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EFFICACY OF LACTULOSE WITH RIFAXIMIN FOR PROPHYLAXIS OF PORTOSYSTEMIC ENCEPHALOPATHY

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ABSTRACT

OBJECTIVE: *To determine the efficacy of lactulose versus refixamine plus lactulose for prophylaxis of portosystemic encephalopathy.*

METHODOLOGY**:** *A randomized controlled trial was conducted in the Department of Gastroenterology at the Asian Institute of Medical Sciences (AMIS) Hospital, Hyderabad. Non-probability purposive sampling technique was used to recruit the sample of 166 patients between aged group of 20 to 70 years, of either gender. Participants had to have a confirmed diagnosis of portosystemic encephalopathy (PSE) were included in the study. Participants were randomized into two equal groups (n=83) by using computer-generated sequential numbers enclosed in sealed envelopes, which were opened at the time of allocation. Group A received a combination therapy of lactulose and rifaximin (400 mg twice daily), while Group B received lactulose alone (30–60 mL daily in 2–3 divided doses). Participants were followed for one week to assess treatment efficacy of the treatment. SPSS version 26.0 was used to analyse the data. The P value ≤ 0.05 was considered as criteria of statistical significance.*

RESULTS: *The mean age of participants in Group A was 46.63 ± 11.75 years, while in Group B, it was 44.19 ± 11.53 years, with insignificant difference between the groups (p = 0.180). In gender distribution group A consist of 66.3% males and 33.7% females while group B included 59.0% males and 41.0% female. Ammonia levels were significantly higher in Group A (131.45 ± 22.42 µmol/L) compared to Group B (119.58 ± 21.72 µmol/L, p = 0.001). Efficacy in Group A versus Group B was noted as (71.1% v/s 53.0%; OR: 2.18; p=0.016).*

CONCLUSION: *The findings of current study shows that combination of lactulose and rifaximin found to be significantly more effective than lactulose alone in the treatment of portosystemic encephalopathy. Patients receiving combination therapy had rates of clinical outcomes, and better biochemical profiles. These findings support lactulose plus rifaximin as a superior treatment option for PSE.*

KEYWORDS*: Antibiotics, Hepatic Encephalopathy, Hepatic Function Tests, Lactulose, Liver Cirrhosis, Microbiome, Rifaximin*

INTRODUCTION

Portosystemic encephalopathy (PSE) is a frequent complication of cirrhosis, causing a significant burden to patients and families [1]. The emergence of portosystemic encephalopathy adversely affects patients' survival [2]. Encephalopathy event resulting in hospitalization carries a 1st and 3rd year survival probability of only 42% and 23% respectively. The most common potentially preventable cause for readmission is portosystemic encephalopathy [3]. The most common clinical presentations of PSE includes altered mentation, psychotic symptoms, and coma [4]. In fact, PSE is relatively common and should be recognized as a frequent complication of advanced liver disease, including hepatitis due to different viruses, cirrhosis, and liver cancer [5]. Management of PSE has primarily been directed at the reduction of both gut-derived ammonia production and absorption [6]. Elevated serum ammonia, and therefore therapy with non-absorbable disaccharides (NAD), rifaximin, L-ornithine-L-aspartate (LOLA), and branched-chain amino acids (BCAA), all of which aim to reduce serum ammonia levels, were observed in 60%–80% of patients with PSE [7]. The most important neurotoxic substance implicated in the pathogenesis of Portosystemic encephalopathy (PSE) is ammonia which is produced in the gut primarily by colonic bacteria [8]. Lactulose reduces ammonia production and increases consumption of ammonia in gut by reducing gut transit, acting on different groups of colonic bacteria, leading to both lower production and increased consumption of ammonia in the gut [9]. In support of this, a study by Ali B et al demonstrated the effectiveness of rifaximin for prophylaxis of portosystemic encephalopathy in cirrhotic patients [9]. Rifaximin also aids PSE through bactericidal action on ammonia-producing gut flora [10]. Lactulose is the preferred and most commonly used among these, while rifaximin, a new non-absorbed oral antimicrobial, has shown its efficacy in recent years [11]. Meta-analysis studies suggested similar clinical effects of the two drugs, such as [12]. Since the pharmacological mechanisms of rifaximin and lactulose for the PSE are essentially different that a combination could increase the clinical efficacy from that of lactulose [13].

The study comparing lactulose alone versus rifaximin and lactulose for the prophylaxis of portosystemic encephalopathy (PSE) in cirrhotic patients was motivated by current therapeutic standards and the need for better treatments. Liver cirrhosis complications like PSE are prevented and treated with lactulose and rifaximin. The non-absorbable antibiotic rifaximin reduces gut flora, while lactulose reduces colon ammonia absorption. They are widely used, but it is unclear if the combined therapy prevents PSE better than lactulose alone. Because both medications synergistically lower serum ammonia levels, they may reduce PSE more effectively than either alone. Local population efficacy is important because genetic, dietary, and environmental factors can affect treatment outcomes. This study fills the literature gap on the optimal prophylactic treatment regimen for PSE in cirrhotic patients and may improve clinical practice therapy.

METHODOLOGY

A randomized controlled trial was conducted in the Department of Gastroenterology at the Asian Institute of Medical Sciences (AMIS) Hospital, Hyderabad. Non-probability purposive sampling technique was used to recruit the sample of 166 patients between aged group of 20 to 70 years, of either gender. Inclusion criteria required participants to have a confirmed diagnosis of portosystemic encephalopathy (PSE), characterized by neuropsychiatric symptoms indicative of significant liver dysfunction (bilirubin > 2 mg/dL, albumin < 3.5 g/dL, INR > 1.5) or portosystemic shunting (hepatic venous pressure gradient (HVPG) > 10 mm Hg, visualization of collateral circulation such as varices, or splenomegaly on ultrasound).

The neuropsychiatric manifestations of PSE included moderate to severe alterations in mental status graded according to the West Haven Criteria (Grades I–IV), elevated serum ammonia levels (>45 µmol/L), intellectual impairments (e.g., confusion, lethargy), and neuromuscular disturbances (e.g., asterixis, hyperreflexia, and muscle rigidity). Diagnosis was established based on the concurrent presence of liver-related and neuropsychiatric symptoms. Patients presenting with symptoms ranging from irritability and confusion to coma (West Haven Grades I–IV) were enrolled following the provision of informed consent.

Exclusion criteria included patients unwilling to participate, those without a history of cirrhosis-related complications, patients receiving nephrotoxic medications, and those with active bacterial infections. Participants were randomized into two equal groups (n=83) by using computer-generated sequential numbers enclosed in sealed envelopes, which were opened at the time of allocation.

Group A received a combination therapy of lactulose and rifaximin (400 mg twice daily), while Group B received lactulose alone (30–60 mL daily in 2–3 divided doses). Baseline demographic and clinical data which include age, gender, PSE grade, and body mass index (BMI), were documented. Baseline laboratory investigations included serum creatinine, serum sodium, and coagulation parameters. Participants were followed for one week to assess treatment efficacy, defined as a ≥ 25% reduction in PSE symptoms, a one-grade improvement in the West Haven Criteria, a 5% increase in serum albumin levels, a 10% decrease in INR and a 50% reduction in serum ammonia levels. The absence of new PSE episodes during the follow-up period was also considered a criterion for treatment success. Blood samples were collected at baseline and post-treatment for comparative analysis of biochemical and coagulation parameters. SPSS version 26.0 was used to analyse the data. Descriptive statistics which include mean ± standard deviation and frequency with percentage was calculated for quantitative and qualitative variable respectively. Inferential statistics was calculated by using Chi-square test at 5% level of significance.

RESULTS

Table I summarizes the baseline and clinical characteristics of the 166 study participants which were divided into two equal groups. Group A (lactulose plus rifaximin) and Group B (lactulose alone). The mean age of participants in Group A was 46.63 ± 11.75 years, while in Group B, it was 44.19 ± 11.53 years, with insignificant difference between the groups (p = 0.180). The MELD score was significantly higher in Group A (24.52 ± 4.87) compared to Group B (22.95 ± 4.68, p = 0.036), while the CTP score showed no significant difference (p = 0.070).

Group A had a lower mean albumin level (2.38 ± 0.66 g/dL) compared to Group B (2.64 ± 0.70 g/dL, p = 0.022), while bilirubin, hemoglobin (Hb), and international normalized ratio (INR) levels were comparable between the groups. Ammonia levels were significantly higher in Group A (131.45 ± 22.42 µmol/L) compared to Group B (119.58 ± 21.72 µmol/L, p = 0.001). Liver enzyme levels, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), were also significantly elevated in Group A, with AST (59.40 ± 6.94 IU/L vs. 54.59 ± 3.74 IU/L, p = 0.0001), ALT (69.06 ± 12.95 IU/L vs. 57.99 ± 8.42 IU/L, p = 0.0004), and ALP (103.45 ± 36.45 IU/L vs. 115.42 ± 30.21 IU/L, p = 0.014).

Gender distribution was comparable, with 55 males (66.3%) and 28 females (33.7%) in Group A, and 49 males (59.0%) and 34 females (41.0%) in Group B (p = 0.336). The grade of hepatic encephalopathy, as classified by the West Haven Criteria, showed no significant difference between the groups (p = 0.735), with the majority of participants in both groups presenting with Grade III or IV encephalopathy. Regarding etiology, alcohol-related liver disease was the most common cause, present in 67.5% of Group A and 62.7% of Group B, followed by HBV and HCV infections, with no significant differences between the groups (p = 0.797).

Table II compares the efficacy between lactulose versus refixamine plus lactulose for prophylaxis of portosystemic encephalopathy. Efficacy was observed in 59 patients (71.1%) in Group A which is significantly higher than in 44 patients (53.0%) in Group B. Conversely, lack of efficacy was reported in 24 patients (28.9%) in Group A as compared to 39 patients (47.0%) in Group B.

The calculated odds ratio (OR) was 2.179 with a 95% confidence interval (CI) of 1.148–4.137, indicating that patients in Group A were approximately 2.18 times more likely to achieve efficacy compared to Group B.

DISCUSSION

Portosystemic encephalopathy also known to be hepatic encephalopathy (HE) is a familiar and major complication of cirrhosis primarily because of the accumulation of toxic substances like ammonia in the bloodstream, due to impaired liver function [14]. The liver's inability to detoxify these substances leads to their buildup, which can adversely affect the brain, causing cognitive dysfunction, altered consciousness, and neuropsychiatric disturbances. Preventing and managing the PSE is crucial, as it significantly affects the quality of life of patients, increases hospital admission frequency and is related to the high morbidity and mortality [15].

Lactulose, a non-absorbable disaccharide, is widely used in the treatment and prevention of PSE. It functions by reducing blood ammonia levels through two primary mechanisms: by acidifying the colon, lactulose

converts ammonia (NH_3) into ammonium (NH_4^+), which is less easily absorbed into the bloodstream, and by acting as a laxative, it accelerates the excretion of ammonia [16]. Lactulose has proven to be effective in lowering the levels of ammonia and preventing episodes of encephalopathy however it needs frequent dosing and can cause gastrointestinal side effects such as bloating, diarrhea, and abdominal discomfort, which can affect patient adherence to treatment. These side effects are particularly problematic in patients, who need the long-term treatment. Despite these challenges lactulose remains one of the most familiar and accessible treatments for PSE, particularly in resource-limited settings.

On the other hand, rifaximin, a non-absorbable antibiotic, has become an important adjunct in managing PSE, particularly for patients who continue to experience episodes of hepatic encephalopathy despite lactulose therapy. Rifaximin works by targeting gut microbiota, which has a vital role in the ammonia creation via bacterial metabolism of nitrogenous compounds [17]. By reducing the bacterial load in the intestines, the rifaximin lowers the production of ammonia, thereby helping to lower ammonia levels in the bloodstream. Multiple researches have stated that the effectiveness of rifaximin in minimizing the incidence of hepatic encephalopathy episodes, and improving cognitive function, especially in patients with cirrhosis. Its use is generally well-tolerated, with fewer gastrointestinal side effects compared to lactulose. Rifaximin is especially beneficial for long-term management, as it requires fewer doses and is better tolerated over time.

In our study, in Group A (Lactulose Plus Rifaximin), efficacy was noted in 71.1% of patients while in Group B (Lactulose Alone), it was reported in 53% of patients. A study by Hussain T et al reported the prevalence of efficacy among rifaximin plus lactulose versus lactulose alone in treating portosystemic encephalopathy was 72.6% and 51.6% respectively [18]. Another study by Paik YH et al showed that rifaximin and lactulose were effective in 84.4% and 95.4% of patients for the treatment of portosystemic encephalopathy [19].

In managing PSE, both lactulose and rifaximin are effective and each has its strengths and weaknesses. The basic strength of lactulose is in its proven efficacy in lowering ammonia levels, and preventing episodes of encephalopathy. It is widely available and affordable making it a first-line therapy for PSE especially in low resource settings however its frequent dosing regimen, and gastrointestinal side effects can reduce patient adherence, particularly in those requiring long-term treatment [20]. The requirement for careful monitoring of dosage and side effects may also complicate its use in some patients.

Rifaximin, by contrast, offers a more targeted approach by reducing ammonia production at the source—the gut microbiota. It has a favorable side effect profile, with fewer gastrointestinal disturbances than lactulose, making it a better option for long-term use. However, the high cost of rifaximin remains a significant limitation, especially in resource-poor regions. Although it is effective at preventing recurrent episodes of hepatic encephalopathy, rifaximin does not address the underlying liver disease or halt its progression [21]. Therefore, it should be used as an adjunct rather than as a standalone therapy. Additionally, while rifaximin has been effective in clinical trials there is still limited long-term safety data particularly concerning the potential for antimicrobial resistance and changes to gut microbiota over extended usage time.

Given the strengths and weaknesses of lactulose and rifaximin, healthcare providers should consider every patient factor when selecting between these strategies. For patients who can tolerate the gastrointestinal side effects of lactulose, it has been an affordable and effective option to prevent PSE, however, for patients who struggle with these side effects or experience frequent recurrence of encephalopathy, rifaximin may be a better choice. In the resource limited settings where cost is a significant contributing factor lactulose remains an important choice while rifaximin may be reserved for the patients who have failed lactulose therapy, or need more targeted treatment.

Further research is needed to assess the long-term safety and efficacy of rifaximin, particularly in regard to its impact on gut microbiota and potential antimicrobial resistance. Additionally the healthcare systems should explore ways to make rifaximin more accessible, such as by negotiating lower prices or promoting the use of generic formulations. The role of lactulose in preventing PSE should continue to be reinforced, but its limitations, particularly with regard to patient compliance, need to be addressed through better patient education and support. Routine monitoring of liver function and ammonia levels as well as a multidisciplinary approach to managing cirrhosis will help optimize outcomes for patients with PSE.

By tailoring treatment to the individual needs of patients, considering both the benefits and limitations of lactulose and rifaximin, healthcare providers can improve the management of PSE and enhance the quality of life for cirrhotic patients.

CONCLUSION

The findings of current study shows that combination of lactulose and rifaximin found to be significantly more effective than lactulose alone in the treatment of portosystemic encephalopathy. Patients receiving combination therapy had rates of clinical outcomes, and better biochemical profiles. These findings support lactulose plus rifaximin as a superior treatment option for PSE

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