A Pilot Randomized Double-Blinded Placebo-Controlled Trial of Prophylactic Sildenafil in Preterm Infants at Risk of Bronchopulmonary Dysplasia

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Background

- Bronchopulmonary dysplasia (BPD), is the need for oxygen therapy at 36 weeks postmenstrual age (PMA) in an infant who is more than 28 days old
- In a rat model experiment, sildenafil was suggested to have possible therapeutic potential for the prevention of BPD
- With increasing survival of very premature neonates, efforts are needed to limit the burden associated with BPD

Objective

- To assess the feasibility and safety of oral sildenafil in <24 hours postnatal, extremely to very preterm infants for reducing the incidence of BPD

Methods

Figure 1. Chart of the study flow

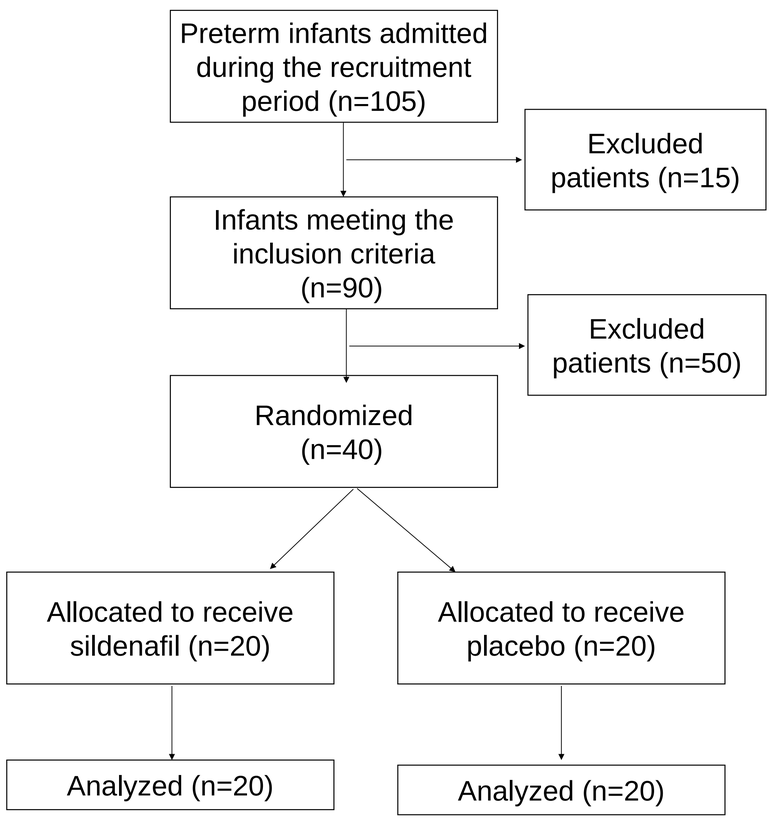

Table 1. Methods *continued*…

Design	**Pilot randomized, double-blinded placebo-controlled clinical trial (RCT), from 2012 to 2014 in Women's Wellness and Research Center, Qatar**
Inclusion criteria	• Gestational age of $24^{0/7}$-$29^{6/7}$ weeks • Postnatal age of <24 hours at randomization • Need of respiratory support or oxygen ≥ to 25% at randomization
Exclusion criteria	• Infants who were not considered viable • Infants with congenital malformation • Infants with severe hemodynamic instability at randomization, and had liver failure
Sample size	Group 1 (n=20) , oral sildenafil (0.5 mg/kg every 6 hours) for one week Group 2 (n=20), placebo solution, for one week
Outcome measures	*Primary outcome measures:* • The incidence of BPD and death at 36 weeks PMA • Side effects that are associated with sildenafil *Secondary outcome measures:* • Incidence of BPD and respiratory support at day 28 of life

Methods…*continued*

Outcome measures	• Duration of oxygen use • Fraction of inspired oxygen (FIO_2) use at 36 weeks & 28 days of life • Duration of hospitalization • Incidence retinopathy of prematurity (ROP), severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), and sepsis • The impact of comorbidities on the study outcomes
Randomiza-tion	• Infants were randomized within 24 hours • Stratification according to gestational age and birth weight

Results

- Baseline infant characteristics were statistically not different between the groups
- Surviving infants until 36 weeks had similar rates of BPD between the groups
- No side effects were reported
- The groups were similar in all secondary outcomes
- The mortality rate at 36 weeks PMA was statistically negatively associated with the gestational age at delivery and the maternity care
- The respiratory support provided by 36 weeks PMA was statistically associated with the occurrences of IVH, NEC, gestational age, and receiving antenatal care or postnatal steroids
- The FIO_2 was statistically related to the presence of ROP, NEC, gestational age, and receiving postnatal steroids

Table 2. Clinical outcomes

Outcome	Sildenafil N(%)	Placebo N(%)	P-value
Mortality at 36 weeks	2 (10)	4 (20)	1
Respiratory support at 36 weeks	6 (30)	5 (25)	0.57

Table 3. The impact of comorbidities on the study outcomes

Variable	P-value	Strength of association
Mortality at 36 weeks		
Gestational age	0.02	-0.42

Results…*continued*

Table 3. The impact of comorbidities on the study outcomes…*continued*

Variable	P-value	Strength of association
Mortality at 36 weeks		
Antenatal care	0.03	-0.4
Respiratory support at 36 weeks		
IVH	0.04	0.58
NEC	0.03	0.64
Gestational age	0.008	0.56
Antenatal care	0.03	0.5
Postnatal steroid	0.002	0.73
FIO_2 at 36 weeks		
ROP	0.004	0.99
NEC	0.03	0.68
Gestational age	0.02	0.53
Postnatal steroid	0.02	0.71

Discussion

- It is possible that a total daily dose of 2 mg/kg is small for the study purpose
- There is only one RCT in literature, by Konig K et al, which was of 10 extremely preterm infants receiving sildenafil (n=10) (3mg/kg/day) versus placebo (n=10)
- Konig K et al study showed no beneficial sildenafil prevention effect with no sides effects
- No side effects were reported. This is anticipated as significant side effects need large sample size and longer duration of sildenafil

Conclusion

- While sildenafil was not associated with side effects, it did not demonstrate benefit as a preventative measure against BPD in the very preterm infants
- Future trials that target varying regimens of sildenafil are needed

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All research members have no conflicts of interest