Efficacy of inhaled iloprost in the management of pulmonary hypertension after cardiopulmonary bypass in infants undergoing congenital heart surgery. A case series of 31 patients

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ABSTRACT

Introduction: Reactive pulmonary hypertension is frequent in children with high pulmonary flow and pressure. Inhaled iloprost and nitric oxide are the only substances approved as selective pulmonary vasodilators, but data about the effectiveness and safety of inhaled iloprost during cardiac surgery in infants and children are limited.

Methods: We retrospectively analysed the effects of inhaled iloprost after cardiopulmonary bypass weaning on the ratio of mean pulmonary artery to mean arterial pressure. The effectiveness of the inhalation set up was tested in an in vitro study.

Results: Thirty-one patients received inhaled iloprost during surgery. The clinically used inhalation set up for inhaled iloprost delivered 20% to 30% (500 to 750 ng * kg⁻¹) of the nebulizer dose and caused a decrease in the ratio of mean pulmonary artery to mean arterial pressure from 0.6 ± 0.2 to 0.4 ± 0.1 and 0.4 ± 0.1 (30 and 60 minutes after) p < 0.05. In eleven (35%) patients norepinephrine infusion was started.

Conclusion: Our data suggest that a single dose of inhaled iloprost significantly decreases the ratio of mean pulmonary artery to mean arterial pressure for at least 60 min. Vasopressor support may be indicated to avoid systemic hypotension. The filled dose in the nebulizer should be high enough to compensate for the high depletion rate of the pediatric inhalation system. However, our study allows no final decision about beneficial or detrimental effects of the off label use of inhaled iloprost to reduce pulmonary artery pressure during congenital heart surgery.

Keywords: pediatric heart surgery, pulmonary hypertension, iloprost, inhalation therapy

INTRODUCTION

Impaired endothelium-dependant vasodilation is frequently present in children with high pulmonary flow and pressure which might be exacerbated by cardiopulmonary bypass (CPB) leading to pulmonary hypertensive crisis (1). This acute increase in pulmonary artery re-
An increase in pulmonary vascular resistance after weaning off CPB is critical in patients with impaired endothelium-dependent vasodilatation, we sought to evaluate the effectiveness and potential side effects of iLo in decreasing pulmonary artery pressure during pediatric cardiac surgery. Our hypothesis is that iLo can be used after weaning off CPB to decrease pulmonary artery pressure without serious side effects.

METHODS

Approval for a retrospective case-note review was obtained from the local ethics committee.

An anesthetic information management system (AMS) NarcoData (IMESO GmbH, Hüttenberg, Germany) was used to identify all infants and children who had: 1) congenital heart surgery associated with an increased risk of post-CPB pulmonary hypertension (closure of common atrium, ventricular or atrioventricular septal defects, correction of total anomalous pulmonary venous return, bidirectional cavopulmonary connection (BCPC) or total cavopulmonary connection (TCPC) in univentricular hearts, and cardiac transplantation), and 2) received iLo or iNO after weaning from cardiopulmonary bypass during congenital heart surgery at the Pediatric Heart Centre Giessen from November 01. 2002 to November 01. 2005.

Anesthesia and hospital records were reviewed from all patients treated with iLo to obtain demographic and perioperative data including dose and timing of iLo therapy, hemodynamic data including vasoactive and inotropic support, as well as postoperative outcome. Anesthesia and Surgery were carried out following our routine clinical procedures including ventilation with 100% oxygen during and after weaning off cardiopulmonary bypass (CPB) and have been published elsewhere (10).

As a part of our clinical standard, an indwelling 3F pulmonary artery catheter was inserted in the main pulmonary artery before weaning off CPB in infants at risk of postoperative pulmonary hypertensive crisis. In patients with BCPC or TCPC, pulmonary artery pressures were measured via the vena jugularis catheter. At the pediatric heart center giessen a mean pulmonary artery pressure (MPAP) > 25 mmHg after biventricular repair, and a MPAP > 18 mmHg or oxygen saturation < 80 % in patients with hemi-fontan or fontan circulation is accepted as indication for pulmonary vasodilators. Furthermore norepinephrine is indicated when mean arterial
pressure (MAP) was < 45 mmHg despite adequate preload and contractility judged by central venous pressure, transesophageal echocardiography and direct visualization of the heart.

The hemodynamic readings from vital data monitors and lung ventilator data were continuously recorded in three minute intervals by the AMS. Great importance was attached to analyze the exact timing of all interventions affecting pulmonary circulation (mechanical ventilation with oxygen, administration of milrinone, inhalation of iloprost). To allow comparison of the concomitant vasoactive therapy a vasoactive-inotropic score described by Gaies et al. was used (12). The time course of all interventions is shown in figure 1.

In all cases illo was started after weaning off CPB. For analysis, stable systemic pressures during the first ten minutes after weaning from CPB and before starting inhalation therapy were taken as baseline (T0) followed by a second (T1) and third (T3) data set 30 minutes, and 60 minutes after starting illo, respectively.

For the inhalation therapy with iloprost an ultrasonic nebulizer (Optineb®; Nebu-Tec, Elsenfeld, Germany) was integrated in the inspiratory limb of a pediatric breathing system (15 cm in front of the Y-piece).

The breathing circuit was connected to a Servo 900C anesthesia ventilator (Siemens, Erlangen, Germany). A single dose of 2.5 μg x kg⁻¹ Iloprost diluted in isotonic saline to obtain a filled-in volume of 3 ml was inhaled over a 20 minutes period. This dosage has previously been shown to be clinically effective in reducing MPAP/MAP (10).

However, the characteristics of an aerosol spray are affected by the nebulizer system, breathing circuit, and ventilator. To assess the effective amount of illo at the tip of the endotracheal tube, the above described ventilator set up was connected to a breathing chamber containing a micro filter. After 20 minutes the residual volume...
in the nebulizer was measured, and the drug concentration in the micro filter was analyzed by high-performance liquid chromatography as described elsewhere (13). The essays were performed twice using an filling volume of 2 and 3 ml, a volume controlled ventilation pattern with a respiratory rate of 20 x min-1, and a tidal volume of 50 and 100 ml, respectively. Statistical analysis was performed using IBM SPSS statistics 19.0 (www.spss.com). Data are expressed as median and ranges, or as mean and standard deviation. A paired t-test was used to compare the hemodynamic effects before and after illo. Differences in baseline hemodynamics between biventricular and univentricular hearts were analyzed using the unpaired t-test.

**RESULTS**

*Patients:* In 31 patients illo was the sole agent exclusively used in the operating room after weaning off CPB. Demographic data, preoperative cardiac diagnosis, and details of surgery are presented in *table 1*. The time course of all interventions affecting pulmonary vascular resistance is shown in *figure 1*. During the observation period from November 01, 2002 to November 01, 2005 corrective or palliative heart surgery with CPB was performed in 312 infants and children at risk of post-CPB pulmonary hypertension.

*Effective delivered iloprost dose:* Analyzing the clinical setup for the inhalation therapy with iloprost, we found that only 20 to 30%

| Table 1 - Patients characteristics and perioperative data | median (range) |
|-----------------------------------------------------------|----------------|
| Age (days)                                                | 165 (3 - 3193) |
| Weight (kg)                                               | 5,3 (2,7 - 14,8) |
| Diagnosis:                                                |                |
| Common atrium (n)                                         | 1              |
| VSD (n)                                                   | 11             |
| AVSD (n)                                                  | 8              |
| TAPVR (n)                                                 | 3              |
| HLHS (n)                                                  | 4              |
| HRHS (n)                                                  | 4              |
| Preoperative Cardiac catheterisation (n = 17):             |                |
| MPAP:MAP                                                 | 0,79 (0,48 - 1,44) |
| Qp:Qs                                                     | 2,17 (1,0 - 4,62) |
| Surgery:                                                  |                |
| Complete repair (n)                                       | 23             |
| BCPC (n)                                                  | 5              |
| TCPC (n)                                                  | 2              |
| HTX (n)                                                   | 1              |
| CPB-time (min)                                            | 112 (50-220)   |
| X-clamp time (min)                                        | 54 (0-186)     |

Ventricular septal defect, VSD; atrioventricular septal defect, AVSD; total anomalous pulmonary venous return, TAPVR; hypoplastic left heart syndrome, HLHS; hypoplastic right heart syndrome, HRHS; mean pulmonary artery pressure, MPAP; mean arterial pressure, MAP; bidirectional cavopulmonary connection, BCPC; total cavopulmonary connection TCPC, heart transplantation, HTX; cardiopulmonary bypass time, CPB-time; aortic cross clamping time, x-clamp time
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Table 2 - Amount of effective administered iloprost after a 20 min inhalation period.

| Essay No.: | Filled-in iloprost (µg) | Filled-in volume (ml) | Vtidal (ml) | Inhaled iloprost (µg) |
|------------|------------------------|-----------------------|-------------|----------------------|
| 1          | 20                     | 2                     | 50          | 2,92                 |
| 2          | 20                     | 2                     | 50          | 3,06                 |
| 3          | 15                     | 3                     | 50          | 2,72                 |
| 4          | 15                     | 3                     | 50          | 2,72                 |
| 5          | 20                     | 2                     | 100         | 4,41                 |
| 6          | 20                     | 2                     | 100         | 3,22                 |
| 7          | 15                     | 3                     | 100         | 4,7                  |
| 8          | 15                     | 3                     | 100         | 2,92                 |

of iloprost is effectively administered using the Optineb® ultrasonic nebulizer together with a pediatric breathing system (Table 2). Hemodynamic data: Inhalation therapy with iloprost after weaning off CPB decreases significantly the ratio of mean pulmonary artery pressure (MPAP) to mean arterial pressure (MAP) (Figure 2) by reducing primarily MPAP. Although great efforts were made to keep right ventricular loading condition stable throughout the observation (a decreased central venous pressure was only observed at T2 in patients undergoing biventricular repair (Table 3), norepinephrine was necessary in 35% of the patients after illo to keep systemic pressure (Table 4). Comparing univentricular and biventricular repair we found a lower base line MPAP/MAP-ration as well as a lower base line oxygen saturation in patients with univentricular physiology. After illo a decrease in MPAP/MAP and trend towards higher oxygen saturation values was observed in both groups (Table 3).

Figure 2 - Time course of post-CPB mean pulmonary artery pressure (MPAP) to mean arterial pressure (MAP)- ratio in 31 patients receiving inhaled iloprost during congenital heart surgery.
Postoperative Therapy: During the postoperative course in the intensive care unit, pulmonary vasodilators were administered in 87% of patients treated with iloprost for a median time of six days (range: 4-30 days). Median time on mechanical ventilation was five days (range: 1-14 days). No patient died during the postoperative stay in the intensive care unit.

DISCUSSION

In this case series, we found a significant decrease in MPAP/MAP ratio in all patients after starting inhalation of 2.5 μg x kg⁻¹ iloprost over 20 minutes. Using the same inhalation apparatus, this dosage has previously been shown to be clinically effective in decreasing pulmonary artery pressure.

Table 3 - Hemodynamic data after weaning off cardiopulmonary bypass in patients undergoing biventricular and univentricular repair.

|                      | BiVH (n = 24) | UVH (n = 7) | BiVH (n = 24) | UVH (n = 7) | BiVH (n = 24) | UVH (n = 7) |
|----------------------|---------------|-------------|---------------|-------------|---------------|-------------|
| Heart rate (x min⁻¹) | 142 ± 16      | 143 ± 33    | 149 ± 18      | 151 ± 25    | 147 ± 18      | 149 ± 24    |
| MAP (mmHg)           | 48 ± 9        | 53 ± 9      | 57 ± 9        | 57 ± 10     | 60 ± 12       | 57 ± 4      |
| MPAP (mmHg)          | 30 ± 6        | 19 ± 3      | 26 ± 4        | 17 ± 3      | 25 ± 6        | 16 ± 3*     |
| MPAP/MAP             | 0.6 ± 0.2     | 0.4 ± 0.1   | 0.5 ± 0.1     | 0.3 ± 0.1   | 0.4 ± 0.1     | 0.3 ± 0     |
| CVP (mmHg)           | 12 ± 3        | 7 ± 4       | 11 ± 3        | 7 ± 4       | 10 ± 3        | 6 ± 4       |
| Oxygen saturation (%)| 95 ± 6        | 85 ± 13     | 97 ± 5        | 88 ± 9      | 97 ± 4        | 90 ± 8      |

T0, before iloprost; T1, 30 min after iloprost; T2, 60 min after iloprost; BiVH, biventricular heart; UVH, univentricular heart; *=p < 0.05 versus T0; +=p < 0.05 versus BiVH; MAP: Mean Arterial Pressure; MPAP: Mean Pulmonary Artery Pressure; CVP: Central Venous Pressure.

Table 4 - Concomitant vasoactive and inotropic therapy after weaning off CPB

| Drug and dosage | n (%) |
|-----------------|-------|
| Milrinone (0,5 μg x kg x min⁻¹) | 30 (97) |
| Dobutamine (10 μg x kg x min⁻¹)  | 1 (3)   |
| Norepinephrine (0,03 - 0,3 μg x kg x min⁻¹) | 11 (35) |
| Epinephrine (0,17 μg x kg x min⁻¹) | 1 (3)   |
| Vasoactive-inotropic score (VAS) |     |
| VAS < 10       | 21 (68) |
| VAS 10 - 14    | 1 (3)   |
| VAS 15 - 19    | 4 (13)  |
| VAS 20 - 24    | 1 (3)   |
| VAS ≥ 25       | 4 (13)  |

Cumulative Vasoactive-inotropic score (VAS) described by Gaies et al.
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(10). Although a tested ultrasonic nebulizer was used that provided an aerosol with a mass median diameter of the droplets of 3.4 μm, the effective dose also depends on the assembly of the breathing system. The effectiveness of administration in our set up was only 20 -30 % of the filled-in dosage of iloprost. Based on this findings, the effective dosage in the present study was 500 to 750 ng x kg-1 which is higher than the previously reported theoretical alveolar deposition of 250 ng x kg-1 over a 10 minutes period (14). However, a dose increase up to 2000 ng x kg-1 has recently been reported to achieve a clinical response (15). This data clearly emphasize the importance of the delivery system when illo is used.

In the presented set up illo decreases MPAP/MAP by 28% and 31% after 30 and 60 min, respectively. This effect was observed in patients with biventricular physiology as well as in patients with univentricular physiology. Favorable effects of illo on MPAP and oxygen saturation after weaning off CPB has been reported by Limsuwan et al. in a small mixed group of patients undergoing corrective biventricular or palliative univentricular surgery (15). A decrease in MPAP together with an improved oxygen saturation suggests an increase in transpulmonary blood flow. However, an improvement in pulmonary mismatch could also explain the increase in oxygen saturation. This effect of illo has been described in animal models of acute respiratory failure and ischemia-reperfusion injury (16, 17). Although we observed a decrease of MPAP/MAP after illo in all patients non-responders to illo were reported during pulmonary vasoreactivity testing in children with long-standing pulmonary hypertension related to congenital heart disease (18). No serious adverse event (i.e. airway irritation, increased postoperative bleeding) was observed in our series. A systemic spill over may be the cause why a vasopressor had to be administered in 35 % of the patients receiving illo to obtain stable hemodynamics (19). Otherwise all patients requiring vasopressor support were treated with milrinone; an inotropic agent with significant vasodilator properties. However, the dosage of milrinone has not been changed during the study period.

The main study limitations are the retrospective nature of the chart review, the absence of a control group, and the limited sample size of 31 patients. However, the presented cohort is larger in size to other published reports. Furthermore, an AMS was used to identify patients treated with illo as well as to generate and review hemodynamic and intervention data. This should minimize the risk of personal bias. The timing of all interventions influencing the pulmonary circulation has been exactly reviewed. It should be pointed out that ventilation with oxygen, and inotropic support were started before weaning from CPB. This therapy was not changed after weaning from CPB indicating that the observed decrease in MPAP/MAP can be attributed to illo or it can be an effect of time. However, 87% of the patients in this series needed pulmonary vasodilators for a median of 6 days during their postoperative course making the passage of time as the main cause for the observed hemodynamic changes after weaning from CPB not very likely.

In summary, we have shown in a retrospective observational study that a single filled-in dose of 2.5 μg x kg-1 iloprost results in an effective delivered dose of 500 to 750 ng x kg-1 after 20 min inhalation with an ultrasonic nebulizer integrated in a pediatric breathing system. This dosage decreases the MPAP/MAP-ratio for at least 60 minutes. In our series, analyzing the off label use of inhaled iloprost, we observed no non-responder and no rebound phenomenon, two problems reported to be of relevance when iNO was used (7, 20). No
major side effects occurred, but vasopressor support was necessary in 35% of the patients. However, the retrospective design and the limited number of patients treated with illo warrants further studies to define the role of inhaled iloprost in the treatment of pulmonary hypertension after congenital heart surgery.

REFERENCES

1. Celermajer DS, Cullen S, Deanfield JE. Impairment of endothelium-dependent pulmonary artery relaxation in children with congenital heart disease and abnormal pulmonary hemodynamics. Circulation 1993; 87: 440-6.
2. Hopkins RA, Bull C, Haworth SG, et al. Pulmonary hypertensive crises following surgery for congenital heart defects in young children. Eur J Cardiothorac Surg 1991; 5: 628-34.
3. Brown KL, Ridout DA, Goldman AP, et al. Risk factors for long intensive care unit stay after cardiopulmonary bypass in children. Crit Care Med 2003; 31: 28-33.
4. Schulze-Neick I, Li J, Penny DJ, Redington AN. Pulmonary vascular resistance after cardiopulmonary bypass in infants: Effect on postoperative recovery. J Thorac Cardiovasc Surg 2001; 121: 1033-9.
5. Bauer J, Dapper F, Demirakça S, et al. Perioperative management of pulmonary hypertension after heart transplantation in childhood. J Heart Lung Transplant 1997; 16: 1238-47.
6. Halioglu O, Dilber E, Celiker A. Comparison of acute hemodynamic effects of aerosolized and intravenous iloprost in secondary pulmonary hypertension in children with congenital heart disease. Am J Cardiol 2003; 92: 1007-9.
7. Bauer J, Thul J, Valeske K, et al. Perioperative management in pediatric heart transplantation. Thorac Cardiovasc Surg 2005; 53: 155-8.
8. Hwang SJ, Lee KH, Hwang JH, et al. Factors affecting the response to inhaled nitric oxide therapy in persistent pulmonary hypertension of the newborn infants. Yonsei Med J 2004; 45: 49-55.
9. Macrae DJ, Field D, Mercier JC, et al. Inhaled nitric oxide therapy in neonates and children: Reaching a european consensus. Intensive Care Med 2004; 30: 372-80.
10. Müller M, Scholz S, Kwapisz M, et al. Use of inhaled iloprost in a case of pulmonary hypertension during pediatric congenital heart surgery. Anesthesiology 2003; 99: 743-4.
11. Gorenflo M, Gu H, Xu Z. Peri-Operative pulmonary hypertension in paediatric patients: Current strategies in children with congenital heart disease. Cardiology 2010; 116: 10-7.
12. Gaiés MG, Gurney JG, Yen AH, et al. Vasoactive-Inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med 2010; 11: 234-8.
13. Scypinski S, Lanzano RL, Soltero RA. Determination of iloprost in 5% dextrose in water solution by reversed-phase high performance liquid chromatography. J Pharm Sci 1990; 79: 934-7.
14. Rimensberger PC, Spahr-Schopfer I, Berner M, et al. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: Vasodilator capacity and cellular mechanisms. Circulation 2001; 103: 544-8.
15. Limsuwan A, Wanitkul S, Khosithseth A, et al. Aerosolized iloprost for postoperative pulmonary hypertensive crisis in children with congenital heart disease. Int J Cardiol 2008; 13: 129-335-8.
16. Schermuly RT, Leuchte H, Ghofrani HA, et al. Zardaverine and aerosolised iloprost in a model of acute respiratory failure. Eur Respir J 2003; 22: 342-7.
17. Lockinger A, Schütte H, Walmrath D, et al. Protection against gas exchange abnormalities by pre-aerosolized PGE1, iloprost and nitroprusside in lung ischemia-reperfusion. Transplantation 2001; 71: 185-93.
18. Limsuwan A, Khosithseth A, Wanichkul S, Khowsathit P. Aerosolized iloprost for pulmonary vasoreactivity testing in children with long-standing pulmonary hypertension related to congenital heart disease. Catheter Cardiovasc Interv 2009; 73: 98-104.
19. Olsewski H, Rohde B, Behr J, et al. Pharmacodynamics and pharmacokinetics of inhaled iloprost, aerosolized by three different devices, in severe pulmonary hypertension. Chest 2003; 124: 1294-304.
20. Atz AM, Adatia I, Wessel DL. Rebound pulmonary hypertension after inhalation of nitric oxide. Ann Thorac Surg 1996; 62: 1759-64.

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