Pulmonary arterial hypertension (PAH) is a progressive and fatal syndrome. Sildenafil citrate (Pfizer, Sandwich, Kent, UK) is a potent and selective PDE5 inhibitor that prevents cGMP breakdown and is FDA-approved only to treat PAH in adults. Studies have raised concerns about the long-term use of high dose sildenafil in pediatric patients with PAH. These data led to the U.S Food and Drug administration safety advisory recommending “against sildenafil treatment for pulmonary arterial hypertension in children”. The FDA has since revised this statement to recommend “…health care professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient.” Our goal was to conduct a systematic review to determine the comparative effectiveness and safety of PDE5 inhibitors in the management of pediatric patients with PAH.

**RESULTS**

We identified 1270 potentially relevant unique papers, and 21 were selected for inclusion: 8 randomized control trials (RCT) and 13 observational studies (Figure 1).

**I. Are PDE5 Inhibitors Effective in Improving Oxygenation and Hemodynamic Outcomes in Pediatric Patients with PH?**

**Oxygenation Parameters**

There is moderate strength evidence that PDE5 inhibitor use improves oxygenation parameters when compared to either baseline measurements or placebo.

- 3 of 4 RCTs reported that sildenafil treatment improved oxygenation when compared with either pre-treatment measurements, placebo, conventional treatment, or MgSO4 (p<0.05 for all studies).

- 5 observational studies reported oxygenation changes (1 pros and 4 retro), 2 showed no significant change in systemic oxygenation after initiation of sildenafil and 3 reported improvement in at least one oxygenation parameter [O2, FiO2, and/or alveolar-arterial oxygen difference] after sildenafil initiation (p<0.05).

**Hemodynamic Outcomes – Cardiac Catheterization Data**

There is moderate strength of evidence that PDE5 inhibitor use improves cardiac catheterization outcomes when compared to placebo or baseline measurements.

- In 4 of 5 RCTs a lower PAP was found in the sildenafil arm (p<0.05). In 1 RCT the milrinone group demonstrated the most significant reduction in systolic PAP (p = 0.003).

- 5 observational studies (3 pros/2 retro) reported significant decreases in mean PAP, systolic PAP, or PVRI with PDE5 inhibitors (p<0.05 for all studies).

**Hemodynamic Outcomes – Echocardiographic Data**

There is moderate strength of evidence that PDE5 inhibitor use improves left and right heart parameters by echo when compared to baseline measurements.

- 1 RCT reported lower mean PAP and higher cardiac index after sildenafil treatment when compared to baseline or after conventional treatments (p<0.05).

- 6 observational studies (2 pros/4 retro), 5 demonstrated improvement after PDE5 inhibitor use, including increased left ventricular output and pulmonary blood flow, and decreased PAP (p<0.05). 1 showed no difference in echo evidence of PH.

**METHODS**

All studies identified by the initial literature search were published before February 2015 and independently screened by two reviewers (Figure 1). We graded the quantity, quality, and consistency of data for each primary outcome by adapting an evidence grading scheme recommended by the GRADE Working Group’s guide for conducting comparative effectiveness reviews.

**II. Mortality and Toxicity**

- **RCT (N=4)**
  - 1 study reported mortality data: 1 study reported no deaths (p<0.05).
  - 1 study reported mortality data: 2 studies reported deaths related to medication administration.
  - 1 study reported mortality data: 1 study reported no deaths involving other reported deaths unrelated to medication administration.

- **PROSPECTIVE (N=3)**
  - 1 study reported mortality data: 1 study reported no deaths involving other reported deaths unrelated to medication administration.
  - 1 study reported mortality data: 1 study reported no deaths involving other reported deaths unrelated to medication administration.

- **RETROSPECTIVE (N=7)**
  - 1 study reported mortality data: 1 study reported no deaths involving other reported deaths unrelated to medication administration.

**III. Clinical Outcomes**

This evidence is insufficient to allow definitive statements about the effects of PDE5 inhibitors on clinical outcomes (including frequency of PH Crises, Exercise Capacity, Inotropic support, Weaning of PH medications, Ventilator time and either ICU or Hospital Length of Stay). This is due to the small number of studies and the inconsistent results for each individual clinical outcome (See Table 1).

**CONCLUSIONS**

This systematic review:

- Strongly suggests that PDE5 inhibitors improve oxygenation and hemodynamic parameters in pediatric patients
- Reiterates the need for additional well-planned, prospective, comparative studies of phosphodiesterase inhibitors, other pulmonary vasodilators, and placebo controls in infants and children with PH.
- Support prior observational studies that suggest that sildenafil is of more benefit than risk to pediatric patients with PAH.
- Mortality data from RCT’s in our study demonstrated no increased risk of death, with the exception of the STARTS-2 trial by Barst et al.

**REFERENCES**

5. FDA Drug Safety Communication: FDA recommends against use of Revatio®/sildenafil in children and adolescent patients with PAH.