Sildenafil in Term and Premature Infants: A Systematic Review

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ABSTRACT

Purpose: Numerous medications are used off-label in term and premature infants, with limited safety or efficacy data. Although sildenafil is approved by the US Food and Drug Administration for the treatment of pulmonary hypertension in adults, it is not approved for use in children. However, sildenafil use in term and premature infants with pulmonary hypertension is increasing. The goal of this study was to review controlled trials evaluating the efficacy of sildenafil use in: (1) term infants with pulmonary hypertension; (2) premature infants at risk for developing bronchopulmonary dysplasia (BPD); and (3) premature infants with BPD-associated pulmonary hypertension.

Methods: MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and International Pharmaceutical Abstracts databases were searched for citations related to sildenafil use in term or near-term infants with pulmonary hypertension or premature infants at risk for BPD or with BPD-associated pulmonary hypertension. Randomized and nonrandomized controlled trials were searched for that evaluated sildenafil use in term and premature infants compared with placebo or inhaled nitric oxide alone. Included studies were limited to English or Spanish language. Risk of bias was determined by using the Cochrane risk of bias tool.

Findings: Five trials (4 full-text articles and 1 abstract) of the 802 screened citations met the criteria for inclusion. All 5 trials were randomized controlled trials; the largest had 51 participants. Four of the trials (with a total of 137 subjects) evaluated the use of sildenafil versus placebo for term or near-term infants with persistent pulmonary hypertension of the newborn in low-resource settings in which inhaled nitric oxide was unavailable; there were no trials of sildenafil in areas in which inhaled nitric oxide is routinely available. The trials showed improvements in oxygenation index and a reduction in mortality in the sildenafil groups (5.9% vs 44%). One trial evaluated early sildenafil use (after day 7 of life) in premature infants for the prevention of BPD (n = 20). More premature infants in the sildenafil group died, were exposed to postnatal steroids, and had higher right-sided ventricular pressures later during hospitalization; these differences were not statistically significant. No trials evaluated sildenafil versus placebo in premature infants with BPD-associated pulmonary hypertension.

Implications: There is currently little evidence to support the use of sildenafil in term or near-term infants with persistent pulmonary hypertension of the newborn in areas in which inhaled nitric oxide is available. More data are needed to determine the effectiveness and dosing of sildenafil in improving outcomes for term and premature infants. Sildenafil dosing and safety studies are needed, especially among premature infants, before efficacy trials are performed. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: premature infant, sildenafil, pulmonary hypertension, bronchopulmonary dysplasia.

INTRODUCTION

The majority of medications are used off-label in infants, with no available studies to adequately determine the safety profile or effectiveness of these agents.[1] Understanding the efficacy and safety of these medications in the pediatric population is a priority.[2] Systematic reviews of existing literature and ongoing large trials to assess the safety and efficacy of these medications are needed. Sildenafil is a medication increasingly being used off-label in term and premature infants with pulmonary hypertension

Accepted for publication July 23, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.07.019
0149-2918/$ - see front matter

and/or bronchopulmonary dysplasia (BPD) with a lack of systematic studies to support its use.[3]

Sildenafil is approved by the US Food and Drug Administration (FDA) for the treatment of pulmonary arterial hypertension (World Health Organization Group I) to improve exercise ability and delay clinical worsening in adults.[4] Sildenafil is a potent inhibitor of type 5 phosphodiesterase, the predominant isoform in the lung that metabolizes cyclic guanosine monophosphate, and produces pulmonary vasodilation by potentiating the effects of endogenous nitric oxide. Since its approval for the treatment of pulmonary arterial hypertension in adults, the off-label use of sildenafil in infants has increased.[3] After noting an increased risk of death at high doses of sildenafil compared with low doses in 1 long-term pediatric clinical trial, the FDA released a black box warning in 2012 recommending against the use of long-term sildenafil use in children aged 1 to 17 years.[5,6] In addition to the concerns regarding mortality, numerous other potential adverse effects of sildenafil have been suggested, including severe systemic hypotension, pulmonary hemorrhage, or increased incidence of retinopathy of prematurity, but none has been consistently reported.[7–12]

Pulmonary hypertension in premature and term infants represents a heterogeneous group of diagnoses that collectively are associated with poor outcomes. Causes of pulmonary hypertension include congenital heart disease, congenital diaphragmatic hernia, and persistent pulmonary hypertension of the newborn (PPHN) secondary to meconium aspiration syndrome or other hypoxic respiratory failure in term infants and premature infants.[13–15] Pulmonary hypertension can also occur in premature infants with BPD later during their hospitalization.[13,15,16] Despite new technologies and therapies, the estimated mortality of infants diagnosed with pulmonary hypertension remains at 10% to 20%.[13,15–18] Infants with pulmonary hypertension may require prolonged mechanical ventilation, need extracorporeal life support, or progress into right-sided heart failure.[13,15,16,19] Surviving infants often also require exogenous oxygen for an extended period of time. Such complications may ultimately have long-term neurodevelopmental consequences for these infants.[20,21]

Trials of sildenafil are challenging because there are a variety of mechanisms to diagnose pulmonary hypertension. Providers often diagnose pulmonary hypertension on the basis of clinical symptoms and ventilatory requirements alone or in conjunction with echocardiography findings demonstrating an elevation in pulmonary pressures. Although cardiac catheterization is considered the gold standard for the diagnosis of pulmonary hypertension, it is often not used because of the invasive nature of the test and the critical condition of the infants with pulmonary hypertension. Adding to the challenge of standardizing studies of sildenafil is the wide clinical spectrum of severity of pulmonary hypertension in infants. As a result of such complexities, systematic studies assessing risks and benefits of sildenafil use in infants are difficult, and the safety and effectiveness of sildenafil as a therapy for pulmonary hypertension in infants remain ill-defined, with limited studies and case reports available to support routine use of this drug in infants.[6,17,22–31]

In the present systematic review, the existing evidence for sildenafil use in term infants with pulmonary hypertension and in premature infants at risk for BPD or with BPD-associated pulmonary hypertension was assessed. We investigated outcomes, including death before discharge, length of hospitalization, duration of mechanical ventilation and the reduction in pulmonary hypertension as evidenced by improvement in oxygenation.

MATERIALS AND METHODS

Research Questions

The primary questions of the present review were the following: (1) Does sildenafil use improve in-hospital mortality in term infants with pulmonary hypertension or premature infants with BPD-associated pulmonary hypertension compared with placebo or inhaled nitric oxide (iNO); and (2) Does sildenafil use in premature infants prevent or treat BPD as defined by oxygen requirement at 36 weeks' corrected gestational age (GA)? We also hypothesized that sildenafil use would reduce the intermediate outcomes of hospital stay and the duration of mechanical ventilation for surviving infants; these end points might confer long-term neurodevelopmental benefits.

Criteria for Selection of Studies

Original trials were included, including randomized and nonrandomized controlled trials regardless of year of publication (with sufficient data published in