**ORIGINAL ARTICLE**

# Comparison of the Effectiveness and Safety Profile of Polyethylene Glycol-Electrolyte Solution with Lactulose in patients of Overt Hepatic Encephalopathy

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## ABSTRACT

**Aim:** To compare the effectiveness and safety profile of polyethylene glycol-electrolyte solution with lactulose in patients of overt hepatic encephalopathy.
**Study design:** Randomized controlled trial
**Place and duration of study:** South Medical Ward, Mayo Hospital, Lahore from 10th January, 2017 to 9th June, 2017.
**Methodology:** A sample size of 94 patients was taken using non-probability purposive sampling technique. Group A consisting of 47 patients were given polyethylene glycol-electrolyte solution (500 ml) and Group B comprising 47 patients were given lactulose (30 ml). Serum sodium and potassium levels were checked at 0, 12 and 24 hours. The data was analyzed using computer software SPSS version17.0.
**Results:** The mean age of all cases was 39.98 ± 13.63 years. Overall there were 56(59.6%) male and 38(40.4%) female cases. Serum sodium and potassium levels remained normal at 0 and 12 hours while at 24 hours, there were 3(6.4%) cases in group-A and 4(8.5%) cases in group-B who developed hyponatremia, p-value > 0.05. Moreover only 2(4.3%) cases in group-A and 3(6.4%) in group-B at 24 hours had low serum potassium levels, p-value > 0.05. The mean hospital stay in group-A was 3.30±1.59 days and in group-B was 4.11± 2.12 days, the mean hospital stay in group-A was significantly lower than group-B, p-value = 0.039. The mean improvement in Modified Orientation Log score in group-A was 11 ± 3.61 and in group-B was 6.81±2.13 with significantly higher improvement in group-A than in group-B, p-value < 0.0001.
**Conclusion:** It was concluded that Polyethylene glycol-electrolyte solution is better in effectiveness and safety in patients of overt hepatic encephalopathy when compared with lactulose.
**Keywords:** Overt hepatic encephalopathy, hyponatremia, Polyethylene glycol-electrolyte solution, Lactulose

## INTRODUCTION

Hepatic encephalopathy(HE) is a brain dysfunction with combination of neurological and psychiatric changes[1]. Pathophysiology of hepatic encephalopathy has 2 different hypotheses, elevated synthesis and absorption by intestinal flora and high levels of blood ammonia[2]. About 50% patients of hepatic cirrhosis develop hepatic encephalopathy at any stage of their disease[3] which if left untreated has a survival rate of 23% at 3 years[4].

Cirrhosis is a serious and advanced stage of liver disease[5]. When complicated by hepatic encephalopathy, treatment mainly revolves around protein restriction alongwith provision of lactulose (synthetic disaccharide), probiotics, Rifaximin, and carnitine (branched chain amino acids)[6].

For catharsis of gut, lactulose has been in use for a long time. It improves cognitive function and quality of life in patients of hepatic encephalopathy[7]. Lactulose creates an acidic environment in the gut which helps in conversion of soluble ammonia to insoluble ammonium ion which results in decreased systemic absorption from the gut[8]. Although lactulose is used as the standard therapy for relieving constipation, polyethylene glycol (PEG) electrolyte solution has also shown better results in this regard. Polyethylene glycol is an osmotic laxative and is a non-absorbable compound given along with extra fluids, thus increasing the water content in the gut leading to distension and passage of large volumes of stool[9].

In a meta analysis published in 2010, polyethylene glycol was found to be more effective than lactulose in relieving constipation.[10] Another study performed in 2014 by Rahimi and colleagues in the University of Texas, USA showed that 91 % patients improved in polyethylene glycol group compared to 52% in lactulose group in patients of overt hepatic encephalopathy.[11] This study suggested that rapid catharsis buys the time which the physician can utilize in focussing on triggering agents and recognizing various other reasons of metabolic encephalopathy that exist in the same patient. [11] Limitation of the study was a small sample size, solely American population with alcohol abuse being the most common cause of hepatic cirrhosis.

Rationale of this study is to compare the efficacy and safety profile of polyethylene glycol-electrolyte solution with lactulose. So far, limited data is available comparing the efficacy of polyethylene glycol solution with lactulose in the Pakistani population. We expect to monitor the safe dosage as well as administration technique to prevent further complications like aspiration.

## METHODOLOGY

This Randomized controlled trial was conducted in South Medical Ward, King Edward Medical University, Mayo Hospital, Lahore from 10th January, 2017 to 9th June, 2017. A sample size of 94 patients was taken using 1%

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level of significance, 95% power of the test and by taking expected percentage of patients improved by at least 1 grade of hepatic encephalopathy using polyethylene glycol-electrolyte solution as 91% when compared with lactulose 52%[11]. The patients were selected via Non-probability purposive sampling technique and were divided into 2 groups, Group A and B, each consisting of 47 patients.

Patients of either gender between the age group of 13-60 years and having confirmatory evidence of cirrhosis with any grade of hepatic encephalopathy ascertained on history, examination and ultrasonography were included in the study. Permission to be enrolled in the study was taken from the first-degree relatives. Patients with acute liver failure, altered sensorium due to cause other than hepatic cirrhosis as ascertained on history and examination, hemodynamically unstable patients on vasopressors, those who have taken lactulose in the last 48 hours and sedatives in the last one week were excluded from the study.

After approval from the Board of Studies (BOS) and Institutional Review Board (IRB) of King Edward Medical University, 94 patients of hepatic encephalopathy conforming to the inclusion criteria were selected from the emergency department of Mayo Hospital, Lahore. Informed consent of the patient was taken from the first degree relatives prior to intervention. Treatment allocation was done by using random number generated by Excel. Patients demographic data and history of precipitating factors was taken. Hepatic encephalopathy modified orientation log assessment score was assessed clinically. Nasogastric tube was passed in all the patients. Baseline Complete Blood Count (CBC), Liver Function Tests (LFTs), Renal Function Tests (RFTs), serum electrolytes including sodium and potassium and PT/aPTT were carried out alongwith Ultrasonography of the abdomen. Etiology leading to cirrhosis was ascertained on history, examination and relevant investigations if needed. A standardized treatment was given to all 94 patients. Infusion Ciprofloxacin 200 mg I/V 12 hourly, Infusion Metronidazole 500 mg I/V 8 hourly, Tab Rifixamin 550 mg P/NG 12 hourly, Injection Vitamin K 10 mg I/V 24 hourly for 3 days and Injection Omeprazole 40 mg I/V 12 hourly was given. Hydration status of all the patients was taken care of.

A total of 47 patients in Group A were given polyethylene glycol-electrolyte solution 500 ml every 4 hours through nasogastric tube whereas 47 patients of Group B were given lactulose 30 ml 4 hourly also through nasogastric tube. Apart from this, standard care of unconscious patient was imparted to all patients by the nursing staff that included chest physiotherapy 12 hourly, posture changing 2 hourly, exercise of joints 4 hourly, nasogastric feeding 6 hourly alongwith bowel and bladder care 8 hourly. Patient was removed from the study if blood work showed serum sodium level less than 128 mEq/L or serum potassium level less than 3mEq/L or both at any time during treatment. Hepatic encephalopathy modified orientation log score was assessed after every 4 hours till 24 hours. Treatment was shifted from curative regimen to preventive regimen once patient was completely out of hepatic encephalopathy. Blood pressure was checked after every 4 hours till 24 hours. Serum sodium and potassium levels were checked at 0, 12 and 24 hours. Other laboratory tests like CBC, LFTs and RFTs were checked again after 24 hours. Total stay in the hospital was noted for all the patients.

The data was analyzed by statistical methods generated on the computer software SPSS version 17.0. Quantitative variables like age, grade of hepatic encephalopathy and duration of hospital stay was presented as Mean±SD. Qualitative variables like sex of the patient were presented as frequencies and percentages. T test was used to see the association between quantitative attributes in relation to the treatment groups. P value ≤ 0.05 was taken as significant.

## RESULTS

The mean age of all cases was 39.98±13.63 years. The mean age in group-A was 39.51±13.27 years and in group-B was 40.45±14.10 years, p-value 0.741. Overall there were 56(59.6%) male and 38(40.4%) female cases while each group had equal gender distribution i.e., 28(59.57%) male and 19(40.43%) female cases. Comparison of the precipitating factors and occurrence of hypotension during the first 24hours of the study are given in tables 1 and 2. Comparison of low levels of serum sodium and potassium, duration of hospital stay and improvement in Modified Orientation Log between the 2 groups are shown in tables 3,4 and 5 respectively.

Table 1: Precipitating factors in both study groups

| | Group –A | Group –B | p-value |
|---|---|---|---|
| Constipation | 40(85.10%) | 42(89.3%) | 0.84 |
| Infection | 5(10.63%) | 6(12.76%) | 0.9 |
| Upper Gastrointestinal bleeding | 3(6.38%) | 5(10.64%) | 0.79 |

Table 2: Comparison of hypotension at different hours in both study groups

| Hypotension | Study Group | | P value |
|---|---|---|---|
| | Group A | Group B | |
| **At 4 hours** | | | |
| Yes | 4(8.5%) | 3(6.4%) | 0.694 |
| No | 43(91.5%) | 44(93.6%) | |
| **At 8 hours** | | | |
| Yes | 4(8.5%) | 3(6.4%) | 0.315 |
| No | 43(91.5%) | 44(93.6%) | |
| **At 12 hours** | | | |
| Yes | 3(6.4%) | 2(4.3%) | 0.646 |
| No | 44(93.6%) | 45(95.7%) | |
| **At 16 hours** | | | |
| Yes | 3(6.4%) | 1(2.1%) | 0.307 |
| No | 44(93.6%) | 46(97.9%) | |
| **At 20 hours** | | | |
| Yes | 1(2.1%) | 2(4.3%) | 0.557 |
| No | 46(97.9%) | 45(95.7%) | |
| **At 24 hours** | | | |
| Yes | 1(2.1%) | 0(0%) | 0.315 |
| No | 46(97.9%) | 47(100.0%) | |

Table 3: Comparison of low levels of Serum Sodium (mEq/L) and Serum Potassium (mEq/L) at 24hr in both study groups

| | Study Group | | P value |
|---|---|---|---|
| | Group A | Group B | |
| ***Serum Sodium (mEq/L) at 24hr*** | | | |
| Low | 3(6.4%) | 4(8.5%) | 0.694 |
| Normal | 44(93.6%) | 43(91.5%) | |
| ***Serum Potassium (mEq/L) at 24hr*** | | | |
| Low | 2(4.3%) | 3(6.4%) | 0.646 |
| Normal | 45(95.7%) | 44(93.6%) | |

Table 4: Comparison of Hospital stay (days) in both study groups

| Study groups | Mean | S.D | Min. | Max. |
|---|---|---|---|---|
| Group A (n=47) | 3.30 | 1.59 | 1 | 6 |
| Group B (n=47) | 4.11 | 2.12 | 1 | 9 |
| Total (n=94) | 3.70 | 1.91 | 1 | 9 |
| t-test (p-value) | 2.094 (0.039) | | | |

Table-5: Comparison of Improvement in Modified Orientation Log in both study groups

| Study groups | Mean | S.D | Min. | Max. |
|---|---|---|---|---|
| Group A (n=47) | 11.00 | 3.61 | 3.00 | 18.00 |
| Group B (n=47) | 6.81 | 2.13 | 3.00 | 12.00 |
| Total (n=94) | 8.90 | 3.63 | 3.00 | 18.00 |
| t-test (p-value) | 6.85 (< 0.0001) | | | |

## DISCUSSION

Hepatic encephalopathy (HE) incorporates a wide range of reversible neuropsychiatric deficits developing in cirrhotic patients who present with symptoms of mild to severe cognitive abnormalities e.g., sleep disturbance, sudden altered behavior, changed mentation or coma. The mechanisms behind brain abnormalities in HE are still obscure, however it is proposed that ammonia synthesized by gut flora plays a significant role[12]. There is a dearth of evidence backed by large, well-controlled clinical trials in favor of specific treatment options currently in use for patients with Minimal HE. However the existing evidence suggests some advantage of lactulose in the treatment of Minimal HE. Treatment of patients with Overt HE is mainly based on the eliminating the underlying precipitating factors, nutritional support, and reduction of blood ammonia level.

Lactulose is the most widely used medication to reduce ammonia production; however its exact mechanism of action is still unclear[13]. Lactulose is currently considered as the first line treatment of patients with Overt HE although there is no high-quality evidence to support it[14]. Polyethylene glycol (PEG) is being studied for the treatment of HE in cirrhotic patients and limited research has shown positive effects[11].

A study conducted by Naderian M et al[15] showed the mean age of cases to be 56.45±10.86 years which was somewhat comparable with the mean age of our sample population i.e., 39.98±13.63 years. Also the gender distribution was quite similar in their study i.e., 67.5% males and 32.5% females compared to 59.6% males and 40.4% females in our study.

The likelihood of electrolyte imbalance or renal function disturbance due to intervention was also evaluated in the follow-up period. The measurement of electrolytes, creatinine and blood urea nitrogen was done at baseline and at 6-24 hours after hospitalization[11]. A study conducted by Rahimi RS showed that Potassium levels reduced from 4.3mmol/L to 3.8mmol/L after PEG administration (p =0 .006)[11]. These findings are different from the findings of our study (p=0.646).

PEG can reduce the hospitalization in overt HE cases based on the contributing factors of the HE. Rahimi and his colleagues showed the duration of hospital stay to be short and resolution of HE quicker and significant in the PEG group[11]. The average length of hospital stay was 8±12 in Lactulose group and 4±3 in PEG groups with no significant difference, p-value 0.07. But in our study, we found significantly shorter mean hospital stay in PEG group i.e. 3.30±1.59 days when compared to Lactulose group i.e., 4.11±2.12 days, p-value = 0.039.

The results of Rahimi's study also showed that 91% patients improved in polyethylene glycol group compared to 52% in lactulose group in patients of overt hepatic encephalopathy, p-value < 0.01.[11] Another study reported by Naderain M et al showed that in comparison with lactulose alone, PEG-lactulose combination improved Hepatic Encephalopathy Score Assessment (HESA) score in 24 hours more effectively ($p$=0.04). A total of 20 patients in PEG-lactulose group had a decrease of at least 1 HESA score after 24 hours, as compared with 14 patients in lactulose group and the difference was significant ($p$ =0.05)[15]. Our outcome was based on mean improvement in Modified Orientation Log score and we found that PEG group mean MOL score was 11±3.61 and Lactulose group mean MOL score was 6.81±2.13 with significantly better improvement in the PEG group, p-value < 0.0001.

Another study was done in 2 groups in which one group received either 20-30 grams of lactulose orally or by a nasogastric tube, or 200 grams of lactulose enema by a rectal tube. The other group was given PEG–lactulose combination, the same amount of oral or rectal lactulose, plus 280 grams of PEG in 4 liters of water orally as a single dose in 30-120 minutes. The study result showed that in comparison with lactulose alone, PEG-lactulose improved HESA score in 24 hours more effectively ($p$=0.04). Overall, PEG-lactulose regimen was related to shorter length of hospital stay compared with lactulose treatment ($p$=0.03) but in subgroup analysis, it was found that PEG-lactulose regimen could only decrease the length of hospital stay in women significantly ($p$=0.01). Thus, the use of PEG along with lactulose in comparison with lactulose alone is more useful in the treatment of HE in cirrhotic patients and results in more rapid discharge from hospital[15].

Further studies need to be conducted on the Asian population showing the role of polyethylene glycol-electrolyte solution as very limited data is available so far. This randomized controlled trial can be conducted on a larger population with longer follow-up period in order to validate the role of PEG as a better treatment option in patients with overt hepatic encephalopathy.

## CONCLUSION

We concluded that Polyethylene glycol-electrolyte solution is better in effectiveness and safety when compared with lactulose in patients of overt hepatic encephalopathy.

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