually ascertain the effects of hemodynamics, Child Pugh's staging, modified MELD score in various variables like rebleeding, salvage therapy, ICU stay in variceal bleeding in each group. So that appropriate initial drug preference may be prioritized, and appropriate variables which have an impact on rebleeding and mortality may be targeted early on.

The result of the study will be no significant difference noted between octreotide and terlipressin in preventing 6 weeks mortality and 5 days rebleeding in esophageal variceal bleed when given along with EVL therapy.

A Double Blind Randomized placebo controlled trial by Abid S et al stated that for the management of acute variceal bleed the effectiveness of terlipressin was not inferior to octreotide as an adjunct therapy [18]. A comparative study by Arzinda Fatima et al found that the subjects treated with terlipressin had

better control of bleeding, less chances of rebleeding, reduced mortality rates than patients treated with octreotide [19].

A prospective randomized hemodynamic study by Baik SK et al had shown that the effects of octreotide on hemodynamics were transient as compared to terlipressin [22].

A comparatively small randomized study of 30 patients by Campisi C et al from Italy stated that terlipressin was more effective than octreotide when given as a single drug therapy in esophageal variceal bleed [23].

A Double Blind Randomized controlled trial by Feu F et al found that octreotide and terlipressin were equal in efficacy which can suppress the EVB [24].

A Cochrane systemic review by Ioannou G et al had suggested that terlipressin could be selected as a first line of drug for the management of EVB as it was able to reduce the mortality rate by upto 34% [25]. As in our study we are expecting to find no any observable difference in the mortality in two treatment groups when given along with EVL.

A Cochrane systemic review by Ioannou G et al had demonstrated the adverse effects of terlipressin such as ischemic heart disease, effects of withdrawal of drug and deaths, also stated no any difference in controlling bleeding, rebleeding in terlipressin and octreotide [25]. But the adverse effects of terlipressin in our study will not be evaluated as cases with ischemic heart disease will be excluded from the study for the ethical purpose. A number of studies on cirrhosis of liver [26-28] and related complications [29-30] were reported. Also a few related studies were reviewed [31-33].

This study will also compare the effects of two drugs terlipressin and octreotide on the ICU stay duration in variceal bleed, but no other studies in the past had evaluated effects of terlipressin and octreotide on the length of stay in ICU, so more extensive trials are needed in this direction.

6. CONCLUSION

There will be no significant difference between octreotide and terlipressin in preventing 6 weeks mortality and 5 days rebleeding in bleeding esophageal varices when given along with EVL therapy.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

Approval will be obtained from the Ethics Committee of Institution and consent will be taken from the patients participating in this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology*. 1995;22(1):332-54. DOI: 10.1002/hep.1840220145. PMID: 7601427.
2. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. *N Engl J Med*. 1988;319(15):983-9. DOI: 10.1056/NEJM198810133191505. PMID: 3262200.
3. Cremers I, Ribeiro S. Management of variceal and nonvariceal upper gastrointestinal bleeding in patients with cirrhosis. *Therap Adv Gastroenterol*. 2014;7(5):206-16. DOI: 10.1177/1756283X14538688. PMID: 25177367; PMCID: PMC4107701.
4. Biecker E. Gastrointestinal Bleeding in Cirrhotic Patients with Portal Hypertension. *ISRN Hepatol*. 2013;2013:541836. DOI: 10.1155/2013/541836. PMID: 27335828; PMCID: PMC4890899.
5. D'Amico G, De Franchis R; Cooperative Study Group. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology*. 2003;38(3):599-612. DOI: 10.1053/jhep.2003.50385. PMID: 12939586.
6. P. A. McCormick and C. O'Keefe, "Improving prognosis following a first variceal haemorrhage over four decades," *Gut*. 2001;49(5):682-685.
7. Augustin S, Muntaner L, Altamirano JT, Gonzalez A, Saperas E, Dot J, et al. Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. *Clin Gastroenterol Hepatol*. 2009;7:1347-1354.
8. Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology*. 1981;80(4):800-9. PMID: 6970703.
9. D'Amico G, Pietrosi G, Tarantino I, Pagliaro L. Emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis: a Cochrane meta-analysis. *Gastroenterology*. 2003;124(5):1277-91. DOI: 10.1016/s0016-5085(03)00269-5. PMID: 12730868.
10. Escorsell A, Ruiz del Arbol L, Planas R, Albillos A, Bañares R, Calès P, Pateron D, Bernard B, Vinel JP, Bosch J. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology*. 2000;32(3):471-6. DOI: 10.1053/jhep.2000.16601. PMID: 10960437.
11. Bildoza M, Kravetz D, Argonz J, Romero G, Suarez A, Jmelnitzky A, Fainberg M, Fassio E, Berreta J, Romero G, Landeira G, Martinez H, Bosco A, Guevara M, Valero J, Chopita N, Berenstein G, Terg R. Efficacy of octreotide and sclerotherapy in the treatment of acute variceal bleeding in cirrhotic patients. A prospective, multicentric, and randomized clinical trial. *Scand J Gastroenterol*. 2000;35(4):419-25. DOI: 10.1080/003655200750024001. PMID: 10831267.
12. Besson I, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, Hochain P, Larricq J, Gourlaouen A, Ribard D, et al. Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med*. 1995;333(9):555-60. DOI: 10.1056/NEJM199508313330904. PMID: 7623904.

13. De Franchis R. Somatostatin, somatostatin analogues and other vasoactive drugs in the treatment of bleeding oesophageal varices. *Dig Liver Dis.* 2004;36Suppl1:S93-100.
DOI: 10.1016/j.dld.2003.11.017.
PMID: 15077917.
14. Burroughs AK. Pharmacological treatment of acute variceal bleeding. *Digestion.* 1998;59Suppl2:28-36.
DOI: 10.1159/000051417.
PMID: 9718416.
15. Douglas JG, Forrest JA, Prowse CV, Cash JD, Finlayson ND. Effects of lysine vasopressin and glypressin on the fibrinolytic system in cirrhosis. *Gut.* 1979;20(7):565-7.
DOI: 10.1136/gut.20.7.565.
PMID: 488751;
PMCID: PMC1412506.
16. Calès P, Masliah C, Bernard B, Garnier PP, Silvain C, Szostak-Talbodec N, Bronowicki JP, Ribard D, Botta-Fridlund D, Hillon P, Besseghir K, Lebrec D; French Club for the Study of Portal Hypertension. Early administration of vaptotide for variceal bleeding in patients with cirrhosis. *N Engl J Med.* 2001;344(1):23-8.
DOI: 10.1056/NEJM200101043440104.
PMID: 11136956.
17. Bañares R, Albillos A, Rincón D, Alonso S, González M, Ruiz-del-Arbol L, Salcedo M, Molinero LM. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. *Hepatology.* 2002;35(3):609-15.
DOI: 10.1053/jhep.2002.31354.
PMID: 11870374.
18. Abid S, Jafri W, Hamid S, Salih M, Azam Z, Mumtaz K, Shah HA, Abbas Z. Terlipressin vs. octreotide in bleeding esophageal varices as an adjuvant therapy with endoscopic band ligation: a randomized double-blind placebo-controlled trial. *Am J Gastroenterol.* 2009;104(3):617-23.
DOI: 10.1038/ajg.2008.147.
Epub 2009 Feb 17.
PMID: 19223890.
19. Fatima A, Chachar AZ, Ahmed SI, Qaisera S. Comparison of Terlipressin with Octreotide in Management of Acute Variceal Bleed in Patients with Liver Cirrhosis. *J Rawalpindi Med College.* 2017;21(3):191-6.
20. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol.* 2005;43(1):167-76.
DOI: 10.1016/j.jhep.2005.05.009. Erratum in: *J Hepatol.* 2005;43(3):547.
PMID: 15925423.
21. Bambha K, Kim WR, Pedersen R, Bida JP, Kremers WK, Kamath PS. Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. *Gut.* 2008;57(6):814-20.
DOI: 10.1136/gut.2007.137489.
Epub 2008 Feb 4.
PMID: 18250126.
22. Baik SK, Jeong PH, Ji SW, Yoo BS, Kim HS, Lee DK, Kwon SO, Kim YJ, Park JW, Chang SJ, Lee SS. Acute hemodynamic effects of octreotide and terlipressin in patients with cirrhosis: a randomized comparison. *Am J Gastroenterol.* 2005;100(3):631-5.
DOI: 10.1111/j.1572-0241.2005.41381.x.
PMID: 15743362.
23. Campisi C, Padula P, Peressini A, Boccardo F, Biraghi M, Casaccia M. Emorragie digestive alte. Confronto fra Terlipressina e Octreotide [Upper digestive hemorrhage. Comparison of terlipressin and octreotide]. *Minerva Chir. Italian.* 1993;48(19):1091-6.
PMID: 8309607.
24. Feu F, Ruiz del Arbol L, Bañares R, Planas R, Bosch J. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. *Variceal Bleeding Study Group. Gastroenterology.* 1996;111(5):1291-9.
DOI: 10.1053/gast.1996.v111.pm8898643.
PMID: 8898643.
25. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev.* 2003;(1):CD002147.
DOI: 10.1002/14651858.CD002147.
PMID: 12535432.
26. Kadam N, Acharya S, Shukla S, Gupta K. "Ascitic Fluid High Sensitive C-Reactive Protein (Hs-CRP). A Prognostic Marker in Cirrhosis with Spontaneous Bacterial Peritonitis." *Journal of Clinical and Diagnostic Research.* 2016;10(4):OC20-24.
Available: <https://doi.org/10.7860/JCDR/2016/17931.7610>.

27. Kirnake V, Arora A, Sharma P, Goyal M, Chawliani R, Toshniwal J, Kumar A. "Non-Invasive Aspartate Aminotransferase to Platelet Ratio Index Correlates Well with Invasive Hepatic Venous Pressure Gradient in Cirrhosis." *Indian Journal of Gastroenterology*. 2018;37:4335–41. Available:<https://doi.org/10.1007/s12664-018-0879-0>.
28. Kirnake, Vijendra, Anil Arora, Praveen Sharma, and Ashish Kumar. "Does Non-Invasive Aspartate Aminotransferase/Platelet Ratio Index (APRI) Correlates with Invasive Hepatic Venous Pressure Gradient (HVP) in Cirrhosis?" *Journal of Gastroenterology and Hepatology*. 2016;358(31):3
29. Jain, Jyoti, Ramji Singh, Shashank Banait, Nitin Verma, and Satish Waghmare. "Magnitude of Peripheral Neuropathy in Cirrhosis of Liver Patients from Central Rural India." *Annals of Indian Academy of Neurology*. 2014;17(4):409–15. Available:<https://doi.org/10.4103/0972-2327.144012>.
30. Andhale, Amol, Sourya Acharya, Samarth Shukla, Sujal Patel, Shubham Nimkar, and Mansi Patel. "An Unusual Case of Hematemesis in a Case of Cirrhosis with Portal Hypertension- in a Realm of Double Jeopardy." *Medical Science*. 2020;24(105):3579–83.
31. Khatib, Mahalaqua Nazli, Abhay Gaidhane, Shilpa Gaidhane, and Zahiruddin Quazi Syed. "Ghrelin as a Promising Therapeutic Option for Cancer Cachexia." *Cellular Physiology and Biochemistry*. 2018;48:52172–88. Available:<https://doi.org/10.1159/000492559>.
32. Tambekar, Anil, Nishant Burnase, Abhay Gaidhane, Punit Fulzele, and Zahiruddin Quazi Syed. "Comparison of Two Microscopic Methods for the Detection of Parasitic Infection in Antenatal Women in Selected Areas." *Medical Science*. 2020;24:102557–64.
33. Tambekar, Anil, Nishant Burnase, Abhay Gaidhane, Punit Fulzele, and Zahiruddin Quazi Syed. "Foldscope Assisted Microscopy for the Examination of Soil Transmitted Helminths (STH)." *Medical Science*. 2020;24(101):102–6.

© 2021 Lomte et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/68601>