INTRODUCTION

Pulmonary hypertension (PH) in neonates is a challenge in neonatal care which causes attenuation in lung perfusion as a result of increased pulmonary vascular resistance that brings hypoxia. Treatment of PH aims selective pulmonary vasodilatation, and inhaled nitric oxide (iNO) is the most effective drug among them. However, the issue that iNO was found to be successful approximately in 70% of infants creates the need of other therapies. Inhaled iloprost, a stable prostacyclin analogue, was stated to be successful in neonatal case reports with some handicaps due to inhalation process as; hypoxia due to connection of inhalation unit among the ventilatory circuit during conventional ventilation and need to pause ventilatory treatment if high frequency oscillatory ventilation (HFOV) are being used. Endotracheal instillation may overcome those problems while resulting beneficial short-term results.

In this report, we present two neonates with PH who were administered iloprost by endotracheal instillation in whom different systemic effects were observed.

CASE REPORT

The presented patients were followed in level-III neonatal intensive care unit (NICU), Gazi University, Turkey.

CASE REPORT

Iloprost Instillation in Two Neonates with Pulmonary Hypertension

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ABSTRACT

Pulmonary hypertension may coexist with certain diseases in neonates. Iloprost inhalation is one of the treatments which cause selective pulmonary vasodilatation. Inhalation is not an easy way of drug administration in mechanically ventilated infants; as some exhibit desaturations during inhalation. Moreover, inhalation of drug requires cessation of mechanical ventilation, if patient is on high frequency oscillatory ventilation. We presented two patients with pulmonary hypertension; term baby with congenital diaphragmatic hernia and preterm baby with respiratory distress syndrome; who had iloprost instillation during mechanical ventilation treatment. Iloprost instillation was well tolerated with no side effects in the term patient with diaphragmatic hernia; whereas severe blood pressure fluctuations were observed in the preterm infant. This report may courage administration of iloprost in term neonates with resistant pulmonary hypertension.


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In this report, we present two neonates with PH who were administered iloprost by endotracheal instillation in whom different systemic effects were observed.

CASE REPORT

The presented patients were followed in level-III neonatal intensive care unit (NICU), Gazi University, Turkey.

Case 1: A 3195 grams male neonate with left congenital diaphragmatic hernia (CDH) was delivered at term. Chest X-ray showed reticulogranular appearance besides the features of CDH. Ultrasound detected the herniated left lobe of liver, spleen, and stomach. Surfactant was administered, sedation and HFOV were started (Draeger-Babylog8000+, Leubeck, Germany). Echocardiography revealed PH (right-to-left shunt from ductus arteriosus, tricuspid insufficiency, dilated right atrium and ventricle with an estimated pulmonary artery pressure (PAP) of 80 mmHg). Our approaches for treatment of hypotension, PH, mechanical ventilation and oxygenation indices of every morning's blood gas analyses are shown in Figure 1. As iNO was unavailable, inhaled iloprost was initiated due to unresponsiveness to other PH treatments. As severe hypoxia after connection of inhaler system occurred, iloprost was instilled via the side tube of double lumen endotracheal tube. Solution containing 20 microgr iloprost in 1 ml (Ilomedin®) was diluted to 10 ml with saline and 1.5 µg iloprost was instilled every 2 hours. Pulse oxygen saturation (SpO₂) were increased above

Figure 1: Case 1: Oxygenation indices of each morning’s blood gas analyses, mechanical ventilation, and approaches for treatment of hypotension and pulmonary hypertension are shown. Vertical bold line indicates the operation time. HFOV = High frequency oscillatory ventilation; NIV = Noninvasive ventilation; OI = Oxygenation index; PH = Pulmonary hypertension; SIMV+VG = Synchronized intermittent mandatory ventilation with volume guarantee.
95% in 15 seconds following instillation. Iloprost was given whenever preductal SpO₂ was below 85%, not frequent than every 2 hours. Dose intervals remained every 2 hours for first 5 days. Operation was performed successfully at fourth postnatal day, and iloprost frequency was decreased by half every 3 day until extubation. During instillation mean arterial blood pressure (MABP) changed not more than 5 mmHg. Estimated PAPs were 50 mmHg on the 8th and 40 mmHg on the 15th day. He was extubated on 16th day, needed oxygen treatment until 40th day and was discharged when he was 3 months old.

**Case 2:** A preterm girl weighting 960 grams, delivered at 29 weeks of gestation by cesarean section due to maternal chorioamnionitis. She was intubated and given surfactant in the delivery room. Synchronized intermittent positive pressure ventilation with volume guarantee (SIMV+VG) was started with 100% oxygen. Chest X-ray was compatible with respiratory distress syndrome. Arterial blood gas analysis showed normocarbia with hypoxemia. Dopamine and dobutamine infusions were started (with MABP of 22 mmHg). Echocardiography revealed PH (PAP=55 mmHg). HFOV was started; however, she did not tolerate HFOV and SIMV+VG was continued. Magnesium sulfate infusion was started for severe hypoxia and increased preductal - postductal SpO₂ difference indicating right to left shunt. Iloprost inhalation and sildenafil treatments were started due to hypoxia. She immediately developed bradycardia when iloprost was given by inhalation unit. Endotracheal iloprost instillation was then performed. Response of MABP and SpO₂ to three iloprost administrations (1.5, 1.0 and 0.5 ug) is shown in Figure 2. Iloprost dose was tapered off because of decline in MABP. Magnesium sulphate was continued for 2 days and sildenafil for 5 days. During NICU follow-up, late-onset sepsis, grade-2 intraventricular hemorrhage, bronchopulmonary dysplasia and stage-III retinopathy of prematurity occurred. She was discharged after 6 months of hospitalization.

**DISCUSSION**

The two reported cases showed that iloprost instillation may be useful in selected patients when other PH treatments were either ineffective or unavailable and inhalation results in side effects. The recommended treatment of severe PH in neonates is iNO. PH associated with respiratory failure in preterms and with CDH are of special interest with some limitations for the administration iNO and may require other pulmonary vasodilatation treatment options. iNO increases cGMP levels thus causes selective pulmonary vasodilatation. However, iNO unresponsiveness was an important issue which occurs in one-third of the treated infants. Prostacyclin activates adenylate cyclase and relaxes vascular smooth muscles. Synthetic prostacyclin (epoprostenol) and prostaglandin analogues (iloprost, beraprost, treprostinil) are one group of the alternative treatment options for PH, which can be administered to neonates. Inhaled prostacyclin is known to improve oxygenation rapidly in neonates with PH and a recent survey stated its common use among neonatologists for refractory hypertension. Iloprost, the stable prostacyclin analog, differs from epoprostenol and seems to be advantageous by having a longer half-life. Iloprost is the most commonly used one among other prostacyclin analogues; and similar to prostacyclin, inhaled iloprost also has shown to be beneficial for increasing saturation and decreasing right-to-left shunts without obvious systemic side effects when administered to preterm with PH due to respiratory distress syndrome, non-ventilated preterms with bronchopulmonary dysplasia, and patients with PH due to cardiac disease, or after surgery. However, inhalation treatment in intubated infants may have some disadvantages as De Luca et al. noticed in their report of two cases; the interruption of mechanical
ventilation treatment if HFOV was being used, and bradycardia-hypoxia due to declines in inspiratory pressures after connecting aerosol unit to ventilatory circuit if conventional ventilation was being used.\textsuperscript{2} We preferred instillation as a way of administration of iloprost to overcome those problems that was also experienced in the presented cases.

Instillation as a route of iloprost administration is reported only in one case report.\textsuperscript{3} Ehlen and Wiebe reported that inhaled and instilled iloprost permanently converted the right-to-left shunting and improved oxygenation in a term neonate with refractory PH and Trisomy 21.\textsuperscript{3} We also experienced rapid oxygenation response in both cases, without an obvious decrease in MABP in the term infant (case 1) contrary to the preterm infant (case 2). Clinical observation of effective pulmonary vasodilation as increase in oxygenation after iloprost instillation lasted for 2 hours as given in literature.\textsuperscript{6} Although PH associated with CDH is a challenge and currently not recommended to be treated with iNO and epoprostenol, three case reports have been reported positive short-term results with inhaled prostacyclin analogues similar to our experience.\textsuperscript{2} Case-1 seems to confirm potential usefulness of iloprost in CDH. Moreover, instillation process avoided disadvantages of inhalation process ventilation.

Epoprostenol, a synthetic prostacyclin, was also reported to result in an improved oxygenation without overt changes in MABP, and achievement of a sustained response when instilled in four preterm infants with persistent PH.\textsuperscript{4} It is excepted that inhaled iloprost and epoprostenol exert similar pulmonary and systemic effects.\textsuperscript{9} On contrary, the authors observed marked decline in MABP with iloprost in the preterm infant, even with a dose of 0.5 µg (case 2), which was less than the doses reportedly administered.\textsuperscript{2} The observed hypotension can be attributed to either relaxation of vascular smooth muscles as a systemic side effect or more probably exaggerated decrease in pulmonary vascular pressure leading to marked left-to-right shunting, as increase in oxygenation occurred simultaneously with hypotension. This observation must be taken into consideration in an NICU, especially that does not perform invasive arterial blood pressure monitorization because blood pressure fluctuations have absolute role in the development of cerebral lesions as intraventricular hemorrhage and adverse long-term outcome.\textsuperscript{10}

In conclusion, instillation, as a way of iloprost administration, seems to be a safe alternative for mechanically ventilated term infants with PH who either unresponsive to iNO or do not tolerate inhalation. It may be particularly useful in NICUs where iNO is unavailable. Iloprost instillation must be avoided in preterms regarding to possible hemodynamic side effects. Further studies are needed to clarify minimal effective dosages for preterms.

REFERENCES