# Continuing Somatostatin Does Not Prevent Rebleeding After Variceal Ligation For Acute Variceal Bleeding

**Yasser A. Abdelghani[1], Reem Yehia[2]**

[1] MD, Tropical Medicine and Gastroenterology, Minia University, Minia, Egypt.
[2]MD, Tropical Medicine and Gastroenterology, Minia University, Minia, Egypt.

***Corresponding Author:** Yasser A. Abdelghani

MD, Tropical Medicine And Gastroenterology, Minia University, Minia, Egypt. Phone No.: (+2). E-Mail: Yasser_Git1@Yahoo.Com ORCID ID: Http://Orcid.Org/0000-0002-2251-6329
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## Abstract

Background: variceal bleeding (VB) is a medical emergency. Endoscopic variceal ligation (EVL) performed quickly is beneficial. Even after EVL, somatostatin is still utilized in the VB band for 2–5 days. The advantage of continuing somatostatin after EVL is uncertain since EVL is the main method for achieving hemostasis.

Aim and objectives: to determine if continuing somatostatin after EVL is effective in reducing mortality and rebleeding.

Subjects and methods: In this study, 75 patients with variceal bleeding were divided into two treatment groups (TG); TG2 & TG5, which received somatostatin (250 microgram bolus + a continuous infusion of 500 microgram/h) for two days and five days, respectively, and one control group (TG0), which received 0.9 percent normal saline and was monitored for six weeks.

Result: There were a total of 8 rebleeds; they happened more often in the TG0 (4%) and TG2 (2.6%) and TG5 (4%) groups, albeit not statistically significantly (P=0.751). The treatment group substantially experienced more adverse drug reactions (ADRs) than the control group (P=0.003). Diarrhoea was the most frequent ADR, followed by hyperglycemia and bradycardia, with 14 patients mentioning two or more ADR. In comparison to the control group, ADR was considerably greater in the treatment groups. As the days of somatostatin medication increased, the length of the hospital stay rose considerably (P=0.041).

Conclusion: We conclude that in acute VB, there is no justification for continuing somatostatin after EVL since it had no beneficial effect on preventing rebleeding and, instead, increased the risk of ADR and length of hospital stay.

**Keywords:** Somatostatin; Variceal; Bleeding; Ligation.

## INTRODUCTION

A common medical emergency is acute variceal bleeding (VB). Endoscopic variceal ligation (EVL) performed promptly serves as a diagnostic and therapeutic tool. The current standard of care for the treatment of varices and VB includes medications that reduce portal pressure (PP) by inducing splanchnic vasoconstriction, such as non-selective beta-blockers (NSBBs; propranolol, nadolol, and carvedilol), somatostatin (SMT), and its analogues (octreotide, vapreotide), as well as vasopressin (VP) (1).

Before performing endoscopic intervention, somatostatin, a vasopressin analogue, is often administered in situations of suspected variceal haemorrhage combined with volume and blood resuscitative techniques. According to the recommended protocol, somatostatin medication is maintained for 2–5 days following EVL (first IV bolus 250 microgram, which may be repeated in the first hour if there is still bleeding, and continuous IV infusion of 250–500 microgram/h to avoid re-bleeding and death). Since these medications work by reducing blood flow to the liver and splanchnic circulation, an improvement in liver function is not something that would be anticipated. As a result, prolonged somatostatin usage is not only costly in environments where resources are few but also not entirely safe.

The advantage of maintaining somatostatin after EVL to avoid rebleeding or death in acute VB is not yet supported by a clinical study. Steatorrhea, which may be managed, diarrhoea, loose stools, malabsorption, gastrointestinal cramps, and infrequent nausea have all been identified to be somatostatin's adverse effects. Because Somatostatin prevents gallbladder contractions, around 27% of people taking it developed gallstones (2). Therefore, the rationale for continuing somatostatin

for 5 days after EVL is debatable since EVL mainly achieves hemostasis and it is yet unknown what the danger vs benefit of somatostatin treatment after EVL is.
Somatostatin use after EVL prolongs in-hospital treatment as well, increasing the financial load on the healthcare system. Evidence on the effectiveness of maintaining somatostatin after EVL in avoiding rebleeding, death, and the prevalence of adverse medication responses in acute VB is currently lacking. The purpose of the current research was to assess the advantages and disadvantages of maintaining somatostatin in acute VB patients following EVL. The study's objective was to assess how well somatostatin continued after EVL prevented an early re-bleed in acute VB.

## PATIENTS AND METHODS

Single-center prospective research was conducted at Minia University Hospital between February 1 of 2018 and February 1 of 2020 after receiving prior clearance from the Institutional Ethics Committee. The sample size was determined to be approximately 75 patients after adjusting for a -error of 0.05 with an 80 percent power and a 10% dropout, for the final analysis. The sample size was determined based on the epidemiological evidence currently available, anticipating a 30 percent incidence of re-bleed in the population with a 15 percent incidence of re-bleed in the treatment group (3). A randomized controlled clinical study with an open-label was conducted.
Three treatment groups (TG), signifying the length of somatostatin therapy following EVL—two treatment groups (TG2 and TG5), and one control group (TG0—were included in the research. Somatostatin was administered to the TG2 and TG5 groups for 2 days and 5 days, respectively, whereas 0.9 percent normal saline was administered to the TG0 control group (NS). After receiving written informed permission, all patients with endoscopically verified acute VB who had been brought to the emergency room were screened and then participated in the study in accordance with the inclusion and exclusion criteria. Early rebleeding was defined in earlier papers as a recurrence of haemorrhage within 6 weeks (4), therefore participants were monitored for 6 weeks by visits in the outpatient clinic.

### Inclusion and exclusion criteria:

All patients with endoscopy-proven acute VB who underwent EVL within 24 hours of admission, regardless of gender or age of more than 18 years, were recruited for the research. Patients with chronic renal illness, EVL, variceal bleeding for more than 24 hours, prior history of these conditions, or pregnancy were excluded from the trial. The research eliminated EVL performed more than 24 hours after admission due to hemodynamic instability or encephalopathy. Patients who had concomitant esophageal and gastric varices or portal vein thrombosis were also disqualified. Patients who were being treated with antiplatelet and/or anticoagulant medications within 4 weeks after their first presentation were also disqualified from the trial. Additionally, those with acute renal damage were disqualified.

### Methods and intervention:

Clinical information was recorded, and baseline blood tests were done on each patient to determine their risk level and develop a future care strategy. For each patient, abdominal ultrasound and an alfa-feto protein test were performed. The FIB 4 test was used as a fibrosis marker. Airway, breathing, and circulation protection received first consideration throughout care. The crystalloid infusion was provided as needed to maintain hemodynamic stability. When haemoglobin (Hb) reached the threshold level of 7 g/dL, to maintain a target Hb of 7-9 g/dL, or when there were indications of hemodynamic instability despite fluid resuscitation, blood transfusion was started. Before endoscopy, somatostatin (250 microgram bolus + 500 microgram/h continuous infusion), proton pump inhibitors, and antibiotics were quickly started in all suspect instances of VB.
The skilled gastroenterologists and hepatologists at the institution performed an endoscopy as quickly as feasible, within 24 hours of the patient's presentation, after their hemodynamics were stable and their airway was secured. EVL was performed when it was determined that the haemorrhage had a variceal origin. Following EVL, patients who met the eligibility requirements were randomly assigned to two treatment groups (TG2 & TG5) and one control group (TG0). The control group (TG0) participants got 0.9 percent normal saline (NS) IV infusion instead of somatostatin, whereas the participants in the TG2 and TG5 groups received 250 µg of IV somatostatin as a bolus plus a continuous infusion of 500 µg/h for 2 and 5 days, respectively.
Following stabilization and hemostasis, all individuals were released from surveillance and then monitored for a further six weeks by attendance visits. Somatostatin was restarted in patients in both the control and treatment groups who were not receiving it at the time of the rebleed (IV somatostatin 250 µg bolus plus a continuous infusion of 500 µg/h). Any severe VB after EVL that required repeat endoscopy, hemodynamic instability, and a large reduction in haemoglobin necessitating blood transfusion was referred to as a "re-bleed." Another effort at endoscopic hemostasis was attempted in the event of rebleeding. The length of the hospital stays, the frequency of rebleeding, and adverse drug reactions (ADRs) were compared across the research groups.

### Outcome:

The participant's occurrence of rebleeding during the 6-week follow-up was the primary outcome. Incidence of ADR, length of hospital stay, and in-hospital complications were secondary outcomes.

## STATISTICAL ANALYSIS

The SPSS 18.0 version was used to conduct the statistical analysis. The categorical data from the descriptive statistics were presented as percentages, proportions, and graphical displays. In order to examine the categorical endpoints, a non-

parametric Pearson's chi-square test was used. The mean, range, and standard deviation of the parametric data were shown. Using one-way ANOVA, the mean values for distinct groups were compared. A P-value of 0.05 or below was regarded as statistically significant.

## RESULTS

All 75 participants had liver cirrhosis, which was verified in all cases; 63 (84%) of them were men. The study population's mean age was similar amongst the groups (P=0.983) and was 47.28 (12.005), 48.22 (10.212), and 47.04 (11.563) in TG0, TG2, and TG5, respectively. Body mass index (BMI) was 24.1 (3.2) kg/m2, which was the average. The research groups had similar gender, age, and BMI distributions (Table 1).

Twelve percent of patients had diabetes mellitus, two had hypertension, and one had the chronic obstructive pulmonary disease as concomitant condition (COPD). Chronic hepatitis B was discovered in 8% of cases, while chronic hepatitis C was found in 2.6%. Only one individual was an alcoholic, while 46.6 percent of participants smoked. The research groups had comparable distributions of comorbidities and risk factors (Table 1). When the study groups were compared, 52 percent of subjects experienced tachycardia (PR 100), 24 percent had hypotension (SBP 90 mmHg), and 6.6 percent were hypoxic (SPO2 90%). (Table 1).

The research population's mean haemoglobin (Hb), total leucocyte count (TLC), and platelet counts were 7.76 (2.3) g/dL, 10.10 x $10^9$ /L (4.8), and 108.5 x $10^9$ /L (85.0), respectively. A Hb 7 gm/dL, which was seen in 39.8% of individuals, was deemed clinically severe anaemia needing a blood transfusion. Among the subjects, 70.3 % had thrombocytopenia. In 55.6 percent of patients, coagulopathy (INR > 1.5) was found (Table 2).

It was possible to follow up with all 75 participants for 6 weeks. During the follow-up, no participant was overlooked. Over the course of an 6-week follow-up, 8 patients (10.6 percent) had rebleeding. Re-bleeding occurred in the TG0 (4%) group, then in the TG2 (2.6%) and TG5 (4%) groups (Table 3). P=0.751) without statistical significance. Rebleeding was further separated into early (within 7 days) and late (beyond 7 days) rebleeding (after 1 week to 6 weeks). All 75 participants could be tracked for six weeks, and only 1 (1.4%) patient in the TG0 group had an early rebleed.

The remaining 7 patients had late re-bleed at rates of 4.6%, 2.6%, and 2.6% in the TG0, TG2, and TG5 groups, respectively (Table 3), although these rates were not statistically significant (P=0.888). At 6 weeks follow-up, the total death rate (15 patients) was 20%. Out of 75 patients, 27 (or 36% of them) had an adverse drug response (ADR). Most often in the TG5 study group (22.6%), then in TG2 (10.6%) and TG0 (2.6%) research groups (Table 3). In comparison to the control group, ADRs were considerably greater in the treatment group (P=0.003). Diarrhoea was the most frequent ADR, followed by hyperglycemia and bradycardia, with 14 patients mentioning two or more ADR. In comparison to the control group, ADR was considerably greater in the treatment groups (Table 3).

Shocking (which affected eight individuals), encephalopathy (which affected seven people), and sepsis were the three most frequent hospital complications (seven patients). Three patients needed mechanical ventilation, and one patient contracted pneumonia hospitalized (Table 3). Even though the TG5 group had a greater rate of hospital sequelae, only shock (P=0.034) was statistically significant. For all patients, the average length of stay in the hospital was 4.19 (around 1.86) days. The average hospital stays in the TG0, TG2, and TG5 groups were 2.60 (0.50), 3.74 (0.57), and 6.73 (0.65) days, respectively (Table 3). Even as the number of days of somatostatin medication increased, the length of the hospital stay rose considerably (P=0.041).

## DISCUSSION

Variceal bleeding is a serious side effect of portal hypertension and the main killer of cirrhotic individuals (5). Over the last three decades, advancements in diagnosis and treatment have significantly improved the prognosis for this condition. Early mortality after an incident of acute variceal bleeding (AVB) is very high (15–24%). (6). Controlling bleeding, preventing early recurrence, and preventing 6-week mortality are the initial goals of treatment (7).

Prompt EVL serves both therapeutic and diagnostic purposes. Before EVL, it is important to evaluate the patient's airways, breathing, and hemodynamic stability by maintaining circulatory volume using crystalloids. The goal of blood transfusion is a Hb of less than 7 g/dL. (8). As soon as feasible, ideally within 24 hours after the presentation, an endoscopy is performed. When the variceal cause of bleeding is identified during endoscopy, EVL should be performed right away. Rebleeding, however, is common and may occur in up to 30% to 40% of instances (9).

Another effort at endoscopic hemostasis is made in the event of rebleeding. Certain therapies using a transjugular intrahepatic portosystemic shunt are used for refractory bleeding. Proton pump inhibitors, antibiotics, and somatostatin are often utilized as adjuvant pharmacotherapy in acute VB. An analogue of vasopressin is somatostatin. Its pharmacological impact is carried out by activating the vascular smooth muscle vasopressin-1 receptors, which results in vasoconstriction of the splanchnic circulation and a reduction in portal flow and hepatic venous pressure gradient (2).

Somatostatin (250 µg bolus + 500 µg/h continuous infusion) is immediately utilized in any suspected instance of VB before the endoscopic operation and maintained for 2–5 days following EVL to avoid re-bleed and death, in accordance with recommendations (1). Somatostatin use over an extended period of time is not entirely risk-free. In countries where resources are few, it raises the burden and cost of medical treatment. Additionally, somatostatin has been linked to several potentially fatal issues related to the heart, the lungs, ischemia circulation, and electrolyte balance (2-4). As EVL is the primary method of achieving hemostasis, the usefulness of continuing somatostatin for a further five days seems questionable. A prospective, open-label randomized controlled clinical trial was used for the current investigation. This study's main goal was to assess the reduction in mortality and rebleeding after successful EVL for acute variceal bleeding.

Somatostatin considerably improves control of bleeding when compared to placebo (63 percent vs. 46 percent), but not survival, according to randomized studies and meta-analyses [10, 11, 12]. However, although having a superior safety profile, it has a comparable positive impact on the management of bleeding, early rebleeding, and mortality as terlipressin. Somatostatin's significant adverse effects are exceedingly uncommon. Up to 21% of individuals have mild side effects such as vomiting and hyperglycemia, which are frequently manageable.

Following an initial 250 µg bolus, somatostatin is typically administered at a constant perfusion dosage of 250-500 µg/h (which can be repeated up to 3 times during the first hour). The infusion has to be continued for 5 days [14] or until there has been no bleeding for 24 hours. Patients with more severe bleeding may respond better to 500 µ/h dosages, which have been linked to larger HVPG reductions [15, 16]. Studies comparing endoscopic sclerotherapy and active medication therapy for acute VB have been conducted. In these 13 trials (8 vs octreotide and 5 versus somatostatin), there were no discernible differences between the two medications in terms of bleeding control or mortality, according to a meta-analysis [17]. Somatostatin was, nevertheless, considerably favoured by variations in major adverse effects. As an endoscopic modality, EVL has not been directly compared with any medications.

So far, there hasn't been a clinical investigation to establish the length and justification of somatostatin treatment after EVL. In this research, we contrasted the various somatostatin treatment durations after successful EVL. In our investigation, there were no significant differences between the groups in the re-bleed rate (TABLE 3; $P > 0.05$). Rebleeding happened in 8 (10.6 percent) of the individuals in our research. Only one patient—in the G0 group, which did not receive somatostatin—experienced an early relapse. Four patients in the treatment group (TG2 & TG5) overall had rebleeding, compared to four in the control group (TG0). Therefore, re-bleeding was comparable across individuals who got somatostatin and those who did not. Early re-bleeding was less common in our research compared to the previous trials since all patients had EVL within 24 hours of their arrival. The use of somatostatin after EVL to prevent re-bleeding was not useful in our trial since hemostasis could be attained with EVL. Using somatostatin after EVL did not improve the ability to manage re-bleed, according to our research.

Transient paroxysmal supraventricular tachycardia, hyperglycemia, bradycardia, and stomach discomfort were all described by Villanueva C et al (18). In our research, we found some ADR. Diarrhoea was the most frequent, then hyperglycemia, bradycardia, and generalized abdominal discomfort (TABLE 3). Some reports of somatostatin-related ischemia problems in internal and external organs, including the heart, have been made (19, 20). None of the subjects in our research reported experiencing chest discomfort, and none had signs of peripheral ischemia or ischemic heart disease. Compared to the TG2 and control groups, the TG5 group had the most ADR. Therefore, our research indicated that utilizing somatostatin for a longer period of time may cause a lot of ADRs. The majority of these ADRs were small, self-limiting, and transient and required constant supervision. Similar to the above, despite the data being statistically insignificant, hospital problems such as the requirement for mechanical ventilation, sepsis, encephalopathy, and shock were more common among patients hospitalized for a longer period of time and who got somatostatin treatment following EVL.

A previous meta-analysis and comprehensive review found that although somatostatin alone was ineffective for treating acute VB, it was successful when combined with EVL to reduce bleeding and avoid in-hospital death (21). The same research also revealed that somatostatin was not entirely risk-free and trouble-free (21). Therefore, EVL is the last type of treatment to establish primary hemostasis, and somatostatin is used to bridge the gap before EVL is used as the final therapy.

The effectiveness of maintaining somatostatin after EVL in acute VB to avoid re-bleeding or death has not yet been shown in a clinical investigation. Continuing somatostatin after attaining hemostasis with EVL, according to the index trial, was not helpful for avoiding re-bleeding and instead increased the risk of ADR, length of hospital stays, and in-hospital complications. Even after attaining hemostasis with EVL, continuing somatostatin inhibits early release and adds to the already high need for emergency care at institutions.

### Study limitations:

The study's first limitation was the limited sample size resulting from stringent exclusion criteria. In order to avoid bias and ensure homogeneity across the research groups, we eliminated any patients who had recurrent bleeding or bleeding that lasted longer than 24 hours.

## CONCLUSION

We come to the conclusion that in cases of acute VB, it is unlikely to be beneficial to continue somatostatin after EVL since it raised the incidence of adverse drug reactions (ADR), length of hospital stay, and in-hospital complications rather than preventing rebleeding.

**Conflict of interest:** None.

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**Table (1):** Baseline data of the study population.

| Baseline data | TG0 (N=25) | TG2 (N=25) | TG5 (N=25) | *P* value |
|---|---|---|---|---|
| Males (N=63) | 19 (25.3%) | 21 (28%) | 23 (30.6%) | 0.630 |
| Females (N=12) | 6 (8%) | 4(5.3%) | 2 (2.6%) | 0.580 |
| Age (years ±SD) | 47.28 (12.005) | 48.22 (10.212) | 47.04 (11.563) | 0.983 |
| BMI (kg/m$^2$) | 24.9 (2.6) | 25.1(3.3) | 23.8(4.3) | 0.913 |
| DM (N=9) | 2 (2.6%) | 3 (4%) | 4 (5.3%) | 0.331 |
| Hypertension (N=2) | 2 (2.7%) | 0 | 0 | 0.118 |
| COPD (N=1) | 1(1.4%) | 0 | 0 | 0.370 |
| Hepatitis B (N=6) | 3 (4%) | 2 (2.6%) | 1 (1.3%) | 0.663 |
| Hepatitis C (N=2) | 1 (1.3%) | 1 (1.3%) | 0 | 0.320 |
| Smoking (N=35) | 11 (14.6%) | 13 (17.3%) | 11 (14.6%) | 0.088 |
| Alcoholic (N=1) | 0 | 1(1.4%) | 0 | 0.370 |
| Tachycardia (PR ≥100) (N=39) | 13 (17.3%) | 12 (16.6%) | 14 (18.6%) | 0.716 |
| Hypotension (SBP ≤90) (N=18) | 4 (5.3%) | 7 (9.3%) | 7(9.3%) | 0.457 |
| Hypoxia (SPO2 ≤90%) (N=5) | 2 (2.6%) | 2 (2.6%) | 1 (1.4%) | 0.681 |
| Ascites (N=32) | 12 (16.6%) | 9 (12%) | 11 (14.6%) | 0.561 |
| Spontaneous bacterial peritonitis (N=9) | 3 (4%) | 3 (4%) | 3(4%) | 001 |
| Significant anemia (Hb ≤7 gm/dL) (N=28) | 13 (17.3%) | 7 (9.3%) | 8 (10.6%) | 0.213 |
| Thrombocytopenia (N=62) | 24 (32%) | 23 (30.6%) | 15 (20%) | 0.324 |
| Transaminitis (N=48) | 15 (20%) | 18 (24%) | 15 (20%) | 0.536 |
| Jaundice (N=41) | 13 (17.3%) | 15 (20%) | 13 (17.3%) | 0.764 |
| Hypoalbuminemia (N=59) | 17 (22.6%) | 22 (29.3%) | 20 (26.6%) | 0.834 |
| INR≥ 1.1 (N=53) | 19 (25.3%) | 18 (24%) | 16 (21.3%) | 0.512 |

**BMI:** body mass index; CLD: chronic liver disease; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease. **INR:** international normalized ratio.

**TABLE (2):** Baseline investigations of the study population.

| Baseline investigation | TG0 (N=25) (Mean ±SD) | TG2 (N=25) (Mean ±SD) | TG5 (N=25) (Mean ±SD) | *P* value |
|---|---|---|---|---|
| Hemoglobin (gm/dL) | 7.13 (1.81) | 8.22 (2.60) | 7.92 (2.41) | 0.079 |
| TLC ($\times 10^9$/L) | 8.22 (5.0) | 9.62 (5.0) | 9.48 (4.3) | 0.629 |
| Platelets($\times 10^9$/L) | 93.56 (62.45) | 120.2 (118.32) | 118.38 (59.194) | 0.404 |
| Urea (mg/dL) | 55.68 (25.32) | 51.88 (30.37) | 53.17 (22.66) | 0.734 |
| Creatinine (mg/dL) | 0.92 (0.37) | 0.77 (0.48) | 1.11 (0.86) | 0.220 |
| Bilirubin (mg/dL) | 2.11 (3.59) | 2.81 (3.98) | 2.9 (9.03) | 0.285 |
| SGOT (IU/L) | 77.9 (66.7.78) | 84.16 (79.83) | 76.68 (43.42) | 0.360 |
| SGPT (IU/L) | 62.64 (46.59) | 63.39 (42.76) | 56.58 (31.24) | 0.663 |
| Albumin (g/dL) | 2.66 (0.71) | 2.75 (0.56) | 2.82 (0.45) | 0.810 |
| PT (seconds) | 22.5 (5.4) | 22.0 (6.2) | 24.3 (7.9) | 0.446 |
| INR | 1.73 (0.39) | 1.65 (0.40) | 1.61 (0.50) | 0.464 |

**TLC:** total leucocyte count; SGOT: aspartate aminotransferase; SGPT: alanine aminotransferase; PT: prothrombin time; INR: international normalized ratio.

**TABLE 3.** Comparison of outcome among the different treatment and control groups.

| Outcomes | TG0 | TG2 | TG5 | *P* value |
|---|---|---|---|---|
| Re-bleed (N=8) | 3 (4%) | 2 (2.6%) | 3 (4%) | 0.751 |
| Early re-bleed (N=1) | 1 (1.3%) | 0 | 0 | 0.414 |
| Late re-bleed (N=7) | 3 (4%) | 2 (2.6%) | 2 (2.6%) | 0.888 |
| Patients with ADR (N=27) | 2 (2.6%) | 8 (10.6%) | 17(22.6%) | 0.003 |
| Diarrhoea (N=18) | 2 (2.6%) | 5 (6.6%) | 11 (14.6%) | 0.003 |
| hyperglycemia (N=9) | 0 | 2 (2.6%) | 7(9.33%) | 0.002 |
| Bradycardia (N=8) | 0 | 2 (2.6%) | 6 (8%) | 0.015 |
| Paroxysmal supraventricular tachycardia (N=7) | 1 (1.3%) | 3 (4%) | 3 (4%) | 0.517 |
| Shock (N=8) | 2 (2.6%) | 1 (1.3%) | 5 (6.6%) | 0.034 |
| Encephalopathy (N=7) | 2 (2.6%) | 2 (2.6%) | 3 (4%) | 0.451 |
| Sepsis (N=7) | 3 (4%) | 3 (4%) | 1 (1.3%) | 0.671 |
| Mechanical ventilation (N=3) | 0 | 1 (1.3%) | 2 (2.6%) | 0.341 |
| Hospital acquired pneumonia (N=1) | 0 | 0 | 1 (1.3%) | 0.348 |
| Duration of hospital stay (days) | 2.60 (±0.50) | 3.74 (±0.57) | 6.73 (±0.65) | 0.041 |

**ADR:** Adverse drug reaction