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Secondary prophylaxis of overt hepatic encephalopathy in cirrhosis: a randomized controlled trial of colistin versus lactulose

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Abstract

Patients who have cirrhosis and have successfully recuperated from an episode of overt hepatic encephalopathy (OHE), should receive secondary prophylactic therapy (lactulose is the first line while rifaximin is add-on therapy) for an indeterminate duration or until they get a liver transplant. This research aimed to evaluate and contrast the effectiveness and safety of colistin and lactulose for the prevention of OHE in individuals with a cirrhotic liver. This was a prospective, parallel, open-label, randomised controlled study performed on 316 individuals who had received enrollment from Tropical Medicine and Infectious Diseases Department, Tanta University Hospital, Egypt. In the lactulose group, the frequency of development of HE was comparable with that of the colistin group (15.83 versus 18.12%) (P= 0.612). No substantial differences were existed in the grades of HE among the studied groups (P=0.786). Colistin is as effective as lactulose for 2ry prophylaxis of OHE. Lactulose treatment is associated with significant gastrointestinal adverse events.

Keywords: Hepatic encephalopathy, lactulose, colistin, secondary prophylaxis.

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1. Introduction

Hepatic encephalopathy (HE) refers to the complex range of neuro-psychiatric alterations that may occur throughout the progression of acute or chronic liver disease [1]. Secondary prophylaxis of hepatic encephalopathy decreases hospital admissions and mortality rates [2]. Lactulose non-adherence treatment is recognized as a precipitating factor of HE, contributing to 20% of hospitalizations for HE correlated to drug use [3]. Rifaximin, a kind of locally-acting antibiotic, is used to enhance cognitive function and treat hyperammonemia [4]. Colistin is an antibacterial agent that kills bacteria and is effective against a wide range of Gram-negative bacteria.; oral colistin is used for selective gut decontamination [5].

2. Patients and Methods

The study was a prospective, parallel, open-label, randomised controlled experiment conducted on 316 individuals who received enrollment from the Tropical Medicine and Infectious Diseases Department at Tanta University Hospital in Egypt. The research lasted a period of 24 months, including both the recruiting and follow-up phases. It began in November 2020 and ended November 2022. The included subjects had been randomised into lactulose group (158 patients) or colistin group (158 patients). Finally, 139 patients were considered for analysis in the lactulose group against 138 individuals in the colistin group.

2.1. Criteria for inclusion

- Must be at least eighteen years old.
- Individuals who have cirrhotic liver and prior histories of recovering from HE.

2.2. Criteria for exclusion

- History of lactulose consumption for the last 7 days.
- Individuals receiving preventive treatment for spontaneous bacterial peritonitis (SBP).
- Individuals who are taking psychoactive medications, including sedatives or anti-depressants.
- History of prior trans-jugular intra-hepatic portosystemic shunts or shunt surgeries.
- Presence of notable comorbidities, including cardiovascular, pulmonary, or neurological conditions.
- Malignant tumors that may reduce life expectancy.
- Infections acquired in the recent past or usage of antibiotics in the past 6 weeks.
- Gastrointestinal bleeding occurring during the last 6 weeks.
- Kidney failure, Myasthenia gravis.

- Colistin sulfate hypersensitivity.
- Breastfeeding or pregnancies.
- Alcohol consumption.

2.3. Sample size calculation and study design

This study was a prospective, parallel, open-labelled, randomised controlled experiment. The individuals participating in the study were randomly assigned utilizing a computer randomized number generator. The randomization process included selecting random permuted blocks with varying block sizes of 4, 6, and 8. The allocation ratio was equal for all blocks. Concealment was ensured by using sequentially numbered, sealed, opaque envelopes [6].

2.4. Outcomes

- **Primary outcome:**
  -Development of OHE.
- **Secondary outcomes**
  - Overall mortality.
  - adverse impacts of treatment.

All the patients in the study had been exposed to the follows:

1- Thorough history is taken.
2- Clinical assessment.
3- Laboratory tests.
4- Modified Child–Turcotte–Pugh score.
5- Abdominal ultrasonography.

2.5. Follow-up

The patients were followed up monthly for 6 months to assess treatment compliance, record side effect of the drugs, recurrence of OHE based on criteria of West Haven, and the determining factor for OHE occurrence in all groups. Baseline assessments recurred following a 3-month follow-up examination and at the conclusion of the research period. Therapy compliance was generally ensured by direct questioning and the retrieval of empty drug envelopes, and counting the number of bottles of lactulose consumed.

2.6. Statistical analysis

The statistical data was provided as the mean ± standard deviation (SD), frequency (number), and percentage as deemed suitable. The research groups have been contrasted utilizing Student's t-test, which is used for contrasting independent samples from both groups when the samples follow a normal distribution. The χ 2 -test has been utilized for contrasting categorical data. A one-way analysis of variance had been performed, followed by a post-hoc Tukey's multiple comparison test to identify any significant variations. The paired t-test can be utilized for contrasting paired samples from both groups, assuming that the samples follow a normal distribution. The χ 2 -test and Student's t-test were used to examine the outcome measures. P-values $\leq$ 0.05 were considered statistically significant. The statistical analyses were conducted utilizing the computer application SPSS (Statistical Package for the Social Sciences; SPSS Armonk, NY: IBM Corp) version 20 for Microsoft Windows.

3. Results and Discussion

Hepatic encephalopathy significantly impacts individuals with cirrhosis, resulting in heightened hospitalization rates, financial expenses, frequent readmissions, diminished health-related life quality, and a decline in socioeconomic standing. Therefore, it is important to take into account the prevention of the reoccurrence of OHE in every individual [7]. In our study, the frequency of development of OHE during follow up period of 6 months in the lactulose group was comparable with that of the colistin group (15.83 versus 18.12%). Our result was in line with Sharma, et al., 2009 [8] who stated that the frequency of cirrhotic patients who developed OHE was 19.6% in the lactulose group versus 46.87% in the placebo group. This was in disagreement with Chang, et al., 2021 [9] who reported that the frequency of patients who developed hepatic encephalopathy was 87.1% in the lactulose group versus 50% in the rifaximin and lactulose group. This may be related to different inclusion criteria as they included both OHE and CHE patients while in our study, we included only patients with overt hepatic encephalopathy. Over a six-month period, management with colistin was as effective as lactulose in reducing the incidence of recurrence of HE among patients with liver cirrhosis. Our results revealed that, four patients out of 138 (2.9%) in the colistin group, developed OHE due to constipation (P=0.043*). Dhariwal and Tullu, 2013 [10]. reported that oral colistin leads to gastro-intestinal disorders (constipation or diarrhea). Pseudomembranous colitis may arise as an uncommon negative consequence of colistin therapy [11] In our study, the percentage of patients with diarrhoea, bloating, distaste to lactulose, flatulence, nausea and abdominal pain had been substantially greater in the lactulose group contrasted to the colistin group (P<0.05). This was in accordance with Stuart et al., 2022[12]. who demonstrated that lactulose is correlated with greater incidence of gastrointestinal symptoms in individuals with decompensated cirrhosis. These undesirable side effects lead to noncompliance. In current work, no substantial variations had been detected among the studied groups as regards the frequency and causes of mortality (6.47% in the lactulose group versus 5.8% in the colistin group) (P> 0.05).Our findings was in accordance with Sharma, et al., 2009[8]. who reportedthat the frequency of mortality was 8.1% in the lactulose group versus 17.18% in the placebo group. However, this was in disagreement with Agrawal, et al., 2012[13]. who stated that the frequency of mortality was (19.11%) in the lactulose group versus 17.18% in probiotics group versus 24.61% in no therapy group. This difference from our study could be attributed to the longer duration of follow up for 12 months in their study compared with 6 months in ours. As regards basic demographic data of the groups under the study, no substantial variations had been existed among lactulose and colistin groups (P > 0.05) (Table 1, Figure 1). Baseline clinical and abdominal ultrasonographic data didn't reveal any substantial variations between groups (P> 0.05) (Table 2). In the lactulose group, the frequency of development of HE was comparable with that of the colistin group (15.83 versus 18.12%) (P= 0.612). no substantial differences in the grades of HE among the studied groups (P=0.786) (Table 3).

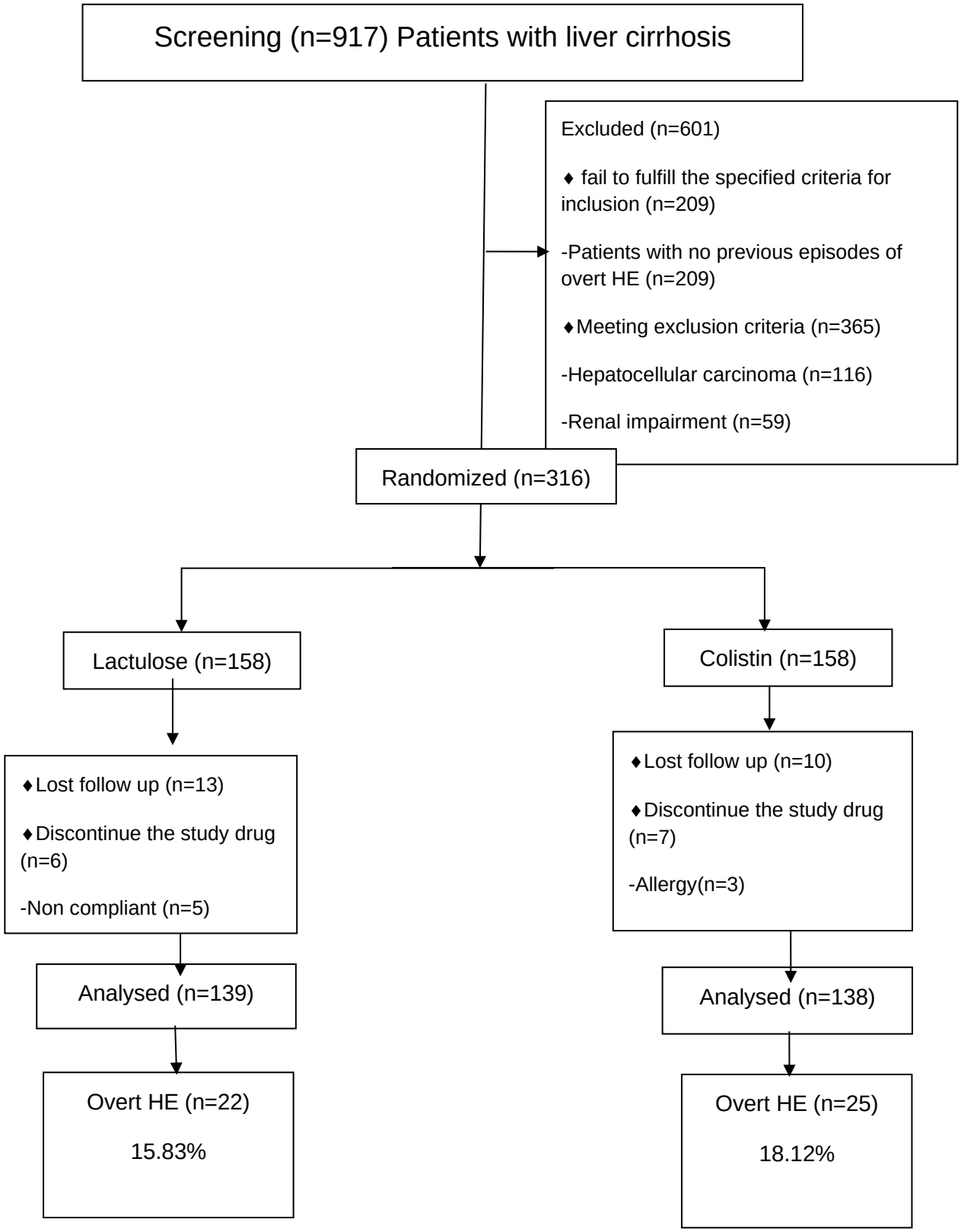

Figure 1: Study flow chart. GIT, gastrointestinal; HE, hepatic encephalopathy; n, number of patients; SBP, spontaneous bacterial peritonitis.

Table 1: Basic demographic data of studied groups

		Group				T-Test or Chi-square	
		Lactulose(n=139)		Colistin(n=138)		t/ X^2	P-value
Age	Range	46 - 73		45 - 75		1.773	0.077
	Mean ±SD	61.655 ± 5.502		60.413 ± 6.140			
		N	%	N	%		
Gender	Male	107	76.98	101	73.19	0.532	0.466
	Female	32	23.02	37	26.81		
Diabetes mellitus	No	97	69.78	98	71.01	0.050	0.823
	Yes	42	30.22	40	28.99		
Etiology of cirrhosis	HCV	117	84.17	114	82.61	0.173	0.917
	HBV	4	2.88	5	3.62		
	Others	18	12.95	19	13.77		
Child-Pugh class	B	25	17.99	30	21.74	0.613	0.434
	C	114	82.01	108	78.26		
Child- Pugh score	Range	8 - 12		7 - 12		-0.519	0.604
	Mean ±SD	10.381 ± 1.017		10.449 ± 1.159			

N, number of patients; PPI, proton pump inhibitors; HE, hepatic encephalopathy; HBV, hepatitis B virus; HCV, hepatitis C virus; SD, standard deviation; significant P ≤0.05

Table 2: Baseline clinical and abdominal ultrasonographic data of the studied groups

		Group				T-Test or Chi-square	
		Lactulose (n=139)		Colistin (n=138)			
		N	%	N	%	t/ X^2	P-value
Jaundice	No	19	13.67	23	16.67	0.484	0.487
	Yes	120	86.33	115	83.33		
Splenomegaly	No	73	52.52	85	61.59	2.328	0.127
	Yes	66	47.48	53	38.41		
Lower limb oedema	No	10	7.19	10	7.25	0.000	0.987
	Yes	129	92.81	128	92.75		
Ascites (U/S)	No	2	1.44	2	1.45	0.000	0.994
	Yes	137	98.56	136	98.55		

N, number of patients; PV diameter, portal vein diameter; SD, standard deviation; U/S, ultrasound; significant P ≤0.05*.

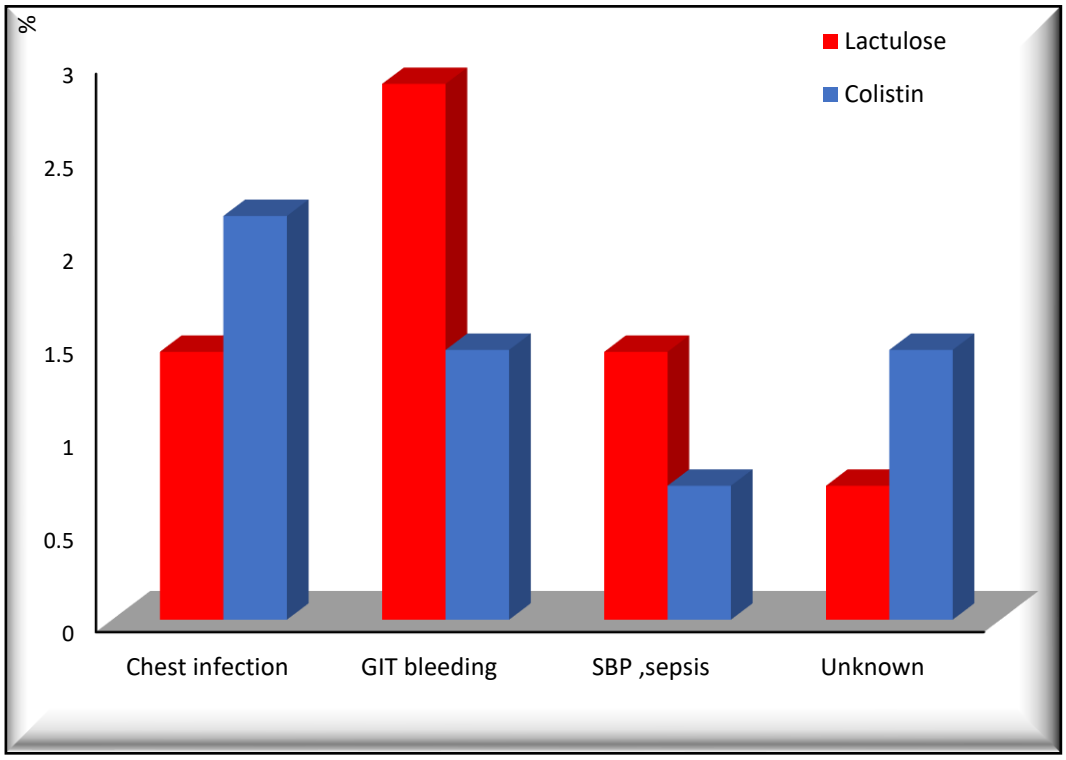

Figure 2: Causes of mortality during follow-up period of 6 months in the studied groups. GIT, gastrointestinal tract; SBP, spontaneous bacterial peritonitis.

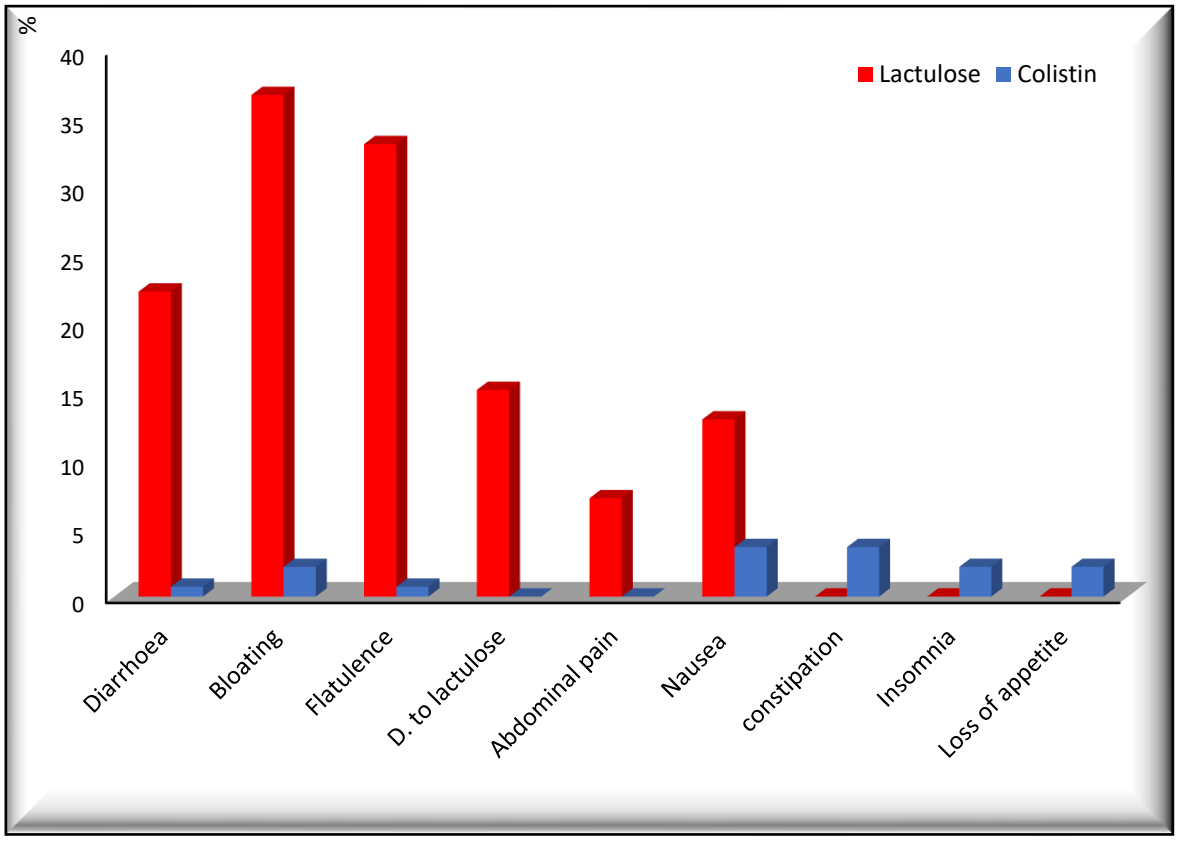

Figure 3: Adverse events in the studied groups. D, distaste

Table 3: Baseline laboratory investigations of the studied groups

		Group		T-Test	
		Lactulose(n=139)	Colistin(n=138)	t	P-value
Hb (g/dl)	**Range**	8.2 - 12.1	8.1 - 13.8	-0.920	0.358
	Mean ±SD	9.868 ± 0.786	9.961 ± 0.884		
PLT(x10^3/mm^3)	**Range**	34 - 139	29 - 146	0.677	0.499
	Mean ±SD	93.468 ± 25.070	91.413 ± 25.445		
WBCs (x10^3/mm^3)	**Range**	2.01 - 10.8	2.2 - 10.7	-0.003	0.997
	Mean ±SD	5.106 ± 1.876	5.107 ± 1.775		
TB (mg/dl)	**Range**	1 - 6.4	0.8 - 6.7	-0.445	0.656
	Mean ±SD	2.873 ± 1.001	2.930 ± 1.116		
DB (mg/dl)	**Range**	0.2 - 2.4	0.3 - 3.5	-0.560	0.576
	Mean ±SD	1.204 ± 0.471	1.239 ± 0.588		
Serum albumin (g/dl)	**Range**	1.9 - 3.3	1.7 - 3.1	0.711	0.477
	Mean ±SD	2.490 ± 0.321	2.462 ± 0.319		
ALT IU/L (up to 40)	**Range**	8 - 69	9 - 55	0.086	0.931
	Mean ±SD	27.338 ± 11.010	27.232 ± 9.470		
AST IU/L (up to 37)	**Range**	18 - 84	14 - 71	-1.077	0.282
	Mean ±SD	44.856 ± 14.236	46.674 ± 13.842		
INR	**Range**	1.17 - 2.69	1.19 - 2.8	-0.951	0.342
	Mean ±SD	1.663 ± 0.257	1.694 ± 0.277		
Serum creatinine (mg/dl)	**Range**	0.5 - 1.2	0.5 - 1.2	1.794	0.074
	Mean ±SD	1.002 ± 0.179	0.962 ± 0.189		
Urea (mg/dl)	**Range**	16 - 67	15 - 69	-0.535	0.593
	Mean ±SD	32.971 ± 10.104	33.688 ± 12.111		
Serum Na (mEq/L)	**Range**	128.5 - 138	128 - 140.9	1.364	0.174
	Mean ±SD	131.932 ± 1.686	131.640 ± 1.876		
Serum K (mEq/L)	**Range**	3.01 - 5.3	3.1 - 5.2	1.840	0.067
	Mean ±SD	4.302 ± 0.556	4.181 ± 0.540		
RBS(mg/dl)	**Range**	81 - 318	87 - 314	-0.155	0.877
	Mean ±SD	155.755 ± 68.345	156.953 ± 60.349		

N, number of patients; Hb: hemoglobin; PLT: platelets; WBCS: white blood cells; DB: direct bilirubin; TB: total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR, interanational normalized ration; K: potassium; Na: sodium; RBS: random blood sugar; SD, standard deviation; significant P ≤0.05*.

Table 4: Development of OHE during follow-up period of 6 months in the studied groups

		Group				T-Test or Chi-square	
		Lactulose(n=139)		Colistin(n=138)		t/ X^2	P-value
		N	%	N	%		
Recurrence of HE	No	117	84.17	113	81.88	0.257	0.612
	Yes	22	15.83	25	18.12		
HE WHC grade	2	15	68.18	19	76.00	0.481	0.786
	3	4	18.18	4	16.00		
	4	3	13.64	2	8.00		
Duration of HE related hospitalization (Days)	Range	3 - 10		1 - 11		0.245	0.808
	Mean ±SD	6.647 ± 2.149		6.450 ± 2.665			
Time to first HE related hospitalization (Days)	Range	40 - 171		45 - 160		-0.507	0.615
	Mean ±SD	110.546 ± 40.001		115.917 ± 31.653			

N, number of patients; HE, hepatic encephalopathy; WHC, West Haven criteria; SD, standard deviation; significant P ≤0.05*.

In patients receiving lactulose, no substantial variations were existed in the mean duration of hospitalization due to HE when compared with the colistin group (6.647 ± 2.149 versus 6.450 ± 2.665 days) (P=0.808). No substantial variation was existed in the meantime to first HE- related hospitalization in the lactulose group against the colistin group ((110.546 ± 40.001versus 115.917 ± 31.653 days)(P=0.615) (Table 4). No substantial variation was existed among the studied groups as regards the frequency and causes of mortality (P> 0.05) (Figure 2). The percentage of patients with diarrhoea, bloating, distaste to lactulose, flatulence, nausea and abdominal pain were substantially greater in the lactulose group contrasted to the colistin group (P<0.05).Adverse impacts had been managed by decreasing the dosage of lactulose. In the colistin group, 6 patients(4.35%) developed constipation which was substantially greater contrasted to that in the lactulose group (P=0.041). Constipation was managed by dietary modification. No serious adverse impacts had been stated in the groups under the study. In the colistin group, no significant differences were detected between baseline and follow up laboratory investigations, Child-Pugh score and MELD score at 3 and 6 months (P> 0.05) (Figure 3).

4. Conclusions

- Lactulose treatment is associated with significant gastrointestinal adverse events.
- Colistin is as effective as lactulose for secondary prophylaxis of OHE.

The study was approved by Ethical Committee of Faculty of Medicine, Tanta University. Ethical committee Number 34375 / 1 / 21 and registered on ClinicalTrials.gov, Identifier: NCT05279586.

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Nil

Conflict of Interest
Nil

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