The Use of Citrulline for Pediatric Pulmonary Hypertension

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Abstract

Pulmonary hypertension can be diagnosed at all ages and characterized by increased vascular resistance in the lungs. Pulmonary hypertension in the pediatric population is less studied than in adults with much of the therapy extrapolated from adult data. Suboptimal survival rate of patients with pulmonary hypertension and the economic impact this disease has on the healthcare system warrant the need for new therapeutic options, such as citrulline. Citrulline is a non-essential amino acid involved in the urea cycle, which ultimately converts to nitric oxide to help dilate the pulmonary vasculature. Based on the available animal and few human studies, citrulline can potentially be a preventive remedy for pediatric patients at high risk of developing pulmonary hypertension after undergoing congenital cardiac surgery. However, new clinical trials are needed before using citrulline as a standard treatment option and incorporating it into practice guidelines.

Keywords

Citrulline; Pediatrics; Pulmonary hypertension

Introduction

Pulmonary hypertension (PH) is a disease characterized by increased vascular resistance of the arteries, veins, or capillaries in the lungs thereby increasing the workload on the heart [1]. PH can be diagnosed in all age groups by measuring a mean pulmonary arterial pressure and/or a pulmonary capillary wedge pressure. Patients with PH have a pulmonary arterial pressure greater than 25 mmHg after 3 months of life, and a pulmonary capillary wedge pressure of 15 mmHg or less with cardiac catheterization [1-4]. PH can also be considered when systolic pulmonary artery pressure is greater than half of the systemic systolic pressure [5].

The leading etiologies of PH in the pediatric population include idiopathic pulmonary arterial hypertension (IPAH), pulmonary arterial hypertension (PAH) associated with congenital heart disease, and pulmonary hypertension of the newborn (PPHN) [2]. The incidence and prevalence of pediatric PH is not well defined in the United States. The United States Registry to Evaluate Early and Long-term Pulmonary Hypertension Disease Management (U.S. REVEAL) registry enrolled approximately 210 pediatric patients with PH from 2007 to 2010 with a median age at diagnosis of 7 years old of which 64% were female patients [6].

Without treatment, the prognosis of PH is poor. According to the National Institutes of Health registry, adult and pediatric patients with PH only have a median survival rate of 10 months after diagnosis if treatment is not initiated [7]. After the development of targeted therapies, the survival rate of pediatric patients diagnosed with this clinical condition has improved. The REVEAL registry showed that the 1-, 3- and 5-year estimated survival rates of children on therapies were 96 ± 4%, 84 ± 5% and 74 ± 6%, respectively [8]. Although the overall survival is better in this modern therapeutic era, pediatric patients still die from this disease each year, justifying a strong need for new preventive and therapeutic treatment options for PH.

Besides the suboptimal survival rates of pediatric patients with PH, the economic impact this clinical condition has on the healthcare system is another reason that warrants new preventive/treatment options. According to the REVEAL registry, 30% and 13% of patients are on either dual or triple therapy to manage this disease, respectively [8]. The cost of these target therapies can be expensive and most of the available cost data are in adults (Table 1). The cost of management for persistent pulmonary hypertension of the newborn was evaluated at the Children's Hospital of Philadelphia between 1991 and 2002 [9]. The cost of conventional treatment averaged $41,609 for each inpatient stay with an incremental cost of $1,141 if inhaled nitric oxide was utilized. Lastly, a recent retrospective cohort study found that children with PH accounted for 0.13% of the 43 million pediatric hospitalizations in the United States between 1997 to 2012. A significant increase in the healthcare financial burden from these admissions was observed with a cumulative hospital charges of $926 million in 1997 to $3.12 billion in 2012 (p=0.0003) [10]. Therefore, the economic impact of PH can be enormous and certainly makes a case for the need of new therapeutic options.

Current Treatment Options

The recently published 2015 Pediatric Pulmonary Hypertension guideline from the American Heart Association and American Thoracic Society (AHA/ATS) and the 2013 Pediatric Task Force of the 5th World Symposium on Pulmonary Hypertension outlined pharmacologic treatments for pediatric patients. Treatment options include calcium channel blockers (CCB), endothelin receptor antagonists (ERA), phosphodiesterase 5-inhibitors (PDE5i), inhaled prostacyclins, and nitric oxide [1-3]. It is recommended that the agent of choice should be dependent on the severity and acuity of the PH based on vasodilator testing, level of risk based on symptoms, functional class, ventricular enlargement or dysfunction, and other hemodynamic parameters. Additional treatments with diuretics, oxygen, anticoagulants, and digoxin are management strategies that can be used based on individual patient’s clinical status [2,3]. Table 1 summarizes the current therapeutic options for PH.

The current therapeutic management for PH has several limitations. PH therapy, though well described in adults, remains less studied in the pediatric population. Additionally, current treatment options are limited because recommendations are previously adopted from PH guidelines in adults and based on current pediatric PH experiences [1,2]. In addition, there are currently few treatment
options and less predictable therapeutic response in pediatric PH [2]. As an alternative, the rest of this article will discuss citrulline as a potential therapeutic option for PH in the pediatric population.

Citrulline as a Therapeutic Option for Pulmonary Hypertension

Overview of citrulline

Citrulline or citrulline malate is a non-essential amino acid often used as a dietary supplement. It is currently regulated by the United States Food and Drug Administration (FDA), but it does not require FDA approval as with other dietary supplements. It is available in tablets and powder formulations sold as supplements in retail pharmacies, health-food stores, and by hospital vendors and suppliers [11].

The L-form of citrulline naturally occurs and can be acquired from food or synthesized in the intestinal mucosa [11]. Watermelons are found to contain high levels of L-citrulline in the amount of 0.7-3.6 mg per gram of fruit [12]. Dietary intake and endogenous sources of L-citrulline pass through the liver unchanged [11,13,14]. It is converted in the kidneys to L-arginine which is then released into the systemic circulation. L-arginine undergoes metabolic reactions in the endothelium of blood vessels to form nitric oxide and regenerates L-citrulline in the process [14]. Supplementation with L-citrulline may be preferable to L-arginine, because L-citrulline is not metabolized in the liver [11] and therefore has a higher oral bioavailability making it a better option in restoring nitric oxide production [14].

Citrulline has been used safely in infants at a dose of 0.17 grams/kg/day for up to 20 months in 2-year-old patients with lysinuric protein intolerances [15]. Recently, citrulline has also been used as a therapeutic option for managing pulmonary hypertension in pediatric patients. L-citrulline is proposed to reduce pulmonary hypertension by increasing the level of arginine and endogenous nitric oxide production. Nitric oxide then dilates the pulmonary vasculature thereby improving blood flow to the lungs [14,16-18]. Additionally, L-citrulline may modulate endothelial nitric oxide synthase (eNOS) coupling. Uncoupled eNOS is believed to be one of the signaling problems that causes reduction in nitric oxide production found in chronic pulmonary vascular diseases such as PH [19-21].

Table 1: Current and Investigative Therapeutic Options for Pulmonary Hypertension in the Pediatric Population [15-18,30-34,36-44].

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>MOA</th>
<th>Adverse Effects</th>
<th>Costs (AWP)</th>
</tr>
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<tbody>
<tr>
<td><strong>CCBs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Amlodipine*</td>
<td>Oral: 1-6 y/o: ID: 0.05-0.1 mg/kg/day; 6-17 y/o: 2.5-5 mg qd</td>
<td>Inhibits slow calcium channels of vascular smooth muscle and myocardium during depolarization, producing coronary vascular smooth muscle relaxation and coronary vasodilation</td>
<td>Fatigue, dizziness, hypotension, palpitations, headache, bradycardia</td>
<td>Amlodipine 2.5 mg (90 tabs) or 5mg (90 tabs)= $155.68</td>
</tr>
<tr>
<td>Diltiazem*</td>
<td>Oral: ID: 1.5-2 mg/kg/day in 3 divided doses Max: 6 mg/kg/day, up to 360 mg/day</td>
<td></td>
<td>As-needed</td>
<td>Diltiazem 30 mg (100 tabs)= $44.94</td>
</tr>
<tr>
<td>Nifedipine*</td>
<td>Oral: 1 to 17 y/o: ID (ER tablet): 0.25 to 0.5 mg/kg/day or in 2 divided doses Max: 3 mg/kg/day up to 180 mg/day</td>
<td></td>
<td>Nifedipine: peripheral edema</td>
<td>Nifedipine ER 30 mg (100 tabs)=$139.40</td>
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<tr>
<td><strong>ERAs</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ambrisentan</td>
<td>Oral: ≤ 20 kg: 2.5 mg/day ≥ 20 kg: 5 mg/day Max: 10 mg/day</td>
<td>Blocks endothelin receptor subtypes</td>
<td>Chest pain, edema, flushing, hypotension, headache, palpitations, syncope</td>
<td>Ambrisentan (Letairis) 5 mg (30 tabs) or 10 mg (30 tabs)= $8,842.73</td>
</tr>
<tr>
<td>Bosentan*</td>
<td>Oral: Fixed dosing: Infants ≤ 7 mo and Children: 5 to &lt;10 kg: ID of 15.6 mg/day x 4 ws; MD of 15.6 mg BID 10 to 20 kg: ID of 31.25 mg/day x 4 ws; MD of 31.25 mg BID &gt;20 to 40 kg: ID of 31.25 mg BID x 4 ws; MD of 62.5 mg BID &gt;40 kg: ID of 62.5 mg BID x 4 ws; MD of 125 mg BID</td>
<td>Inhibits ET&lt;sub&gt;α&lt;/sub&gt; receptors, located primarily in pulmonary vascular smooth muscle cells, leading to vasodilatation of the pulmonary vasculature</td>
<td>Chest pain, edema, flushing, hypotension, headache, palpitations, syncope</td>
<td>Bosentan (Tracleer) 62.5 mg (30 caps) or 125mg (30 caps)= $4,932</td>
</tr>
<tr>
<td><strong>PDE5i</strong></td>
<td>Oral: Infants: ID of 0.25 mg/kg/dose Q8H or 0.5 mg/kg/dose Q12H; titrate by 0.5 mg/kg/dose Q4-6H PRN Max: 1 to 2 mg/kg/dose Q6-8H Children and Adolescents: 8 to 20 kg: 10 mg TID &gt;20 kg: 20 mg TID &gt;45 kg: 40 mg TID IV: Infants &gt;60 d/o and Children: LD: 0.04 to 0.35 mg/kg over 5 mins MD: 0.015 to 0.4 mg/kg/h x 24-72h</td>
<td>Inhibits PDE5 in smooth muscles of pulmonary vasculature responsible for the degradation of cGMP, thereby increasing cGMP concentration and resulting in pulmonary vasculature relaxation and vasodilation</td>
<td>Sildenafil 20 mg (90 tabs)= $1,800.26</td>
<td></td>
</tr>
<tr>
<td>Sildenafil*</td>
<td>Oral: 1 mg/kg/day (Max 40 mg/day)</td>
<td></td>
<td>Sinusomal, erythema, headache</td>
<td>Sildenafil 10 mg/mL (112 mL suspension)= $6,561.89</td>
</tr>
<tr>
<td>Vardenafil*</td>
<td>Oral: limited experience in pediatrics</td>
<td></td>
<td>Nausea</td>
<td>Tadalafil (Adcirca) 20 mg (60 tabs)= $3,002.4</td>
</tr>
<tr>
<td><strong>Volume 1 • Issue 1 • 1000101</strong></td>
<td></td>
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<td><strong>Page 2 of 6</strong></td>
<td>Vardenafil (Staxyn) 10 mg (4 tabs)= $98.89</td>
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</table>
Efficacy of citrulline

Animal data: Currently, few studies exist investigating the effects and use of citrulline in animals and humans with pulmonary hypertension. Animal studies using newborn piglets and rats reported promising results to support the use of citrulline for pulmonary hypertension. Fike et al. [22,23] investigated pulmonary arterial endothelial cells and its dependent transport on L-citrulline in newborn piglets. They found a transporter known as Na⁺-dependent neutral amino acid transporter-1 (SNAT-1) expressed on pulmonary arterial endothelial cells and its dependent transport on L-citrulline in pulmonary arterial vasculature.

found increased NO production and PH improvements with oral supplementation of L-citrulline in newborn piglets. The pulmonary arterial pressure and pulmonary vascular resistance were significantly lower in the hypoxic newborn piglets treated with L-citrulline compared to the untreated group [24]. Alveolar growth and PH in newborn rats were studied by Vadivel et al. [25] Hypoxia-induced newborn rats without L-citrulline supplementation had a higher right ventricular hypertrophy when compared to the treated group. Newborn rats treated with L-citrulline were found to have significant increased circulating L-citrulline and L-arginine levels, decreased pulmonary arterial medial wall thickness, and preserved alveolar and vascular growth when compared to newborn rats without treatment [25]. Based on these three animal studies, citrulline was shown to impact nitric oxide signaling and production and improved different pulmonary parameters in newborn animals.

Human data: Investigational studies of citrulline’s effects in humans are limited. In human studies, L-citrulline supplementation safely increased serum citrulline levels, lowered pulmonary pressures, and reduced pulmonary hypertension [17,18]. Researchers observed that plasma levels of citrulline were reduced in pediatric patients after congenital cardiac surgery, and they hypothesized that supplementation with citrulline perioperatively protected against the development of PH. A study by Smith et al. [18] included forty children undergoing cardiopulmonary bypass surgery at risk of developing pulmonary hypertension. They were randomized to either oral L-citrulline 1.9 grams/m² for 5 doses or placebo. The first dose of L-citrulline was given via a nasogastric tube at the induction of anesthesia, followed by doses immediately after surgery and at 12, 24, and 36 hours post-surgery [18]. Oral citrulline supplementation increased citrulline levels safely, and PH did not develop in patients with plasma citrulline concentrations greater than 37 µmol/L (p=0.036). The data also suggested that L-citrulline could reduce the incidence of postoperative pulmonary hypertension from 30% in the placebo group to 15% in the treated group of children 6 years of age or younger status post congenital heart surgery, though no statistical significance was shown. The study also did not control for patients with PH before surgery. The only adverse effect observed with citrulline in this study was hypotension. The hypotension observed was adequately treated with either volume resuscitation and/or pharmacological therapy with no major events in the trial [18].

Barr et al. [17] investigated the pharmacokinetics and safety of intravenous (IV) citrulline in seventeen pediatric patients under 6 years of age undergoing congenital heart surgery as a therapeutic option for postoperative pulmonary hypertension. A target citrulline trough of 80 to 100 µmol/L was used in this study. An intravenous bolus dose of 150 mg/kg followed by 9 mg/kg/hour for 48 hours yielded a citrulline trough within this range. The half-life observed in this study was 60 minutes, the volume of distribution was 0.9 L/kg, and the clearance was 0.6 L/(ht x kg) with a calculated clearance of 0.52 L/(ht x kg). None of the patients had a 20% drop in their mean arterial blood pressure. Also, there were no major adverse events reported in this study that were related to the IV citrulline administration [17]. The IV formulation used in this study was an investigational drug that was prepared as a 50-µg/mL isotonic solution compounded with distilled water [17]. The brand name of this IV formulation is Citrupress®, and it is still under investigation by Asklepion Pharmaceuticals, LLC and is currently unavailable in the United States market [16,26,27].

Besides these aforementioned human trials, there are also two completed studies listed on clinicaltrials.gov that investigated the use of citrulline in children. The postulation for both studies involved the safe increase in plasma levels with IV citrulline supplementation to prevent pulmonary vascular tone, thereby decreasing the duration of postoperative mechanical ventilation hours [26,27]. One of these studies was a phase III single-blind, randomized, placebo-controlled clinical trial exploring the safe and effective use of IV L-citrulline in children undergoing cardiopulmonary bypass surgery [26]. The primary outcome of this study was to evaluate the duration of mechanical ventilation post-surgery between the groups. A secondary outcome was the incidence of a sustained mean pulmonary artery pressure ≥ 20 mmHg for at least 2 hours during the 1st 48 hours of the study period. Seventy-seven patients up to 17 years of age were enrolled in the study. The treatment arm received an intravenous citrulline bolus dose of 150 mg/kg after initiation of the bypass surgery followed by a continuous infusion of 9 mg/kg/hour for 48 hours [26].

The second clinical trial was a double-blind, randomized, placebo-controlled study researching a revised protocol for postoperative IV L-citrulline use to target a plasma citrulline level of > 100 µmol/L in children undergoing surgical septal defect repair of the atrium, ventricle, or antroventricle [27]. Twenty-two patients less than 7 years old were enrolled in the study. This study also had the duration of postoperative mechanical ventilation in hours from the end of surgery until extubation between the treatment and placebo groups as a secondary outcome. Similar to the previous study, the treatment arm was given 150 mg/kg intravenous bolus x1 at the initiation of the bypass surgery. L-citrulline at a concentration of 200 µmol/L was also added to the filtration and hemoconcentration fluids that were used during the surgery. Thirty minutes after the patients were separated from the bypass, a 20 mg/kg intravenous bolus of L-citrulline was given to the subjects followed by a continuous infusion of 9 mg/kg/hr for 48 hours [27]. The data and final results from these two trials are pending and cannot be obtained from the investigators. It will be interesting to see how the results of these studies add to the body of literature supporting the use of citrulline for the prevention of pulmonary hypertension from cardiac surgery in the pediatric population.

Clinical application of citrulline

Citrulline offers benefits for lung cell regeneration, increases nitric oxide production, and improves lung pressures in newborn animals. Based on the current available animal and human studies evaluating citrulline for pulmonary hypertension, it can potentially be used in postoperative cardiac pediatric patients who are at high risk of developing pulmonary hypertension. Factors of high risk for pulmonary hypertension in children include evidence of right ventricular failure, progression of symptoms, elevated B-type natriuretic peptide, right ventricular dysfunction, pericardial effusion, and failure to thrive [2]. Even though these data are promising, more studies with a larger sample size are needed to translate these outcomes into daily clinical practice. In addition, researchers will need to address what is an optimal duration of therapy for this indication.

Another potential investigative area is the use of L-citrulline for treating refractory pediatric pulmonary hypertension. L-citrulline dosed at 150 mg/kg/dose orally or per tube every 6 hours has been used for few patients with refractory pulmonary hypertension at our institution with good outcomes. The citrulline is compounded into an oral solution by weighing 5 g of L-citrulline powder and mixing it with quantity sufficient of sterile water to 50 mL for a final concentration of 100 mg/mL; a beyond-use-date of 7 days is assigned to the product [28]. This dosing, however, is investigational and extrapolated based
on adult data [29]. Well-designed studies are needed before such route and dose of administration can be incorporated into practice guidelines as an adjunct therapy to current medications for the treatment of PH in the pediatric population.

Conclusions

Despite the available therapeutic options for PH in the pediatric population, survival rate is still suboptimal, and the economic impact on the healthcare system is tremendous warranting the need for new therapeutic options such as citrulline. Currently, there are limited human studies investigating citrulline’s efficacy for pediatric PH. Available human studies are only in pediatric patients undergoing cardiopulmonary bypass who were at high risk of developing pulmonary hypertension. Larger studies are needed to evaluate the efficacy and safety of citrulline before implementing it into daily practice for pediatric pulmonary hypertension management.

References


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