Comparative study of the combined use of Isosorbide Mononitrate Plus Propranolol versus Propranolol alone in the management of portal hypertension in Pediatrics

Thesis

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List of Abbreviations

AA	: Diameter of abdominal aorta
AIH	: Autoimmune hepatitis
Alb	: Albumin
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
BCs	: Budd Chiari syndrome
Bil. HSM	: Bilharzial hepatosplenomegaly
Bun	: Blood urea nitrogen
Cc	: Cryptogenic cirrhosis
CE	: Capsule endoscopy
CHF	: Congenital hepatic fibrosis
Cholestatic LD	: Cholestatic liver disease
CI	: Congestive index
COPD	: Chronic Obstructive Pulmonary Disease
Cr	: Creatinine
D.bil	: Direct bilirubin
Dbp	: Diastolic blood pressure
EC	: Endothelial cell
EDRF	: Endothelium-Derived Relaxing Factor
eNOS	: Endothelial nitric oxide synthase
ET-1	: Endothelin1
GSD	: Glycogen storage disease
HARI	: Hepatic artery resistive index
Hb	: Haemoglobin concentration
HDL	: High density lipoprotein
Hr	: Heart rate
HVPG	: Hepatic venous pressure gradient
idiopathic PTH	: Idiopathic portal hypertension
INR	: International normalized ratio
ISMN	: Isosorbide mononitrate
Kg	: Kilogram
LDL	: Low density lipoprotein

List of Abbreviations (Cont.)

μg	: Micrgram
MLCK	: Activated myosin light chain kinase
mm	: Millimetre
NO	: Nitric oxide
No	: Number
NSAIDs	: Non-steroidal anti inflammatory drugs
OM	: Lesser ommental thickness
OMAA	: Ratio of lesser omental thickness to abdominal aorta diameter
OV	: Oesphageal Varix
P. Falciparum	: Plasmodium Falciparum
PHG	: Portal hypertensive gastropathy
Plt	: Platelets count
PT	: Prothrombin time
PVd	: Portal vein diameter
PVsa	: Portal vein surface area
PVT	: Portal vein thrombosis
PVv	: Portal vein velocity
SARI	: Splenic artery resistive index
Sbp	: Systolic blood pressure
SD	: Standard deviation
sec	: Seconds
SVd	: Splenic vein diameter
SVv	: Splenic vein velocity
T.bil	: Total bilirubin
T.protein	: Total protein
TIPS	: Transjugular intrahepatic portosystemic shunting
Tlc	: Total leucocytic count
VLDL	: Very low density lipoprotein

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INTRODUCTION

In patients with cirrhosis, increased intra-hepatic vascular resistance and portal blood flow contribute to the development of portal hypertension and its complications ***(Moreau and Lebrec, 1995)***. Portal hypertension is defined as a pathological increase in portal pressure (i.e. portal pressure gradient between portal vein and inferior caval vein) beyond 5 mmHg. When the portal pressure gradient exceeds the threshold of 12 mmHg, complications such as variceal hemorrhage can arise, defining the stage of clinical significant portal hypertension ***(Schiedermaier et al., 2004)***.

Variceal bleeding is a serious complication of portal hypertension. Varices are present in nearly half of the patients at the time of diagnosis of cirrhosis and 20% of patients have large varices **(Chalasani *et al., 1999)***. One-third of the patients with varices will suffer variceal hemorrhage with a death rate between 30% and 5o% during each bleeding episo*de* ***(D'Amico and de Franchis, 2003).*** In view of this high bleeding rate, as well as the high rate of mortality, the aim of primary prophylaxis is prevention of a first episode of variceal hemorrhage. Two different approaches exist to accomplish this goal:

- Decreasing portal hypertension by either pharmacological intervention or shunting
- Treating esophageal varices by means of endoscopy.

(Schiedermaier et al., 2004).

Accordingly, the goal of pharmacological treatment is to reduce portal pressure and thus variceal pressure. This beneficial effect may be obtained by decreasing portal blood flow or intrahepatic vascular resistance, or both. Certain drugs cause splanchnic vasoconstriction and thus reduce portal blood flow and portal pressure e.g. b-blockers, others cause intrahepatic vasodilatation and thus reduce intrahepatic vascular resistance and portal pressure e.g. nitrates ***(Lebrec, 1998)***.

The use of b-blockers is well established for preventing the first variceal bleeding ***(Binmoeller and Borsatto, 2000)***. Vasodilators, which have been evaluated for long-term prophylaxis of variceal hemorrhage, include nitrates, adrenergic antagonists such as clonidine and prazosin and angiotensin blockers such as irbesartan and lorsartan ***(Albillos et al., 1995)***.

The combined use of Nitrates plus propranolol in the management of portal hypertension is controverserial.

While ***Orban Schiopu et al. (2005)*** states that the combined therapy with propranolol and isosorbide mononitrate is superior to the mono-therapy with propranolol in decreasing the hemodynamic parameters in portal hypertension, ***Schiedermaier et al. (2004)*** states that no difference was found between propranolol and both in the probability of variceal hemorrhage.

The utility of adding a vasodilator to b-blockers needs to be studied further.

AIM OF THE WORK

This study aims at evaluation of the effect of the combined use of Isosorbide Mononitrate and Propranolol on the haemodynamic state and endoscopic findings in children with portal hypertension in comparison to the use of Propranolol alone.

PORTAL HYPERTENSION

A portal system is one, which by definition, begins and ends with capillaries. The major portal system in humans is one in which the capillaries originate in the mesentery of the intestines and spleen and end in the hepatic sinusoids. Capillaries of the superior mesenteric and splenic veins supply the portal vein with nutrient and hormone rich blood supply. The partially oxygenated portal venous blood supplements the oxygenated hepatic arterial flow to give the liver unique protection against hypoxia ***(Shneider, 2007)***.

Portal hypertension is defined by a raised portal pressure above the normal values of 1–5 mmHg. Clinically significant portal hypertension is defined as that above the threshold of 12 mm Hg at which there is the potential development of portal hypertensive bleeding, the most serious complication of portal hypertension, as it is associated with high morbidity and mortality rate ***(Samonakis et al., 2004)***.

Portal hypertension is an almost unavoidable complication of cirrhosis, and it is responsible for the more lethal complications of this syndrome: gastro-esophageal varices and massive gastrointestinal bleeding, ascites, hepatorenal syndrome, portopulmonary syndrome and hepatic encephalopathy ***(Bosch et al., 2003)***.