Berberine nanomicelles attenuate cirrhotic cardiomyopathy induced by bile duct-ligation in a rat model: Possible involvement of NO-cGMP signaling

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Research Objectives: Cirrhosis is associated with cardiac chronotropic and inotropic dysfunctions, which are known as cirrhotic cardiomyopathy. In this condition, a rise in pro-inflammatory cytokines results in up-regulation of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) overproduction. cGMP is a NO-induced effector molecule. Berberine (BBR), an isoquinoline-derived alkaloid isolated from *Rhizoma coptidis*, possesses anti-inflammatory and anti-oxidative effects. However, poor bioavailability and short half-life have limited its clinical applications. Accordingly, this study aimed to examine effect of BBR loaded micells in cirrhotic cardiomyopathy in a rat model of bile duct-ligation (BDL) and further to clarify possible NO-cGMP role.
Methodology: BBR-loaded micells contained 0.3 mg/mL of the drug. Three days following BDL induction, the rats were orally treated with nanoberberine (50 mg/kg, p.o.), BBR (50 and 100 mg/kg, p.o.) and silymarin (100 mg/kg, p.o.) for 28 consecutive days. To clarify the role of NO-cGMP, a selective iNOS inhibitor, aminoguanidine (AG) 100 mg/kg, i.p., on days 14-28, was administered. Moreover, expression of iNOS in the left ventricle and nitrite concentration in plasma were calculated using immunohistochemistry (IHC) and Griess reagent methods, respectively. Ventricular tumor necrosis factor alpha (TNF-α), interleukin -1beta (IL-1β) and cGMP were measured using ELISA method.
Findings: Ventricular TNF-α, IL-1β, iNOS, cGMP, and serum nitrite increased significantly in BDL rats. In contrast, BBR, nanoBBR and silymarin treatments markedly lowered their levels. AG increased nanoBBR50 mg/kg effect and it significantly had lower levels of the cardiac markers compared with nanoBBR 50 mg/kg.
Conclusion: NanoBBR restored impaired cardiac markers and its effect was in a significantly lower dose in comparison with BBR and silymarin. NanoBBR probably improve the cardiac state by down regulations of inflammatory mediators. As a result, a decrease in iNOS, nitrite and cGMP was observed. Consequently, this effect could be mediated at least in part by NO-cGMP pathway.

KeyWords: Cirrhotic cardiomyopathy; Bile duct-ligation; nanoberberine; NO- cGMP; rat.