Original Article

Assessment of the Therapeutic Effect of Polyethylene glycol and Lactulose in Patients with Hepatic Encephalopathy

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Abstract

Background: The mechanism of cerebral dysfunction in hepatic encephalopathy is unknown, although ammonia produced by intestinal bacteria is an essential factor. This study was performed to compare the effect of polyethylene glycol with lactulose in patients with hepatic encephalopathy.

Materials and Methods: In this interventional study, which was performed as a three-blind randomized clinical trial, 60 patients with hepatic encephalopathy referred to Imam Hossein Hospital in Tehran were randomly selected and divided into two groups receiving polyethylene glycol or lactulose were divided and the levels of creatinine, ammonia, platelets, hemoglobin, albumin and bilirubin and Hepatic Encephalopathy Scoring Algorithm, Model for End-Stage Liver Disease and Child-Turcotte-Pugh scores in the patients were compared in the two groups.

Results: The results showed the frequency distribution of creatinine, ammonia, platelets, hemoglobin, albumin, and bilirubin and Hepatic Encephalopathy Scoring Algorithm, Model for End-Stage Liver Disease, and Child-Turcotte-Pugh scores of patients in the two groups were not statistically significant (P>0.05).

Conclusion: In general, based on the results of this study, it is inferred that polyethylene glycol and lactulose have similar efficacy in patients with hepatic encephalopathy and, therefore, the use of each of them according to the condition of patients and the discretion of the treating physician Recommended.

Keywords: Polyethylene glycol, Lactulose, Hepatic encephalopathy

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Introduction

Hepatic encephalopathy includes a range of reversible neuropsychiatric disorders that occur in a significant number of patients with cirrhosis. Symptoms include mild to severe cognitive impairment, such as reversed sleep patterns, sudden behavioral changes, mental state changes, or coma[1]. The mechanism of cerebral dysfunction in hepatic encephalopathy is unknown, although ammonia produced by intestinal bacteria is an essential factor. Cirrhosis of the liver is defined as the last stage of progressive liver fibrosis, which is characterized by the destruction of the liver structure and regenerative nodules[2]. The global prevalence of cirrhosis from autopsy studies is 4.5-9.5% of the general population[3-5]. More than 50 million adults worldwide have chronic liver disease. The prevalence of cirrhosis is probably lower than expected because approximately one-third of patients remain asymptomatic. Cirrhosis is the sixth leading cause of death in developed countries and one of the ten most common causes of death in the various

world[6-9].

This rate is expected to increase in the coming years due to the increasing prevalence of cirrhosis associated with HCV[1] (Hepatitis C Virus) and NASH[2] (Nonalcoholic Steatohepatitis). The majority of patients with cirrhosis eventually develop some degree of hepatic encephalopathy, which leads to a significant increase in mortality and hospital costs[10-12].

Hepatic encephalopathy is divided into overt hepatic encephalopathy and mild hepatic encephalopathy[13]. Patients with cirrhosis eventually develop overt hepatic encephalopathy and mild hepatic encephalopathy in 30-45% and 60-80% of cases, respectively[12-15]. Treatment of this disorder plays an essential role in preventing the complications of this disease and reducing community costs, and improving the quality of life. There are few extensive clinical studies on specific treatment of patients with mild hepatic encephalopathy[16]. However, existing studies suggest using lactulose to treat mild hepatic encephalopathy[17, 18]. Treatment of patients with overt hepatic encephalopathy is based on the elimination of predisposing factors, nutritional support, and reduction of blood ammonia levels[19, 20]. Lactulose and rifaximin are the most common drugs used to reduce blood ammonia, although the exact mechanism of action is still unknown[19]. Rifaximin is a non-absorbable antibiotic used to treat patients with overt hepatic encephalopathy that acts against coliforms such as E. coli and reduces the amount of serum ammonia, and improves hepatic encephalopathy. A meta-analysis of nineteen randomized controlled trials showed that rifaximin had beneficial effects in patients with hepatic encephalopathy and may also reduce mortality in these patients[22]. Of course, there are concerns about the cost, and even one study Decision-analysis concluded that rifaximin monotherapy is not Efficient in treating patients with hepatic encephalopathy[23]. About 70% of patients with overt hepatic encephalopathy recover with lactulose therapy[24]. When lactulose is used for secondary prophylaxis, it reduces recurrent episodes of hepatic encephalopathy but does not affect mortality[25].

Lactulose is commonly used as the first line of treatment for patients with overt hepatic encephalopathy, although there is no substantial evidence to support it[26]. No significant difference was observed in a review study in patients with and without lactulose treatment[27]. When the patient is hospitalized due to overt hepatic encephalopathy, predisposing factors are eliminated during the improvement of the mental state, so it is difficult to understand the main role of lactulose in this improvement[28, 29]. Polyethylene glycol has been studied in treating patients with hepatic encephalopathy with cirrhosis, and few studies have shown its positive effects[1]. Since polyethylene glycol solution is a low-complication drug and performs intestinal cleansing more effectively, the initial hypothesis was that since immediate bowel cleansing is essential in treating acute hepatic encephalopathy, polyethylene glycol may be It is preferable to lactulose in this regard. In this study, due to the lack of comparison of lactulose and polyethylene glycol separately in previous studies, we compared the therapeutic effect of polyethylene glycol and lactulose solution in the treatment of patients with hepatic encephalopathy by recognizing the best practice, in this case, take effective steps to improve the therapeutic process and prognosis for the patients.

Methods

This study was performed in a prospective blind three-way clinical trial, from April 2016 to April 2017, in 60 patients with hepatic encephalopathy referred to Imam Hossein Hospital in two groups of 30 people.

To find the minimum difference in the mean HESA[3] (Hepatic Encephalopathy Scoring Algorithm) changes between the two groups of -0.7 with a test power of 80%, the first type error of 0.05 was determined based on reference (16) and based on the formula below 27 people. Considering the 10% drop in each group, 30 people were determined.

$$n = \frac{(S]_1^2 + S_2^2[\square)\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{d^2}$$

α= 5%, 1-β=80%, $\mathbf{S}_1^2$= 94%, $\mathbf{S}_2^2$= 95%, d= -7%, and n= 27

Sampling method as carried out in the available form. The interview, observation, and field examination methods were used (using a researcher-made data

collection form).

This study's inclusion criterion included documented cirrhosis with any underlying cause, hepatic encephalopathy of any grade, age 18 to 80 years.

Exclusion criteria include acute liver failure: acute liver injury with encephalopathy and an INR[4] greater than or equal to 1.5 in a patient without previous liver disease, acute mental change due to non-hepatic encephalopathy, renal failure or hepatorenal syndrome, Hemodynamic instability that requires vasopressor to resolve, pregnancy, LAR[5] (Legally authorized representative) disagreement, patient reluctance.

Patients who, after giving explanations about the project to them by the research facilitators (relevant assistant and supervisor), wish to participate in the study and complete the written consent form by randomization with permutation blocks with block size two polyethylene glycol and lactulose were assigned to one of the two treatment groups. Hepatic encephalopathy was defined as the onset of disorientation or asterixis. In the group receiving lactulose, 20-30 g of lactulose was administered orally (at least three doses in 24 hours) either by NG[6] (Nasogastric) tube or 200 g by rectal enema tube. The dose of lactulose was increased until at least two loose stools formed. In patients receiving polyethylene glycol, 17 g of polyethylene glycol was dissolved in 8 ounces of water and eaten every ten minutes until two liters or clear defecation was consumed. In order to perform blinding in the people performing the treatment, the drugs were prescribed in a visual form. In addition to the facilitators, patients and data analysts were unaware of the therapeutic group.

Physical examination was performed at the beginning of the visit and 24 hours after treatment.

HESA[3] score was used to assess the severity of hepatic encephalopathy, and to avoid interpersonal differences, HESA[3] score was calculated at baseline and 24 hours after treatment. Blood ammonia levels and serum biochemical studies in all patients were checked at baseline and 24 hours after treatment.

CTP[7] (Child- Turcotte- Pugh) score and MELD[8] (Model for End-Stage Liver Disease) score Calculated for all patients. The cause of cirrhosis was determined based on the patients' history, and the cause of encephalopathy was determined based on the patient's history, physical examination, and tests. The usual treatment of the patient was continued according to the opinion of the responsible treatment team, and the research team decided on the choice of lactulose or polyethylene glycol.

Finally, after collecting the required information from all 60 patients studied, we analyzed the data, in which we used the statistical software SPSS[9] (Statistical Package for Social Sciences) version 26. The tests used included Chi-square and Fisher and Kolmogorov-Smirnov and independent t-test, and the significance level was 0.05.

In this study, the information of the subjects remained confidential and written consent was received from the patients, no cost was imposed on the patients, and the code of ethics was obtained from Shahid Beheshti University of Medical Sciences (To Code Ir.SBMU.MSP.REC.1397.428). The provisions of the Helsinki Convention were also observed. In addition, according to the study population, no treatment regimens or treatment processes were stated outside the protocols and were not performed without the patients' permission.

Hepatic encephalopathy scoring algorithm[29]

Hepatic encephalopathy score	Neuropsychological assessment	Clinical evaluation	Grading of hepatic encephalopathy
All three criteria exist	- Invaluable	- Eyes closed - No verbal answers - No reaction to simple commands	4
There are at least three criteria, clinical or neuropsychological	-Psychological control = 0	- Drowsiness - Confusion - Lack of awareness of the place - Strange behavior / agitation / madness - Clone / rigidity / nystagmus / Babinski	3

There are at least two clinical criteria and three neuropsychological criteria	- Slow answers - Anxiety - Forgetting recent events - Simple calculations	-Lethargy - Lack of awareness of time - Speak slowly - Hyperactive reflexes - Improper behavior	2
There are at least four criteria, clinical or neuropsychological	- Complex calculations - Ability to build - Decreased concentration - Depression	- sleep disorder -Tremor	1

Results

This study was performed on 60 patients with hepatic encephalopathy in two equal groups. There was no difference between the two groups in terms of age (Table 1) and sex (Table 2) (P>0.05). The frequency distribution of the cause of cirrhosis was the same in the two groups, and cryptogenic and viral cases were the most common causes (Table 3) (P>0.05).

The frequency distribution of the cause of encephalopathy in the patients was similar in the two groups, and the cases of infection, hypokalemia, and constipation were the most common causes (Table 4) (P>0.05). Ascites was observed in 50% of patients in the polyethylene glycol group and 66.7% in the lactulose group, which was not a statistically significant difference (Table 5) (P>0.05).

There was no statistically significant difference in the distribution of creatinine, ammonia, and platelets in the two groups (Table 6) (P>0.05). There was no statistically significant difference in the frequency distribution of INR[4], hemoglobin, albumin, and bilirubin in the two groups (Table 7) (P>0.05).

HESA[3], MELD[8] and CTP[7] scores of patients in the two groups were not a statistically significant difference (Table 8) (P>0.05).

Discussion

In this study, due to the lack of comparison between lactulose and polyethylene glycol separately in previous studies, we compared the therapeutic effect of polyethylene glycol and lactulose solution in treating patients with hepatic encephalopathy. Since polyethylene glycol solution is a low-complication drug and performs intestinal cleansing more effectively, the initial hypothesis was that since immediate intestinal purification is important in treating acute hepatic encephalopathy, and therefore polyethylene glycol, is important It may be preferable to lactulose in this regard. In the present study, the frequency distribution of patients' creatinine, ammonia, platelets, hemoglobin, albumin, and bilirubin and HESA[3], MELD[8] and CTP[7] scores in the two groups of polyethylene glycol and lactulose were not statistically significantly different.

In a randomized clinical trial in 2017 in Iran by Naderian et al., The therapeutic effect of polyethylene glycol and lactulose compared to lactulose alone was compared in two groups of 24, resulting in the simultaneous use of polyethylene glycol and lactulose

Table 1: Age frequency distribution of patients in two groups.

		Age(Year)		
		<60	**>60**	**Total**
Group	**Polyethylene glycol**	14(46.7%)	16(53.3%)	30(100%)
	Lactulose	10(33.3%)	20(66.7%)	30(100%)
Total		24(40%)	36(60%)	60(100%)

Table 2: Frequency distribution of sex of patients in two groups.

		Sex		
		Male	**Female**	**Total**
Group	**Polyethylene glycol**	22(73.3%)	8(26.7%)	30(100%)
	Lactulose	16(53.3%)	14(46.7%)	30(100%)
Total		38(63.3%)	22(36.7%)	60(100%)

Table 3: Frequency distribution of the cause of cirrhosis in the studied patients in two groups.

		Cause of Cirrhosis						
		Alcohol	**Chronic Viral Hepatitis**	**Biliary Cirrhosis**	**Cardiac Cirrhosis**	**Cryptogenic**	**Others**	**Total**
Group	**Polyethylene glycol**	0 (0%)	9 (30%)	2 (6.7%)	2 (6.7%)	8 (26.7%)	9 (30.0%)	30 (100%)
	Lactulose	2 (6.7%)	9 (30.0%)	0 (0%)	0 (0%)	14 (46.7%)	5 (16.7%)	30 (100%)
Total		2 (3.3%)	18 (30%)	2 (3.3%)	2 (3.3%)	22 (66.7%)	14 (23.3%)	60 (100%)

Table 4: Frequency distribution of the cause of encephalopathy in two groups.

		Cause of Encephalopathy						
		Hypokalemia	**GIB**	**Azotemia**	**Infection**	**Constipation**	**Others**	**Total**
Group	**Polyethylene glycol**	4 (13.3%)	3 (10%)	7 (23.3%)	9 (30.0%)	5 (16.7%)	2 (6.7%)	30 (100%)
	Lactulose	8 (26.4%)	4 (13.3%)	2 (6.7%)	6 (20.0%)	8 (26.7%)	2 (6.7%)	30 (100%)
Total		12 (20.0%)	7 (11.7%)	9 (15.0%)	15 (25.0%)	13 (21.7%)	4 (6.7%)	60 (100%)

Table 5: Frequency distribution of ascites in patients in two groups.

		Ascites		
		Positive	**Negative**	**Total**
Group	**Polyethylene glycol**	15(50.0%)	15(50.0%)	30(100%)
	Lactulose	20(66.7%)	10(33.3%)	30(100%)
Total		35(58.3%)	25(41.7%)	60(100%)

compared to lactulose Alone is more effective in the treatment of hepatic encephalopathy in cirrhotic patients and causes more improvement in HESA^3 score within 24 hours and faster discharge from the hospital[30]. Given the excellent efficacy of these two drugs in our study, it will not be useless to evaluate their combined effect in future studies.

A randomized clinical trial conducted in the United States in 2014 by Rahimi et al. In which 50 patients with hepatic encephalopathy were randomly assigned to receive polyethylene glycol and lactulose; as a result, patients receiving polyethylene glycol were cured faster than patients receiving lactulose, suggesting that polyethylene glycol may be used to treat patients with cirrhosis due to acute hepatic encephalopathy. However, it should be noted that in our study, both drugs had the same efficacy.

In that study, the HESA^3 score had a significant decrease in the lactulose group and in the polyethylene glycol group on average after 24 hours of treatment, which is in line with the results obtained in our study[1].

A randomized clinical trial was conducted in Japan in 1997 by Watanabe et al. In which 75 cirrhotic patients with hyperammonemia were randomly divided into two treatment groups with and without lactulose. In patients with SHE^{10} (Subacute Hepatic Encephalopathy) who were prescribed lactulose, the results of the quantitative psychometric evaluation showed a clear improvement in weeks 4 and 8 from the start of lactulose administration, and SHE^{10} improved in 50% of patients treated at week 8 but in 85% of patients untreated with lactulose remained resistant. As a result, lactulose therapy in cirrhotic patients with SHE^{10} was effective in improving psychometric tests[18]; this issue can be studied in future studies in Iranian patients.

Table 6: Frequency distribution of creatinine, ammonia and platelets of patients in two groups.

	Group	Mean	St. Deviation
Initial Creatinine	Polyethylene glycol	1.49	0.95
	Lactulose	1.39	0.68
Final Creatinine	Polyethylene glycol	1.81	1.10
	Lactulose	1.42	0.54
Initial Amonium	Polyethylene glycol	223.92	49.10
	Lactulose	279.00	119.50
Final Amonium	Polyethylene glycol	269.11	93.96
	Lactulose	224.00	96.32
Initial Platelet	Polyethylene glycol	119.53	79.09
	Lactulose	123.93	91.89
Final Platelet	Polyethylene glycol	152.36	45.74
	Lactulose	114.09	77.22

Table 7: Frequency distribution of INR, hemoglobin, albumin and bilirubin in patients in two groups.

	Group	Mean	St. Deviation
INR	Polyethylene glycol	1.36	0.12
	Lactulose	1.35	0.15
Initial Albumin	Polyethylene glycol	2.65	0.73
	Lactulose	2.81	0.47
Final Albumin	Polyethylene glycol	2.32	0.62
	Lactulose	2.62	0.46
Initial Hemoglobin	Polyethylene glycol	10.91	0.71
	Lactulose	10.77	1.82
Final Hemoglobin	Polyethylene glycol	10.69	0.75
	Lactulose	9.96	1.25
Bilirubin Total	Polyethylene glycol	2.10	1.86
	Lactulose	2.77	2.03
Bilirubin Direct	Polyethylene glycol	1.49	1.83
	Lactulose	1.74	1.58

In a 2012 randomized clinical trial in India by Agrawal et al., 235 patients who recovered from hepatic encephalopathy were randomly divided into three groups: one received lactulose, one received probiotics, and the third did not receive medication. Psychometric tests and blood ammonia levels assessed patients, and there was a clear difference between the lactulose group and the non-drug group and between the probiotic group and the non-drug group. However, there was no difference between the two groups receiving lactulose and probiotics. In general, lactulose and probiotics were effective for the secondary prophylaxis of hepatic encephalopathy in patients with cirrhosis, like our study, which shows no difference between drugs[25].

A randomized clinical trial in 2017 in Iran by Naderian et al. Examined the therapeutic effect of polyethylene glycol and lactulose compared to lactulose alone. This study was performed in the emergency room of Shariati Hospital in two groups of 24 people. As a result, the simultaneous use of polyethylene glycol and lactulose is more effective in treating hepatic encephalopathy in cirrhotic patients than lactulose alone (further improvement in $HESA^3$ score within 24 hours with $p = 0.004$) and causes faster discharge from the hospital. ($P = 0.03$)[30].

A Cochrane's systematic review study was conducted in Denmark in 2004 by Nielsen et al. On 22 different clinical trials of lactulose, as a result, there was insufficient evidence to support the use of non-absorbable disaccharides in hepatic encephalopathy[22]. However, in our study, a good efficacy was observed for lactulose in the studied patients, which was not different from polyethylene glycol.

Table 8: Frequency distribution of patients' HESA, MELD and CTP scores in two groups.

	Group	Mean	St. Deviation
Initial HESA Score	Polyethylene glycol	2.80	0.41
	Lactulose	2.90	0.31
Final HESA Score	Polyethylene glycol	1.77	0.77
	Lactulose	1.60	0.86
Meld Score	Polyethylene glycol	18.03	3.38
	Lactulose	19.10	7.10
CTP Score	Polyethylene glycol	11.10	1.30
	Lactulose	11.13	2.10

Studies show that hepatic encephalopathy is caused by the liver's inability to detoxify toxins in the blood and brain, including ammonia. Astrocytes convert ammonia to glutamine to protect neurons from side effects. An increase in glutamine, in turn, changes the osmotic pressure and volume of interstitial fluid in the brain. On the other hand, an increase in ammonia also stimulates immune cells in the brain and causes nerve inflammation. High levels of ammonia and the resulting neuroinflammation alter the levels of neurotransmitters, which in turn cause cognitive impairments such as learning and memory impairments and impaired movement and motor coordination.

It seems that the mechanism of therapeutic effect of polyethylene glycol and lactulose solution in treating patients with hepatic encephalopathy is due to intestinal purification.

Polyethylene glycol solution is a low side effect drug and effectively cleanses the intestines similar to lactulose.

Of note, the limitations of our study included the following:

1- The relatively small number of people surveyed in our study resulted in moderate power, which may have led to non-significant results in some of the items surveyed.

2- Due to sampling from a training and referral center, the generalizability of the results decreases.

Finally, it is recommended that more studies be performed to confirm the findings obtained in this study with larger sample size and as a multicenter in other medical centers. Further studies on other treatments for patients with hepatic encephalopathy should be considered for future studies. In addition, it is suggested that we seek the prevention of liver cirrhosis in the community with the necessary preventive planning.

Conclusion

Overall, based on the results of this study, which was performed as a three-blind randomized clinical trial, it is concluded that polyethylene glycol and lactulose have similar efficacy in patients with hepatic encephalopathy, Moreover, therefore, the use of each of them two according to the patients' condition and physician's discretion is recommended.

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