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Medical treatment for hepatopulmonary syndrome: a systematic review

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ABSTRACT

Introduction: Hepatopulmonary syndrome (HPS) is known as a chronic liver disease associated with severe pulmonary deoxygenation due to intrapulmonary vascular vasodilation. Although liver transplantation is accepted as a main treatment of HPS, identifying effective drugs for recovery of HPS can be effective in postponing the transplantation and decreasing the mortality rate of patients before the transplantation. In this study we briefly reviewed the pathogenesis of HPS and also systematically reviewed the current pharmacological treatment of HPS.

Method: Pubmed, Scopus, and Google scholar were searched for the relevant English language clinical and experimental articles about the medications used in the treatment of HPS.

Results: A total of 38 articles were included in this study which mostly resulted in decreasing NOS expression, NO production, endothelin-1 activation, intrapulmonary angiogenesis and increasing oxygenation.

Conclusion: Various drugs have been proposed in treatment of HPS but more large controlled trial studies, is necessary to determine the exact efficacy of each drugs for HPS recovery.

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Introduction

Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is known as a liver disease associated with pulmonary gas exchange disturbances which

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results in arterial hypoxemia and evidence of intrapulmonary vascular dilatations. The diagnosis of HPS is based on the presence of arterial deoxygenation, liver disease, and pulmonary vascular dilation (1). HPS can be diagnosed mostly in patients with liver cirrhosis. Acute liver failure such as fulminant hepatitis A and ischemic hepatitis are other diseases which can increase the occurrence rate of HPS. Due to lack of certain diagnosis benchmarks, the prevalence of HPS can vary in a wide range from 4% to 33% (2).

HPS was firstly described by Kennedy and Knudson in 1997 which was characterized by hypoxemia as a major consequence of vascular vasodilation (3). Although liver transplantation can be proposed as the main therapeutic strategy of HPS which have shown the most efficacy in treating HPS patients, pharmacological treatments can also result in beneficial effects not only as a bridge to transplant but also as an ultimate treatment of HPS. Here we aimed to briefly review the pathophysiology of HPS and then systematically review the current evidence for applying medical therapies as a therapeutic approach for patients with HPS.

Method

This review is conducted based on the PRISMA guideline. PubMed and SCOPUS, and Google scholar were searched for all the English language literature. Two authors performed the literature search separately without time limit. All the human and animal studies are included in this review, only language limitation was considered in our search strategy. All the obtained articles were studied and appraised for the inclusion in the study.

Inclusion criteria

All the clinical trials, experimental studies, and case reports which evaluated the beneficial effects of any specific drug in treating the HPS were included in this review. All the studies which considered the efficacy of liver transplantation and other nonmedical strategies were not included. All the editorials, hypotheses, genetically studies, and unpublished reports were excluded.

Results

Total of 451 studies were retrieved according to our search strategy. After exclusion the irrelevant articles including those which were not match with the purpose of our review, and irrelevant types of articles such as editorial, only 39 articles were included in our study. Results obtained from the included articles are summarized in different subsections.

Pathophysiology

The exact pathogenesis of HPS is still unclear. Inequality of ventilation/perfusion ration (V/Q), pulmonary shunt (right to left shunt), and gas transferring limitation are three possible pathological factors responsible for pulmonary complication in HPS patients. These three factors are mainly resulted from irregular intrapulmonary vascular dilatation and also increased numbers of these dilated vessels (4). Nitric oxide synthesis, pulmonary angiogenesis, and endothelin-1 are the main factors responsible for pulmonary vascular bed alternations in HPS patients and also the target of various treatment strategies. The major underlying molecular mechanism responsible for the further alternations during the HPS might be the overexpression of TNF-alpha due to endotoxin shock (5) and overexpression of endothelial and inducible nitric oxide synthase which leads to over production of nitric oxide as a major vasodilator factor in HPS (6). Several clinical symptoms can be mentioned according to literatures including: dyspnea, platypnea, orthodeoxia, spider nevi, and finger clubbing (7).

Pathogenesis and mechanisms of hypoxia

Nitric oxide

Nitric oxide as an effective endogenous vasodilator which relaxes the smooth muscles cells is over-produced from L-arginine through the activity of NO synthase. Based on clinical and experimental studies, overproduction of NO is proposed as a responsible mechanism of HPS development (6). Exhaled NO evaluated was three times higher in patients with HPS compared with normal patients (8). It is also demonstrated that the NO concentration would be increased in patients with chronic liver disease and cirrhotic patients prone to HPS development and an important role in oxygenation is also suggested for NO (9-11). In cirrhotic rats increased level of microphagous is accounted for increased level of NO synthase (6).

Pulmonary capillary proliferation

Intrapulmonary vasculature angiogenesis is another vasculature alternation of vasculature bed due to cirrhosis and HPS. Aggregation of monocytes due to increased phagocytosis of bacterial endotoxin can induce the intrapulmonary vascular angiogenesis through higher activity of endothelial growth factor and its subsequent mechanisms (12). Although the mentioned mechanisms are responsible for increased angiogenesis of pulmonary capillaries, genetic condition might also affect the regulation of vascular proliferation (13).

Endothelin-1

Increased level of plasma endothelin-1 and over expression of endothelin-B receptor are involved in vasodilation and pathogenesis of HPS (14,15). According to the experimental and clinical studies endothelin-1 can induce the nitric oxide synthase activity and eventually the nitric oxide production which leads to the development of HPS (16).

In this study current pharmacological therapies used in clinical investigations for limiting the pathogenesis mechanisms underlying HPS are discussed and summarized in Table 1.

Table1. Clinical investigation on pharmacological treatments of HPS

Author Reference	Patients characteristics	Drug	Dose	Outcome
Nakos (67)	6 male patients with hepatic cirrhosis Mean age: 51 years	Almitrine bismesylate	At doses of 50 mg orally, twice a day for 4 days	Increased pulmonary vascular resistance Increased pulmonary artery pressure Increased alveolar arterial oxygen content difference and shunt fraction
Milhe (64)	1 man with dyspnea, hypoxemia, and respiratory alkalosis Age: 51 years old	Almitrine bismesylate	One hour intravenously infusion of 2 mg/kg/day for 2 days and then 50 mg twice daily orally for 3 month	Improvement of PaO2,exercise aggravated Dyspnoea and respiratory alkalosis persisted
Krowka (65)	5 patients (2;3) women Age: 28-58 years old with hypoxemia and chronic liver disease	Almitrine bismesylate	Starting dose: 50 mg orally twice a day for 3 days. Increased to 100 mg orally twice a day for 5 weeks	Improvement of PaO2
Caldwell (33)	1female patient with Cirrhosis, Age: 60 years old	Garlic	4 teaspoons 4 times/day for 4 months	Improvement of cyanosis Increased PaO2
Abrams and Fallon (35)	15 cirrhotic patients (7;8)	Garlic	2 Capsule (500mg) 2 times/day for 6 month	Deceased Alveolar–arterial gradien Decreased dyspnea on exertion

Sani (36)	15 (10;5) pediatric patients with cirrhosis Age: 9.4 years old	Garlic	0.5–2 g/1.73 m 2 per day for 4 weeks	Increased PaO2 Improvement of dyspnea
De (37)	41 cirrhotic patients, 21 patients received garlic, 20 received placebo Age: 37.6 years old	Garlic	1 capsule (250mg) 2 times/day for 18 months	Increased PaO2 Deceased Alveolar–arterial gradient Reversal of HPS in 14 from21 patients
Krug (60)	1 female patient with alcoholic cirrhosis Age: 46 years old	Inhaled Iloprost	30 μg/day Nebulized for 2 months	Decreased subjective dyspnea Increased exercise tolerance Increase in PaO2
Maniscalco (43)	1 male patient with-cryptogenic cirrhosis Age:31 years old	L-NAME	8 mg/kg in normal saline intravenously for 5 minutes	Decreased NO production No improvement in arterial oxygenation
Gomez (44)	7 male, 3 female with cirrhosis and HPS Age: 60 years old	L-NAME	Single dose, 162.0 mg dissolved in 4.0mL 0.9% saline over 12 minutes	Decreased exhaled NO Increased systemic vascular resistance No change in ventilation/perfusion mismatch, intrapulmonary shunting, and arterial oxygenation
Brussino (45)	64-year-old man with HPS associated with hepatitis-C-virus-related cirrhosis	L-NAME	m 99·5 mg of inhaled L-NAME in 3 mL ⁄90 saline	Improved oxygenation
Rolla (29)	1 female with alcoholic cirrhosis. Age: 45 years old	MB	3mg/kg intravenous one dose	Improvement in PaO2 Improvement in O2 saturation
Schenk (32)	5 male, 2 female with liver cirrhosis	MB	3mg/kg intravenous, one dose	Improvement of PaO2 Improvement of A-a PaO2 Increased mean pulmonary arterial pressure and pulmonary vascular resistance
Jounieaux (31)	1 male with alcoholic cirrhosis Age: 61 years old	MB	3 mg/kg intravenous, one dose	Increased mean pulmonary arterial Pressure No change in shunt fraction
Roma (30)	1 female with liver transplant patient for AIH Age: 15 years old	MB	3mg/kg intravenous, one dose	Increased O2 saturation As abridge for weaning of from ventilator
Moreira Silva (51)	1 male with autoimmune lympho proliferative Syndrome Age:13 years old	MMFL	500 mg twice/day for 9 month	Improvement of cyanosis, clubbing, and spider nevi Normalization of PaO2 No need for supplemental oxygen Improvement of intrapulmonary shunt
Anel and Sheagren (40)	1 man with Cirrhosis Age:44 years old	Norfloxacin	400 mg 2 times/ day for 4 weeks	Increased O2 saturation Resolution of platypnea and orthodeoxia
Gupta (41)	8 men and 3 women with Cirrhosis Age: 69 years old	Norfloxacin	400 mg 4 times/ day for 1 month	No improvement in HPS
Yilmaz (54)	1 man with noncirrhotic portal hypertension Age: 18 years old	Paroxetine	20 mg/day for 6 months	No improvement in HPS
Gupta (27)	5 men and 4 women with liver cirrhosis Age: 40 years old	PTX	400 mg 3 times/ day	Improvement of clinical symptoms Improvement of PaO2 Decreased TNF-α
Kianifar (26)	10 pediatric patients (6;4) with cirrhosis Age: 9.2 years old	PTX	20 mg/kg/day for 3 months	Increase in PaO2 and A-a PaO2 Improvement of O2 saturation No Improvement in Clinical symptoms
Tanikella (25)	9 cirrhotic patients (3;6) Age:55 years old	PTX	400 mg/day (1week) 400 mg twice/day (1 week) 400 mg 3 times/ day (42 days)	No significant change in PaO2 No significant change in A-a PaO2 No significant change in TNF-α

Krowka (61)	22 patients (12;10) with cirrhosis or chronic active hepatitis (8 patients received the drug)	Somatostatin analogue	150 μg every 8 hours subcutaneously for 4 days	No improvement in subjective dyspnea No improvement in arterial Oxygenation at the end of study
Theysohn (56)	4 patients (3;1) with advanced hepatocellular carcinoma Aage: 64.1 years old	Sorafenib	Maximum daily dose of 800 mg orally for 138 days	Mild to moderate diarrhea, nausea, and fatigue Reduction of HPS

Pharmacological treatments and management of HPS

Pentoxifylline

Pentoxifylline[1-(5-oxohexyl)-3,7-dimethylxanthine;PTX], is a nonspecific phosphodiesterase inhibitor derived from methylxanthine. The inhibitory effects of pentoxifylline on cytokines production lead to different anti-inflammatory and immunomudulatory outcomes. According to different studies, administrating pentoxifylline has revealed beneficial outcomes on proteinuria by reducing the monocyte chemoattractant protein (MCP)-1(17). Suppressing the granulocyte-macrophage colony-stimulating factor (GM-CSF) (18), intercellular adhesion molecule-1 (19), serum levels of interleukin-6 (IL-6), hepatic stellate cells (HSCs) proliferation (20), blood viscosity, increasing erythrocyte flexibility, microcirculatory flow, and tissue oxygen concentration are dose dependent effects of PTX (21). The therapeutic function of PTX on vascular dementia, alcoholic hepatitis, and hepatorenal syndrome, has been also proposed in various studies (22,23).

Based on clinical and experimental studies on lung diseases and liver fibrosis, pentoxifylline has favorable effects by selectively restricting the circulating tumor necrosis factor-alpha (TNF-α) expression in inflammatory cells. Through several experimental and clinical studies, the efficacy of application of PTX and the underlying mechanisms are investigated during the HPS and PTX is suggested as a potent therapeutic strategy. Experimental studies which were mostly on HPS induced rats by common bile duct ligation (CBDL) showed that PTX could act through diminishing the aortic NO overproduction by suppressing the blood TNF- alpha to prevent the development of HPS. According to these studies increased levels of TNF-alpha is a result of macrophages activation or bacterial translocation. Sztrymf et al resulted that PTX can decrease the number of macrophages by macrophages sequestration, which produced TNF-alpha in cirrhotic rats, but did not reveal any bacterial translocation changes. The suppression of TNF led to reduced activity of NOS which is proposed as the main reason for preventing HPS in cirrhotic rats treated with PTX. According to this study prophylactic administration of PTX will be beneficial in liver cirrhosis (6). These results are confirmed in another experimental survey with the same protocol by applying 50 mg/kg/day PTX 1 week after CBDL for 2 weeks. PTX led to down-regulation of endotelin B receptors, NOS expression and activation, and monocytes accumulation which reduced the following molecular cascade including TNF-alpha and NF-κB and AKT activation (24).

Although PTX application has become beneficial during experimental studies, its efficacy on human is not clear. Nausea and vomiting are observed as the major side effects of PTX on patients with advanced HPS, which reduced its tolerability. In one pilot trial PTX was not successful in improving the arterial oxygenation and declining the TNF-alpha levels which might be due to dose limiting gastrointestinal toxicity, severe HPS in patients, and intense oxygenation abnormalities compared with

experimental models (25).

Unlike the mentioned study, kianifar et al revealed significant increase in arterial oxygenation of pediatric patients at early stages of HPS after 3 months treatment with 20 mg/kg/day PTX in a pilot trial (26). Similar results obtained in another study by applying 400 mg PTX 3 times a day in cirrhotic patients with HPS and a considerable reduction was also observed in their TNF-alpha after the treatment (27).

Methylene blue

Methylene blue is an oxidizing factor and acts as another inhibitor of NOS and nitric oxide on guanylate cyclase which might be useful in preventing the pulmonary vasodilation in patients with HPS. The therapeutic capacity of methylene blue has been previously investigated in patients with septic shock and refractory shock, and methemoglobinemia. In patients with cirrhosis or hypotension, application of methylene blue has been able to rise the blood pressure (28). In 3 different case reports patients with alcoholic cirrhosis or cirrhosis due to autoimmune hepatitis who had HPS, intravenous injection of 3 mg/kg methylene blue, increased the arterial oxygenation which resulted in significant decrease of pulmonary shunting (29-31).

Although continues application of methylene blue results in some adverse effects such as cardiovascular, dermatologic, and gastrointestinal complications, its temporary administration might have beneficial effects on arterial oxygenation of hypoxemic patients with HPS (30). Improvement of arterial oxygenation and hypoxemia is also shown by administrating one bolus of 3 mg/kg methylene blue in one controlled trial on 7 patients with cirrhosis and HPS (32). Application of intravenous methylene blue revealed beneficial effects in reducing cardiac output, pulmonary artery pressure, improving systemic vascular and pulmonary vascular resistance (32).

Garlic

Garlic (Allium sativum L.) is not only a food but also a medicinal herb which can be applied as medical supplementation. It is mostly used for hearth diseases, lowering blood pressure, rheumatoid arthritis, applied as an antibiotic. Since 1992, in different articles the efficacy of garlic has been investigated on patients with HPS. Improving the cyanosis, oxygen saturation are the proposed consequences of administrating garlic powder by a patients with HPS which let to further investigations (33,34). In one pilot trial, applying one capsule of garlic per day revealed increased arterial oxygenation which were with unclear responsible mechanisms (35).

Arterial oxygen saturation was also increased in pediatric patients who applied 1 capsule of garlic every day (36). Unlike the previous mentioned medication (PTX and methylene blue) one recent randomized controlled trial has been performed on the efficacy of garlic on HPS patients. In this regard improved arterial oxygenation, reversal of intrapulmonary shunts, and decreased mortality rate was resulted in treatment group compared with controls (37).

Norfloxacin

Norfloxacin is an antibacterial agent (a potent fluoroquinolone antibiotic eliminates the gram-negative bacteria) which might be effective in preventing bacterial translocation that leads to endotoxemi and eventually results in increased activation of NOS in pulmonary intravascular macrophages (38). Based on literature suppressing the bacterial translocation can be helpful in preventing HPS. 5 weeks application of norfloxacin resulted in decreased translocation of gram-negative bacteria, reduced pulmonary microvessels with macrophages, normalized

the activity of inducible NOS in rats with CBDL induced cirrhosis. According to this experimental investigation, norfloxacin application can suppress the severity of HPS (39). To investigate the effectiveness of norfloxacin in clinical situation, a cirrhotic patient with HPS was treated with 400mg 2 times a day oral norfoxacin for four month, which resulted in improvement of patients hypoxemia (40). In a recent randomized controlled trial, controversial results were obtained and showed no significant improvement of HPS symptoms which necessities performing larger clinical trials on the efficacy of norfloxacin (41).

NG-nitro-L-arginine methyl ester (LNAME)

L-NAME is known as an NOS inhibitor which is widely applied in biological surveys (42). According to one experimental study, 5 mg/kg/day application of L-NAME in CBDL induced rats for 6 weeks, decreased the NOS activity and prevented the HPS in animal models (6). Because of the considerable effect of L-NAME on NOS activity its efficacy is investigated on HPS patients. According to one case report, although administering L-NAME reduced the exhaled NO and cardiac output of the patient with HPS, no significant improvement was observed in patient's arterial oxygenation (43).

These results are confirmed in another clinical study on 10 patients with HPS and suggested that oxygenation abnormalities in HPS condition might be mainly due to pulmonary vasculature remodeling than vascular vasodilation as a result of over production of NO (44). In contrary, in one case of HPS, using L-NAME, increased the arterial oxygenation (45).

Quercetin

Quercetin is among flavonoids (polyphenols) are known as antioxidant agents which are widely distributed broad spectrum of vegetables and fruits including apple, broccoli, crowberry, blueberry, tea, onion, etc. (46). Quercetin has been used in experimental study to investigate its possible effects on free radicals due to hypoxemia during the HPS. In the study of Tieppo et al. on cirrhotic induced rats quercetin application resulted in reduced DNA damage and increased the genomic stability of the animal models which might be due to its antioxidant properties (47). Similar results were obtained in anothe experimental study on induce cirrhotic rats due to CBDL. In this study, application of quercetin resulted in diminished oxidative stress, reduced NF-kB expression as a mediator of HPS development (48). Results obtained through experimental studies are necessary to be investigated on human.

Mycophenolate Mofetil (MMF)

MMF acts as an immunosuppressive agent which is used in treatment of autoimmune diseases. According to some experimental studies, MMF might be useful in suppression of cytokines necessary NO production, including TNF-alpha and INF (49). MMF reduces the NO production and angiogenesis through inhibition of inosine monophosphate dehydrogenase (IMPDH)-dependent synthesis, guanosine nucleotide-dependent expression of iNOS gene, and ET-1 synthesis in endothelial cells (50). In one patient with HPS and severe hypoxemia, applying MMF increased oxygenation and decreased intrapulmonary shunt and eventually improved HPS and associated clinical sings (51). Clinical trials are needed to exactly reveal the MMF efficacy in HPS.

Paroxetine

Paroxetine is used as an antidepressant drug which is among selective serotonin reuptake inhibitors. It is also proposed as a novel NOS inhibitor which results in decreased NO

production (52,53). The efficacy of paroxetine in improving HPS is investigated in one case report with a patient with idiopathic portal hypertension. Paroxetine was administered orally for six month at the dose of 20 mg/day. Although paroxetine is NO-reducing agent, no progression was achieved regarding the patient oxygenation (54).

Sorafenib

Sorafenib is known as an inhibitor of tyrosine protein kinases such as vascular endothelial growth factor receptors (VEGFR), VEGF, and various signaling cascades. It is also used as a treatment of hepatocellular carcinoma (HCC) which reduces the tumor cell proliferation and angiogenesis. In an experimental study sorafenib was used as an anti-angiogenesis therapy in CBDL induced HPS rats. Increased oxygenation, decreased intrapulmonary shunting, reduced plasma VEGF concentrations and AKT protein expression were achieved by applying sorafenib which eventually decreased intrapulmonary angiogenesis and improved HPS (55). Similar results were obtained in a retrospective clinical study which proposed beneficial effects for sorafenib in improving HPS of patients with HCC (56).

Iloprost

Iloprost is a prostacyclin analogue which has been highly effective for the treatment of pulmonary hypertension as a potent pulmonary vasodilator in human (57). Dramatic increase of pulmonary vascular resistance, headache, flushing and jaw pain are the reported adverse effects of applying iloprost (58,59). Improvement of HPS, decreased clinical symptoms, and hypoxemia is observed by applying iloprost after the transplantation (60).

N-acetylcysteine

N-acetylcysteine is as an antioxidant factor and thiolic compound, inhibits reactive oxygen species and has antigenotoxic effects. Reversed vasodilation and improvement of oxygenation, are reported as results of applying N-acetylcysteine. In one experimental study on HPS induced rats by CBDL, administering n-acetylcysteine resulted in beneficial effects on HPS animal models by suppression of NO production and DNA damages.

Somatostatin analogue

Applying somatostatin analogue is studied only in one retrospective clinical study. According to this study no significant improvement of arterial oxygenation and other clinical sings were observed in patients with HPS (61).

Caffeic acid phenethyl ester (CAPE)

According to articles CAPE can lead to inhibitory effects on NOS gene expression and activation (62). This effect is investigated in one experimental study on HPS induced rats by CBDL and resulted in improvement of HPS through reduction of plasma NO concentration (63).

Almitrine bimesylate

Almitrine bimesylate is a pulmonary vasoconstrictor which thought to be effective in reducing intrapulmonary vascular vasodilation of HPS. In one case report administrating this medication was successful in increasing oxygen saturation and improving the HPS symptoms (64). This achievement of almitrine bimesylate administration did not observed in all the patients of the study conducted by krowka et al. and the improvement was observed only in one patient (65).

Corticosteroids

In 2006, applying corticosteroids as a treatment of HPS in one case with idiopathic granulomatous hepatitis resulted

in reversion of HPS by refining the portal hypertension, improving of oxygenation and reducing dyspnea (66).

Conclusion

Although various drugs have been proposed in treatment of HPS, Each medication is only studied through case reports or small trials, so revealing an effective therapeutic modality is essential to be based on powerful evidence. A major limitation regarding the applied drugs is the lack of large sample size randomized placebo controlled trials which are needed to carefully investigate the efficacy of medications especially for PTX, MB, and MMF.

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Conflict of Interest

The authors declare no conflict of interest.

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