Effect of pentoxifylline on survival, cardiac function and both portal and systemic hemodynamics in advanced alcoholic cirrhosis: a randomized double-blind placebo-controlled trial


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ABSTRACT

Objective: to assess the effect of pentoxifylline (a potent inhibitor of tumor necrosis factor alpha) on survival, on systemic and portal hemodynamics, and on cardiac function in patients with alcoholic cirrhosis.

Design: a randomized double-blind placebo-controlled trial.

Setting: a single center using parallel groups of patients to compare pentoxifylline with placebo.

Patients: we recruited 24 patients with alcoholic cirrhosis (8 Child-Pugh Band 16 Child-Pugh C).

Interventions: patients were randomly assigned to receive pentoxifylline (400 mg tid; n = 12) or placebo (n = 12) over a 4-week period.

Outcome measures: the primary outcome was to extend short-term and long-term survival. Secondary outcomes included hemodynamic benefits (improvement in cardiac function and/or systemic vascular resistance index, or decrease in portal pressure).

Results: portal pressure and cardiac function remained unchanged and there were no significant differences in short-term or long-term survival between treatment and placebo groups. The group on pentoxifylline increased systemic vascular resistance and decreased cardiac indices (from 1.721 ± 567 to 2.082 ± 622 dyn.sec⁻¹ cm⁻⁵ m⁻² and from 4.17 ± 1.4 to 3.4 ± 0.9 l.m⁻², p = 0.05).

Conclusions: although pentoxifylline seems to provide some short-term hemodynamic benefits in patients with advanced alcoholic cirrhosis, this drug has no effect on survival or portal pressure in these patients.

Key words: TNF-α inhibition. Haemodynamics. Cirrhotic cardiologyopathy. Human cirrhosis.

RESUMEN

Objetivo: valorar el efecto de la pentoxifilina (un potente inhibidor del factor de necrosis tumoral alfa) en la supervivencia, en la hemodinámica sistémica y portal y en la función cardíaca en la cirrosis alcohólica avanzada.

Diseño: estudio aleatorizado, doble-ciego, controlado con placebo.

Contexto: estudio unicéntrico utilizando grupos de pacientes en paralelo para comparar pentoxifilina y placebo.

Pacientes: se incluyeron 24 pacientes con cirrosis alcohólica (8 en estadio B de Child-Pugh y 16 en estadio C de Child-Pugh).

Intervención: los pacientes fueron aleatorizados a recibir pentoxifilina (400 mg, 3 veces al día, n = 12) o placebo (n = 12) durante 4 semanas.

Determinaciones: el objetivo principal fue la supervivencia a corto/largo plazo. Los objetivos secundarios fueron observar beneficios hemodinámicos (mejoría en la función cardíaca y/o en el índice de resistencias vasculares sistémicas o disminución de la presión portal).

Resultados: la presión portal y la función cardíaca no se modificaron y no hubo diferencias en la supervivencia a corto y largo plazo entre los grupos tratados y placebo. Los índices de resistencia vascular sistémica y cardíaco cambiaron en el grupo de pentoxifilina (de 1.721 ± 567 a 2.082 ± 622 Din.sec⁻¹ cm⁻⁵ m⁻² y de 4.17 ± 1.4 a 3.4 ± 0.9 l.m⁻², p = 0.05).

Conclusiones: aunque la pentoxifilina parece producir algún beneficio hemodinámico a corto plazo en pacientes con cirrosis alcohólica avanzada, no tiene efecto sobre la tasa de supervivencia, la función cardíaca ni sobre la presión portal en estos pacientes.

INTRODUCTION

Patients with decompensated cirrhosis frequently display hemodynamic changes that include low systemic vascular resistance and increased cardiac output with increased blood volume (1-4). These changes are thought to cause a decrease in arterial effective blood volume and play a crucial role in the activation of vasopressor, sodium, and water retention systems leading to ascites and renal dysfunction (5). These hemodynamic changes predicted lower survival rates in these patients (6). In addition to these changes, these patients often have subclinical cardiac changes such as diastolic dysfunction and decreased cardiac contractility when undertaking physical effort or when subjected to pharmacological strain, all of which contributes to systemic hemodynamic derangements (7,8). First described by Ma and Lee (8), this cardiomyopathy is often associated with ventricular patchy fibrosis, focal edema and hypertrophy or dilatation (9,10). The precise cause of this condition is unknown but it is believed to result from autonomic dysfunction with reduced β-adrenergic receptor function (11), or from cardiac depressant factors such as endotoxins or nitric oxide (NO)-mediated cytokines, mainly TNF-α (12). Enteric bacterial translocation triggers an increased synthesis of pro-inflammatory cytokines, particularly TNF-α, in experimental portal hypertension (13). More recently, Wiest et al. observed enhanced eNOS-derived NO production has been observed in cirrhotic rats with bacterial translocation (14,15). Further, inhibition of TNF-α ameliorated hyper-dynamic circulation of portal hypertensive rats (13,16), and increased TNF-α production has been observed in mesenteric lymph nodes of decompensated cirrhotic patients undergoing liver transplant (17).

Pentoxifylline is a potent inhibitor of TNF-α synthesis. Also, it appears to have antioxidant and anti-fibrogenic properties (18,19), and prolongs survival in patients with severe alcoholic hepatitis (20) while improving cardiac function and survival in patients with dilated cardiomyopathy (21).

We designed the present study to determine the effects of pentoxifylline on survival, cardiac function, hemodynamic disturbances in cirrhosis, and portal hypertension.

PATIENTS AND METHODS

This was a single-center, placebo-controlled trial of parallel groups comparing pentoxifylline with placebo. The local ethics committee approved the protocol. The study was conducted according to the Declaration of Helsinki for medical research involving human subjects. Written details regarding the nature of the study were provided to patients before a written consent to participation was obtained from each study subject, or a responsible relative.

Patients (n = 24) had cirrhosis of alcoholic etiology; 8 at Child-Pugh stage B and 16 at Child-Pugh stage C (Table I).

Patients excluded were those with an etiology other than alcohol abuse (infection with B or C hepatitis viruses, with active or recent gastrointestinal bleeding (one week prior to inclusion), grade III-IV hepatic encephalopathy, primary renal or cardiopulmonary disease, insulin-requiring diabetes mellitus, ongoing bacterial infection, complete portal vein thrombosis, receiving drugs with hemodynamic effects such as β-blockers, nitrates or non-steroidal anti-inflammatory drugs (NSAIDs) within the week prior to recruitment. All patients were admitted due to ascitic decompensation. The Child-Pugh score was used to grade the degree of hepatic dysfunction in patients (22).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Pentoxifyline</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; y</td>
<td>56±10</td>
<td>49.7±7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>11/1</td>
<td>9/3</td>
<td>NS</td>
</tr>
<tr>
<td>Child-Pugh; 9 B, 15 C</td>
<td>9.3±1.5</td>
<td>10.8±1.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Maddrey DF; ≥ 32</td>
<td>3(12)</td>
<td>(9/12)</td>
<td>0.04</td>
</tr>
<tr>
<td>Creatinine clearance; ml/min</td>
<td>75.8±20</td>
<td>68±39</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium excretion; mEq/L</td>
<td>75±52</td>
<td>44.5±38</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary output; ml/min</td>
<td>0.9±0.46</td>
<td>0.76±0.54</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma sodium; mEq/L</td>
<td>137±3.8</td>
<td>135±7.9</td>
<td>NS</td>
</tr>
<tr>
<td>SBP; mmHg</td>
<td>109±11</td>
<td>114±15.7</td>
<td>NS</td>
</tr>
<tr>
<td>DBP; mmHg</td>
<td>63±12</td>
<td>61±13.6</td>
<td>NS</td>
</tr>
<tr>
<td>MAP; mmHg</td>
<td>79±11.4</td>
<td>79±13</td>
<td>NS</td>
</tr>
<tr>
<td>HR; bpm</td>
<td>77±17</td>
<td>84±14</td>
<td>NS</td>
</tr>
<tr>
<td>CVP; mmHg</td>
<td>2.8±1.2</td>
<td>3.5±4.27</td>
<td>NS</td>
</tr>
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<td>Cardiac index; l.min⁻¹.m⁻²</td>
<td>3.3±0.9</td>
<td>4.17±1.27</td>
<td>NS</td>
</tr>
<tr>
<td>SVR index; Dyn.sec.cm⁻¹.m²</td>
<td>2699±795</td>
<td>1721±567</td>
<td>NS</td>
</tr>
<tr>
<td>WSHVP; mmHg</td>
<td>23±8</td>
<td>26.7±8.33</td>
<td>NS</td>
</tr>
<tr>
<td>FSHVP; mmHg</td>
<td>8±5.6</td>
<td>11.7±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>HPVG; mmHg</td>
<td>15.5±4</td>
<td>15±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>SMAFB; ml.min⁻¹</td>
<td>476±169</td>
<td>489±167</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; CVP: central venous pressure; SVR: systemic vascular resistance; WSHVP: wedged supra-hepatic venous pressure; FSHVP: free supra-hepatic venous pressure; HPVG: hepatic venous pressure gradient; SMAFB: superior mesenteric arterial blood flow.

Of 30 patients screened, 6 were transferred out of the study because of infection by HCV (n = 2), iron overload (n = 1), complete portal vein thrombosis (n = 1), a very poor clinical condition (n = 1), and requirement of methylprednisolone for the treatment of severe alcoholic hepatitis (n=1) (Fig. 1).

The group of eligible patients (mean age: 53 ± 9 years) was composed of 20 males and 4 females. Pa-
Patients were randomized in a 1:1 ratio to receive either pentoxifylline 400 mg t.i.d. postprandial, or placebo of identical appearance. After the first phase of the study, participants were reviewed on an outpatient basis at weeks 2 and 3 of treatment to assess treatment compliance and side effects. At the 4th week, participants were admitted to hospital to complete the other measurements in the study protocol.

Enrolment commenced in March 2001, and the trial concluded in April 2007. Follow-up was extended to April 28, 2008. The randomization was performed according to the Child-Pugh score (22) but without stratification because only patients belonging to Child’s B and C class had been recruited. Sample size was calculated for an 80% power and an α-error of 0.05, assuming a reduction of portal pressure with pentoxifylline of the same magnitude as that reported by Elephteriadis et al. using intravenous pentoxifylline (23).

Patients were placed on relative rest and on an 80 mMol/day sodium diet for 5 days. Blood samples were drawn for routine analysis after overnight fasting, and a 24 hour urine sample was collected for renal function studies. On the 5th day, at 9 a.m., blood samples from a peripheral vein were drawn for routine analysis, and plasma samples were frozen at -70 °C until the trial was ended for determinations for plasma renin activity (PRA), plasma aldosterone concentration (PAC), and IL-6, sTNF-R1 and NO₂/NO₃ determination.

Hemodynamic studies

After fasting overnight an echocardiograph in the left recumbent position was performed in all participants. Stroke volume was measured by 2-dimensional Doppler echocardiography using the left ventricle outflow method. This technique has been shown to correlate well with the thermo-dilution method (24-27). To minimize inter-observer variation, the same observer (PS) performed the procedure throughout the study. Intra-observer variation was less than 5%. Cardiac output was calculated as the product of stroke volume and heart rate.

Echocardiography baseline values were compared to those of 14 age- and gender-matched healthy volunteers. Blood pressure was measured non-invasively. Systemic vascular resistance was calculated as:

\[
SVR: \left\{ \frac{(MAP-CVP)}{CO} \right\} \times 80
\]

Where the MAP is mean arterial pressure in mm Hg and CO is cardiac output in L/min.

The cardiac and systemic vascular resistance indices were calculated as:

\[
CI: \frac{CO}{BSA}
\]
\[
SVR_i: \left\{ \frac{(MAP-CVP)}{CI} \right\} \times 80
\]

Where the BSA is body surface area and CVP is central venous pressure in mm Hg.

The left ventricular stroke work index (LVSWI) was used as a marker of left ventricular contractility (28), and was calculated as:

\[
LVSWI: \left( \frac{SBP \times SV}{0.0136} \right) \times \frac{BSA}{h(LVIDs)}
\]

Where the LVID is left ventricular end-systolic diameter and h is posterior left ventricular thickness.

Echocardiographic studies were also performed in a group of 15 age- and gender-matched healthy volunteers.

Wedged, free supra-hepatic venous pressures and hepatic venous pressure gradient were obtained for portal hemodynamic assessment in all but 1 patient. For hepatic hemodynamic measurements an occlusion balloon catheter was used (OB/5/5/100, Boston Scientific, Cork, Ireland) coupled to a viridian 24CT monitor (Hewlett-Packard) and a pressure transducer 6f-HF-1019-01 (Monitoring kit Transpac, Abbott, Sligo, Ire-
land). Central venous pressure was recorded throughout the procedure. Upper mesenteric arterial blood flow (MABF) was calculated by echo Doppler according to Iwao et al. (29).

**Blood constituent measurements**

Plasma renin activity was determined by radioimmunoassay for angiotensin-I (angiotensin radioimmunoassay test; Diasorin, Saluggia, Italy). Plasma aldosterone concentration was measured by direct radioimmunoassay (aldosterone II RIA diagnostic kit; Diasorin, Saluggia, Italy). Serum samples for sTNF-α-R1 measurement were available from 17 patients (11 from the treatment group). Since serum soluble TNF-α-R1 levels have been shown to better predict short-term survival than TNF-α (30), we chose sTNF-α-R1 instead of TNF-α as a marker of TNF activation. Measurement of sTNF-α-R1 was performed by enzyme amplified sensitivity immunoassay (Biosource Europe, Nivelles, Belgium). ELISA (IBL Immunobiological Laboratories; Hamburg, Germany) was used to measure interleukin-6. Nitrates and nitrites were measured by colorimetric assay (Cayman Chemical; Ann Arbor, MI, USA). This assay is based on the conversion of nitrate ion into nitrite by the action of nitrate reductase. The excess NADPH is then removed by lactate dehydrogenase, and nitrites measured using Griess reaction at 540 nm. The tritrus automatic immunoassay system was used to minimize the random error associated with manual handling.

**Randomization**

A member of the hospital’s pharmacy who was not a member of the trial investigation team performed the assignment according to a computer-generated random series. The sequence was concealed until intervention was assigned. An allocation code was kept in sealed envelopes in the hospital’s pharmacy until data analysis. Patients, as well as researchers, were blinded to treatment assignment. Tablets of pentoxifylline (400 mg) and placebo of identical appearance were supplied according to the random code. Results were analyzed on an intention-to-treat basis.

**Endpoints**

The two major endpoints of the study were predetermined. The 1st endpoint was to assess the safety and effect of pentoxifylline on long-term survival. The 2nd end-point was to evaluate cardiac function, and systemic hemodynamic parameters. The effects on PRA, PAC, TNF-α, IL-6, NO₂/NO₃, hepatic and renal functions were measured on a post-hoc basis after the investigators were un-blinded with respect to treatment allocation.

**Statistical analyses**

Results were expressed as mean and standard deviation in case of a normal distribution of values, and as median and ranges for those values with a non-Gaussian distribution. Delta values were used for comparison between groups. Wilcoxon’s signed rank test and Student’s paired t-test were used for comparison of paired values. Correlations between variables were tested by Pearson and Spearman rank regression analysis. P values < 0.05 were considered statistically significant. Log-ranked Kaplan-Meier curves (Fig. 2) and the adjusted Cox proportional-hazards survival analysis were used to assess survival at the end of the follow-up period.

**RESULTS**

The median period of follow-up was 42 months (range: 1-84). There were no significant differences with respect to baseline liver and renal function or systemic or portal hemodynamic parameters or SMA blood flow (Table I). Patients assigned to the pentoxifylline group had
poorer liver function (as indicated by the higher Child-Pugh score), and a significantly higher number of patients had a Maddrey discriminant function (MDF) ≥ 32.

Compared to the control group, patients had a smaller left ventricular end-systolic diameter (30.38 ± 2.8 vs. 26 ± 6.4; p = 0.03), and a higher LV-ejection fraction (70.5 ± 8 vs. 62 ± 6; p < 0.01). In addition, patients had lower E/A ratio (1.12 ± 0.25 vs. 1.54 ± 0.36; p < 0.001).

Most patients in both groups remained abstinent from alcohol, or substantially reduced alcohol intake, during the trial. Hence, patients in the placebo as well as the pentoxifylline group significantly improved their hepatic function.

The dose of diuretics was similar in both groups throughout the study (spirolactone: 117±19 vs. 68±64 ± 64 and furosemide 24.44±28 vs. 12.7 ± 18.5; NS).

HVPG and superior mesenteric blood flow remained unchanged following treatment (Table II). There were no changes in creatinine clearance or urinary sodium excretion.

Compared to the placebo group, patients treated with pentoxifylline had an increase in SVRi (Fig. 2) and a reduction in cardiac index (Fig. 3). Despite this increase in SVRi, there were no changes in left ventricular ejection fraction, left ventricular stroke work index or left ventricular wall stress. In addition, pentoxifylline did not appear to exert any effect on the E-A ratio, or on left ventricular wall thickness (Table III).

There was a direct correlation between the baseline values of superior mesenteric blood flow and HVPG (r = 0.62; p < 0.01).

There were no changes in sTNF-α-R1, IL-6, NO2/NO3, PRA or PAC (Table IV).

Side effects, mainly epigastric pain and discomfort, were more common in the pentoxifylline group (Table V); 2 patients were unable to tolerate treatment because of dyspepsia, and a 50% reduction of dose was administered to a 3rd patient due to epigastric pain.

Survival was not significantly different between groups (Fig. 4). There were no deaths among the patients in Child-Pugh class B in the pentoxifylline group. However, the small number of patients in this category precluded sub-group analyses. Following ad-
justment for covariates known to influence survival (such as the Child-Pugh score or the Maddrey discriminant function values and cardiac output), an adjusted Cox proportional hazard analysis did not show differences in survival between the 2 groups on an intention-to-treat basis (HR = 1.46; 95% CI: 0.5-4.28; p = 0.48).

There was no effect of gender on survival (HR = 1.32, 95% CI: 0.41-4.22; p = 0.46).

## DISCUSSION

Our main findings are a lack of clinical benefit of pentoxifylline on survival, cardiac function, splanchnic circulation, and portal pressure in patients with advanced alcoholic cirrhosis. The increased systemic vascular resistance index and decreased cardiac index did not translate into clinical benefit, therefore might have been produced by chance, considering the small sample size. Furthermore, probability values were p = 0.05 and, therefore of only borderline significance.

Compared with the control group, patients had a lower end-systolic left ventricular diameter and higher ejection fraction, which is consistent with reduced systemic arterial afterload in patients with cirrhosis and ascites.

Unadjusted analysis of the primary outcome revealed no differences in long-term survival between treatment and placebo groups. A potential bias regarding survival comparisons is that patients assigned to the pentoxifylline group had poorer hepatic function, as assessed by the Child-Pugh score and Maddrey’s discriminant function. After controlling for these potentially confounding covariates, an adjusted Cox proportional hazard analysis showed no statistically significant differences between groups.

A limitation of this study was the modest sample size in each group. It is also likely that a larger sample size would have resulted in clearer differences regarding systemic hemodynamic changes. Conversely, it is unlikely that a larger sample size would have produced any significant effect on cardiac function or portal pressure since, with current patient numbers, no trend could be observed with treatment.

As commented, the observed short-term hemodynamic benefit in the pentoxifylline group was not translated into clear clinical benefits. It is plausible that detecting any effect on survival would have required a more sustained hemodynamic improvement, for which a longer treatment period with pentoxifylline would...
have been needed. No discernible effect of treatment on E/A ratio changes or any measured cardiac structural parameter had been noted. This implies that either the drug is not effective for this purpose or that longer periods of treatment would be needed to induce myocardial structure changes. In patients with dilated myocardopathy, a benefit in survival had been observed after 6 months of pentoxifylline administration (21). Compared to healthy controls, patients had reduced LV end-systolic volume and higher LVEF, which further confirms that patients with decompensated cirrhosis have a systemic arterial territory of low resistance (31-35). Free supra-hepatic venous pressure was slightly higher than usually reported. However, it is of note that the same observer (TH) had performed the measurements in all but one of the patients, and there were no significant reductions in HPVG following pentoxifylline administration.

The reduction of the cardiac index after pentoxifylline treatment might in part be explained by a reduction in preload or by a negative chronotropic effect, since central venous pressure, FSHVP, and heart rate were reduced with treatment. The markers of inotropic function, such as LV stroke volume, LVEF% and LVWI, remained unchanged. In addition, there were no reductions of surrogate markers of effective arterial blood volume, such as PRA or PAC, following treatment with pentoxifylline. The dose of diuretics throughout the study cannot explain this difference as they were similar between groups. Therefore, the effect on the systemic vascular resistance index may be secondary to a reduction in cardiac index, without significant changes in arterial effective blood volume.

There was no reduction in splanchnic arteriolar vasodilation (as measured by superior mesenteric arterial blood flow) in patients treated with pentoxifylline.

Liver function improved in both treatment and placebo groups. This was due, most likely, to the abstinence from, or substantial reduction in, alcohol intake that most patients declared to have maintained during the trial. We were unable to detect any specific clinical benefit of pentoxifylline on liver function.

Although the mechanism underlying hemodynamic improvement is unknown, the amelioration of hepatic function observed in treatment as well as in placebo groups is unlikely to account for the hemodynamic improvement, as this had been significant only in the pentoxifylline group. In addition, we could not demonstrate that inhibition of TNF-α synthesis contributed to this improvement, as indicated by a lack of significant reduction in sTNF-α-R1 in the pentoxifylline group.

The intravenous administration of pentoxifylline reduced portal pressure in an experimental model (36), and intra-variceal pressure in cirrhotic patients by decreasing blood viscosity (23). We did not observe any reduction in portal pressure or in upper mesenteric blood flow following the chronic administration of pentoxifylline. Two additional studies published in abstract form revealed conflicting results, i.e., no effect on portal pressure or splanchnic hemodynamics (37), or a modest reduction by 13.6% in portal pressure with no effect on systemic hemodynamics (38). In experimental studies with portal-vein-ligated rats and with CCl4-induced cirrhosis in rats, there were no effects on mean arterial pressure, cardiac output, peripheral resistance, portal venous flow, hepatic artery flow, or portal-systemic shunting in either group of rats with portal hypertension; although there had been a reduction of portal pressure in cirrhotic rats (39). However, the intravenous doses of pentoxifylline used in the experiments were much higher than those used in clinical practice.

In an open-label study, Austin et al. (40) showed no effect of pentoxifylline on portal pressure or systemic hemodynamics in 9 patients, whereas thalidomide (another inhibitor of TNF-α) induced a significant reduction in portal pressure. However, there had been 7 dropouts from the study, and patients had received treatment for only two weeks despite documentation indicating that clinical benefit only becomes apparent after the second week of treatment (20). Another reason for these discrepancies may be the different doses used; pentoxifylline may decrease viscosity at low-dose levels while hemolysis may be induced at higher concentrations (36). Conventional doses of pentoxifylline were used in the present study. Although blood viscosity measurements were not performed, any reduction of viscosity would, according to Poiseuille’s law, decrease systemic vascular resistance rather than cause an increase. Further, any reduction in blood viscosity would be associated with an increase in blood velocity. However, such changes in peak blood flow velocity were not detected by Doppler measurements. As such, it is unlikely that rheological changes were relevant in causing the hemodynamic changes observed.

Pentoxifylline has been shown to improve survival in patients with severe alcoholic hepatitis (20). However, the population of our study is not comparable to that studied by Akriviadis et al., since only patients with a Maddrey discriminant function > 32 were included in the trial by Akriviadis et al. while only 12 of 24 patients in our trial had a MDF > 32.

The external validity of our trial may be compromised because of our stringent inclusion criteria. Clinical presentation of advanced cirrhosis often includes renal dysfunction, encephalopathy or bacterial infection, all of which were exclusion criteria in our trial. Although there were no dropouts, 2 patients in the pentoxifylline group were unable to tolerate treatment, and 1 required a 50% reduction in overall dose. In clinical practice, a gradual escalation of the dose to improve tolerance and compliance might be more appropriate in future studies addressing efficacy and tolerability for this drug.
In summary, pentoxifylline has no significant effect on short-term or long-term survival, cardiac function, splanchnic circulation, or portal pressure.

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REFERENCES


