Prophylactic sildenafil in preterm infants at risk of bronchopulmonary dysplasia: A systematic review and meta-analysis

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Abstract

Objective: This study aimed to investigate the efficacy and safety of prophylactically administered sildenafil during the early life stages of preterm infants to prevent mortality and bronchopulmonary dysplasia (BPD). **Data Sources:** MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, and Ichushi. **Study Selection:** Published randomized controlled trials (RCTs), non-RCTs, interrupted time series, cohort studies, case–control studies, and controlled before-and-after studies were included. **Data Extraction:** Two reviewers independently screened the title, abstract, and full text, extracted data, assessed the risk of bias, and evaluated the certainty of evidence (CoE) following the Grading of Recommendations Assessment and Development and Evaluation approach. The random-effects model was used for a meta-analysis of RCTs. **Results:** This review included three RCTs (162 infants). The prophylactic sildenafil and placebo groups demonstrated no significant differences in mortality (risk ratio [RR]: 1.32; 95% confidence interval [CI]: 0.16–10.76; very low CoE) and BPD (RR: 1.20; 95% CI: 0.79–1.83; very low CoE), as well as in any other outcome assessed (very low CoE). **Limitations:** The sample sizes were less than the optimal sizes for all outcomes assessed, indicating the need for further trials. **Conclusions:** The prophylactic use of sildenafil in individuals at risk of BPD did not indicate any advantageous effects in terms of mortality, BPD, and other outcomes, or increased side effects.

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Author contribution: Katsuya Hirata: Conceptualization; writing – original draft; investigation; data curation; formal analysis; methodology. Atsuko Nakahari: Investigation; data curation; methodology; validation. Mami Takeoka: Investigation; data curation; methodology; validation. Masahiko Watanabe: investigation; data curation; validation. Yutaka Nishimura: Conceptualization; investigation; data curation; methodology; validation. Yoshinori Katayama: Conceptualization; investigation; data curation; methodology; validation. Tetsuya Isayama: Writing–review and editing; supervision; validation

Abbreviated title : Sildenafil to prevent bronchopulmonary dysplasia

ABSTRACT

Objective: This study aimed to investigate the efficacy and safety of prophylactically administered sildenafil during the early life stages of preterm infants to prevent mortality and bronchopulmonary dysplasia (BPD).

Data Sources: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, and Ichushi.

Study Selection: Published randomized controlled trials (RCTs), non-RCTs, interrupted time series, cohort studies, case–control studies, and controlled before-and-after studies were included.

Data Extraction: Two reviewers independently screened the title, abstract, and full text, extracted data, assessed the risk of bias, and evaluated the certainty of evidence (CoE) following the Grading of Recommendations Assessment and Development and Evaluation approach. The random-effects model was used for a meta-analysis of RCTs.

Results: This review included three RCTs (162 infants). The prophylactic sildenafil and placebo groups demonstrated no significant differences in mortality (risk ratio [RR]: 1.32; 95% confidence interval [CI]: 0.16–10.76; very low CoE) and BPD (RR: 1.20; 95% CI: 0.79–1.83; very low CoE), as well as in any other outcome assessed (very low CoE).

Limitations: The sample sizes were less than the optimal sizes for all outcomes assessed, indicating the need for further trials.

Conclusions: The prophylactic use of sildenafil in individuals at risk of BPD did not indicate any advantageous effects in terms of mortality, BPD, and other outcomes, or increased side effects.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) persists as one of the foremost factors contributing to mortality and morbidity in extremely preterm infants[1]. BPD is associated with unfavorable respiratory and neurodevelopmental outcomes that endure throughout childhood and extend into adulthood [2]. No singular therapy

has been definitively validated in significantly reducing the incidence or severity of BPD despite the use of various pharmaceutical agents aimed at BPD prevention and treatment [3].

Sildenafil, which is a discerning phosphodiesterase-5 (PDE-5) inhibitor, acts by impeding cGMP degradation, thereby protracting the effects of cGMP and inducing smooth muscle relaxation. A PDE-5 inhibitor emerges as a promising contender for BPD treatment because PDE-5 prevails as the predominant isoform within the pulmonary system. The United States Food and Drug Administration (FDA) approved sildenafil for pulmonary arterial hypertension management in adults [4]. However, mortality rates observed in children with pulmonary arterial hypertension who received increasing doses of sildenafil beyond one year increased [5], thus the FDA issued a recommendation against the long-term usage of sildenafil in this pediatric population[6]. Nevertheless, the employment of sildenafil in neonatal intensive care units, although off-label, has witnessed a surge in recent years [7,8]. Sildenafil has been administered to infants afflicted with BPD-associated pulmonary hypertension (BPD-PH) as a rescue therapy in most instances [8]. Conversely, the prophylactic use of sildenafil in neonatal rats exposed to hyperoxia has enhanced alveolarization, facilitated angiogenesis, and reduced lung inflammation, and fibrin deposition. Consequently, these effects help with BPD mitigation via the activation of the hypoxia-inducible factor signaling pathway [9,10]. However, the effectiveness of administering sildenafil early on to prevent BPD remains uncertain.

Hence, this comprehensive systematic review and meta-analysis aimed to investigate the efficacy and safety of administering sildenafil prophylactically during the early stages of life in preterm infants, to prevent severe BPD, and mortality.

METHODS

This systematic review follows the standard methods from the Cochrane Handbook for Systematic Reviews of Interventions. The protocol of this systematic review was developed before the literature search and was registered at PROSPERO (CRD42022358641).

Selection criteria for the systematic review

This systematic review included studies that compared the effectiveness of prophylactic administration of sildenafil compared with standard treatment without sildenafil, targeting preterm infants (gestational age of <37 weeks) necessitating respiratory support (mechanical ventilation, non-invasive respiratory support, nasal continuous positive airway pressure, high-flow nasal cannula, or oxygen supplementation) within 14 days of birth. This study excluded newborns who received inhaled nitric oxygen within the initial 14 days of life, as well as infants with chromosome abnormalities and major congenital anomalies. Studies about sildenafil administration for established BPD or BPD-PH were not incorporated. This review included all published RCTs, non-RCTs, interrupted time series, cohort studies, case–control studies, and controlled before-and-after studies. Unpublished RCTs were only eligible if sufficient information on the risk of bias assessment was obtained. The language was not restricted, but the selected articles were required to have an English abstract. This systematic review excluded studies without sufficient data regarding the outcomes to be summarized, duplicate studies or data, and animal studies.

The primary outcome for this systematic review includes mortality at discharge from the neonatal intensive care unit, and secondary outcomes were long-term neurodevelopmental impairment, BPD, severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC; Bell's criteria of [?]2a) or focal intestinal perforation (FIP), retinopathy of prematurity (ROP; international stage [?]2 or requiring treatment), BPD-PH, and adverse side effect (hypotension, arrhythmia, gastrointestinal symptoms, cutaneous symptoms, and irritability).

BPD was defined as oxygen use or respiratory pressure support at the postmenstrual age of 36 weeks. Severe IVH was defined as Papile's grade III or IV. BPD-PH was defined as pulmonary hypertension associated with BPD diagnosed by cardiac catheterization or echocardiography (e.g., tricuspid regurgitant jet velocity of >2.8 m/s; bowed interventricular septum systolic flattening; estimated pulmonary artery pressure/systolic blood pressure ratio of >0.5 or time to peak velocity to right ventricular ejection time ratio of <0.35).

Search methods and strategy

A literature search was performed in the following databases from their inception to November 3, 2022: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, and Ichushi, which is a Japan's largest database for medical journals and abstracts. The reference lists of the review articles on this topic were manually searched. E-table 1 shows the full search strategy used for MEDLINE.

Study selection and data extraction

Two reviewers (AN and MT) independently screened the titles and abstracts of the selected articles derived from the literature search and reviewed the full text of all potentially relevant articles. Any discrepancy between the two reviewers was first resolved by discussion, and a third reviewer (KH) adjudicated it when no consensus was reached.

Risk of bias assessment

The two authors (AN and MT) used the Revised Cochrane Risk of Bias tool for RCT (RoB2.0) to independently assess the risk of bias of the included studies for each outcome [11]. Conflicts of assessment between the two reviewers were resolved through discussion, with the other reviewers (KH, YK, and YN) adjudicating them if needed.

Assessment of the Certainty of Evidence

Two reviewers (KH and AN) used the Cochrane Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE) to rate the certainty of evidence (CoE) [12]. We resolved any disagreements through discussion with other reviewers (MT, YK, and YN).

Data Analysis

This meta-analysis was performed using the random-effects model with the Mantel-Haenszel method using Review Manager (RevMan), version 5.4 (The Nordic Cochran Center, The Cochrane Collaboration). The effect estimates were reported as risk ratios (RRs) and absolute risk differences with 95% confidence intervals (95% CIs). Statistical significance was set at p-values of <0.05. Heterogeneity was assessed by visual inspection of the forest plot using the $\chi 2$ test ($p < 0.10$ indicates significance) and I2 statistic ($I2 > 40\%$ indicates significant heterogeneity).

RESULTS

Search results

Out of the 2914 records initially identified in the literature search, 1967 were assessed based on their title and abstract after removing duplicates. The full text of 16 articles was reviewed, and 3 RCTs were included in this systematic review (König 2014 [13], Abounahia 2019 [14], Dehdashtian 2019[15]) (Figure 1). Not a single observational study was found.

Characteristics of the included studies

Table 1 shows the characteristics of the studies. Overall, the included three RCTs enrolled 162 preterm infants. The mean or median gestational age of the infants in the three studies was 24–28 weeks. Sildenafil was orally administered at a dose of 2–3 mg/kg/day in all the studies. Dehdashtian 2019 solely assessed ROP and did not evaluate mortality, BPD, or other outcomes [15].

Risk of bias assessment

Table 2 shows the risk of bias in all the studies. The risks associated with the randomization process, deviations from the intended intervention, and outcome measurement were low in all studies. The risk of mortality outcome was deemed of some concern due to the exclusion of 2 out of 10 mortalities in the sildenafil group, which resulted from participant transfers during the study conducted by König et al.[13] Regarding the

domain of missing outcome data. The study conducted by Abounahia et al. [14] considered the risk of BPD outcome as high due to missing outcome data exceeding 20%. However, the risks of IVH, PVL, NEC, and ROP outcomes were regarded as some concerns since the missing outcome data were <20%. The risks in most of the studies were low for the selection of the reported result domain. However, the risk of the study conducted by Dehdashtian et al [15]. was deemed high as it did not specify prespecified analysis plans in the methods.

Effects of interventions and quality of the evidence

Figure 2 presents forest plots displaying the results of the meta-analysis of RCTs. The GRADE evidence profile table provides a summary of the CoE for each outcome (Table 3). The sample sizes of the included studies achieved no optimal information size for all outcomes assessed (E-table 2). Two studies reported the primary outcome of mortality. No significant difference in mortality was observed between prophylactic sildenafil and placebo (RR: 1.32, 95%CI: 0.16–10.76, I2 = 62%; 2 studies, 57 infants, very low CoE).

No significant differences were observed in secondary outcomes, including BPD, severe IVH, PVL, NEC, ROP, or side effects, between prophylactic sildenafil and placebo (very low CoE). No studies evaluated long-term neurodevelopmental outcomes, FIP, and BPD-PH.

DISCUSSION

This study represents the inaugural systematic review and meta-analysis using the GRADE approach to examine the use of prophylactic sildenafil in preterm infants at risk of BPD. The study encompassed three RCTs (162 infants) and revealed results indicating no statistically significant reduction or elevation in any of the assessed outcomes for the infants (mortality, BPD, severe IVH, PVL, NEC, ROP, and side effects) with prophylactic sildenafil administration than with placebo (very low CoE). Very low CoE was attributed to the risk of bias and imprecision due to the small sample size.

Infants with BPD exhibit varying degrees of severity[16], but particular attention has been directed toward those cases characterized by an exceedingly severe course of the condition, necessitating long-term mechanical ventilation or tracheostomy [16-18]. The prevention of BPD exacerbation assumes critical importance because severe BPD can impose substantial medical, social, and economic burdens on parents, the healthcare sector, and society as a whole [19]. Existing evidence has not substantiated its efficacy presumably due to its pharmacological properties although sildenafil holds theoretical promise as an agent capable of averting BPD progression. Perez et al. conducted a systematic review in 2015 on sildenafil usage in both term and premature infants[20], which encompassed a single RCT involving a preterm cohort [13]. The present review includes two additional RCTs [14,15]; however, their small sample prevented meta-analyses from attaining sufficient evidence.

The present review encapsulates the current body of evidence about the prophylactic sildenafil administration. However, further investigations are imperative to ascertain the veracity of these findings. A multicenter randomized placebo-controlled study is currently ongoing to evaluate the safety, pharmacokinetics, and preliminary effectiveness of intravenous and enteral sildenafil in premature infants at risk of BPD[21,22]. Conducting a future iteration of the systematic review and meta-analysis that encompasses additional studies is desirable.

The study has several limitations. First, this review included only tree trials with a small sample size, thereby attaining no optimal information size for all outcomes assessed. The insufficient sample size was due to the negative findings in this meta-analysis. Second, the studies revealed very low CoE in the primary outcome and other outcomes.

In conclusion, this systematic review revealed a level of evidence characterized by very low certainty, indicating that the prophylactic use of sildenafil in individuals at risk of BPD demonstrated no benefits in terms of mortality, BPD, severe IVH, PVL, NEC, ROP, or increased side effects. Further investigations in the future are necessary to comprehensively assess all the outcomes due to the inadequate sample size used in this systematic review.

Acknowledgement

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Figure legends

Figure 1. Flow chart of literature search.

CENTRAL, Cochrane central register of controlled trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; RCT, randomized clinical trial.

Figure 2. Comparison of mortality and morbidities between sildenafil and placebo. The

analyses were conducted using random effects models.

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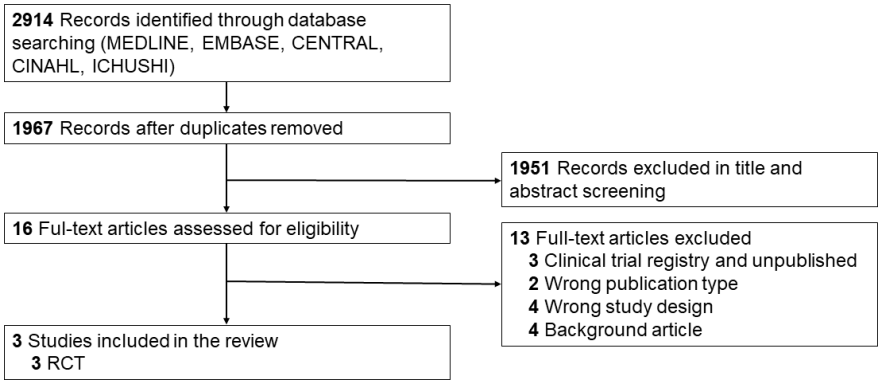
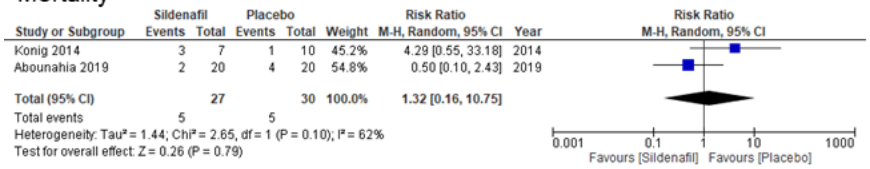


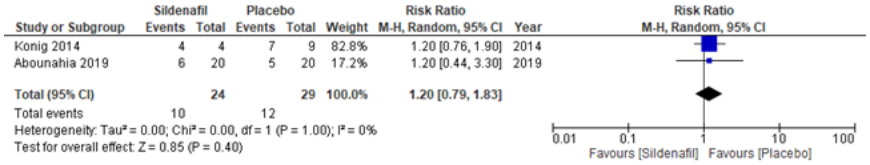
Primary outcome

Mortality

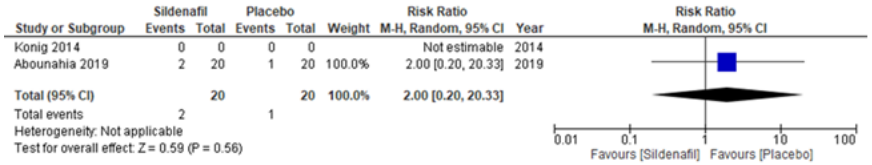


Secondary outcomes

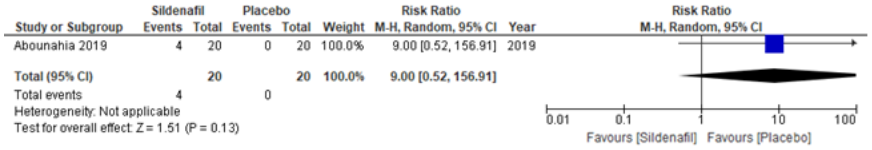
Bronchopulmonary dysplasia



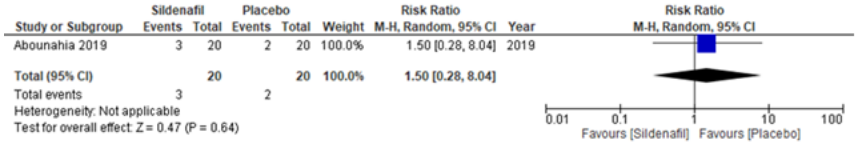
Severe intraventricular hemorrhage



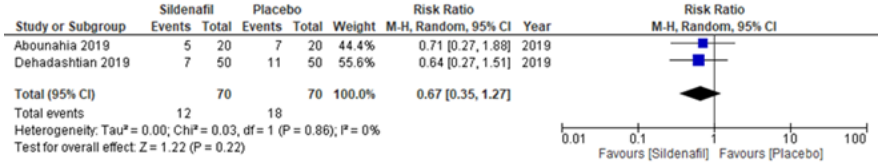
Periventricular leukomalacia



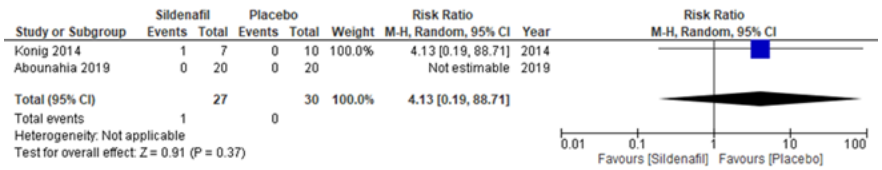
Necrotizing enterocolitis



Retinopathy of prematurity



Side effect



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