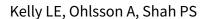


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Sildenafil for pulmonary hypertension in neonates (Review)



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[Intervention Review]

Sildenafil for pulmonary hypertension in neonates

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ABSTRACT

Background

Persistent pulmonary hypertension in the neonate (PPHN) is associated with high mortality. Currently, the therapeutic mainstay for PPHN consists of assisted ventilation and administration of inhaled nitric oxide (iNO). However, nitric oxide is costly, and its use may not be appropriate in resource-poor settings. Approximately 30% of patients fail to respond to iNO. High concentrations of phosphodiesterases in the pulmonary vasculature have led to the use of phosphodiesterase inhibitors such as sildenafil or milrinone.

Objectives

To assess the efficacy and safety of sildenafil for treatment of pulmonary hypertension in neonates.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 3), MEDLINE via PubMed (1966 to 18 April 2017), Embase (1980 to 18 April 2017), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 18 April 2017). We searched clinical trials databases, conference proceedings, and reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

We included randomised and quasi-randomised controlled trials of sildenafil compared with placebo or other pulmonary vasodilators, irrespective of dose, route, and duration of administration, in neonates with pulmonary hypertension, if investigators reported any of the prespecified outcomes.

Data collection and analysis

We assessed the methodological quality of trials regarding how bias was minimised at study entry, during study intervention, and at outcomes measurement. We extracted data on relevant outcomes; we estimated the effect size and reported it as risk ratio (RR), risk difference (RD), or mean difference (MD), as appropriate. We applied the I² test of heterogeneity and used GRADE to assess the quality of evidence.

Main results

For this update, we identified two additional studies, for a total of five eligible trials that enrolled 166 infants. The methodological quality of these studies ranged from low to high risk of bias. Three studies were performed in resource-limited settings, where iNO and high-frequency



ventilation were not available at the time of the study. One study compared sildenafil versus active controls, and another study evaluated sildenafil as adjuvant therapy to iNO. When comparing sildenafil with placebo, investigators noted significant reduction in mortality in the sildenafil alone group (three studies, 77 participants; typical RR 0.20, 95% confidence interval (CI) 0.07 to 0.56; I² = 0% - none; typical RR -0.36, 95% CI -0.53 to -0.18; number needed to treat for an additional beneficial outcome 3, 95% CI 2 to 6; I² = 39% - low). Trials reported no significant differences in mortality upon comparison of the sildenafil group versus the active control group (one study, 65 participants; typical RR 0.55, 95% CI 0.05 to 5.75), or when iNO was administered to both groups (one study, 24 participants; typical RR 1.27, 95% CI 0.26 to 6.28). Physiological parameters of oxygenation (oxygenation index, partial pressure of oxygen in arterial blood (PaO₂)) suggested steady improvement after the first dose of sildenafil. None of the included trials identified any clinically important side effects. We rated the quality of evidence as low to very low owing to imprecision related to small sample size and unclear methodological features.

Authors' conclusions

Sildenafil used for treatment of pulmonary hypertension has potential for reducing mortality and improving oxygenation in neonates, especially in resource-limited settings where iNO is not available. However, large-scale randomised trials comparing sildenafil versus active controls (other pulmonary vasodilators) and providing follow-up for survivors are needed to assess the comparative effectiveness and long-term safety of sildenafil versus other pulmonary vasodilators.

PLAIN LANGUAGE SUMMARY

Sildenafil for pulmonary hypertension in neonates

Review question

Is sildenafil safe and effective in newborn babies with pulmonary hypertension?

Background

When a baby is born, pressure in the blood vessels of the lungs is high, and when normal breathing is established, this pressure starts to fall. In some babies, this transition does not occur and pressure remains high; this does not allow blood to go to the lungs to get adequate oxygen. This situation is called persistent pulmonary hypertension of the neonate (PPHN). Other events can lead to development of high pressure in lung blood vessels that can manifest within a few days after birth. Persistent high pressure in these vessels leads to delivery of less oxygen to all organs of the body. A medication called sildenafil may cause lung blood vessels to relax, allowing improved blood flow and improved delivery of oxygen to all organs.

Study characteristics

We identified five studies that evaluated effects of sildenafil: three studies that compared sildenafil with placebo (no sildenafil); one that compared sildenafil with other medication (magnesium sulphate); and one that used sildenafil in combination with another medicine (nitric oxide). These studies included 166 newborns and were conducted in Colombia, Mexico, Turkey, and Qatar.

Key results

Three studies that compared sildenafil and placebo (no sildenafil) reported that sildenafil reduced the number of deaths. Studies that compared sildenafil against another medication or that used another treatment with sildenafil described no significant reduction in the number of deaths. Sildenafil was more effective than placebo in improving oxygen levels. None of the five included studies reported safety concerns. However, these studies enrolled small numbers of infants, and most were conducted in settings where other treatments were not available. Sildenafil may be useful in settings where other treatment approaches are not available. However, additional studies are needed to compare sildenafil against existing treatment in a resourceful environment to assess its effectiveness and safety.

Quality of evidence

The quality of evidence for reducing mortality or improving respiratory parameters was low owing to the small number of included studies and the small number of babies evaluated. Some of the included studies have methodological issues, resulting in low to very low quality of evidence.