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Nebulized nitroglycerin in children with pulmonary hypertension secondary to congenital heart disease

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Abstract

Pulmonary hypertension continues to be a major cause of morbidity and mortality, despite new treatments. Since inhaled nitric oxide has been reported to be effective in some cases, we investigated using nebulized nitroglycerin to treat pulmonary hypertension in children with congenital heart disease. Four children (ages 6-72 months) with severe pulmonary hypertension secondary to congenital heart disease (all with membranous ventricular septal defect, undergoing cardiac catheterization) were given 3 cc of nebulized normal saline over 10 min as placebo control, followed by nebulized nitroglycerine (20µg/Kg in 3cc normal saline). Normal saline administration did not elicit any change, but nitroglycerine administration resulted in the following changes (mean ±SE, paired statistics): systolic pulmonary artery pressure from 68±8 to 53±6 at 10 min into treatment (P 0.006), mean pulmonary artery pressure 47±4 to 38±4 (P 0.005), heart rate 131±8 to 127±7 (P 0.13), systolic blood pressure 85±8 to 88±3 (P 0.7), mean blood pressure 59±6 to 63±4 (P 0.5). These results indicate that nebulized nitroglycerine may be an effective, easy to administer, inexpensive, and safe alternative for treatment of severe pulmonary hypertension in children with congenital heart disease, especially in areas where other treatments such as extracorporeal membrane oxygenation or inhaled nitric oxide are inaccessible.

Introduction

Pulmonary hypertension (PHT) continues to be a major cause of morbidity and mortality in the pediatric age group. One common cause of pulmonary hypertension is congenital heart disease, unless the congenital heart lesions are surgically corrected early in life (1). Conventional therapy with mechanical ventilation is not always effective and use of intravenously administered vasodilators is limited because of the systemic effects, such as hypotension. Extracorporeal membrane oxygenation (ECMO) can be effective, but it is invasive and not feasible in small hospitals and rural areas. The discovery of the endothelium-derived relaxing factor (EDRF, 2) and its identification as nitric oxide (NO, 3) made it potentially possible to use inhaled NO for treatment of persistent pulmonary hypertension.

Reports of beneficial effects of inhaled NO in infants with persistent PHT (4), as well as in children with congenital heart disease (CHD, 5), are promising. Delivery of inhaled NO, however, requires special equipment (5,6) and may also be toxic. Many rural areas in the U.S. and the world have no access to either ECMO or inhaled NO. Nitrovasodilators are believed to release NO during their metabolism (7) and thus their vasodilatory mechanism is similar to that of NO.

In this study, we sought to determine if nebulized nitroglycerine (NTG) can be effective in reducing pulmonary artery pressure without significant change in systemic BP in children with pulmonary hypertension secondary to CHD.

Methods

This study was approved by the Research Administration at Zhejiang Medical University Children's Hospital and consent was obtained for each of the four children, ages 6 months to six years. These children were spontaneously breathing with uncorrected ventricular septal defect and severe PHT undergoing diagnostic cardiac catheterization. Severe pulmonary hypertension was defined as pulmonary artery pressure at least half of systemic blood pressure (Table 1). Baseline pulmonary artery pressure, systemic blood pressure, oxygen saturation, and heart rate were measured. Each patient received 3 cc of nebulized normal saline (NS) as placebo control and these vital signs were recorded at 5 min intervals.
Next, each patient received a dose of 20 g per kilogram body weight of NTG in total volume of 3 cc NS nebulized and their vital signs were recorded at 5 min intervals.

Results

Nebulized NS failed to produce any changes in any of the patients. Nebulized NTG, on the other hand, significantly reduced pulmonary artery pressure without changing the systemic BP or heart rate (Table 2). This study was terminated at the end of the catheterization procedure with no long-term follow-up.

Discussion

Treatment for severe PHT continues to be difficult and often is not successful, despite the promising role of nebulized NO and ECMO as well as other treatment modalities. The fact that the mechanism of action of nitrovasodilators involves metabolism to NO led us to investigate of their potential.

To study the potential benefits of nebulized NTG on PHT, we selected four stable patients undergoing a diagnostic procedure. The lack of effect of NS eliminated the possibility of a placebo effect when using NTG. The significant reduction of both systolic and mean pulmonary artery pressures is encouraging, knowing that patients with uncorrected VSD tend to have sustained high diastolic pressure which would not respond well to any treatment.

Administering nebulized NTG had no effect on systemic BP or heart rate, presumably because of the fast local metabolism and short half-life. This finding is also promising because of the limitations of any treatments associated with systemic effects.

Conclusion

Nebulized NTG appears to be an effective, easy to administer, inexpensive and safe alternative for treatment of severe PHT in children with CHD, especially in areas where other treatment modalities such as ECMO or inhaled NO are inaccessible.

Larger studies on similar patients and also on patients with different etiologies are needed to confirm our preliminary findings.

Acknowledgement

We thank Bertha Romine for her secretarial assistance.

References


Table 1. Characteristics of the Four Pediatric Patients.

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Diagnosis</th>
<th>Baseline PAP</th>
<th>Baseline BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>VSD</td>
<td>80/32</td>
<td>84/51</td>
</tr>
<tr>
<td>36</td>
<td>VSD</td>
<td>85/33</td>
<td>93/39</td>
</tr>
<tr>
<td>18</td>
<td>VSD</td>
<td>56/35</td>
<td>99/62</td>
</tr>
<tr>
<td>6</td>
<td>VSD</td>
<td>45/20</td>
<td>64/34</td>
</tr>
</tbody>
</table>

VSD = ventricular septal defect
PAP = pulmonary artery pressure
BP = blood pressure

Table 2. Effects of Administration of Nebulized Nitroglycerine.

<table>
<thead>
<tr>
<th></th>
<th>Before NTG</th>
<th>At 10 minutes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAP</td>
<td>68 ± 8</td>
<td>53 ± 6</td>
<td>0.006</td>
</tr>
<tr>
<td>MPAP</td>
<td>47 ± 4</td>
<td>38 ± 4</td>
<td>0.005</td>
</tr>
<tr>
<td>SBP</td>
<td>85 ± 8</td>
<td>88 ± 3</td>
<td>0.7</td>
</tr>
<tr>
<td>MBP</td>
<td>59 ± 6</td>
<td>63 ± 4</td>
<td>0.5</td>
</tr>
<tr>
<td>HR</td>
<td>131 ± 8</td>
<td>127 ± 7</td>
<td>0.13</td>
</tr>
</tbody>
</table>

SPAP = systolic pulmonary artery pressure
MPAP = mean pulmonary artery pressure
SBP = systolic blood pressure
MBP = mean blood pressure
HR = heart rate

Combined statistics for the four patients. Student's t-test (paired statistics) was utilized.