Original Article

Therapeutic Effect of Captopril, Pentoxifylline, and *Cordyceps Sinensis* in Pre-Hepatic Portal Hypertensive Rats

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ABSTRACT

Background/Aim: Portal hypertension is an important and potentially fatal complication of liver disease whereby cellular and fibrotic alterations manifest to increase portal venous pressure. The aim of this study is to investigate the effect of captopril, pentoxifylline (PTX), and *cordyceps sinensis* in pre-hepatic portal hypertensive rats. **Settings and Design:** Wister male rats were divided at random into 3 main groups: the first group: control rats. The second group: sham-operated rats and the third group: prehepatic portal hypertensive rats (PHPHT) induced by regulated pre-hepatic portal vein ligation. After 14 days, Group 3 was subdivided into 5 subgroups. Subgroup (1): portal vein–ligated (PVL) was killed at once; Subgroup (2): received distilled water for 30 days (untreated PVL group); subgroups 3–5 were treated with captopril (60 mg/kg, orally); PTX (100 mg/kg, orally); and *C. sinensis* (200 mg/kg, orally), respectively, as a single daily dose for 30 days. **Patients and Methods:** Portal pressure, nitric oxide (NO), antioxidant enzymes, Liver enzymes, and creatinine levels were measured to evaluate the status of the liver state. **Results:** Portal vein ligation produced significant increments in liver enzymes, NO, creatinine and portal pressure concomitant with significant decrements in glutathione content and superoxide dismutase activity. Treatment with captopril, PTX, and *C. sinensis* resulted in a significant reduction in liver enzymes, NO, creatinine and portal pressure and observable increase in antioxidant enzymes. **Conclusions:** captopril, PTX, and *C. sinensis* have promising effect in controlling PHPHT and reducing hyperdynamic circulatory state through reduction of portal pressure and NO level.

Key Words: Captopril, nitric oxide, pentoxifylline, portal hypertension, reactive oxygen species

Received: 14.08.2011, Accepted: 19.11.2011

How to cite this article: Ahmed AF, El-Maraghy NN, Abdel Ghaney RH, Elshazly SM. Therapeutic effect of captopril, pentoxifylline, and *cordyceps sinensis* in pre-hepatic portal hypertensive rats. Saudi J Gastroenterol 2012;18:182-7.

Chronic liver diseases generally progress slowly from inflammation to fibrosis and in many cases to portal hypertension (PHT) and cirrhosis.[1]

PHT resulted in a hyperdynamic circulatory state. Nitric oxide (NO) and reactive oxygen species (ROS) may play important roles in the pathogenesis of hemodynamic changes of PHT.[2]

Captopril may inhibit production of superoxides, scavenge free radicals, and increase expression of endothelial nitric oxide synthase.[3]

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

PubMed ID: 22626797

DOI: 10.4103/1319-3767.96451

Pentoxifylline (PTX) is an inhibitor of phosphodiesterases, resulting in an elevated intracellular pool of the second messenger cyclic adenosine monophosphate (cAMP).[4] PTX also possesses an antioxidant effect.[5]

C. sinensis is a fungus that develops stroma. Previous studies have demonstrated its multiple pharmacologic actions, such as reducing damage to renal tubules and protecting the Na^+, K^+-ATPase on cellular membranes, an action that is associated with a reduction in cellular lipid peroxidation.[6]

The aim of this work is to investigate the effect of captopril, PTX, and *C. sinensis* on repairing and hence management of the induced prehepatic portal hypertension (PHPHT) in male rats.

PATIENTS AND METHODS

Experimental animals and ethical approval

Adult male albino rats 220–250 g (Zagazig University, Zagazig, Egypt) Rats were housed in stainless steel cages at constant temperature of 25°C ± 2°C, relative humidity of

approximately 50%, illumination (12 h light/dark), and had free access to standard pellet chow and water ad libitum. All experimental procedures were approved by the local authorities at the Faculty of Pharmacy, Zagazig University, Egypt (Ethical Committee for Animal Handling at Zagazig University, ECAHZU).

Experimental design

After 1 week of acclimatization, rats were randomized and separated into 3 main groups: (1) control rats (n=8), (2) Sham-operated rats (n=12), and (3) Pre-hepatic portal vein ligated (PVL) rats (n=48). Group 3 was subdivided into 5 subgroups. Subgroup (1): portal vein–ligated (PVL) was killed at once; Subgroup (2): received distilled water for 30 days (untreated PVL group); Subgroup (3): received captopril (60 mg/kg, orally); Subgroup (4): received PTX (100 mg/kg, orally); and Subgroup (5) received *C. sinensis* (200 mg/kg, orally). Subgroups (2, 3, and 4) received single oral daily dose of drugs for 30 days. At the end of the experiment, all animals from each group were anesthetized with urethane (1.3 g/kg) and the portal pressure was determined [Table 1]. Rats were then killed by decapitation; blood was collected by direct cardiac puncture for serum biochemical estimation. Blood samples were kept at room temperature for 30 min and centrifuged at 3000 rpm for 30 min to obtain the serum, which was kept at -20°C until the assay. The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), NO, and creatinine were measured spectrophotometrically. Livers were perfused with phosphate buffer solution (pH=7.4) containing 0.16 mg/mL heparin. Then livers were isolated and immersed immediately in liquid nitrogen and kept at -80°C for estimation of antioxidants parameters (glutathione (GSH) content, superoxide dismutase activity (SOD), catalase).

Induction of prehepatic portal hypertension

PHT was induced by a calibrated portal vein stenosis according to the procedure of Vorobioff *et al*.[7] In brief, rats were anesthetized with sodium pentobarbital (40 mg/kg body weight, i.p.) and then a midline abdominal incision was made. The portal vein was located and isolated from the surrounding tissues. A ligature of 3-0 silk was placed around the vein and snugly tied it to a 20-gauge blunt end needle placed alongside the portal vein. The needle was subsequently removed to yield a calibrated stenosis of the portal vein. Sham rats underwent an identical procedure except that portal vein was isolated but not stenosed. Each rat was injected with 0.5 mL of benzyl-penicillin (diluted in 4 mL distilled water) for 3 days to avoid infection. Fourteen days after the operation, rats of group 2 developed PHT.

Table 1: Drugs and chemicals

Drug name	Dose	Source
Captopril•	60 mg/kg (oral)	Egyptian International Pharmaceutical Co. (EPICO), Egypt
Pentoxifylline•	100 mg/kg (oral)	Sanofi Aventis Co., Egypt
Cordyceps sinensis•	200 mg/kg (oral)	Mycology Laboratories Ltd., UK
Ethylcarbamate (urethane)	1.3 g/kg (I.P.)	Prolabo, Paris

(•) the drug was dissolved in distilled water. All other chemicals were of analytical grades. All drug solutions were freshly prepared just before use. All the first three drugs were taken by oral cavage. *C. sinensis* is biomass powder

Biochemical analysis

Measurement of portal venous pressure:

Fourteen days after portal vein ligation (PVL), the rats were anesthetized with urethane (1.3 g/kg I.P.) given as 25% freshly prepared solution.[8] The ileocolic vein was cannulated with polyethylene tubing (PE-50) to measure portal venous pressure (PVP) through pressure transducer "PT_{400}" that was attached to FC_{137} strain gauge coupler of oscillograph 400 MD 4C (Palmar–Bioscience).

Liver function tests

Serum ALT and AST activities were determined by a colorimetric method using Diamond Diagnostic Kits (Egypt) according to Reitman and Frankel.[9]

Catalase activity

Catalase activity was assayed calorimetrically by the method of Johansson and Borg.[10]

Glutathione content (GSH reduced form)

Glutathione was measured in 10% liver homogenate according to the colorimetric method of Beutler *et al*.[11]

Superoxide dismutase activity

SOD activity is measured in 10% liver homogenate according to the method of Minami and Yoshikawa *et al*.[12]

Creatinine

Creatinine in serum was determined by a colorimetric method using a diagnostic kit supplied by Diamond Diagnostic Kits (Egypt) as described by Henry *et al*.[13]

Nitric oxide in liver

NO in liver homogenates was determined by a colorimetric method using a diagnostic kit supplied by Biodiagnostic Company (Egypt) as described by Hirvonen *et al*.[14]

Statistical analysis

Results were expressed as mean ± SE. Statistical evaluation was done using one-way analysis of variance (ANOVA), and Tukey's multiple comparison test using SPSS software version 12, SPSS Science, Chicago, IL, USA. values of $P<0.05$ were considered significant.

RESULTS

Effect of portal vein ligation on normal rats

Effect on liver enzymes

Portal vein ligation induced a significant elevation in the serum levels of ALT and AST compared with sham-operated rats. On the other hand, sham-operated rats didn't induce a significant change in the level of liver enzymes compared with normal group. Portal vein–ligated (PVL) rats which were left for 4 weeks without treatment (PVL-untreated) showed a significant decrease in ALT (U/L) level compared with PVL rats [Table 2].

Administration of captopril or PTX to PVL rats induced a significant reduction in ALT and AST levels compared with non-PVL rats. PVL rats treated with *C. sinensis* decreased AST level only [Table 2].

Effect on antioxidant status

PVL rats showed a significant reduction in GSH content and SOD activity compared with sham-operated rats. Results also illustrated that, administration of captopril to PVL rats caused a significant increase in GSH content and SOD activity, compared with non-PVL rats. In addition, Treatment of PVL rats with PTX or *C. sinensis* to PVL rats induced observable increase in SOD and catalase activities, compared with non-PVL rats [Table 3].

Effect on nitric oxide, creatinine, and portal pressure

PVL caused a significant elevation in the levels of NO, creatinine, and portal pressure compared with sham-operated group. Oral administration of captopril, PTX, or *C. sinensis* significantly reduced NO, creatinine, and portal pressure compared with non-PVL rats [Table 4 and Figure 1].

DISCUSSION

Partial portal vein ligation model has been widely used in the study of the pathophysiology of PHT.[7] PHT is often accompanied with a hyperdynamic circulatory state. ROS and NO (vasodilatory agent) play an important role in this hyperdynamic state.[15]

In the present study, pre-hepatic portal hypertensive rats demonstrated a reduced hepatic antioxidant activity. The mechanisms responsible for this antioxidant power inhibition include (1) the increase in mitochondrial

Table 2: Effect of oral treatment with captopril, pentoxifylline, or *cordyceps sinensis* on liver enzymes levels in portal vein–ligated rats

Parameters	ALT (U/L)	AST (U/L)
Normal	9.5±0.6	43.06±2.1
Sham	6.7±0.23	42.66±1.46
PVL	23.15±1.6#	62.28±2.6#
PVL-untreated	16.35±1.5**,#	58.15±3.17#
Captopril	10.13±0.86*	40.08±1.7*
Pentoxifylline	11.8±1.05*	39.86±1.5*
Cordyceps sinensis	15.9±0.83	47.23±4.2*

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PVL: Portal vein ligated. Results are presented as the mean ± S.E.M. #Significantly different from the corresponding mean value of sham group at $P<0.05$. **Significantly different from the corresponding mean value of PVL group at $P<0.05$. *Significantly different from the corresponding mean value of PVL-untreated group at $P<0.05$

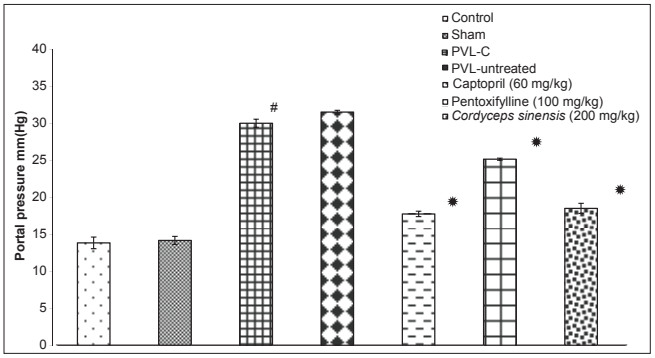

Figure 1: Effect of oral treatment with captopril, pentoxifylline, or *Cordyceps sinensis* on portal pressure in adult male PVL rats. Results are presented as the mean ± SEM; #significantly different from the corresponding mean value of sham group at $P<0.05$; *significantly different from the corresponding mean value of non-PVL group at $P<0.05$)

Table 3: Effect of oral treatment with captopril, pentoxifylline, or *cordyceps sinensis* on antioxidants status in adult male PVL rats

Parameters	GSH (mg/g tissue)	SOD activity (µg/mL reaction mixture)	Catalase activity
Normal	80.32±2.62	49.26±4.48	28.31±1.43
Sham	66.45±4.42	54.6±4.5	25.14±2.46
PVL	39.49±1.47#	33.64±1.47#	19.74±1.36
PVL-untreated	16.35±1.5**,#	37.65±1.78#	20.63±2.4
Captopril	58.25±2.02*	63.9±2.77*	26.43±1.87
Pentoxifylline	50.7±5.3	62.9±2.64*	28.43±1.57*
Cordyceps sinensis	45.45±4.8	45.03±2.17*	31.03±3.44*

PVL: Portal vein ligated. Results are presented as the mean ± SEM. #Significantly different from the corresponding mean value of sham group at $P<0.05$. **Significantly different from the corresponding mean value of PVL group at $P<0.05$. *Significantly different from the corresponding mean value of PVL-untreated group at $P<0.05$

Table 4: Effect of oral treatment with captopril, pentoxifylline, or *cordyceps sinensis* on nitric oxide and creatinine levels in adult male PVL rats

Parameters	Nitric oxide (μmol/L)	Creatinine in serum (mg/dl)
Normal	11.72±1.5	1.88±0.086
Sham	11.93±1.3	1.89±0.075
PVL	30.9±2.57#	4±0.21#
PVL-untreated	24.96±1.86#,**	2.8±0.11#,**
Captopril	13.73±1.48*	2.36±0.145*
Pentoxifylline	14.1±1.26*	1.79±0.072*
Cordyceps sinensis	12.6±1.81*	2.3±0.13*

PVL: Portal vein ligated. Results are presented as the mean ± SEM. #Significantly different from the corresponding mean value of sham group at $P<0.05$; **Significantly different from the corresponding mean value of PVL group at $P<0.05$; *Significantly different from the corresponding mean value of PVL-untreated group at $P<0.05$

superoxide radical and H_2O_2; and (2) the induction of the microsomal cytochrome P-450. Liver will be more susceptible to oxidant-induced liver injury by decreasing portal blood flow. Oxidative damage-associated liver injury is evidenced by decreased cell viability and enhanced liver enzyme levels,[16] which are similar to the significant elevation in liver enzymes in portal vein–ligated rats in our results.

NO is a gas that freely diffuses across cell membranes. In the physiological state, the generation of NO is regulated mainly by NOS, which has several isoforms, the two major ones of which are calcium- and calmodulin-dependent constitutive form and calcium-independent inducible form; and they can be expressed by vascular smooth muscle and other cells in response to stimuli, such as cytokines and endotoxins.[17]

Kanwar *et al*.[18] reported that after the portal vein stenosis, calcium-dependent NOS activity was increased. The explanation for the increased Ca^{+2}-dependent NOS appears to lie in the mesenteric hyperemia in experimental animal models of PHT. Many factors including shear stress, vasopressin, angiotensin II, and norepinephrine can increase the constitutive form of NOS, and these factors are all increased in PHT.[19] This study was found in agreement with the present results that portal vein ligation for 14 days caused a significant increase in NO level.

There was a statistically significant difference in portal pressure between PVL and control groups.

A clear relationship between PHPHT and central (hypothalamus and medulla oblongata) as well as peripheral (portal vein) norepinephrine metabolism exists.[20] Several reports demonstrated that homodynamic changes characteristic of PHT are accompanied by an increase in the activity of the sympathetic nervous system, as reflected by elevation of plasma norepinephrine and it is considered to play an important role in the pathogenesis of PHT and elevation of portal pressure.[21] Several investigators have sought to establish a relationship between renal function and elevations in PVP. The acute elevations in PVP resulted in significant diminutions in glomerular filtration rate and renal blood flow. The elevation in PVP in the present study was produced by partial occlusion of the portal vein, which resulted in significant alterations in renal function demonstrating an increased serum level of creatinine. These changes may be attributed to a fall in renal arterial pressure.[22]

Captopril ([S]-1-[3-mercapto-2-methyl-1-oxo-propyl]-l-proline) is the first marketed orally active angiotensin converting enzyme inhibitors (ACEI) designed to treat hypertension by blocking the conversion of angiotensin I into angiotensin II.[23] The specific inhibitory properties of captopril have been attributed to its structure containing thiol groups that provide specific binding to ACE as well as to indirect suppression of expression of gene encoding ACE. In addition, this thiol compound can react with superoxide anion radical acting as a scavenger or with hydroxyl radical and improved the oxidative balance.[24] Treatment of portal vein–ligated rats in the present study with captopril caused a significant elevation in GSH content and SOD activity.

Antioxidant effect of ACEI may be through direct effect on enzyme synthesis or activity or a secondary effect resulting from the consequences of ACE metabolic actions: inhibition of angiotensin II synthesis, inhibition of aldosterone formation and release, stimulation of renin production, increasing cellular sensitivity to catecholamine, and potentiation of bradykinins.[25] De-Cavanagh *et al*.[26] showed that captopril treatment increased antioxidant enzymes and nonenzymatic antioxidants in several mouse tissues. Furthermore, in erythrocytes the augmentation of antioxidants by ACE inhibitors was associated with protection against oxidant damage.

This is in accordance with the current results that increasing enzymatic antioxidant defenses by ACE inhibitor (captopril) may protect cell components from ROS-mediated damage, and therefore reducing liver enzyme activities of ALT and AST.

TNF-α plays a leading role in activating and sustaining inflammatory responses. It was also shown to stimulate inflammatory cells recruitment, synthesis of cytokines and NO. It has previously been established that ACE inhibitors suppress TNF-α synthesis *in vivo* and *in vitro*.[27] These observations can explain the present data that treatment of PVL rats with captopril resulted in a significant reduction in NO level.

In the present investigation, treating PVL rats with captopril showed a significant decrease in portal pressure compared with non-PVL rats. The reduction in portal pressure after captopril administration could be related to the improvement of portal venous outflow brought about by a decrease in the intrahepatic vascular resistance.[28]

Antioxidant effect of captopril can protect the kidney from damage. This protection was clearly reflected by the decrease in serum creatinine and urea levels.[29] These findings are in agreement with the present results that demonstrated that PVL rats treated with captopril showed a significant reduction in serum creatinine level.

PTX is a xanthine derivative, which has inhibitory effects on xanthine oxidase. Xanthine oxidase is considered as a candidate for oxygen free radical formation in cells. PTX is also a phosphodiesterase inhibitor capable of increasing cAMP and cGMP levels.[30] In our research, we found that treatment of PVL rats with PTX caused a significant increase in antioxidants activity (catalase and SOD). PTX reduces oxygen radical production and protects against tissue damage *in vivo* by the action of its metabolites, suggesting that PTX could scavenge ROS and potentiates the activity of the antioxidant enzymes.[31]

It has been found that the rise in plasma pro-inflammatory cytokine levels coincided with the augmentation of ROS-induced lipid peroxidation and accompanied by the suppression of antioxidant mechanisms.[32] Besides both IL-1β and TNF-α have an ability to induce iNOS expression and increasing NO production. Their inhibition by PTX, ameliorated the hyperdynamic circulation syndrome and reduced PHT, through intracellular accumulation of cAMP.[33] This is confirming our observations that PTX treatment in PVL rats showed a significant reduction in NO and portal pressure level.

In addition, the inhibition of injurious pro-inflammatory cytokines, specifically TNF-α and IL-1β by PTX has a role in the renal protective effect. It has been demonstrated that renal cells can produce and release TNF-α and that the kidney is highly sensitive to this cytokine.[34] The resultant beneficial renal effect also may have been, at least in part, mediated by the vascular effect of PTX and resulted in an impressive increase in glomerular filtration rate.[35]

Results of this work demonstrated that oral treatment of PVL rats with *C. sinensis* caused a significant increase in antioxidants activity. *C. sinensis* has many different effective components capable of scavenging free radicals, such as polysaccharides, mannitol, and cordycepin.[36]

The polysaccharide cordycepin is one of active components in *C. sinensis* that has multiple pharmacologic activities, such as inhibiting the tumor development, protecting liver function, and having antioxidant effect by counteracting the decline of SOD and GSH activity. It also possesses rather potent peroxide eliminating and free radical scavenging capabilities.[37]

Cordycepin suppresses the production of NO and iNOS. The molecular mechanism by which cordycepin inhibits the expression of inflammatory mediators appear to involve the inhibition of NF-κB activation. In addition, events necessary for the activation of NF-κB (such as IκB phosphorylation and nuclear translocation) were suppressed by cordycepin.[38] NF-κB-activating cytokine such as TNF-α was also downregulated, leading to a decrease in NO production.[39] All the previous facts explain our data in the present work that oral treatment of PVL rats with *C. sinensis* caused a significant decrease in NO level compared with non-PVL rats.

The increase in TNF-α in PVL rats, which, in turn, increases NO and prostacyclin synthesis is partially responsible for the vasodilation found and is one of the factors to which the hyperdynamic syndrome is attributed. Inhibition of TNF-α synthesis by cordycepsin administration reduces NO synthesis and blunts the development of the hyperdynamic circulation as well as reduces portal pressure in PVL rats.[40]

In summary, the current data showed that captopril, PTX, and *C. sinensis* have a promising effect in controlling PHPHT through the reduction of portal pressure and reducing hyperdynamic circulation.

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Source of Support: Nil, **Conflict of Interest:** None declared.