Research Paper

Antibiotic prophylaxis in the prevention of rebleeding in acute variceal hemorrhage: A randomized trial

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ABSTRACT

Objective: To assess the role of antibiotic prophylaxis in the prevention of rebleeding in acute variceal hemorrhage. **Materials and Methods:** A total of 60 patients who underwent endoscopic therapy for bleeding esophageal varices were randomized into the prophylaxis group and the on-demand group. Patients in the prophylaxis group received antibiotic prophylaxis using intravenous ofloxacin till the patient resumed oral fluids, followed by oral ofloxacin tablet for a total of 7 days. In the on-demand group, antibiotics were used only when infection was evident. Patients were monitored for rebleeding and infection during the hospital stay. **Results:** A total of 30 patients in the prophylaxis group and 26 patients in the on-demand group were analyzed. The clinical characteristics in both the groups were similar. The Child–Pugh score was around 7 in both the groups. The incidence of infection was 5/30 (16.7%) in the prophylaxis group and 7/26 (26.9%) in the on-demand group (P = 0.52). The incidence of early rebleeding in the prophylaxis vs. the on-demand group was 3 vs. 5 (P = 0.69), and the incidence of late rebleeding was 6 vs. 8 (P = 0.48). The differences were not significant. **Conclusion:** The present study shows a trend toward lower rate of early and late rebleeding, infection rate and mortality in the prophylaxis group; hence, routine use of antibiotics in all such patients may not be necessary. Further studies with a larger sample size and a longer follow-up period are required to validate the usefulness of antibiotics in these patients.

Key words: Child–Pugh score, endoscopic variceal ligation, hemetemesis, esophageal varices, ofloxacin prophylaxis, rebleeding index

INTRODUCTION

Variceal hemorrhage is a dreaded complication in patients with cirrhosis and portal hypertension. Each bleeding episode carries an increased risk of mortality. About one-third of the patients succumb to an initial bleeding episode due to failed conservative management. The survivors carry a 33% risk for rebleeding within 6 weeks, and this figure approaches 80% in the next 2 years.[1] The development of new vasoactive agents, endoscopic variceal ligation (EVL), glue injection for gastric varices and transjugular intrahepatic portacaval shunt (TIPS) has improved the prognostic outcome of the patients with variceal hemorrhage. However, the rebleeding rates are still in the vicinity of ~ 25%, which calls for further improvement in management.[2-9]

Patients with cirrhosis are vulnerable to infection and aerobic Gram negative bacilli are attributed more commonly.[10] It has been shown in various studies that infection can have a negative impact on the hemostasis, and an association between infection and failed control of variceal bleeding has been reported.[11-13]

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Some studies have reported that use of prophylactic antibiotics reduces the incidence of infection, rebleeding rates and mortality in patients with cirrhosis and portal hypertension; however, the evidence is limited and routine use of antibiotics in such patients is not universally followed.[14-17] Data regarding the use of antibiotics in Indian patients are sparse. This study was, therefore, undertaken to analyze the effect of antibiotics in the prevention of rebleeding in patients with acute variceal hemorrhage.

MATERIALS AND METHODS

This study was a nonblinded randomized control trial conducted in the Department of General Surgery JIPMER, Puducherry, India over a period of 2 years. Ethical clearance for the study was obtained from the Institute Ethical Committee and all provisions of the Declaration of Helsinki were followed in this study.

All consecutive patients with cirrhosis who presented with acute variceal hemorrhage were included in the study. The patients who had infection at the time of admission, bleeding gastric varices, patients with noncirrhotic portal hypertension, history of antibiotic use in the last 2 weeks and history of surgical or endoscopic treatment for varices in the past were excluded from the study. Informed consent was obtained from the stable patients. Consent was taken from the spouse/parents or immediate close relative in situations where the patient was unable to give consent.

Patients were initially admitted and resuscitated in the emergency medical services department where the first clinical assessment of the patients was carried out. Volume resuscitation was performed initially using 2 L of crystalloids in all patients. Packed cell blood transfusion was given to patients with systolic BP less than 90 mmHg after initial volume resuscitation or in whom the hemoglobin was less than 8. Fresh frozen plasma was transfused to patients with increased prothrombin time. Octreotide was given as 50 μg bolus and as 25 μg/h intravenous infusion to all patients who had clinical or sonographic evidence of cirrhosis and portal hypertension for 24 h or till there is no evidence of fresh bleeding. A Sengstaken Blakemore tube was inserted in the patient with uncontrolled bleeding till fresh bleeding stopped and the patient was fit to be taken up for emergency endoscopy.

Esophageal variceal hemorrhage was diagnosed by:

- Presence of hemetemesis or coffee ground vomitus and melena
- Signs of active bleeding on endoscopy, adherent clots, erosions on varices and white nipple signs
- Red-color sign over large varices without other bleeding sources.

The severity of cirrhosis was graded according to Pugh's modification of Child's scoring.

Endoscopic treatment

Endoscopy was performed as soon as possible and EVL or endoscopic variceal sclerotherapy (EVS) was performed as indicated. The severity of esophageal varices was graded based on the system suggested by Beppu *et al*.[18] EVL was performed using Saeed's six-shooter multiband ligator (Cook Medical Inc., Bloomington, IN, USA). Around six bands or less were applied in a single session. EVS was performed using 5–20 cc of polidocanol according to the grade of varices where EVL was not possible.

Post endoscopic therapy, patients were kept nil per oral and intravenous fluids for at least 24 h. Patients were discharged with nonselective β-blocker therapy (propranolol) for prophylaxis of variceal hemorrhage when hemodynamically stable and there were no evidence of hemorrhage or infection.

Patient groups

After the endoscopic therapy, patients included in the study were randomized into two groups using a computer-allocated electronic random number method with the sealed envelope technique. The groups were as follows:

Prophylaxis group

Patients in this group, after randomization, received antibiotic prophylaxis with intravenous ofloxacin 200 mg q12h for 2 days or till the oral fluids were allowed followed by oral ofloxacin 200 mg q12h for a total of 7 days.

On-demand group

Patients in this group did not receive antibiotic prophylaxis on presentation. Antibiotics were used only when infection was suspected or established.

Assessment for infection

Patients were suspected of having infection when there was fever (>38°C), hypothermia (<36°C), unexpected hemodynamic instability, tachypnea, new onset of chest symptoms like cough, dysuria, abdominal pain or distension, as well as alteration of mental state. Patients were assessed for development of septicemia, urinary tract infection, spontaneous bacterial peritonitis and pneumonia. Accordingly, patients were investigated with WBC count, chest radiography, culture and antibiotic sensitivity of urine, sputum and blood.

Patients who had no identifiable source of infection but had fever >38°C and leukocytosis >11,000/μL with neutrophilia were considered as having infections and received antibiotics on demand. For calculating incidence, the infections that occurred during the hospitalization or within 10 days of admission were taken into account. Appropriate antibiotics

were started for those patients with infection, both in the prophylactic and the on-demand group according to sensitivity pattern.

Assessment of rebleeding

Rebleeding was defined as new onset of hemetemesis, coffee-ground vomitus or melena, with an increasing pulse rate over 110 per minute and decreasing blood pressure below 90 mmHg after a 24-h period of stable vital signs following endoscopic treatment. Rebleeding within 7 days after initial control of bleeding was defined as *early rebleeding*. If rebleeding occurred, patients were treated akin to the first episode protocol. *Treatment failure* was defined as failure to control active bleeding after two attempts of endoscopic treatment, rebleeding more than twice or bleeding to death. Patients were called for follow-up endoscopy every 2–3 months after the initial management and continued till all the varices get obliterated. On the follow-up visit, they were asked for any history suggestive of bleeding. Patients were followed-up until death or till before conclusion of the study period. *Rebleeding index* for each patient was calculated by dividing the months of follow-up by the number of rebleeding episodes plus one.

The incidence of early rebleeding, incidence of late rebleeding, rebleeding index, incidence of infection and mortality were the parameters studied in both the groups.

Statistical analysis

GraphPad InStat 3 was used for statistical analysis. The continuous parameters between the two groups were analyzed using Student's "*t*" test. Categorical data were analyzed using Fisher's exact test. A P value of < 0.05 was considered significant.

RESULTS

A total of 80 patients were assessed for eligibility. Twenty patients did not meet the inclusion criteria and hence were excluded from the study. Four patients in the on-demand group were lost to follow-up and hence excluded from the analysis [Figure 1].

Patients in both groups were comparable with regard to age, chronic alcoholism, mean Child–Pugh score, variceal grade and period of follow-up [Table 1]. EVL was possible in all the patients during initial and subsequent endoscopy except

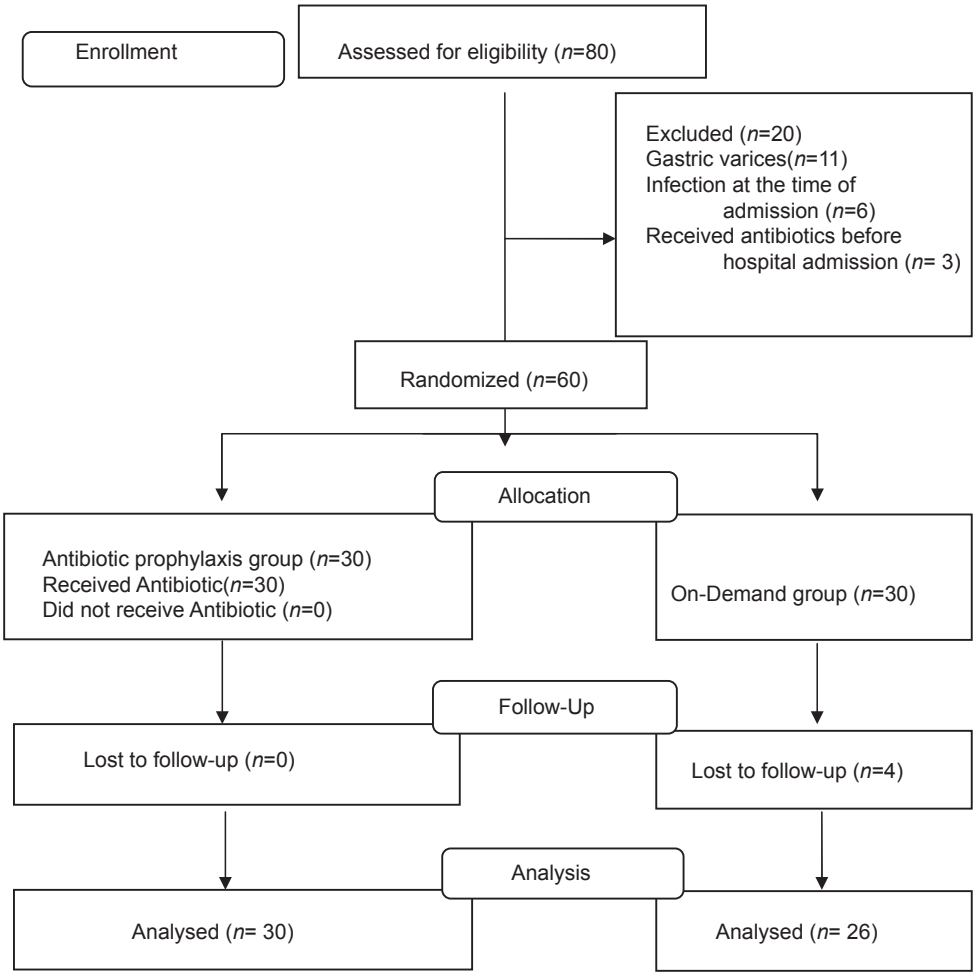

Figure 1: Consort flow chart

in two patients in the prophylaxis group in whom EVS was performed during the initial endoscopy. Two patients in each group died 24–48 h after initial endoscopic treatment due to early rebleeding. Two patients in the prophylaxis group died due to late rebleeding during the follow-up of 18 and 20 months. Three patients in the on-demand group died due to late rebleeding during the follow-up of 6, 8 and 13 months.

On analysis, no significant difference was observed between the prophylaxis and on-demand groups with regard to the early and late rebleeding rates, although the incidence of both early (3/30 vs. 5/26) and late (6/30 vs. 8/26) rebleeding were lower in patients who received antibiotic prophylaxis [Table 2]. The rebleeding index also failed to show any significant difference between the two groups [Table 2].

Similarly, no significant difference was observed with regard to mortality (4/30 vs. 5/26) between the prophylaxis and on-demand groups [Table 3]. Although the incidence of infection (5/30 vs. 7/26) was lower in patients who received antibiotic prophylaxis, this difference was not statistically significant [Table 4]. Urinary tract infection was diagnosed in two patients in the prophylaxis group and three patients in the on-demand group. Bacteremia was diagnosed in three patients in the prophylaxis group and four patients in the on-demand group.

Table 1: Demographic and clinical characteristics of the patients included in the study

	Antibiotic prophylaxis group	On-demand group	*P* value[a]
No of patients	30	26	
Age (years±SD)	41.53±2.19	44.15±2.66	0.43
Gender (m/f)	15/15	17/9	0.91
Alcohol intake (%)	40	53.84	0.67
Mean child-pugh score	7.03±1.24	7.07±0.93	0.98
Varices grade	2.13±0.62	2.1±0.65	0.94
Follow-up (mean days)	308±166.89	279±184.19	0.67

[a]Unpaired t test. SD=Standard deviation

Table 2: Comparison of the rebleeding incidences between cases and controls

	Antibiotic prophylaxis group *N* (30)	On-demand group *N* (26)	*P* value
Early rebleeding no. of patients (incidence %)	3 (10)	4[a] (15.4)	0.69[c]
Late rebleeding no. of patients (incidence %)	4[b] (13.33)	6[b] (23)	0.48[c]
Rebleeding index+SD	9.64+5.78	8.29+6.08	0.39[d]

[a]1 patient in the control group had 2 episodes of early rebleeding. [b]2 patients each in cases and control groups had 2 episodes of late rebleeding.[c]*P* value calculated for number of patients with early/late rebleeding using Fisher's exact test.[d]*P* value calculated using Unpaired *t* test. SD=Standard deviation

DISCUSSION

Variceal hemorrhage is one of the most important consequences of portal hypertension. One-fourth of the patients with varices develop hemorrhage within 2 years. The prognosis of patients with variceal hemorrhage has improved over the last two decades as our understanding of the pathophysiology of portal hypertension has improved; however, the rebleeding rate is still considerably high, around 25%. Therefore, there is still a need for a better approach to bring this rate down further.[2-7]

Studies have shown that infection adversely affects the coagulation parameters of the patients with hepatic cirrhosis and leads to prolongation of the clotting time.[12,13] It has been hypothesized that response to infection and endotoxemia results in release of multiple vasoactive substances that cause an increase in the variceal pressure due to contraction of stellate cells and also affects primary hemostasis, resulting in variceal hemorrhage. Antibiotic prophylaxis can decrease the incidence of infection in the patients with liver cirrhosis, but whether this reduction has an impact on variceal hemorrhage is still not clear. In our study, we tried to assess whether prophylactic antibiotic therapy has any effect on the rebleeding rates in patients with variceal hemorrhage.

In the present study, it was found that the early rebleeding rate was 10% for the prophylaxis group. This early rebleeding rate is slightly higher than that in the study reported by Hou *et al.* from Taiwan, where they found the rate to be 6.77%.[17] In the present study, the early rebleeding rate in the

Table 3: Comparison of the mortality between cases and controls

	Antibiotic prophylaxis group	On-demand group	*P* value[a]
Mortality due to early rebleeding (%)	2 (6.67)	2 (7.69)	1.00
Mortality due to late rebleeding (%)	2 (6.67)	3 (11.54)	0.65

[a]Fisher's exact test

Table 4: Comparison of the incidence of infections between the prophylaxis and control groups

Group	Total (%)	Infection (%)	*P* value[a]
Prophylaxis	30 (100)	5 (16.7)	0.51
Controls	26 (100)	7 (26.9)	

[a]Fisher's exact test

control group was higher at 15.4%; however, this increased early rebleeding rate in the on-demand group failed to show a statistically significant difference ($P = 0.69$). Hou *et al.* also reported a higher early rebleeding rate in the control group at 34.4%, which was significantly different than the prophylaxis group in their study ($P = 0.022$). Jun *et al.* from Korea found that none of the patients in their series had early rebleeding in the prophylaxis group. In the control group, three patients experienced early rebleeding (3/59, 5%). This difference was not statistically significant ($P = 0.24$).[16] In the same study, it was found that there was a significant difference in the early rebleeding rate when calculated for a period of 6 weeks (3/62, 4.8% vs. 12/58, 20.7%, $P = 0.01$). Hou *et al.*'s study used Terlipressin and Somatostatin as vasoactive agents whereas in the present study and in the study by Jun *et al.,* Octreotide was used. Terlipressin is the only agent that has been shown to improve survival. The efficacy of Octreotide in controlling hemorrhage has been questioned due to the development of tachyphylaxis vis-a-vis bleeding. Use of superior vasoactive agents might have contributed to reducing the rebleeding rates in the study by Hou *et al.* compared with the present study.

In our study, the late rebleeding rate was 13.33% for the prophylaxis group and 23% for the control group, which is comparatively lesser than that in the study by Jun *et al.* (34% for prophylaxis group and 57% for controls).[16] The present study was conducted over a period of 18 months, whereas Jun *et al.* conducted their study over 4 years. A shorter follow-up period might be the reason behind lower rebleeding rates in the present study. The study by Hou *et al.,* which was conducted over a period of 25 months, had a late rebleeding rate of 13.5% in the prophylaxis group, and this figure is closer to the late rebleeding rate for the prophylaxis group in the present study. The late rebleeding rate for controls was lower in their study (10%).[17]

The overall rebleeding rate in this study was 23.33% for the prophylaxis group and 38.5% for the controls. In the study by Jun *et al.,* the rebleeding rates were 34% and 62% for cases and controls, respectively, which are higher than that in the present study.[16] In the study by Hou *et al.,* the rates were 20% for the cases, which is closer to the finding in the present study, and 44.2% for the controls, which is higher than our study.[17] The cause of lower overall rebleeding rate in the present study might be the exclusion of patients with gastric varices. In a study by Sarin *et al.,* gastric varices were found to be significantly more common in bleeders than in nonbleeders (27% versus 4%), perhaps indicating that gastric varices develop at a more advanced stage of portal hypertension.[19]

In the present study, 20% of patients in the prophylaxis and 30% of patients in the control group expired. Two patients each from the prophylaxis and control groups died due to early rebleeding. Two patients from the prophylaxis and three patients from the control group died of late rebleeding. The mortality rate was 13.33% for the prophylaxis group and 19.23% for the control group in the study by Jun *et al.,* whereas in the study by Hou *et al.,* the mortality rate was 27% for the prophylaxis and 21.3% for the control groups.[16,17] The mortality in the present study is lower compared with the above studies. The reason behind this might be a shorter follow-up period and a lower Child–Pugh score of the patients in the present study. It has been shown in various studies that increase in the Child–Pugh score increases the risk of rebleeding.[20,21] The mean Child–Pugh score for the prophylaxis group was 7.03 ± 1.2 and 7.07 ± 0.9 for the control group in our study. The mean Child–Pugh score in the study by Jun *et al.* was 8.7 ± 1.9 for the prophylaxis group and 8.3 ± 2.1 for the control group. Similarly, it was 8.54 ± 1.9 for the prophylaxis group and 7.9 ± 2.04 for the control group in the study by Hou *et al*.

There were 11 patients who developed infection during the study period, five (16.7%) patients from the prophylaxis group and seven (26.9%) patients from the control group. Urinary tract infection was diagnosed in two patients in the prophylaxis group and three patients in the control group. Bacteremia was diagnosed in three patients in the prophylaxis group and four patients in the control group.

The infection rate in our study was higher than that seen in other studies. Xu *et al*. in their study had significantly less infection rate in the prophylaxis group (16%) than the no prophylactic antibiotic group (38.1%).[22] The antibiotic used in their study was intravenous cefazolin, which has a wider bacterial cover than ofloxacin, including community-acquired *Escherichia coli* and *Klebsiella pneumonia* strains. We used IV ofloxacin initially and switched to the oral route once the patient was started on a fluid diet. Bioavailability of ofloxacin during intravenous to oral switchover is excellent (>90%) compared with the intravenous cefazolin to oral cephalexin (60–90%). Switchover therapy reduces the risk of cannula-related infections and risk of thrombophlebitis and is less expensive than IV therapy, with reduction in the hidden costs that are of concern in developing countries like India and helps in earlier discharge of the patient from the hospital.[23] The incidence of infection was 3.39% in the prophylaxis group and 26.2% in the control group in the study by Hou *et al.,* which was again less than that in the present study. In the present study, all the patients were put on continuous bladder drainage whereas only 8.35% patients in the study by Hou *et al.* were catheterized. Routine catheterization might have contributed to a higher infection incidence in our study as catheterization is known to predispose to infection.

CONCLUSION

The present study shows a trend toward lower rate of early and late rebleeding, infection rate and mortality in the prophylaxis group when compared with the control group, but the differences were not significant probably due to small sample size and short follow-up and patients with moderate Child–Pugh score. Further studies with a larger sample size, a longer follow-up period and varying Child–Pugh score are required to validate the usefulness of antibiotics in patients with variceal hemorrhage.

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