Effect of treatment with midodrine in non azotemic Cirrhotic patients with tense ascites

Thesis

Submitted in partial fullfilement for M.Sc. degree of internal medicine

By

Youseff Botross Ishac Khalil

M.B.B.CH.

Supervision by

Dr. Nouman El Garem

Professor of internal medicine

Faculty of medicine - Cairo University

Dr. Mohamed Ahmed Abo seif

Assistant professor of internal medicine

Faculty of medicine - Beni Suef University

Dr . El-Sayed Abdallah El-Sayed

Assistant professor of internal medicine

Faculty of medicine - Cairo University

Cairo University

2009

Acknowledgment

First to all thanks to Allah, who gave me the power to perform and complete this work.

I would like to express my profound gratitude and appreciation to **Prof. Dr. Nouman El Garem**, Professor of Internal Medicine, Faculty of Medicine, Cairo University, for his continuous encouragement and valuable supervision and guidance throughout this work.

Also, I would like to express deep gratitude and deepest thanks to **Ass. Prof. Dr. Mohamed Ahmed Abo seif,** Assistant professor of Internal Medicine, Faculty of Medicine, Beni Suef University, For his continuous guidance, advises and supervision.

I wish also to express my gratitude and deep thanks to **Ass. Prof. Dr. El-Sayed Abdallah El-Sayed,** Assistant professor of Internal Medicine, Faculty of Medicine, Cairo University, for giving me much of his effort & time and his continuous guidance, correction and explanation to finish this work.

I would like also to thank **Ass. Prof. Dr. Khaled El-Sayed El-Hadidy**, Assistant professor of Internal Medicine, Faculty of Medicine, Beni Suef University, for his guidance and advises throughout this work.

Also, I would like to thank **Dr. Waleed Mohammed El-Nabway,** Lecturer of Internal Medicine, Faculty of Medicine, Beni Suef University for his support throughout this work.

Lastly but not least, my thanks to my father, my mother, my fiancée and my best friend Mr. Azzer Yousef Atta who suffered a lot throughout this work.

Abstract

This study was conducted to evaluate the effects of 7 days treatment with midodrine, an alpha 1-agonist, in non azotemic cirrhotic patients with tense ascites.

Midodrine group: (Patients subjected to Midodrine and Diuretics) shows a significant decrease in body weight and a significant increase in B.U.N. at the end of the 7 days study compared to day 1 of the study.

Control group: (Patients subjected to Diuretics) shows a significant decrease in body weight at the end of the 7 days study compared to day 1 of the study.

In a comparison between the above two groups There was a significant increase in urine output and a significant decrease in serum creatinine in patients of Midodrine group as compared with patients of Control group.

So the present study shows that administration of Midodrine with diuretics in patients with tense ascites led to a significant diuresis as well as a significant improvement of renal functions as compared to patients who were administered diuretics only.

Key Words

Midodrine-liver cirrhosis-non azotemic-tense ascites- diuretics - renal functions.

LIST OF CONTENTS

Title	Page No.

Introduction 1

Aim of the work 2

Review of literature:

- Liver Cirrhosis 3
- Ascites in Liver Cirrhosis 14
- Midodrine in Ascites 30

Patients and methods 36

Results 41

Discussion 65

Summary and conclusion 69

References 70

Arabic summary .....__

LIST OF TABLES

Table No.	Page No.
Table(1): Demographic data between the studied groups ...	41
Table(2): Clnical and Laboratory parameters at the beginning and the end of the 7 days study among patients of group1 (Midodrine group)	42
Table(3): Clnical and Laboratory parameters at the beginning and the end of the 7 days study among patients of group2 (Control group)	43
Table(4): Comparison of clinical and laboratory parameters at the end of the 7 days study between patients of group1 and group2	45

LIST OF DIAGRAMS AND GRAPHS

Figure No. **Page No.**

Diagram(1): Overflow hypothesis 16

Graph(1): Changes in Body weight in Midodrine group, at the beginning and end of the study 47

Graph(2): Changes in Urine output in Midodrine group, at the beginning and end of the study 48

Graph(3): Changes in serum Sodium concentration in Midodrine group, at the beginning and end of the study..... 49

Graph(4): Changes in serum Potassium concentration in Midodrine group, at the beginning and end of the study 50

Graph(5): Changes in Plasma osmolality in Midodrine group, at the beginning and end of the study 51

Graph(6): Changes in B.U.N. in Midodrine group, at the beginning and end of the study 52

Graph(7): Changes in serum creatinine in Midodrine group, at the beginning and end of the study ……... 53

Graph(8): Changes in serum albumin in Midodrine group, at the beginning and end of the study ……... 54

Graph(9): Changes in 24 hours urinary sodium excretion in Midodrine group, at the beginning and end of the study 55

Graph(10): Changes in Body weight in Control group, at the beginning and end of the study 56

Graph(11): Changes in Urine output in Control group, at the beginning and end of the study 57

Graph(12): Changes in serum Sodium concentration in Control group, at the beginning and end of the study 58

Graph(13): Changes in serum Potassium concentration in Control group, at the beginning and end of the study 59

Graph(14): Changes in Plasma osmolality in Control group, at the beginning and end of the study 60

Graph(15): Changes in B.U.N. in Control group, at the beginning and end of the study 61

Graph(16): Changes in serum creatinine in Control group, at the beginning and end of the study 62

Graph(17): Changes in serum albumin in Control group, at the beginning and end of the study 63

Graph(18): Changes in 24 hours urinary sodium excretion in Control group, at the beginning and end of the study 64

LIST OF ABBREVIATIONS

ADH ..... Antidiuretic hormone.

ANP ..... Atrial natriuretic peptide.

BFGF ..... Basic fibroblast growth factor.

BMPs ..... Bone morphogenic proteins.

BUN ..... Blood Urea Nitrogen.

CO ..... Cardiac output.

DIC ..... Disseminated intravascular coagulopathy.

FGF ..... Fibroblast growth factor.

GFR ..... Glomerular filtration rate.

HBV ..... Hepatitis B virus.

HCV ..... Hepatitis C virus.

HGF ..... Hepatocyte growth factor.

HRS ..... Hepatorenal syndrome.

HSC ..... Hepatic Stellate Cells.

IHD ..... Ischemic heart disease.

INR ..... International normalized ratio.

LVPs ..... Large volume paracentesis.

MAP ..... Mean arterial pressure.

MELD ..... Model for end-stage liver disease.

NASH ..... Non alcoholic steatohepatitis.

NSAIDs ..... Non steroidal anti-inflammatory drugs.

PDGF ..... Platelet-derived growth factor.

PRA ..... Plasma renin activity.

RAAS ..... Rennin- angiotensin-aldosterone system.

SNS ..... Sympathetic nervous system.

SVR ..... Systemic vascular resistance.

TGF-β1.....Transforming growth factor β1.

TIMP ..... Tissue inhibitor of metalloproteinase.

TIPS ..... Transjugular intrahepatic portosystemic shunt.

TNFα ..... Tumour necrosis factor alpha.

UNaV ..... Urinary sodium excretion.

Introduction

The development of cirrhosis of the liver is associated with a total derangement of the normal architecture due to the presence of regeneration nodules and fibrous bands or septae running between them. Thus cirrhosis results in a distortion, compression, and even obliteration of the hepatic vasculature, with increased portal venous compression, increased resistance to portal venous blood flow, or portal hypertension.

(Blendis and Wong 2001).

Portal hypertension is a progressively debilitating complication of cirrhosis and a principal cause of mortality in patients who have hepatic decompensation. Through the persistent elevation of pressures in portosystemic collaterals, varices develop, enlarge, and gain the potential to bleed. Variceal hemorrhage is the primary cause of bleeding episodes and occurs in 25% to 35%of patients who have cirrhosis and large esophagogastric varices. ***(Minor and Grace 2006).***

Ascites is the most common major complication of cirrhosis; It is associated with poor quality of life, increased risk of infection, and renal failure. Twenty percent of patients with cirrhosis have ascites at the time of the diagnosis. While 30% and 50% of patients with compensated cirrhosis will develop ascites in 5 and 10 years of follow up, respectively. Ascites, which is a sign of poor prognosis, characteristically develops during late stages of the disease. Patients with cirrhosis and ascites have 50% mortality at two years. ***(García Leiva et al. 2007).***

Aim of the work

The aim of the work is:

To verify the therapeutic effects of administration of vasopressor alpha1-adrenergic agonist (Midodrine) in non-azotemic cirrhotic patients with tense ascites as regards body weight, urine output, sodium, potassium, plasma osmolality, B.U.N., serum creatinine, serum albumin and urinary sodium excretion.

Liver Cirrhosis

Definition:

Cirrhosis, which can be the final stage of any chronic liver disease, is a diffuse process characterized by fibrosis and conversion of normal architecture to structurally abnormal nodules.These "regenerative" nodules lack normal lobular organization and are surrounded by fibrous tissue. The process involves the whole liver and is essentially irreversible.

(Guadalupe Garcia-Tsao 2007).

Causes: *(Guadalupe Garcia-Tsao 2007).*

MAIN FACTORS CAUSING CIRRHOSIS:

- Chronic hepatitis C
- Alcoholic liver disease
- Nonalcoholic fatty liver disease
- Chronic hepatitis B

OTHER CAUSES OF CIRRHOSIS (<2% OF ALL CASES):

A)Cholestatic and autoimmune liver diseases:

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Autoimmune hepatitis

B)Intrahepatic or extrahepatic biliary obstruction:

- Mechanical obstruction
- Biliary atresia
- Cystic fibrosis

C)Metabolic disorders:

- Hemochromatosis
- Wilson's disease
- α_1-Antitrypsin deficiency
- Glycogen storage diseases
- Abetalipoproteinemia
- Porphyria

D)Hepatic venous outflow obstruction:

- Budd-Chiari syndrome
- Veno-occlusive disease
- Right-sided heart failure

E)Drugs and toxins

F)Intestinal bypass

G)Indian childhood cirrhosis

Pathophysiology:

Tissue fibrosis is mediated by fibroblasts and myofibroblasts. Potential contributors to the hepatic myofibroblast population in areas of inflammation include the hepatic stellate cell (HSC), portal myofibroblast and myofibroblast derived from stem cells. Of these, the HSC is the most thoroughly studied. ***(Iredale and Guha 2007).***

Stellate cell activation:

Activation involves the transdifferentiation of the quiescent, retinoid-storing HSC, lying in the space of Disse, into the activated, contractile 'myofibroblast'.

There are a number of potential initiators for HSC activation, including soluble signals released by sinusoidal endothelium, hepatocytes, Kupffer cells, platelets and leukocytes. ***(Iredale and Guha 2007).***

They are able to interact with the HSC using a variety of mediators ranging from fibronectin release from damaged endothelium to platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β1 and epidermal growth factor from platelets.

Kupffer cells, which are resident macrophages in the liver, have a significant interaction with HSCs. They are able to activate stellate cells and stimulate matrix synthesis via the release of cytokines, in particular TGF-β1. ***(Bachem et al., 1989).***

Pathways of stellate cell activation:

There are two major phases of activation**:** initiation and perpetuation.

(Friedman 2004).

Initiation of stellate cell activation:

The earliest changes in stellate cells are likely to result from paracrine stimulation by all neighbouring cell types, including sinusoidal endothelium, Kupffer cells, hepatocytes and platelets.