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# A Comparative Study to Determine the Fate of Arterial Blood Ammonia Level in Patients of Decompensated Chronic Liver Disease with Short Course (7days) Therapy with Rifaximin And Or Lactullose.

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***Abstract:*** *90 patients of decompensated chronic liver diseases were selected and randomised to treat with either lactulose or rifaximin or both lactulose and rifaximin (30 patients in each group) for 7 days. Pre-treatment and post-treatment arterial blood ammonia level were measured amongst each group of treatment. The study was to review the comparison of the effectiveness of Rifaximin (1200mg/day , in 3 divided doses ) alone or in combination with Lactulose (60gram/day,in divided doses) or Lactulose (60gram/day) alone to reduce the arterial blood ammonia level in hepatic encephalopathy of any grade of any cause in adult (>18 years) admitted patients decompensated chronic liver diseases.*
*Arterial blood ammonia was significantly reduced with treatment in all three groups of treatment. Post-treatment decrement of blood ammonia was not significantly different when compared amongst each of three modes of treatment (lactulose or rifaximin or both of them) for 7 days in hepatic encephalopathy.*
***Keyword:*** *Chronic, Liver, Disease ,Blood, Ammonia*

## I. Introduction

Hepatic encephalopathy is a potentially reversible neuro-psychiatric and functional syndrome occurring in 50% - 70% of patients with advanced liver disease and or porto-systemic shunting [1] Hepatic encephalopathy occurs in presence of insufficient hepatic clearance of toxic products absorbed from the intestine resulting in neuro-chemical abnormalities after crossing the blood brain barrier [2]. The toxic products possibly implicated in the aetiology of hepatic encephalopathy are ammonia, false neuro-transmitters ( octopamine , phenyl-ethanolamine), gamma-amino butyric acid, short chain fatty acids, mercaptanes , neurosteroids and manganese [3]. Elevated serum ammonia level is the best described marker of hepatic encephalopathy and is detected in 60% -80% of affected patients [4, 5]. Acute hyperammonia appears to have a direct effect on brain oedema, astrocyte swelling, and the transport of neurally active compounds such as myoinositol and thereby contributes to hepatic encephalopathy.

There is alteration of neuronal membrane fluidity, expression and activation of neurotransmitter and neurotransmitter receptor. The gamma-amino butyric acid (GABA) – benzodiazepine system is activated.

Hyperammonia increases astrocyte glutamine production via glutamine synthetase. The increased astrocyte glutamine and glutamate concentration leads to CNS dysfunction.

The clinical diagnosis of overt hepatic encephalopathy is based on two concurrent types of symptoms: impaired mental status, as defined by the Conn score (also called West Haven criteria) with higher score indicating more severe impairment [10], and impaired neuro-motor function [6, 7] .Conn score (West Haven score) is recommended by the working party on hepatic encephalopathy [8] for assessment of overt hepatic encephalopathy in clinical trial. In healthy persons, the ammonia level in venous blood is similar as that of arterial blood. However in liver insufficiency, the muscles become the most important organ for detoxification of ammonia by the conversion of glutamate into glutamine [10]. The ammonia level in venous blood reflects therefore not only hepatic detoxification but also ammonia clearance by the muscles, kidneys and brain. As a consequence, in these patients, the ammonia level in venous blood is always lower than in arterial blood. On the other hand , tourniquet induced ischemia or muscle contraction can cause the release of ammonia in venous blood , resulting in false high venous ammonia level [11]. For these reason, arterial blood ammonia measurements are more logical. Ammonia measurement still is affected by various variables such as specimen handling, transport, storage, cigarette smoking [12]. Laboratory should be smoke free, free of open urine

samples or open bottles containing high ammonia . Blood should be analysed within 15 minutes of collection [13]. Current treatment strategies are aimed to reduce the serum ammonia and it is done by introducing agents that decrease or inhibit intestinal ammonia production or reduce its absorption by antibiotic such as rifaximin or lactulose / lactitol from gastrointestinal tract or correcting precipitating factors, such as gastrointestinal haemorrhage, constipation, dyselectrolytaemia [9].

Lactulose, non-absorbable disaccharide reduces the absorption of ammonia through cathartic effect and by altering colonic pH. [14]. Lactulose is currently recommended as the first-line pharmacological treatment for hepatic encephalopathy by the practice guideline proposed by American College of Gastroenterology.[14].

Rifaximin is a semi-synthetic, gut-selective, minimally absorbed broad spectrum oral anti-microbial agent which has in vitro activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria and has low risk of resistance and less side effects [15]. Rifaximin received approval from the US Food and Drug Administration in March 2010 for the treatment of hepatic encephalopathy because of its few side effects and pharmacological benefit in reducing the risk of recurrence of overt hepatic encephalopathy.Several studies have been conducted to support the use of rifaximin instead of or in addition to lactulose in the treatment of acute hepatic encephalopathy [16].

Our study is to review the comparison of the reduction of blood ammonia level using the treatment of Rifaximin (1200mg/day , in 3 divided doses ) alone or in combination with Lactulose (60gram/day ,in divided doses) or Lactulose (60gram/day) alone to reduce the short term mortality and clinical improvement in hepatic encephalopathy of any grade of any cause in adult (>18 years) admitted patients decompensated chronic liver diseases.

## II. Aims And Objectives

Hepatic encephalopathy is a potentially reversible neuro-psychiatric disorder developed from acute or chronic liver failure. The mainstay of treatment of hepatic encephalopathy in addition to correcting precipitating factors, is to use lactulose, which results in colonic acidification. More recently, rifaximin has been very effective in treating hepatic encephalopathy with out the known side effects. The purpose of this study is to compare the effectiveness of three different modes of treatment for hepatic encephalopathy for 7 days in terms of fate of blood ammonia levelThese three modalities of treatment in hepatic encephalopathy are :

Group- A : Lactulose ( 60 gram /day ) with Rifaximin ( 1200 mg/day )
Group- B : Lactulose ( 60 gram /day ) alone
Group- C : Rifaximin ( 1200 mg/day ) alone

**Specific Objectives**

The specific objectives of this study is to determine the treatment benefit in each group of patient in regard to decreasing arterial blood ammonia level

## III. Materials And Methods

**A) Opertational Defination:** Hepatic Encephalopathy: It refers potentially reversible neuro-psychiatric problem, results from any cause of chronic liver diseases with or without ascites/ jaundice , in an adult of greater than 18 years of age without hematemesis or melena / spontaneous bacterial peritonitis/ hepato- pulmonary syndrome/ hepato- renal syndrome/ ,chronic kidney diseases/ congestive cardiac failure /sepsis/ dyselectrolytaemia.

**B) Study Type**: Prospective Study

**C) Study Design**: A)Allocation – Randomised B) End Point Classification - Efficacy Study C) Model - Parallel Assignment D)Primary Purpose Medical Treatment And Data Analysis

**D) Study Area**: Indoor Medicine Ward (Male And Female), Dept. Of Medicine R. G. Kar Medical College And Hospital, Kolkata-4.

**E) Study Population**: Adult (>18years) Admitted Patients Of Hepatic Encephalopathy Of Any Grade Of Any Cause With Decompensated Chronic Liver Disease.

**F) Study Period**:1 Year

**G) Sample Size**: A) Rifaximin And Lactulose - 30 Patients B) Lactulose Alone - 30 Patients C) Rifaximin Alone - 30 Patients

**H) Sample Design**: Patients Of Decompensated Chronic Liver Diseases Of Any Cause Of Any Grade Of Hepatic Encephalopathy Were Randomised To Treat With Either Rifaximin And Lactulose / Lactulose / Rifaximin For 7 Days With The Doses –A) Rifaximin - 1200 Mg. /Day (400 Mg. Thrice A Day) B) Lactulose - 60 Gram /Day (20 Gm. Thrice A Day)C) Rifaximin -1200 Mg/Day (400 Mg Thrice A Day) And Lactulose, 60gm/Day (20 Gm Thrice A Day)

**I) Eligibility Criteria:**

A) Inclusion Criteria:

- adult (>18years) admitted patients of both sexes
- decompensated chronic liver disease of any cause
- hepatic encephalopathy of any grade

B) Exclusion Criteria- hepatic encephalopathy patients complicated with - haematemesis and or melena
- hepatic encephalopathy with hepato-renal syndrome
- hepato -pulmonary syndrome
- hepato-cellular carcinoma
- hepatic encephalopathy complicated with spontaneous

spontaneous bacterial peritonitis
- dyselectrolytaemia, metabolic encephalopathy
- severe comorbidities such as congestive cardiac failure,

pulmonary diseases, kidney diseases
- neuro-psychiatric illness
- sepsis

**J) Promotion Of Study**: Approval from Ethical Review Committee, R. G. Kar Medical College was sought by December, 2010 before data collection.

**K) Parameters To Be Compared** - Arterial blood ammonia level

**L) Study Tools**: Predesigned and Pretested proforma :

Clinical history

Clinical examination : general survey, systemic examination including vitals.
- West Haven criteria of altered mental status in hepatic encephalopathy Glassgow coma scale
- Laboratory Examination –

a) **arterial blood ammonia level** (Enzymatic method b) Hb, TC, DC, Platelet count,c) LFT d) Serum sugar, urea , creatinine, Na+, K+ e) Prothrombin time f) HBsAg, Anti-HCV, ICTC g) Ascitic fluid for cell count, cell type, protein, albumin, sugar - Imaging study a) U.S.G. of abdomen b) Upper G.I. Endoscopy

**M) Study Technique:** After obtaining approval from Institutional ethical committee, collection of data were taken from cases after taking consent from patients parties of hepatic encephalopathy of any grade of any cause admitted in medicine ward by the following process:
- clinical examination., as in clinical proforma (annexure-3)
  arterial blood ammonia level estimation at the beginning before treatment .
- randomisation of the patients with assignment
- treated the patients with rifaximin and lactulose or lactulose or rifaximin for 7days
- after treatment clinical and mental function examination and grading of hepatic encephalopathy
- at the end of treatment repeat blood ammonia estimation was done.
- short- term mortality after treatment.
- clinical deterioration and improvement with the treatment

**N) End Point Of Study:**- after the completion of proposed therapy for 7 days- repeat arterial blood ammonia estimation was done.

**O) Results** : At the end of study different data would be collected, compiled and interpreted into suitable charts, diagrams, table, graphs.

**P) Analysis Of Data**:After collecting all the data , a grand chart was prepared using Microsoft Office Excel 2007 and statistical analysis was performed using SPSS-16 statistical software . Data would be analysed with appropriate statistical test to determine the significance level and p value of $< 0.05$ was taken as significant.

**Q) Limitation Of Study**: Statistical power of the test might be reduced due to small sample.

## IV. Results And Analysis

In our study, 90 patients of decompensated chronic liver diseases were selected and randomised to treat with either lactulose or rifaximin or both lactulose and rifaximin for 7 days. Clinical outcome and short term mortality were noted in each group of treatment. Pre-treatment and post-treatment arterial blood ammonia level were measured amongst each group of treatment.

The table 1shows the number and percentage of study patients having different pre- treatment arterial blood ammonia level . Only 20% of patients had arterial blood ammonia level over and above the upper normal limit ( > 86 µg./dl) . Mean pre-treatment arterial blood ammonia was 74.16 µg./dl.

Paired sample t test, t=4.701, df=80, p=0.000 ,Figure 1 support the statement.

Table 2 shows mean and standard deviation ( S.D.) of blood ammonia at pre-treatment stage were 73.50µg./dl and 15.327 and in post treatment stage were 63.40 µg./dl and 15.805 respectively in paired sample (n=81) .

By paired sample t test it is found that arterial blood ammonia level showed significant change with treatment ($p = 0.000$). Figure 2 support the statement.

## V. Discussion

**Arterial Blood Ammonia:** From various studies , it reveal that elevated serum ammonia level is the best described marker of hepatic encephalopathy and is detected in 60% - 80% of affected patients [4,5]. However some comatose patients have normal or near normal arterial ammonia level (Sherlock et. al, 1956). Multiple studies have shown that arterial blood ammonia level correlates to some extent with the severity with the hepatic encephalopathy but the ammonia level substantially overlap among the patients with differing grades of hepatic encephalopathy [19].

In our study it was found that 20% of hepatic encephalopathy patients had pre-treatment arterial blood ammonia level greater than upper limit of normal level ,i.e, 30 – 86 µg./dl. and the the mean pre-treatment blood ammonia of sample population was 74.16 µg./dl.

**Treatment Effect In Blood Ammonia:** Arterial blood ammonia showed statistically significant ($p =0.000$) change with the treatment and net decrement in amount of blood ammonia was 9.61% from pre-treatment ammonia level. Mean post-treatment ammonia decrement from mean pre-treatment value was 10.10 µg./dl in our study. There is a study which reveals that patients receiving rifaximin showed lower serum ammonia level (weighted mean difference was -10.65; $p=0.10$) better mental status and less asterixis without reaching statistically significance [17].

We found that post-treatment decrement of blood ammonia level was more in combined drug treatment group (77%) than rifaximin group (70%) and lactulose group (53%) in our study patients of decompensated chronic liver diseases. But these apparent differences of post treatment blood ammonia decreament among three modes of treatment are not statistically significant ($p = 0.142$). Our study reveals that there is no significant difference in post-treatment decrement of blood ammonia among three treatment groups; no one is superior than others in this regard. There is a study which demonstrates significantly more improvement in blood ammonia level, with rifaximin, 1200 mg/day compared with lactulose, 60 gm/day [18].

## VI. Conclusion

The comparison of the effectiveness of Rifaximin (1200mg/day , in 3 divided doses ) alone or in combination with Lactulose (60gram/day ,in divided doses) or Lactulose (60gram/day) alone to reduce the arterial blood ammonia level in hepatic encephalopathy of any grade of any cause in adult (>18 years) admitted patients of decompensated chronic liver diseases was shown that arterial blood ammonia was significantly reduced with treatment in all three groups of treatment. Post-treatment decrement of blood ammonia was not significantly different when compared amongst each of three modes of treatment (lactulose or rifaximin or both of them) for 7 days in hepatic encephalopathy.

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## Tables and figures:

**Table -1. Distribution of patients according to pre-treatment of arterial blood ammonia level**

| | | |
|---|---|---|
| > 86 | 18 | 20.00 |
| ≤86 | 72 | 80.00 |
| Total | 90 | 100.00 |

**Figure-1. Pie-distribution of patients according to pre-treatment of arterial blood ammonia (µg./dl)**

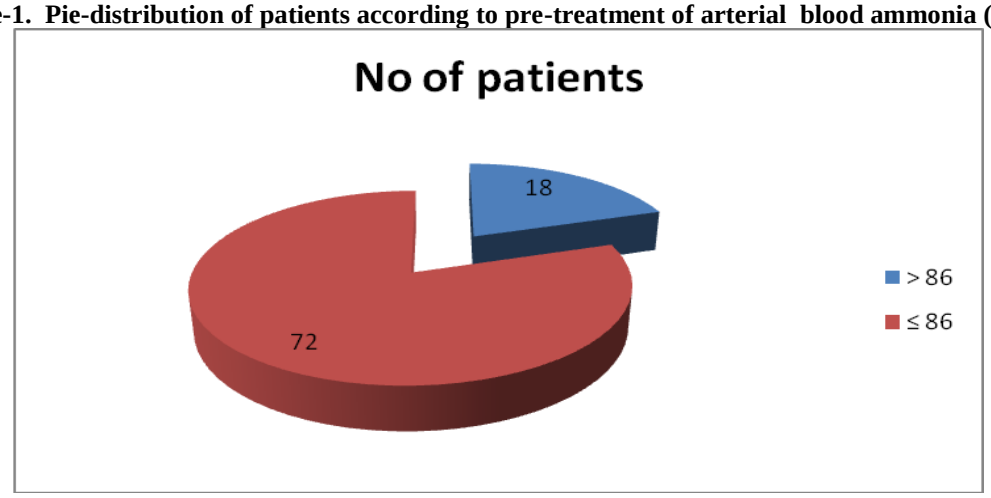


**Table-2. Comparison between pre-treatment and post-treatment of arterial blood ammonia level (n = 81)**

| | Blood ammonia Level | Mean (µg/dl) | Standard Deviation | Standard Error of Mean |
|---|---|---|---|---|
| Pair-1 | Pre-treatment blood NH3 | 73.50 | 15.327 | 1.703 |
| | Post-treatment blood NH3 | 63.40 | 15.805 | 1.756 |

**Figure-2. Comparison between mean arterial blood ammonia before and after treatment in µg./dl (n=81).**