ORIGINAL ARTICLE

Role of oral antibiotics "Neomycin vs Ciprofloxacin" for Secondary Prophylaxis of Porto-Systemic Encephalopathy in Liver Cirrhotic patients

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ABSTRACT

Background: Liver cirrhosis is a leading cause of morbidity and mortality worldwide [(1,2)] but exact prevalence of cirrhosis is not known. Prevalence of Hepatic encephalopathy (HE) also known as porto-systemic encephalopathy (PSE) is 24% in cirrhotic patients

Aim: To compare efficacy of Neomycin and Ciprofloxacin for secondary prophylaxis of portosystemic encephalopathy (PSE) in liver cirrhotic patients.

Study Setting& duration: Two years in East Medical Ward Mayo Hospital Lahore, Pakistan

Study Design: Randomized Control Trail

Sample Size: 280 cases randomly assigned into two groups

Methods: Patients coming with PSE were included after they became conscious. Patients were divided into two groups. One group received Ciprofloxacin &other group was given Neomycin at discharge. Patients were followed for relapse of PSE for 6 months.

Results: Among 280 subjects the mean age of the patients in Neomycin group was 50.35±6.72 where as in the ciprofloxacin group that was 50.33±7.09. Total 59.6% patients were male and 40.4% patients were female. In Grade I hepatic encephalopathy 1.07% patients were presented,37.14% in Grade II,39.28% were in Grade III,22.5% patients were in Grade IV hepatic encephalopathy. In follow up at 3 months in neomycin group 46.32% patients did not developed porto systemic encephalopathy, 13.23% patients developed porto systemic encephalopathy, 26.47% patients expired, In ciprofloxacin group 10.41% patients did not developed porto systemic encephalopathy, 50.69% patients developed porto systemic encephalopathy, 31.94% patients expired, 9.94% patients lost the follow up. Pearson chi-sq. = 66.619 P = 0.000. In follow up at 6 months in neomycin group 46.32% patients did not developed porto systemic encephalopathy, 13.23% patients developed porto systemic encephalopathy, 26.47% patients expired. In ciprofloxacin group 10.41% patients did not developed porto systemic encephalopathy, 50.69% patients developed porto systemic encephalopathy, 31.94% patients expired.

Conclusions: Neomycin is more effective in preventing Porto-systemic encephalopathy than ciprofloxacin. Mortality rate among neomycin group is less as compared to ciprofloxacin groups.

Keywords: Liver Cirrhosis, PSE, Secondary prophylaxis.

INTRODUCTION

Liver cirrhosis is a leading cause of morbidity and mortality worldwide[1,2]but exact prevalence of cirrhosis is not known[3]. An estimate shows that up to 1% of population is affected worldwide but percentage is even higher in most developing countries of Asia and Africa where chronic viral hepatitis B and C is more prevalent[4].Liver Cirrhosis is becoming an epidemic in Pakistan due to a high prevalence rate of viral hepatitis B and C in ourcommunity[14]. Unfortunately, prognosis of livercirrhotic patients is poor in long term. Mortality rate of50 to 70 percent have been observed at one year follow-up[9].Most often is due to advanced stage of liver cirrhosis resulting to catastrophic complications[9]. Fibrosis is the key event leading to liver cirrhosis and life threatening complication[5]. Liver cirrhosis and its complications are affecting the socio-economic values at gross level[11].

One of the major complications of liver cirrhosis is hepatic encephalopathy (HE). Prevalence of HE also known as portosystemic encephalopathy (PSE) in cirrhotic patients is 24%[2]. It is characterized by neuropsychiatric expression that can vary in severity from a mild modification in mental state to a coma, while sometimes neuromuscular symptoms can be examined[6]. An important outcome of the disease is distraction of portal blood circulation into the systemic circulation through porto-systemic collateral vessels thus bypassing the hepatic metabolism[7]. HEis also illustrated in patients without liver cirrhosis with either

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spontaneous or surgically producedporto-systemic shunts. It can occur in patients with quickly occurring liver disease without evidence of porto-systemic shunting[8].

Advance research in recent years has made significant progress toward prevention and treatment of common complications of liver cirrhosis[4]. HE is often precipitated by identifiable factors such as variceal bleeding, gut infections, constipation and electrolyte imbalance[10,11].Proper identification and management of precipitating factors is the key to prevent these complications of cirrhosis.[(10)(11)]To prevent of episodicporto-systemic encephalopathy is an important deal in the treatment of chronic liver diseas[15,16,17,18,19] especially since symptoms of overt encephalopathy are debilitating and decrease the ability for self-care, leading to improper nutrition and non adherence to a therapeutic regimen, which in turn leads to severe symptoms, frequent hospitalizations, and a poor quality of life.

Use of lactulose and antibiotics play important role in changing gut flora and thus preventing HE[12].By using effective oral antibiotics to prevent the recurrence of PSE, we can reduce the morbidity and mortality of liver cirrhosis, thus reducing the socio-economic burden associated with this illness. In antibiotics Neomycin is widely used for prophylaxis[13]. Due totoxicity of neomycin its use has been limited to either topical or oral preparations . Benefits from neomycin, the most widely used drug, are attributed to effects on colonic bacteria[23].Although gastrointestinal absorption of orally administered neomycin is reported to be as low as 0.58% on average[21,24].Plasma levels of "Neomycin" are negligible[21,22]. It should not be used for more than six months and to be alert for signs of renal and auditory toxicity[22].

While Ciprofloxacin is also rationally being used in clinical practice but evidence regarding the benefit of these medicines in secondary prophylaxis is far from being established. [(14)]A large sized randomized trial is needed to establish the role of Ciprofloxacin in prevention of PSE.

Management of these patients in our country is not only difficult but also complicated as these patients present at a very late stage. Few treatment options are available. Neomycin and ciprofloxacin for management of these patients is cost effective and easily available in our setup. Objective of this study is to assess the treatment efficacy of these two drugs so that we can delineate guidelines for management of such patients that will avoid complications in patients with portosytmatic hepatic encephalopathy but also patients will benefits from these treatment options.

MATERIAL AND METHODS

This randomized longitudinal trial was carried out in East Medical wards, Mayo Hospital, Lahore during a period of two years. The samplesize of this study was 280 cases calculated fromRaosoft calculator as described by Ezechi et al. The margin of error was 5% and confidence level was 95%.Consecutive patients of PSE were randomized in ciprofloxacin and neomycin group.

Inclusion Criteria:

All those patients between the age of between 18-60 years with liver cirrhosis established and those patients recovered from current episode of Porto systemic Encephalopathy in hospital and being discharged were included in the study.

Exclusion Criteria:

- Patients with history of psychiatric illness or history of tranquilizer intake
- Patients with portal vein thrombosis on Ultrasonography
- History of alcohol intake
- Altered conscious level due to drug poisoning
- Hypersensitive to Neomycin or Ciprofloxacin
- Patients with co-morbid condition like glomerulonephritis, renal failure, and congestive heart failure
- Patients already receiving oral antibiotics on regular basis
- Patients with contraindication for use of Aminoglycosides and Fluoroquinolones

Clinic visits occurred on days 7, 14, 56, 112, and thereafter through day 168 (end of the treatment period). Patients were also monitored during the weeks without due clinic visits for any side effect of drugs or episode of PSE.SPSS 13.0 was used for statistical analysis. Chi-square test was use on qualitative as well quantitative data to assess the significance between the two groups for out of intervention with statistical significant at $P < 0.05$.

RESULTS

Hematological parameters, BUN and Prothrombin time of both groups taken afterinclusion of the patients in study has no significant difference ($P > 0.05$).The mean age of the patients in Neomycin group was 50.35±6.72 where as in the ciprofloxacin group that was 50.33±7.09. ($P = 0.981$) (Table1) Total 59.6% patients were male and 40.4% patients were female. In neomycin group were 56.6% patients were male and female patients were 43.4%. In ciprofloxacin group 62.5% male while 37.7% were female patients. Pearson's chi- square =1.005 $P = 0.316$. In neomycin group 26.47% patients expired, 13.67% patients lost the follow up. In ciprofloxacin

group 31.94% patients expired, 9.94% patients lost the follow up. These patients were excluded from final analysis model.

In follow up at 3 months, overall 27.85% patients did not develop porto systemic encephalopathy while 32.26% patients developed porto systemic encephalopathy, 29.28% patients expired, 10.35% patients lost the follow up. Statistically significant number (Pearson chi-sq=66.619 *P* value =0.000) of patients in ciprofloxacin group (50.69%) developed porto systemic encephalopathy as compared to neomycin group 13.23%.

With follow up period up to 6 months overall 27.85% patients did not develop porto systemic encephalopathy, 32.26% patients developed porto systemic encephalopathy, 29.28% patients expired which were again excluded from final analysis. In neomycin group 46.32% patients did not developed porto systemic encephalopathy, 13.23% patients developed porto systemic encephalopathy, 26.47% patients expired. In ciprofloxacin group 10.41% patients did not developed porto systemic encephalopathy, 50.69% patients developed porto systemic encephalopathy, 31.94% patients expired.Pearson chi-sq. = 63.138 P = 0.000.

Table 3: Comparison of two group's laboratory values

Characteristics	Neomycin	Ciprofloxacin	Pvalue
Haemoglobin level (g/dl)	8.98± 1.9	9.18±2.02	0.390
Total leukocyte count×10^3/mm^3	10.0 ± 16.9	9.88±9.23	0.935
Platelet count×10^3 /mm^3	105.29±76.9	151.88±53.3	0.314
Serum bilirubin(mg/dl)	1.87±1.86	1.68±1.35	0.328
Serum albumin(g/dl)	3.19±0.55	3.18±0.7	0.957
Serum creatinine(mg/dl)	1.23±0.44	1.36±0.59	0.041
Blood urea nitrogen(mg/dl)	34.34±16.61	36.33±16.61	0.318
Prothrombin time(seconds)	2.63±0.7	2.50±0.78	0.135

Table 4 Comparison of TP score and follow up days

	Treatment group	Mean	Std. Deviation	p-value
CTP class score	Neomycin	11.47059	5.524278	0.271
	Ciprofloxacin	10.93056	1.945599	
Days of Follow up	Neomycin	106.9118	64.95018	0.000
	Ciprofloxacin	47.6111	48.09884	

Clinical sign and symptom of the patients in both groups are follow.

Table-6: Sign and Symptoms among treatment group

Sign and Symptoms	Treatment group of patient		
	Neomycin	Ciprofloxacin	Total
Pusle>100/min	11.76%	14.58%	13.21%
BP< 90 systolic	0.73%	1.38%	1.07%
Ascites	84.55%	87.5%	86.07%
Spiderangioma	11.02%	13.19%	12.14%
Ankle edema	77.94%	74.30%	76.07%
Malena	83.82%	77.77%	80.71%
GI Bleeding	64.70%	63.88%	64.28%
Splenomegaly	98.52%	95.13%	96.7%
Dilated portal vein	4.41%	4.86%	4.64%

Table 7:Grades of Hepatic Encephalopathy:

Grade of Hepatic encephalopathy	Treatment group of patient		Total
	Neomycin	Ciprofloxacin	
Grade I	0.73	1.38	1.07
Grade II	37.5	36.80	37.14
Grade III	40.44	38.19	39.28
Grade IV	21.32	23.61	33.5

Chi- square= 0.540 p-value=0.910

Grade 1- Trivial lack of awareness, shortened attention span. Impairment noted on arithmetical testing

Grade 2- Lethargy, disorientation in time, clear personality change, or inappropriate behavior

Grade 3- Very drowsy, semi-comatose but responsive to stimuli, confused, gross disorientation in time or space, bizarre behavior

Grade 4- Coma

DISCUSSION

The prevention of overt hepatic encephalopathy is an important goal for the treatment liver cirrhosis patients, particularlywhile symptoms of recurrent encephalopathy are devastating and decrease the capability for self-care, leading to inappropriate nutrition and nonadherence to a remedial regimen, which consecutively leads to severe symptoms, repeated hospitalizations, and a poor feature of life. In recent decades no major advances in HE therapy has been achieved[26].Hopeful results regarding benefit versus risk of antibiotics use are the most favorable[27,28]. Oral antibiotics that nearby low absorption can reduce the small intestinal bacterial overgrowth (SIBO) which is habitually associated with liver cirrhosis[29, 30]. For this reason, antibiotics can be predominantly useful in disaster settings to control ammonia production, but head-to-head comparisons in HE treatment are insufficient.

This study has reported that neomycin reduced the risk of episode of hepatic encephalopathy during a 6 month period among patients having a new history of evident recurrent hepatic encephalopathy[31].

The efficiency of a specific treatment with neomycin sulfate has so far not been submitted to experimental trials. Strauss *et al*studied for the period

of five years, 102 cirrhotic patients developed hepatic encephalopathy at admission or during hospitalization, and 39 were randomized for treatment with either neomycin sulfate or placebo. The group of disqualified patients (n=63) was compared with the randomized group (n = 39), and no statistical differences were found concerning, Child-Pugh classification, etiology of cirrhosis, precipitating factors and grade of hepatic encephalopathy. The remedy for hepatic encephalopathy consisted in the control of precipitating factors associated with 6 g of neomycin sulfate "per os" or placebo. The time beyond between the initiation of the therapeutic procedure and falling off to grade zero of hepatic encephalopathy was 39.11 +/- 23.04 hours for the group of active neomycin, and 49.47 +/- 21.92 hours for the placebo group, but this difference did not achieve statistical significance[32].

According to Child-Turcotte-Pugh (CTP) class, 76.78% patients were presented in class C, 22.5% were in class B, 0.71% was in class A. In neomycin group 77.20% were in class C, 22.05% were in class B, 0.73% were in class A.In follow up at 3 months in neomycin group 46.32% patients did not developed porto systemic encephalopathy, 13.23% patients developed porto systemic encephalopathy, 26.47% patients expired, and at follow up at 6 months in neomycin group 46.32% patients did not developed porto systemic encephalopathy, 13.23% patients developed porto systemic encephalopathy, 26.47% patients expired.

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Also this study shows the superiority of neomycin therapy over treatment with Ciprofloxacin. It was first time performed the comparison of neomycin 500mg OD and ciprofloxacin 750 weekly for secondary prophylaxis of hepatic encephalopathy. All patients received concomitant lactulose during the study period, and a significant treatment effect was noted within 6 month follow up after randomization.

In the current, prospective study, neomycin therapy reduced the risk of hospitalization involving hepatic encephalopathy, reflecting the clinical significance of efficacy findings. Also, this reduced risk supports the results of retrospective chart reviews which have shown that use of neomycin is associated with a significantly lower frequency of hospitalization.

In one study the modifications of colon microflora in 14 patients under oral ciprofloxacin therapy were examined. All patients were affected by hepatic encephalopathy. A marked decrease in enterobacteria with both doses was noticed in the first few days, with a complete disappearance from days 3-6 of therapy and a return to normal within 2 weeks after interruption of treatment. Gram-positive and Gram-negative aerobic and anaerobic flora was not affected significantly. As a consequence of these results, the treatment of six patients affected by PSE (grade 2-3) was studied, testing the colon microflora changes, the presence of circulating endotoxins and blood ammonium levels before, during and after 12 days of therapy. A marked reduction or suppression of enterobacteria was observed, and a prompt normalization of blood ammonium levels, the disappearance of circulating endotoxins and a clear clinical improvement in (83%) 5 out of 6 patients[33].

The limitations of the present study were that it was not a blinded study and did not assess health related quality of life. Treatment with antibiotics of both group were done through longitudinal randomized trial, therefore, it was not possible to perform a blinded study. However, low dose of neomycin and ciprofloxacin were well tolerated by all the patients and none of the patients had to discontinue drug due to its side effects.

Present study is unique comparing to other studies underwent for secondary prophylaxis of portosystemic encephalopathy, as no randomized control trail of ciprofloxacin vs neomycin were performed with such a large sample size, with 6months follow up and minimum neomycin 500mg OD dose vs ciprofloxacin 750mg weekly dose. “Neomycin” therapy reduced the risk of hospitalization involving porto-systemic encephalo-pathy, reflecting the clinical significance of our study. Our study has shown that “neomycin” as compared with “ciprofloxacin”,is associated with a significantly reduced episodes of overt porto-systemic encephalopathy. The incidences of adverse events in general and adverse events consisting of infection in particular were similar in the “neomycin” group and the “ciprofloxacin” group. In summary, this study showed a robust protective effect of “neomycin” against episodes of Porto-systemic encephalopathy as compare to ciprofloxacin.

CONCLUSION

Present study strongly suggests that Neomycin is more effective in preventing Porto-systemic encephalopathy than ciprofloxacin.

REFERENCES

1. Bosch J. Burroughs A.K. Lammert F. Lebrec D. Sauerbruch T. Liver Cirrhosis: From Pathophysiology to Disease Management Series: Falk Symposium, Vol. 162 2008, XIII, 334 p. Dustjacket.
2. Almani SA, Memon AS, Memon AI, Shah MI, Rahpoto MQ, Solangi R. Cirrhosis of liver: Etiological factors, complications and prognosis. J LiaquatUni Med Health Sci. 2008. 7:61-67.
3. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. Am Fam Physician. 2006. 74:756-62.
4. Schuppan D, Nezam H. Afdhal. Liver Cirrhosis. Lancet 2008 8;371:838–851.
5. Butt JA, Ahmed SI, Zafar S, Chohan AR. The Role of Antifibrotics in the Treatment of Chronic Hepatitis Pak J Gastroenterol Mar 2003; 17(1):33-6.
6. Lizardi-Cervera J, Almeda P, Guevara L, Uribe M. Hepatic encephalopathy: a review. Ann Hepatol. 2003 ;2:122-30.
7. Riggio O, Efrati C, Catalano C, Pediconi F, Mecarelli O, Accornero N, et al. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: a case-control study. Hepatology. 2005; 42:1158-65.
8. Av SP. Hepatic encephalopathy: pathophysiology and advances in therapy. Trop Gastroenterol. 2007; 28:4-10.
9. Koulaouzidis A, Bhat S, Saeed AA. Spontaneous bacterial peritonitis.World J Gastroenterol 2009 7; 15:1042–1049.
10. Zakaria M, Hussain SR, Butt MRA, RanaGF. Hepatic encephalopathy; precipitating factors in patients with cirrhosis. Professional Med J Jul - Sep 2008; 15(3):375-9.
11. Maqsood S, Saleem A, Iqbal A, Butt JA. Precipitating factors of hepatic encephalopathy; Experience at PIMS Islamabad. J Ayub Med Coll Abbottabad 2006; 18(4).
12. Sheth AA, Garcia-Tsao G. Probiotics and liver disease. J ClinGastroenterol. 2008 Jul; 42Suppl 2:S80-4.
13. Shah VH, Kamath P. Management of portal hypertension. Postgrad Med 2006 Sep-Oct;119(3):14-8.
14. H. Kojima, K.D.E. Kaita, K. Hawkins, J. Uhanova, and G. Y,Minuk Use of Fluoroquinolones in Patients with Chronic Hepatitis C Virus-IndicedFailure.Antimicrob Agents Chemother. 2002. 46(10):3280-3282.
15. Munoz SJ. Hepatic encephalopathy. Med Clin North Am 2008; 92:795-812.
16. Leevy CB, Phillips JA. Hospitalizations during the use of rifaximinversuslactulose for the treatment of hepatic encephalopathy. Dig Dis Sci2007; 52:737-41.
17. Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepaticEncephalopathy in patients with cirrhosis. J Hepatol 1999; 30:890-5.
18. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with endstag liver disease. Liver Transpl 2007; 13 1366-71.
19. Waksman, S. A., and H. A. Lechevalier. 1949. Neomycin a new antibiotic active against streptomycinresistant bacteria, including tuberculosis organisms. Science 109:305-307.
20. Breen, K. J., R. E. Bryant, J. D. Levinson, and S. Schenker. 1972. Neomycin absorption in man: studies of oral and enema administration and effect of intestinal ulceration. Ann. Intern. Med. 76:211-218.
21. J.Lizardi-Cervera et al. Hepatic encephalopathy.Annals of Hepatology 2(3)2003:122-130.
22. Strauss E, Tramote R, Silva EP,Caly WR, Honain NZ, Maffei RA, de Sa MF Clinic of Gastroenterology, Hospital Heliópolis, São Paulo, Brazil. PubMed - indexed for MEDLIN 1483668.
23. Cottone S, Pagliaro L. Ital J,Gastroenterol. 1991; 23(7):403-7.
24. Orlandi F, Freddara U, Candelaresi MT, Morettini A, Corazza GR, Di Simone A, Dobrilla G, Cavallini G. Dig Dis Sci. 1981 Jun;26(6):498-506.
25. Poordad FF: Review article: the burden of hepatic encephalopathy. Aliment PharmacolTher 2007, 25:3-9.
26. Liver Transplantation 2003, 9(9):993-994. Cardenas A.Ginès P: Management of complications of cirrhosis in patients awaiting liver transplantation.
27. J Hepatol 2005, 42:S124-S133. Bass N: Review article: the current pharmacological therapies for hepatic encephalopathy. Aliment PharmacolTher 2006, 25(Suppl):23-31.
28. Als-Nielsen B, Gluud LL, Gluud C: Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004, 328:1046.
29. Lakshmi CP, Ghoshal UC, Kumar S, Goel A, Misra A, Mohindra S, et al.: Frequency and factors associated with small intestinal bacterial overgrowth in patients with cirrhosis of the liver and extra hepatic portal venous obstruction. Dig Dis Sci 2010, 55:1142-1148.
30. Pande C, Kumar A, Sarin SK: Small-intestinal bacterial overgrowth in cirrhosis is related to the severity of liver disease. Aliment PharmacolTher 2009, 29:1273-1281.
31. Gunnarsdottir SA, Sadik R, Shev S, Simrén M, Sjövall H, Stotzer PO, et al.: Small intestinal motility disturbances and bacterial overgrowth in patients with liver cirrhosis and portal hypertension.
32. Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA, de Sá MF. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology. 1992 Dec; 39(6):542-5.
33. Esposito S, Barba D, Galante D, Gaeta GB, Laghezza O. Intestinal microflora changes induced by ciprofloxacin and treatment of portal-systemic encephalopathy (PSE). Drugs ExpClin Res. 1987; 13(10):641-6.