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EVALUATION OF POLYETHYLENE GLYCOL 4000 SOLUTION (PEG) EFFICACY VERSUS LACTULOSE IN TREATMENT OF HEPATIC ENCEPHALOPATHY

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ABSTRACT

Background: Hepatic encephalopathy is a common complication of patients with hepatic cirrhosis and results in the alteration of mental status with a broad range of signs and symptoms based on its clinical severity. Lactulose or a nonabsorbable antibiotic are the mainstays of therapy for patients with persistent encephalopathy. **Objective**: The aim of this study was to evaluate the efficacy of Polyethylene glycol (PEG) versus lactulose in management of hepatic encephalopathy. **Patients and Methods**: This study was carried out at Tropical Medicine Department (Al-Hussein and Sayed Galal University Hospitals). The study population included 100 patients who were diagnosed to have signs of the first to third degrees of HE, during the period from January 2016 to August 2016. The patients were divided and classified into two groups: **Group I:** Included 50 patients who had hepatic encephalopathy and were treated with lactulose, and **Group II:** Included 50 patients who had hepatic encephalopathy and were treated with 4 liters of PEG. **Results:** A total of 100 patients were randomized to each treatment arm. Clinical efficacy was determined using HE index improvement. PEG was considered effective in 38 patients (76%) and lactulose in 40 patients (80.0%), which was not significantly different. **Conclusions:** PEG and lactulose decrease hepatic encephalopathy index with no statistically significant difference.

INTRODUCTION

The treatment of HE has focused on reducing both the production and absorption of gut-derived ammonia. Non-absorbable disaccharides and antibiotics are the mainstay of therapy **(Paik et al., 2005).**

Lactulose or a nonabsorbable antibiotic are the mainstays of therapy for patients with persistent encephalopathy. Lactulose has traditionally been considered the first line therapy to reduce absorption of nitrogenous compounds from the intestinal tract. It is metabolized by colonic bacteria into acetic and lactic acid, thus acidifying the colon and increasing fecal nitrogen excretion **(Sharma et al., 2009).** Lactulose is the first choice for treatment of episodic overt HE (GRADE II-1, B, 1 - ***EASL , 2015).***

Laxative agents such as magnesium salts were used prior to the introduction of lactulose suggesting that catharsis alone may be effective for treatment of HE. However, since the first report of the efficacy of lactulose in 1966, and the consequent widespread adoption of non-absorbable disaccharides for treatment of HE, there have been few studies comparing their effect with cathartic methods. Since PEG is a safe commonly used, and highly effective purgative, we hypothesized that if immediate catharsis

of the gut is important in the treatment of HE, then PEG may be superior to lactulose in this capacity **(Rahimi et al., 2013).** This study aimed to evaluate the efficacy of polyethylene glycol (PEG) versus lactulose in management of hepatic encephalopathy.

PATIENTS AND METHODS

This was a prospective double-blind randomized controlled trial done in Tropical Medicine Department (Al-Hussein and Sayed Galal University Hospitals), within the period from January 2016 to August 2016.The study protocol adopted was approved by the Medical Ethics Committee,Al-Azhar Faculty of Medicine. The protocol was explained to at least one relative of each patient selected for the study, and written informed consent was obtained from all patients who participated or from their relatives. At the beginning of the trial, patients underwent a full assessment, including a detailed history taking, and physical and neurological examinations. The following parameters were evaluated before and at the end of the treatment period: Complete blood count, liver function test, kidney function test, serum electrolyte, blood sugar, prothrombin time, international normalized ratio, arterial ammonia, viral markers (hepatitis B surface antigen and anti-hepatitis C virus), and abdominal ultrasound. Ascitic fluid analysis was done for spontaneous bacterial peritonitis. Child–Turcotte–Pugh (CTP). The end point of the study was complete reversal of HE as per West Haven criteria. A total of 150 patients with cirrhosis and HE were screened. Of these, 50 patients were excluded because of serum creatinine >2 mg/dl at admission (*n*=22), hepatocellular carcinoma (*n*=3), patients with GIT bleeding (*n*=14), patient on rifaximin within previous 7 days (*n*=5) and significant comorbidities (*n*=6). Finally, 100 patients who met the inclusion criteria were included in the study. Of these, 50 patients received lactulose (group A) and 50 patients received PEG (group B).

Drug Administration: Group A patients were treated with Lactulose **(beta-1, 4-galactosido-fructose) (**Lactulose syrup® EPICO, Pharmaceutical, Cairo, Egypt), 20 to 30 g administered orally or by nasogastric tube (3 or more doses within 24 hours). Group B patients were treated with 4 L of PEG (Fortrans® sachets Elhayatt, Pharmaceutical, Cairo, Egypt) administered orally or via nasogastric tube, one liter every 6 hours. After PEG administration, no lactulose or other potential HE therapy was allowed for 24 hours, at which time the follow-up was obtained, close monitoring of sign of dehydration and electrolyte disturbance. All patients were given a nutritious diet containing a maximum of 40g of protein per day**.** Recovery of HE was assessed twice daily independently by two expert hepatologists. In case of treatment failure, patients in group B were given rifaximin plus lactulose and those in group A were given rifaximin plus L-ornithine and L-aspartate.

Serum ammonia level: Blood samples were collected from a stasis-free vein (that is, without using a tourniquet and taking care not to cause turbulence or hemolysis) and immediately transported on ice to the laboratory to be analyzed within 20 min. Normal ammonia level was considered <75 umol/L **(Yong-Han et al., 2005).**

Blood ammonia levels: Blood ammonia was measured before and after the treatment using Cobas Integra 800 (Roche, Basel, Switzerland). Grade 0: < 75 μM/L; Grade 1: 76-150 μM/L; Grade 2: 151-200 μM/L; Grade 3: 201-250 μM/L; and Grade 4: > 251 μM/L **(Yong-Han et al., 2005).**

Grade of mental state: This was examined semi-quantitatively using Conn's modification of the Parsons-Smith classification.[21] Grade 0: no abnormality; Grade 1: trivial loss of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction performance; Grade 2: lethargy, disorientation with respect to time, obvious personality change, inappropriate behavior; Grade 3: somnolence to semi-stupor, responsive to stimuli, confusion, gross disorientation, bizarre behavior; and Grade 4: coma, unable to test mental function **(Conn et al., 1977).**

The severity of flapping tremor: Severity was determined by extending the patients' arms and forearms with the wrists dorsiflexed for at least 30 seconds. We adopted a simplified grading system to minimize inter-observer variance. Grade 0: no flapping motion; Grade 1: infrequent flapping motion; Grade 2: continual flapping motion; and Grade 3: unable to test **(Conn et al., 1977).**

Number connection test (NCT): The time taken to connect 25 progressive numbers, i.e. part A of the number connection test. Grade 0: < 30 sec (normal); Grade 1: 31-50 sec; Grade 2: 51-80 sec; Grade 3: 81-120 sec; and Grade 4: > 120 sec ***(Reitan 1955)*.**

HE index: The above items were determined before treatment and on hours 6, 12, 18 and 24 of the trial period. The grades for the above four components were weighted in proportion to their importance. Thus, HE grade awarded a weighting factor of three, while the other variables were each assigned a factor of one. The HE index was defined as the total of the weighted grades, and had a possible range of 0 to 23 points, i.e., HE index= (grade of mental state) × 3+(grade of number connection test)+(grade of flapping tremor)+(grade of blood ammonia) **(Paik et al., 2005).**A decrease of HE index by at least one point was defined as 'improved', and increment of the HE index by one point or more was defined as 'worsened'**(Paik et al., 2005).**

Statistical analysis: Data were expressed as mean±SD for a comparison of categorical variables, χ^2 and Fisher's exact tests were used, and for continuous variables, Mann–Whitney test was used as appropriate. The probability level of $P<0.05$ was set for statistical significance. Statistical analysis was performed with SPSS software, version 19 (SPSS, Chicago, IL).

RESULTS

A total of 150 patients with cirrhosis and HE were screened. Of these, 50 patients were excluded because of serum creatinin >2 mg/dl at admission (*n*=22), hepatocellular carcinoma (*n*=3), Patients with GIT bleeding (*n*=14), patient on rifaximin within previous 7 days (*n*=5) and significant comorbidities (*n*=6). Finally, 100 patients who met the inclusion criteria were included in the study. Of these, 50 patients received lactulose (group A) and 50 patients

received PEG (group B). The enrolled patients were 55 males and 45 females, aged between 40 and 71 (mean age 54.46±8.22 years in group A and 55.12±8.98 in group B). At the start of the study, the demographic and clinical parameters of the patients in the two groups showed no significant differences (Tables 1&2).

Table (1): Baseline characteristics of study patients.

Groups / Characteristics		Lactulose (*n*=50)	PEG (*n*=50)	P value
Age (years)		54.64±8.22	55.12±8.98	>.005
Male/female		26:24	29:21	>.005
HBV		5 (10%)	2 (4%)	>.005
HCV		42 (84%)	46 (92%)	>.005
Other		3 (6 %)	2 (4%)	>.005
CTP	B	35 (70%)	33 (66%)	>.005
	C	15 (30%)	17 (34.2%)	>.005
CTP score		9.9±2.8	9.4±2.5	>.005
HE grade (1/2/3/4)		0/15/30/5	0/14/32/4	>.005
H/o previous HE		40 (80%)	42(82%)	>.005

CTP, Child–Turcotte–Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; H/o, history of

In this study, the cause of the liver disease was HCV infection in 78 patients (78%), HBV infection in 7 patients (7%) and other cause was in 5 patients (5%). 88 patients (88%) was child B and22 patients (22%) child C and 82(82%) patients had history of HE.

Table (2): Baseline laboratory parameters of study patients.

Groups / Parameters	Lactulose (*n*=50)	PEG (*n*=50)	P value
Hb (gm%)	9.92±1.25	10.29±1.14	>.005
Platelet($\times 10^3/\mu L$)	14,8±22,3	79,0±20,8	>.005
WBCs	5148±1118.7	5106.64±1141.3	>.005
Bilirubin(mg/dL	2.4±1.1	2.1±1.3	>.005
Albumin (g/dL)	2.1±0.9	2.3±0.8	>.005
AST (IU/l)	62.76±17.89	59.4±13.2	>.005
ALT (IU/l)	50.9±13.92	51.4±14.94	>.005
INR	2.2±1.1	2.5±1.3	>.005
Urea (mg/dL)	27.8±9.5	31.4±6.3	>.005
Creat (mg/dL)	0.9±0.5	0.7±0.4	>.005
Na (mEq/l)	135.84±5.6	137.3±4.2	>.005
K (mEq/l)	3.5±0.7	3.9±0.5	>.005

ALT, alanine transaminase; AST, aspartate transaminase; Creat, serum creatinine; Hb, hemoglobin; INR, international normalized ratio; K, potassium; Na, sodium;

Table (3): Precipitating factors of HE in both groups.

Precipitating factors \ Groups		Lactulose group (50)	PEG group (50)	Total (50)
High protein diet	**N**	23	30	53
	%	46.00	60.00	53.00
Infection	**N**	6	4	10
	%	12.00	8.00	10.00
Constipation	**N**	13	6	19
	%	26.00	12.00	19.00
Unknown precipitating factor	**N**	8	10	18
	%	16.00	20.00	18.00
Total	**N**	50	50	100
	%	100.00	100.00	100.00
Chi-square	**X^2**	0.372		
	P-value	0.186		

Identified precipitating factors included, protein overload (n=**5**3), infection (n=**10**), constipation (n=1**9**) and unknown (n=1**8**). There was no significant difference between the two groups in terms of factors precipitating HE.

Table (4): Changes in HE Index and HE-related Parameters after Treatment.

Parameters \ Groups	Lactulose		P value	PEG		P value
	Pre	**Post**		**Pre**	**Post**	
NH3 level	179.4±19.37	135.76±21.2	00 0.001	175.88±50.85	137.88±50.85	0.001
Blood NH3 grade	1.8±0.9	0.9±0.6	0.001	1.9±0.8	1.1±0.7	0.001
Mental status grade	1.4±0.8	0.3±0.2	0.001	1.5±0.7	0.5±0.4	0.001
Grad of flapping tremors	1.8±0.8	0.4±0.3	0.001	1.9±0.7	0.6±0.4	0.001
Grade of NCT	2.8±1.1	1.9±1.00	0.001	3.1±0.9	2.0±1.1	0.001
HE index	11.2±3.1	4.5±2.6	0.001	10.9±3.7	4.8±3.1	0.001

Compares the therapeutic effects of PEG and lactulose, Mean blood levels and grades of blood NH3 significantly decreased with both PEG ($p = 0.000$) and lactulose treatment ($p = 0.001$). Mean blood NH3 concentrations were similar after both forms of therapy. Mental state was significantly improved by PEG (1.5→0.5) and by lactulose (1.4→0.3) ($p = 0.001$ and $p < 0.01$, respectively). Grades of flapping tremor and NCT were improved to nearly equal degrees by PEG and lactulose treatment. Mean HE indexes improved both in the PEG group (10.9→4.8, p=0.000) and in the lactulose group (11.2→4.5, p=0.000). No significant difference was found between the two groups in terms of the grades of HE components at any given time.

Table (5): Changes in HE Index, Blood Ammonia and HE Grade after PEG or Lactulose Treatment in Patients with HE.

Parameters \ Groups		Lactulose n= 50	PEG n= 50	P value
Improvement of blood NH3 level		40 (80%)	36 (72%)	>.005
Improvement of HE grade		42(84%)	40 (80%)	>.005
HE index	Improved	40(80%)	38 (76%)	>.005
	Unchanged	10(20%)	10(20%)	>.005
	Worsened		2(4%)	>.005

At the completion of treatment, in group A blood NH3 level improved in 40 patients (80.0%) while in group B was 36 patients (72%). In the lactulose group, 42 patients (80%) improved HE grades. These group differences were not statistically significant (Table 4). Clinical efficacy was determined using HE index improvement. PEG was considered effective in 38 patients (76%) and lactulose in 40 patients (80.0%), which was not significantly different

Overall, treatment regimens were similar in terms of tolerability, with the exception that in the lactulose group, there was more bloating, while PEG group patients experienced more diarrhea symptoms. Furthermore, over 50%of patients who received PEG not only preferred the “salty” taste over the sweet flavor of lactulose, they requested this therapy at discharge to replace their current outpatient lactulose regimen. The possibility that treatment may alter electrolyte levels or renal function in the follow-up period was also assessed. Electrolytes, creatinine, and blood urea nitrogen were measured at baseline and at 6 to 24 hours after admission. There were no significant changes in levels of serum potassium, sodium, creatinine, or blood urea nitrogen after either PEG or lactulose treatment.

DISCUSSION

Depending on its cause, HE can be categorized as either type A, which occurs in patients with acute liver failure; type B, which occurs in patients with bypass shunts or type C, which occurs in patients with chronic liver disease **(Frederick, 2011).**

Although a number of other possible factors have been proposed to play a role in the pathogenesis of HE, such as, the production of central benzodiazepine agonists, endogenous opioids and false neurotransmitters, ammonia is still viewed as the key contributor,Thus the mainstay treatment for HE revolves about reducing the production and absorption of ammonia in the gut, and to improve its excretion by drug therapy or diet modification. Current treatment strategies are aimed at reducing the serum level of ammonia. This is done by introducing agents that reduce or inhibit production of intestinal ammonia or minimize its absorption from the gastrointestinal tract as well as correcting

any detectable precipitating factors **(Eltawil et al., 2012).**

Lactulose is currently recommended as the first-line pharmacological treatment for HE by the practice guidelines proposed by the American College of Gastroenterology. However, the use of lactulose may be associated with nausea, flatulence, abdominal cramps, severe diarrhea, and dehydration **(Kircheis and Haussinger, 2002).** Protracted diarrhea may result in hypertonic dehydration with hypernatremia, which may aggravate the patient's mental state.

Laxative agents such as magnesium salts were used prior to the introduction of lactulose, suggesting that catharsis alone may be effective for treatment of HE **(Rahimi et al., 2014)**. Colon cleaning agents as oral mannitol have been shown to be effective, safe, simple, inexpensive, and tolerated medicine in the prevention of HE after upper GI- bleeding in patient with liver cirrhosis **(Massoud et al., 2011).**

PEG is not absorbed and, unlike lactulose, lacks the unabsorbed carbohydrate load that lowers stool pH and increases stool water losses. Furthermore, ammonia excretion in the stool is greater with PEG than with lactulose **(Rahimi et al., 2014**).

The present study is the first, prospective randomized study to compare the efficacy of PEG with that of lactulose for the short-term treatment of HE in EGYPT. Our study confirms that PEG is as effective as lactulose for the treatment of HE in Egyptian patients.

The identification and correction of factors precipitating HE is of primary concern during the management of HE**(Kircheis and Haussinger., 2002)** because the correction of such factors usually results in improvement. Thus patients' precipitating factors should be carefully considered in any future trial. In our study, most patients had an identifiable precipitating factor, and the two treatment groups had reasonably similar precipitating factors profiles. Therefore, we believe that any potential bias caused by precipitating factors was minimal in the present study.

In this study, ammonia levels was examined from 6 to 24 hours after medication ingestion, a time at which ammonia levels might be expected to be rapidly changing as a result of therapy.

Regarding blood ammonia level and grades of blood NH3 in this study, there was statistically significantly decreased in both PEG group and lactulose group after treatment with no statistically significant difference between two groups these results were similar to the results reported by **(Rahimi et al., 2014).**

An important consideration with the use of PEG is that it causes a substantial catharsis and thus in theory may result in dehydration, electrolyte disturbances, and even acid-base abnormalities. However, it also contains electrolyte additives that help balance water and electrolyte loss across the gastrointestinal tract and is the most commonly used cathartic for patients requiring a colon preparation. Indeed, it has been shown to be safe and effective in a wide variety of patients **(Wexner et al., 2006)**.Lactulose, which functions as an osmotic diarrheal agent, causes much more severe electrolyte disturbances than does PEG **(Rahimi et al., 2014**).

In this study, grades of flapping tremor and NCT were improved to nearly equal degrees by PEG and lactulose treatment with no statistically significant difference.

After 1 day, 40 patients (80%) became in grade 0 in lactulose group

with versus 36 patients (72%) in the PEG group .

Clinical efficacy was determined using HE index improvement. PEG was considered effective in 40 of 50 patients (80%) and lactulose in 42 of 50 patients (84%), which was not significantly different (p=0.315)this in agreement with **Rahimi et al., (2014)** who found that Patients receiving PEG had a significantly lower mean(SD)HE score at 24 hours as in patients receiving lactulose.

An important consideration with the use of PEG is that it causes a substantial catharsis and thus in theory may result in dehydration, electrolyte disturbances, and even acid-base abnormalities. However, it also contains electrolyte additives that help balance water and electrolyte loss across the gastrointestinal tract and is the most commonly used cathartic for patients requiring a colon preparation.

In this study, electrolytes (Na and K), creatinin, and blood urea nitrogen were measured at baseline and at 6 to 24 hours after admission. There were no significant changes in levels of serum potassium, sodium, creatinine, or blood urea nitrogen after either PEG or lactulose treatment.

The major strengths of the present study were its innovative approach and potential generalizability. PEG preparations are widely available, commonly used, and inexpensive. One potential benefit of using PEG for overt HE was that it may result in shorter lengths of stay, depending on the causes of the HE; HE resolution was shown to be significantly more rapid in the PEG group, and the length of hospital stay was shorter. This could potentially result in a decrease in the total direct costs of hospitalization nationally.

We recognized potential limitations of this study. First, it was from a single center and thus may not be generalizable to other centers. However, we would emphasize that it was performed in a center with a highly diverse population. Second, this study could not be blinded, since giving a placebo in the place of PEG was not possible. Thirdly, the duration of our study was one day.

CONCLUSION

PEG improves the various subjective and measurable components of hepatic encephalopathy including mental status, asterixis, behavior and serum ammonia concentration but less effective than lactulose. In HE of grade 1 to grade 3, PEG was an alternative to non-absorbable disaccharides. It was also well tolerated and associated with less frequent side effect.

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تقييم فاعلية محلول البولي إيثيلين جلايكول4000 مقارنة باللاكتيلوز في مناجزة الإعتلال الكبدي الدماغي

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خلفية البحث : إعتلال الكبد الدماغي هو مضاعفات للمرضى الذين يعانون من تليف الكبد والذي ينتج عنه تغيير في الحاله العقليه .اللاكتيلوز أو المضادات الحيوية غير الممتصه هي الدعائم الأساسية لعلاج المرضى الذين يعانون من إعتلال الدماغ المستمر.

الهدف من الدراسة: هو تقييم فاعلية البولي إيثيلين جليكول مقارنة باللاكتيلوز في علاج إعتلال الكبد الدماغي .

المرضى وطرق البحث : أجريت هذه الدراسة في قسم الأمراض المتوطنة بمستشفي الحسين وسيد جلال الجامعي وتضمنت الدراسة 100 مريضاً يعانون من الإعتلال الكبدي الدماغي من الدرجة الأولى وحتى الدرجة الثالثة خلال الفترة بين يناير 2016 وحتى أغسطس 2016.وقد تم تقسيم المرضي إلي مجموعتين : المجموعة الأولي تضمنت 50 مريضاً تم علاجهم باللاكتيلوز والمجموعة الثانية تضمنت 50 مريضاً أيضا تم علاجهم بالبولي إيثيلين جلايكول .

النتائج: أدى استخدام محلول البولى إيثيلين جلايكول إلي تحسين أعراض الإعتلال الدماغي الكبدى في 38 مريض مقارنة بتحسن 40 مريض عند إستخدام اللاكتيلوز ولم تكن هناك فروق ذات دلالة إحصائية بين المجموعتين.

الخلاصة : يعمل كل من اللاكتيلوز والبولي إيثيلين جلايكول علي تخفيض مؤشر إعتلال الكبدي الدماغي مع عدم وجود فروق ذات دلالة إحصائية .