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Best evidence topic - Congenital

Is sildenafil effective for treating pulmonary hypertension after pediatric heart surgery?

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Summary

A best evidence topic in pediatric cardiac surgery was written according to a structured protocol. The question addressed was whether sildenafil was effective in treating postoperative pulmonary hypertension after pediatric heart surgery. Altogether 28 papers were found using the reported search, of which three represented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results, and study weaknesses were tabulated. We conclude that oral sildenafil may be useful in reducing pulmonary vascular resistance and can be considered for treatment of postoperative pulmonary hypertension after pediatric heart surgery. However, evidence from a large, multicenter, randomized controlled trial is needed to validate the safety and efficacy of sildenafil for use in postoperative pediatric cardiac surgical patients.

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Keywords: Evidence-based medicine; Sildenafil; Pulmonary hypertension; Pediatric heart surgery

1. Introduction

A best evidence topic was constructed according to a structured protocol. This protocol is fully described in the ICVTS [1].

2. Clinical scenario

You are reviewing a postoperative patient in pediatric intensive care unit (ICU) who has pulmonary hypertension not responsive to inhaled nitric oxide (iNO) and intravenous pulmonary vasodilators. The ICU consultant suggests prescribing sildenafil to this patient. You are not sure if sildenafil will be of any benefit. Rather than prescribing blind treatment you decide to review the literature before making your decision.

3. Three-part question

Is [sildenafil] effective for treating [pulmonary hypertension] after [pediatric heart surgery]?

4. Search strategy

Medline 1966 to Oct 2005 using the OVID interface. [exp sildenafil/OR Viagra.mp] AND [exp pulmonary hypertension.mp] AND [exp congenital heart surgery/OR pediatric heart surgery/OR pediatric cardiac surgery/OR paediatric heart surgery/OR paediatric cardiac surgery.mp].

5. Search outcome

Twenty-eight papers were found of which three were relevant. One randomized controlled trial (RCT) was identified and the other two were cohort studies with small sample/population sizes. These are presented in Table 1.

6. Discussion

Of the three studies, the RCT by Stocker et al. [2] investigated the acute effects of intravenous sildenafil on hemodynamics and oxygenation, and its interaction with iNO in infants at risk of pulmonary hypertension early after cardiac surgery. In this trial by Stocker et al. [2], sixteen ventilated infants early after closure of ventricular or atrioventricular septal defects were randomly assigned to one of two groups. The study was completed in 15 infants. Studies were commenced within 7 h of separation from bypass. Seven infants received iNO (20 ppm) first, with the addition of intravenous sildenafil (0.35 mg/kg over 20 min) after 20 min. Eight infants received sildenafil first, iNO was added after 20 min. Vascular pressures, cardiac output and a blood gas were recorded at 0, 20 and 40 min. In infants receiving iNO first, iNO lowered the pulmonary vascular resistance index (PVRI) from 3.45 to 2.95 units ($P=0.01$); sildenafil further reduced PVRI to 2.45 units ($P<0.05$). In those receiving sildenafil first, PVRI was reduced from 2.84 to 2.35 units ($P<0.05$) with sildenafil, and fell to 2.15 units ($P=0.01$) with the addition of iNO. In both groups, sildenafil reduced the systemic blood pressure and systemic vascular resistance ($P<0.01$) and worsened arterial oxygenation and the alveolar-arterial gradient ($P<0.05$).

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Table 1
Best evidence papers

| Author, date and country | Patient group | Study type (Level of evidence) | Outcomes | Key results | Comments/Weaknesses |
|---|--|---|--|--|--|
| Stocker et al. (2003), Intensive Care Med., Australia [2] | 16 ventilated infants early after closure of VSD or AVSD at risk of pulmonary hypertension | Prospective RCT (level 1b) | Vascular pressures, Cardiac output and a blood gas were recorded at 0, 20 and 40 min after administration of iNO (20 ppm) first, with the addition of intravenous sildenafil (0.35 mg/kg over 20 min) after 20 min to 7 infants and sildenafil first, followed by iNO after 20 min to 8 patients | IV sildenafil augmented the pulmonary vasodilator of iNO in infants after cardiac surgery | None of the patients had clinically significant pulmonary hypertension at the time of study Small sample size |
| Schulze-Neick et al. (2003), Circulation, Germany [3] | 12 children with congenital heart disease and increased mean PAP and 12 postoperative children with raised PVR | Prospective non-randomized study (level 2b) | Systemic arterial and pulmonary arterial as well as right and left atrial pressures and endtidal CO ₂ and systemic oxygen consumption were measured before and after the stepwise infusion of sildenafil ('cath laboratory', 1 mg/kg; postop, 0.25 mg/kg) in the presence of iNO (20 ppm) | IV sildenafil more effectively reduced PVR than NO | Lack of randomization Small sample size |
| Kothari et al. (2002), Indian Heart J, India [4] | 14 patients (age range 5-30 years) with 3 postop pediatric patients | Case series (level 4) | Functional status, 6-min walk tests, Doppler echo, hemodynamic study | Significant improvement in functional status and 6-min walk test with significant decline in right ventricular systolic pressure | Uncontrolled study Non-randomized Small sample size |

VSD=ventricular septal defect; AVSD=atrioventricular septal defect; RCT=randomized controlled trial; PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; iNO=inhaled nitric oxide.

In a prospective non-randomized study, Schulze-Neick et al. [3] compared the effects of iNO before and after the specific inhibition of the phosphodiesterase-5 (PDE-5) by intravenous sildenafil in pre- and postoperative children with increased PVR because of congenital heart disease. Twelve children with congenital heart disease (age 0.2 to 15.7 years, median 2.4 years) and increased mean pulmonary arterial pressure, and 12 postoperative children (age 0.11 to 0.65 years, median 0.32 years) with increased PVR (8.3 ± 1.0 Wood Units.m²) were studied during cardiac catheterization ('cath laboratory'), or within 2 h after return from cardiac surgery ('post op'), respectively. All were sedated, tracheally intubated and paralyzed. During alveolar hyperoxygenation (FiO₂=0.65), the effects of iNO (20 ppm) were compared before and after the stepwise infusion of sildenafil ('cath laboratory', 1 mg/kg; post op, 0.25 mg/kg). Intravenous sildenafil more effectively reduced PVR than iNO (11.5% vs. 4.3% in the 'cath labora-

tory' patient group, $P < 0.05$, and 25.8% vs. 14.6% in the post op patient group, $P = 0.09$). The increase in cGMP in response to iNO was potentiated (2- to 2.4-fold) by PDE-5 inhibition. While the vasodilating effects of sildenafil showed pulmonary selectivity, its infusion was associated with increased intrapulmonary shunting in the postoperative patients ($Q_s/Q_t = 16.5 \pm 4.7\%$ to $25.5 \pm 18.2\%$; $P = 0.04$).

Kothari et al. [4], in their prospective case series, reported their experience of using sildenafil in 5 postoperative congenital heart disease patients. In this series, fourteen patients, aged 5-30 years, with severe pulmonary artery hypertension (9 with primary pulmonary hypertension, 5 with operated congenital heart disease including 3 pediatric patients), received oral sildenafil in addition to conventional therapy. Twelve patients were in New York Heart Association functional class III or IV. The drug was started in low dose and empirically increased. Finally, a median dose of 87.5 mg/day was used in children weighing less

than 30 kg, and 150 mg/day in those with weight more than 30 kg. The patients were followed up by assessing their functional status, six-minute walk test, Doppler echocardiography and hemodynamic study (in selected cases). On mean follow-up of 7.3 ± 2.4 months (range 3–14 months), New York Heart Association functional class improved from 3.31 ± 0.75 to 2.00 ± 0.71 ($P < 0.002$). There was a remarkable improvement on the six-minute walk test from a baseline of 264.1 ± 193.7 m to 408.2 ± 156.97 m at 3 months ($P < 0.001$) and 453.2 ± 159.81 ($P < 0.0001$) at 6 months. The right ventricular systolic pressure estimated echocardiographically declined from 112.40 ± 45.21 mmHg to 101.86 ± 47.86 mmHg ($P < 0.002$). The mean pulmonary artery pressure (PAP) decreased from 62 mmHg to 47 mmHg in 4 patients of primary pulmonary hypertension recatheterized after a mean of 7 months of sildenafil treatment. Clinical improvement was seen even when no decrease in PAP was demonstrated in one patient with secondary pulmonary artery hypertension. However, 2 patients died during follow-up despite clinical improvement.

7. Clinical bottom line

Currently available limited published experience of sildenafil usage for treating postoperative pulmonary hypertension after pediatric heart surgery seems to suggest that sildenafil can ameliorate the clinical condition of pediatric patients with postoperative pulmonary hypertension. However, a large, multicenter, randomized controlled trial is warranted to validate the safety and efficacy of sildenafil for use in postoperative pediatric cardiac surgical patients.

References

- [1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. *Interact CardioVasc Thorac Surg* 2003;2:405–409.
- [2] Stocker C, Penny DJ, Brizard CP, Cochrane AD, Soto R, Shekerdemian LS. Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery. *Intensive Care Med* 2003;29:1996–2003.
- [3] Schulze-Neick I, Hartenstein P, Li J, Stiller B, Nagdyman N, Hubler M, Butrous G, Petros A, Lange P, Redington AN. Intravenous sildenafil is a potent pulmonary vasodilator in children with congenital heart disease. *Circulation* 2003;108 (Suppl 1):II167–173.
- [4] Kothari SS, Duggal B. Chronic oral sildenafil therapy in severe pulmonary artery hypertension. *Indian Heart J* 2002;54:404–409.

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