The Evaluation of the Role of Rifixamine and Zinc in Secondary prevention of Spontenous Bacterial Pertonitis

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Abstract

Spontaneous Bacterial Peritonitis (SBP) is an infection of a previously sterile ascitic fluid which represents a fatal complication of liver cirrohsis. Abdominal pain, tenderness and hepatic encephalopathy are the most frequent symptoms and signs in patients with SBP. Treatment with cefotaxime, with maximum dose 2gm IV, every 8 hours start just after taking ascitic fluid sample of PMN more than 250 cells?mm3 for at least 5days is the first choice of treatment.

Rifxamine is abroad spectrum antibiotic which is used in treatments of hepatic encephalopathy and many other diseases as crohns disease and travelers diahrrea had agreat effect in prophylaxsis against SBP.

Zinc is an essential trace element which affects many organ systems, including the skin, gastrointestinal tract, central nervous system, and immune, skeletal, and reproductive systems. affects multiple aspects of the immune system, from the barrier of the skin to gene regulation within lymphocytes. its deficient in most of cirrhotic patients.

We conducted astudy on 60 cirrhotic patients, 20 of them received rifxamine for 4 months the other 20 patients received rifxamine and zinc for 4 moths and the last 20 patients did not receive any medication as prophylaxsis

Our study revealed that rifxamine can decrease the recurrence of SBP in 85% of the patients .although zinc is very effective in prevention of infections and it was deficient among nearly all of these patients and full sufficient dose of zinc supplementation were taken by group one it has no signicficant role in prevention of recurrence of SBP in cirrhotic patients.

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List of Abbreviations

BT:	**Bacterial translocation**
CYP:	**Cytochrome p450**
C3:	**Third component of complement system**
CNNA:	**Culture negative neurocytic ascitis**
CRP:	**c-reactive protein**
DNA:	**deoxy ribonucleic acid**
E coli:	**Eschrechia coli**
GIT:	**gastrointestinal tract**
HRS:	**hepato renal syndrome**
HE:	**Hepatic encephalopathy**
IL:	**Interleukin**
IBO:	**Intestinal bacterial over growth**
LDH:	**lactate dehydrogenase hormone**
MNB:	**Monomicrobial non neutrocytic bacterascitis**
NFKB:	**Nuclear factor kappa beta pathway**
OHE:	**overt hepatic encephalopathy**
PMN:	**Polymorphnuclear leucocytes**
RDA:	**Recommended dietary allowance**
RNA:	**ribonucleic acid**
SBP:	**Spontenous bacterial pertonitits**
TH:	**Thymus helper cells**
TLC:	**Total leucocytic count**
TNF alpha:	**Tumor necrosis factor alpha**
US:	**United states**
TIPS:	**transjugular intrahepatic portosystemic shunt**
WBC:	**White blood cells**

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Introduction

Cirrhosis is characterized by an increased susceptibility to infection. In this way, spontenous bacterial peritonitis is a major complication of liver cirrhosis. The incidence in hospitalized patients with ascitic cirrhosis ranges between 7% and 23%, but increased when ascitis is associated with low protein concentration (below 1g/100 ml) and severe hepatic impairment ***(D' Amico et al., 2006).***

In most cases, Spontanous bacterial peritonitis is a mono microbial infection.The culture of the ascitic fluid reveals a single micro organism and the neutrophils being above 250/mm. The essential pathogenic elements are the intestinal bacterial overpopulation, bacterial translocation, increased intestinal permiability and immune deficiency .Translocation of bacteria is defined as the passage of viable bacteria from the gastrointestinal tract to extra intestinal sites such as mesenteric lymph nodes (MLN), liver, spleen, kidneys, and blood flow. Overgrowth of the intestinal gram negative bacilli will be followed by translocation in mesenteric lymph nodes, in the conditions of disruption of the intestinal barrier(***Wells et al.,1987).***

Unlike the aerobic bacteria which translocate through an intact mucosa, the anaerobic bacteria translocates through an intestinal mucosal defect***.(Marteau et al.,2001).***

In fact, by eliminating the anaerobic bacteria, the intestinal bacterial overgrowth is facilitated, which is one of the main factors promoting bacterial translocation***(Wells.,1996).***

Introduction

The long term prognosis of patients with spontenous bacterial peritonitis is unfavorable, the recurrence rate being 43% at 6 months .Despite the use of empirical antibiotic therapy, particularly cefotaxime as well as antibiotic prophylaxis, currently mortality ranges from 10 to 30%***(Garcea-Tsao.,2003).***

In cirrhotic patients with low protein ascitis (<1.5g/dL) but no prior spontanous bacterial peritonitis (primary prophylaxis) oral norfloxacin (400 mg/day) is recommended .

This has been shown to reduce the probability of spontenous bacterial peritonitis and hepato renal syndrome and improved the 3-month survival . Likewise, oral ciprofloxacin (500 mg/day) will reduce the 1-year mortality rate in patients with ascitic protein levels <1.5 g/dL without prior spontenous bacterial pertonitis episode***.(Fernandez et al.,2007).***

Rifxamine is an antibiotic with a broad-spectrum activity against gram-positive and gram-negative micro-organisms within the gastrointestinal tract. The main advantage of rifxamine is that it is virtually un absorbable, which minimizes the antimicrobial resistance and adverse events and renders the drug safe in all patient populations. In addition, rifxamine has a better activity against gram-positive organisms than norfloxacin***.(Koo et al.,2010).***

By studying its effects on circulating endotoxins level and ascitic fluid neutrophil count in cirrhotic patients with sterile ascitis, Findings strongly suggest that rifxamine induces subclinical activation of ascitic fluid defense mechanisms from prior silent colonisation with bacteria in cirrhotic patients with sterile ascitis. The reduction of endotoxemia by rifaximine may further reduce bacterial translocation by causing a fall in portal pressures. ***(Vlachogiannakos et al.,2009***).

considering that portal hypertension induces structural abnormalities in intestinal mucosa leading to an enhanced permeability.

The appreciation of the potential role of enteric flora in the pathogenesis of several gastrointestinal diseases has broadened the clinical use of rifxamine , which is now used for hepatic encephalopathy, small intestine bacterial overgrowth, inflammatory bowel disease, and Clostridium difficile infection. Theoretically, by reducing the total number of the gut bacteria, rifaximine could also be used to achieve intestinal decontamination in patients with liver cirrhosis and ascitis, thus preventing spontaneous bacterial peritonitis.***(Jeong-hoon Lee.,2014).***

Zinc is known to play an important role in the immune system. Zinc deficient subjects may experience increased susceptibility to a variety of pathogens. Characteristically during zinc deficiency, the serum thymulin activity (a thymic hormone) was decreased which was restored following zinc supplementation.

Studies showed that zinc deficiency caused an imbalance between TH1 and TH2 functions. The production of IFN-g, IL-2, TNF-a (products of TH1 cells) were decreased, whereas the production of IL-4, IL-6 and IL-10 (products of TH2) were not affected.T- cell subpopulation studies revealed that the ratio between CD4+ CD45RA+ and CD4+ CD45RO+ was decreased as a result of zinc deficiency, suggesting that zinc may be required for the regeneration of new CD4+ T cells.

Zinc deficiency also decreases NK cell lytic activity and cause a decrease in the percentage of CD8+ CD73+ T cells which are known to be predominantly precursors of cyto toxic T cells. In a suitable cell culture model studies revealed

that the gene expression of a DNA synthesizing enzyme TK was affected adversely which resulted in delayed cell cycle and decreased cell growth. The above immunological consequences of zinc deficiency may be responsible for decreased cell mediated immune functions in zinc deficient subjects., So zinc may also be used in prophylaxis of spontaneous bacterial peritonitis.(***Fraker et al.,1977)***

Zinc deficiency/altered metabolism is observed in many types of liver disease, including alcoholic liver disease (ALD) and viral liver disease. Some of the mechanisms for zinc deficiency/altered metabolism include decreased dietary intake, increased urinary excretion, activation of certain zinc transporters, and induction of hepatic metallothionein. Zinc deficiency may manifest itself in many ways in liver disease, including skin lesions, poor wound healing/liver regeneration, altered mental status, or altered immune function. Zinc supplementation has been documented to help in stabilization of gut-barrier function, decreasing endotoxemia, decreasing proinflammatory cytokine production, decreasing oxidative stress, and attenuating apoptotic hepatocyte death. It is clear that zinc supplementation reverses clinical signs of zinc deficiency in patients with liver disease. Some studies suggest improvement in liver function in hepatitis C following zinc supplementation, and improved fibrosis markers in hepatitis C patients. The dose of zinc used for treatment of liver disease is usually 50 mg of elemental zinc taken with a meal to decrease the potential side effect of nausea***.(Mohamed et al.,2012).***

Aim of work

Evaluation of the efficacy of administration of oral rifixamine with or without zinc in the secondary prevention of Spontaneous bacterial peritonitis in a Child C Egyptian cirrhotic patient.