Iloprost Inhalation for the Treatment of Severe Persistent Pulmonary Hypertension of the Newborn, Experience at QSNICH

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Background: *Persistent pulmonary hypertension of the newborn (PPHN) is the most serious condition that causes high mortality in term and post term infants. The authors have an experience of using high frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (iNO) for treatment of this condition with a good result. However, due to high cost of iNo, other pulmonary vasodilators have been use. Sildenafil had some side effects of systemic hypotension. Thus, inhaled iloprost was introduced for treatment of PPHN at our institute.*
Objective: *To evaluate the outcome of inhaled iloprost for the treatment of PPHN.*
Material and Method: *This was a retrospective study. The data from medical records of newborns, diagnosed as persistent pulmonary hypertension of the newborn and had received inhaled iloprost from October 1st, 2008-October 31 st, 2012, were reviewed.*
Results: *Nineteen cases of PPHN treated with inhaled iloprost were reviewed. Male to female ratio was 1.37:1 (11:8). Mean birth weight and gestational age of these patients were 2,997±531.63 grams and 37.9±2.51 weeks, respectively. Meconium aspiration syndrome was the leading underlying cause of this condition. The mortality rate in this study was 21% (4 from 19 cases). After the addition of inhaled iloprost, the oxygen index (OI) in the survivor group decreased significantly at one hour after treatment (from 32.89 to 22.06, 18.76, 13.76 at 1, 6, 12 hours, respectively). Oxygen saturation (SpO_2) continued increasing after treatment in the survivor group (from 82.40% to 92.20%, 95.00%, 95.80% at 1, 6, 12 hours, respectively) with significant difference at one hour. There was a significant difference of OI and SpO_2 between the survivor and non-survivor groups after treatment. Low Apgar score at 5 minutes and early diagnosis of PPHN were found statistically significant different in the non- survivor compared to the survivor groups.*
Conclusion: *Inhaled iloprost could be used as an alternative treatment of PPHN without side effects of systemic hypotension.*

Keywords: *Inhaled iloprost, PPHN*

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Persistent pulmonary hypertension of the newborn (PPHN) is the most serious condition that causes high mortality in term and post term infant. The authors have an experience in using HFOV with iNO for the treatment of this condition with good outcomes[1]. However, the use of sildenafil results in significant systemic hypotension. Inhaled nitric oxide decreases pulmonary vascular resistance in newborns but the cost of treatment is too high for developing country. Olschewski et al report the use of aerosolized iloprost for severe pulmonary hypertension[2]. Iloprost is a carbacyclic analogue of PGI2 that has a plasma half-life of 20 to 30 min[3,4]. When inhaled iloprost can cause preferential pulmonary vasodilation that lasts for 1 to 2 hours[2]. The authors have previously reported a neonate with persistent pulmonary hypertension who failed to respond to oral sildenafil but showed improvement after aerosolized iloprost[5]. Here we report four years experience with using inhaled iloprost for the treatment of severe hypoxemia in infants with

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persistent pulmonary hypertension at QSNICH.

Material and Method

In this retrospective study, cases of PPHN treated with inhaled iloprost from October 2008 to October 2012 in the neonatal intensive care unit at Queen Sirikit National Institute of Child Health were reviewed. Demographic data, vital signs, treatment, complication and laboratory results including echocardiogram were obtained from the medical records of these patients: PPHN was diagnosed based on echocardiogram, which showed right to left shunt at foramen ovale with or without patent ductus arteriosus. Cardiotonic agents were used to support cardiac performance when indicated. The present study was approved by the institutional ethical reviewed board. Inhaled iloprost 500 nanogram per kilogram diluted with normal saline was administered via jet nebulization every two hours.

Exclusion criteria

The newborns, who had cyanotic congenital heart diseases, congenital diaphragmatic hernia, maternal anti-HIV positive, severe congenital anomalies incompatible with life, were excluded.

Statistical analysis

Demographic data are presented as mean $\pm$ SD. Continuous variables were analyzed using t-test or Wilcoxon rank sum tests. Discrete variables were compared by Chi-squared analysis. Multiple two-sided unpaired t-test or one-way analysis of variance with repeated measurement at a level of significance of $p<0.05$ were used to determine any significant change between survivor and non-survivor groups.

Results

Nineteen neonates diagnosed as PPHN were reviewed. The mortality rate was 21.1 percent (4/19). Male to female ratio was 1.4:1 (male 11: female 8 cases). The data was analyzed dividing the patients into survivor and non-survivor groups. There were no statistical significant differences in sex, birth weight, gestational age, number of referral cases and underlying diseases except that the non-survivors were diagnosed earlier as compared to the survivors as shown in Table 1. Meconium aspiration syndrome (MAS) was the leading cause of PPHN (47.37%). Four babies died, two cases from MAS and one from pneumonia and one from hydrops fetalis. Sixteen patients treated with high frequency oscillatory ventilation (16/19 cases, 84.2%). The non-survivors had shorter ventilator and admission days as shown in Table 2. Fourteen cases were initially treated with sildenafil of which thirteen cases failed treatment; inhaled iloprost was added. Five cases were also initially treated with iNO of which two cases showed no improvement; inhaled iloprost was added as shown in Table 3. Before treatment with inhaled iloprost, the survivor group had a higher oxygen saturation level than the non-survivor group and also had a lower oxygen index as shown in Table 4 and 5. At 1, 6, 12 hours after treatment with iloprost, the survivor group showed significant improvement of oxygen saturation and oxygen indexes

Table 1. Demographic data between infants, survivor and non-survivor groups

Characteristic	Survivor (%)	Non-survivor (%)	*p*-value
Number, (cases)	15	4	
Male, (cases)	10(66)	1(25)	0.245
Birth weight, (gram)*	3,050$\pm$523	2,800$\pm$593	0.317
GA, (week)*	38.13$\pm$2.5	37.00$\pm$2.94	0.289
Refer, (cases)**	9(60)	2(50)	1
Apgar score at 5 min*	9.0$\pm$1.77	6.5$\pm$3.80	0.019
Age at diagnosis, (hour)*	39.10$\pm$2.2	9.0$\pm$1.28	<0.0001
Underlying disease, (cases)			
MAS	7(46.6)	2(50)	1
Pneumonia	6(40)	1(25)	0.02
Pneumothorax	2(13.33)	1(25)$^{+}$	0.53
Hydrops fetalis	0 (0)	1(25)	0.21

* = mean $\pm$ SD; refer = from other hospital except Rajavithi hospital; GA = gestational age; MAS = meconium aspiration syndrome; Pneumothorax in MAS^{+}

Table 2. Compare mode of respirators and type of drugs used with iloprost between survivor and non-survivor groups

Characteristics	Survivor n = 15 (%)	Non-survivor n = 4 (%)	*p*-value
Mode of ventilator			
CMV	3 (20)	0 (0)	0.530
HFOV	12 (80)	4 (100)	0.530
Mean airway pressure, cmH_2O*	13.20±3.70	13.50±2.51	0.286
Dopamine + dobutamine	9 (60)	1 (25)	0.300
Dopamine + dobutamine + adrenaline	5 (33.33)	3 (75)	0.250
Length of stay (days)*	26.00±17.76	2.00±1.41	<0.0001
Ventilator needed (days)*	7.86±4.25	2.0±1.41	<0.0001

* = mean ± SD, HFOV = high frequency oscillatory ventilation; CMV = conventional mechanical ventilation

Table 3. Types of vasodilators in this report

Type of drugs: vasodilator	Case (%)
Total sildenafil + iloprost	14 (73.7)
sildenafil (fail)	13 (68.42)
sildenafil + iloprost	1 (5.3)
Total iNO + iloprost	5 (26.32)
iNO (fail)	2 (10.53)
iNO + iloprost	3 (15.79)

decreased consistently. Before treatment, the non-survivor group had lower oxygen saturations and higher oxygen indexes and even after treatment with inhaled iloprost there was little improvement of oxygen saturations and oxygen indexes was still high as shown in Table 4, 5 and Fig. 1. There were no complications seen from inhaled iloprost in any of the patients.

Discussion

Iloprost is a stable analogue of prostacyclin that is associated with a longer duration of vasodilation[2]. The authors have previously reported the use of iNO[1] and aerosolized iloprost for the treatment PPHN[5]. Although iNO is the standard treatment for PPHN and was first reported in 1992[6,7], its use is limited in developing countries due to its high cost. Since 2007[5], there have been some anecdotal reports on the use of inhaled iloprost for the treatment of PPHN from in both term and preterm infants[8-11]. Here, we report 19 cases of PPHN treatment with aerosolized iloprost. The present study shows more positive evidence for the use of inhaled iloprost in PPHN. Meconium aspiration syndrome (47%), which was similar to the other reports, was the most common underlying cause of this condition[1,12]. The mortality rate in this present was 21% which is higher than our previous report of using iNO[1] but less than another report from Thailand by Nakwan N et al which showed mortality rate 34.1%[13]. Nakwan N et al reported on predicting mortality of infants with PPHN from 2008-2010. The response to inhaled iloprost was observed within minutes to one hour with significant difference in oxygen saturation after treatment as in previous reports[5]. In the non-survival group, two patients received only inhaled iloprost and showed an initial response but suddenly deteriorated due to undetected pneumothorax. Regarding the other two non-survivors, one received three vasodilator drugs (iNO, sildenafil and iloprost) and the other got two vasodilator drugs (sildenafil and iloprost) after no response to single therapy. Prostacyclin and sidenafil have different vasodilator effects. The combination of both have a synergistic vasodilator effect[14]. Unfortunately, these patients expired because of severe respiratory failure (each from hydrops fetalis and severe pneumonia). Khorana M et al reported the use of sildenafil for the treatment of PPHN in a prospective study[15]. Systemic hypotension was a significant complication with some patients who did not respond to either volume expander or inotropes[15]. There were no complications with the use of inhaled iloprost in the present study. Therefore, we introduce inhaled iloprost for our patients and no any side effect was reported. There have been reports of fewer side effects with inhaled prostacyclin as compare to intravenous form in adults. However, there has also been concern that the inhaled route may be less effective than the intravenous route of treatment[16]. The responsiveness in treatment of PPHN was shown by significant reduction in OI and improvement in oxygen saturation within minutes and had significantly changed in SpO_2, OI at one and twelve hours after

Table 4. Postduct SpO_2 before and after treatment with iloprost at 1, 6, 12 hours

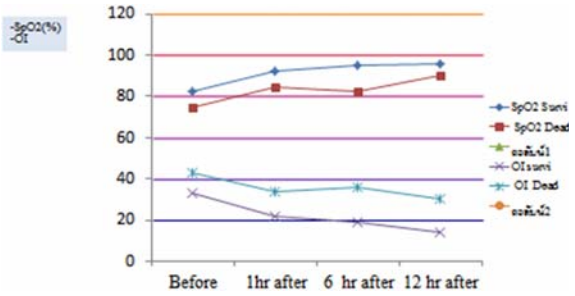
Characteristic SpO_2	Survivor n = 15	Non-survivor n = 4	*p*-value
Before*	82.40±9.48[a]	74.50±9.47	0.55
1 hr after*	92.20±5.78[a]	84.75±9.07	0.02
6 hrs after*	95.00±4.49	82.50±20.73	0.131
12 hrs after*	95.80±3.21[a]	90.00±9.76	<0.0001

* = mean ± SD, a = $p<0.05$

Table 5. Postduct OI before and after treatment with iloprost at 1,6,12 hours

Characteristic OI	Survivor n = 15	Non-survivor n = 4	*p*-value
Before*	32.89±12.29[a]	43.16±11.5	0.10
1 hr after*	22.06±11.87[a]	33.79±10.35	0.003
6 hrs after*	18.76±13.83	36.17±22.04	0.56
12 hrs after*	13.76±9.89[a]	30.7±16.69	0.02

* = mean ± SD, a = $p<0.05$



OI = oxygenation index, SpO_2 = oxygen saturation, hr = hour

Fig. 1 Show SpO_2 and OI before and after 1, 6, 12 hours of treatment.

treatment, respectively.

Conclusion

Inhaled iloprost has a role as an alternative treatment of PPHN without major side effects in a situation where inhaled nitric oxide is not available**.** This is the first report of a cases series of the use of inhaled prostacyclin for the treatment of PPHN.

Potential conflicts of interest

None.

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การใช้ iloprost ชนิดพ่นละอองฝอยในการรักษาภาวะความดันหลอดเลือดปอดสูงในผู้ป่วยทารกแรกเกิดประสบการณ์ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

อุไรวรรณ โชติเกียรติ, มณีวรรณ แจ่มประเสริฐ, มิรา โครานา, วราภรณ์ แสงทวีสิน, วิบูลย์ กาญจนพัฒนกุล

ภูมิหลัง: *ภาวะความดันหลอดเลือดปอดสูงในทารกแรกเกิดเป็นสาเหตุนำของการเสียชีวิตของเด็กทารกที่คลอดครบกำหนดและเกินกำหนด ได้มีการนำ HFOV มาใช้รักษาผู้ป่วยที่มีภาวะความดันหลอดเลือดปอดสูง ร่วมกับการใช้ยาขยายหลอดเลือดในปอดคือ iNO ซึ่งได้ผลดีและต่อมามีการใช้ sildenafil แต่พบมีผลข้างเคียงคือ พบภาวะความดันโลหิตต่ำจึงได้มีการนำยา iloprost ชนิดพ่นมารักษาภาวะความดันหลอดเลือดในปอดสูง*

วัตถุประสงค์: *ศึกษาผลของการใช้ iloprost ชนิดพ่นละอองฝอยในการรักษาภาวะความดันหลอดเลือดปอดสูงในผู้ป่วยทารกแรกเกิด*

วัสดุและวิธีการ: *การศึกษาย้อนหลังโดยรวบรวมข้อมูลจากเวชระเบียนผู้ป่วยทารกคลอดครบกำหนดที่วินิจฉัย PPHN และได้รับการรักษาโดยใช้ inhaled iloprost ศึกษาข้อมูลโดยใช้แบบบันทึกข้อมูลที่ออกแบบไว้ เก็บข้อมูลย้อนหลังตั้งแต่วันที่ 1 ตุลาคม พ.ศ. 2551 ถึง ตุลาคม พ.ศ. 2555*

ผลการศึกษา: *มีทารกเข้าศึกษาจำนวน 19 ราย เป็นเพศชาย 11 ราย (ร้อยละ 57.9) อัตราส่วน ชาย:หญิง 1.37:1 น้ำหนักเฉลี่ย 2,997±531.63 กรัมและอายุครรภ์เฉลี่ย 37.9±2.51 สัปดาห์และโรคดั้งเดิมเป็น MAS เป็นส่วนใหญ่ (47.4%) อัตราการเสียชีวิต 21.1% (4 จาก 19 ราย) หลังจากได้รับยาพบว่า OI มีค่าลดลงโดยกลุ่มรอดชีวิต OI เฉลี่ยก่อนเริ่มยา 32.89 และมีค่าลดลงที่ 1, 6, 12 ชั่วโมง เท่ากับ 22.06, 18.76, 13.76 ตามลำดับ โดยมีนัยสำคัญทางสถิติที่ 1 ชม. และ SpO_2 เริ่มต้น 82.40% มีค่าเพิ่มขึ้น ที่ 1,6,12 ชม. เท่ากับ 92.2.0%, 95.00%, 95.80% ตามลำดับมีนัยสำคัญทางสถิติตั้งแต่ที่ 1 ชม. เป็นต้นไป ค่า OI และ SpO_2 ระหว่างกลุ่มรอดชีวิตและเสียชีวิต มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ หลังให้การรักษาการศึกษานี้พบว่ากลุ่มที่เสียชีวิตมีค่า Apgar score ที่ 5 นาที และระยะเวลาที่ใส่ท่อช่วยหายใจรวมทั้งวันที่นอนโรงพยาบาลต่ำกว่ากลุ่มรอดชีวิตอย่างมีนัยสำคัญทางสถิติ*

สรุป: *การให้ Iloprost ชนิดพ่นละอองฝอย เป็นอีกทางเลือกหนึ่งที่จะช่วยรักษาผู้ป่วยความดันหลอดเลือดปอดสูง ในทารกแรกเกิดทำให้ค่าออกซิเจนดีขึ้น โดยไม่พบมีผลข้างเคียงความดันโลหิตต่ำหลังให้*