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PULMONARY VASODILATORS EFFECT IN BIDIRECTIONAL GLENN ANASTOMOSIS FOR HIGHER GLENN PRESSURES

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Abstract

OBJECTIVE: Bidirectional Glenn operations are commonly performed on patients with a single ventricle as part of the staged surgical management process. Inhaled nitric oxide is a famous pulmonary vasodilator that can be used to treat elevated Glenn pressure following surgery, but still is not offered in many cardiac centers of developing countries. The purpose of this study was to compare the results of inhaled nitric oxide therapy in comparison with a combination of milrinone and sildenafil for management of significant rise in Glenn pressures after this procedure.

Methods: An eighteen-year retrospective study was conducted. After starting pulmonary vasodilator therapy, the change in Glenn pressures was assessed in both groups and compared with baseline parameters. The impact of inhaled nitric oxide therapy was compared with milrinone and sildenafil combination in postoperative marked elevations of Glenn pressures.

Results: Twelve patients were treated with nitric oxide (NO) therapy in group (A) for high rises of **Glenn pressure** (23.4± 2.3 mm Hg). There were significant decrease in Glenn pressure in 10 patients (from 23.2 mm Hg to 18.2 mm Hg, $p < 0.00001$) and significant rise in **partial pressure of oxygen to fraction of inspired oxygen ratio** (from 49.7 to 72.4, $p < 0.01$). There were insignificant reductions in **inotrope score** (from 14.5 to 11.2, $p < 0.3$) in the responsive patients. There were two patients who did not respond at all. **Thirteen** patients were placed on milrinone and sildenafil Combination therapy in group (B) for marked rises in Glenn pressures (25.1± 3.1 mm Hg). In the eleven patients, there were decreases in **Glenn pressures** (from 25.1 mmHg to 17.9 mm Hg, $p < 0.00001$) and significant rise in **partial pressure of oxygen to fraction of inspired oxygen ratio** (from 50.2 to 74.3, $p < 0.01$). There was coincident insignificant decrease in **inotrope score** (from 15.1to 13.9, $p < 0.68$) in the responsive patients. There were three patients who did not respond.

Conclusion: Patients who have markedly elevated Glenn pressures following bidirectional Glenn anastomosis benefit from inhaled nitric oxide versus combination therapy of milrinone and sildenafil, which both significantly lower Glenn pressures and improve systemic blood pressure and pulmonary function. Failure of management is attributed mostly for surgical problems.

Introduction

In children with single ventricle physiology, the bidirectional Glenn shunt (BDG) is a procedure that effectively provides pulmonary blood flow by redirecting systemic venous blood from the superior vena cava to both lungs. In the staged surgical management of children with single ventricle, this procedure has become a well-established practice, based on the early experimental work of Carlon and colleagues (1) and later carried out for the first time by Haller and colleagues (2) in 1966. However, despite preoperative evaluations that include cardiac catheterization, some of these children exhibit postoperative complications, such as low systemic oxygen saturations (3), higher Glenn pressures, and superior vena cava syndrome (4). For these patients, inhaled nitric oxide (NO), a selective pulmonary vasodilator, is usually used the first line of management in the early postoperative phase.

The prototype phosphodiesterase-5 inhibitor sildenafil is authorized for use as an enteral pulmonary vasodilator in the treatment of infants (5). When NO is unavailable or not advised for use in neonates, sildenafil is currently used to treat pulmonary hypertension (6). Another potential treatment option for NO-resistant pulmonary hypertension is milrinone, an intravenous phosphodiesterase-3 inhibitor. It has also been referred to as an "inodilator" due to its dual effects as a vasodilator that occurs independently of β1-adrenergic receptor stimulation (6).

Lack of NO in many cardiac centers stimulates us to provide alternatives in cases of pulmonary hypertension. There is little data supporting the use of NO after surgery in children undergoing BDG, and the results are conflicting (7– 10). The aim of the present study was to compare the results of inhaled nitric oxide therapy in comparison with a combination of milrinone and sildenafil for management of significant rise in Glenn pressures after this procedure.

Methodology

A retrospective study was performed in two different cardiac centers. The influence of inhaled nitric oxide treatment in comparison with milrinone and sildenafil combination was analyzed in postoperative marked rises of Glenn pressures. Group (A) included cases in the pediatric cardiac intensive care unit of the Leipzig Heart Center, Germany, from April 1999 to November 2010. Group (B) patients came from pediatric postoperative cardiac surgery intensive care unit of the Assiut University Children Hospital, Egypt, from March 2010 to December 2017. The following demographic information was recorded: baseline oxygen saturations, preoperative cardiac defect, age, weight, and sex. Cardiopulmonary bypass time, aortic cross-clamp time, and surgical operations were investigated in the operation data. Postoperative echocardiography was performed to check for stenosis or pressure gradient across the Glenn shunt.

All of the patients were put on mechanical ventilation using SIMV (synchronized intermittent mandatory ventilation) mode with low pressure support (PEEP 1–4 cm H2O) and tidal volume breaths of 7–11 mL/kg. The goal of the oxygen supply was to maintain an oxygen saturation level of 75–85%. After initial stability and improving in systemic perfusion, patients were quickly weaned and extubated to promote spontaneous ventilation. Epinephrine, dopamine and dobutamine were continuously infused to provide inotropic support. Crystalloid solutions were used to restore fluid volume if the patient needed. The appropriate use of inotropes and fluid intake were based on O2 saturation, pH, systemic blood pressure and heart rate in order to maintain sufficient systemic perfusion (11).

All postoperative Glenn pressures were observed. Patients were put on low (0-2 cm of water) positive end expiratory pressures (PEEP), and their Glenn pressures were recorded. Higher Glenn pressures (> 20 mm Hg) in conjunction with hemodynamic instability and reduced systemic perfusion were considered to be clear elevation of Glenn pressures (11). Inhaled nitric oxide (iNO) therapy was started for **group (A)** patients whose Glenn pressures were noticeably elevated. The patient received a continuous flow of iNO into the ventilatory circuit's inspiratory limb.

Patients were started on 20 ppm of iNO and were raised to 40 ppm if their Glenn pressures did not significantly decrease. If there was no reaction at 40 ppm, the patients were classified as non-respondents. In order to rule out anatomic lesions, non-respondents underwent additional evaluation, which included cardiac catheterization and echocardiography. If a patient's systemic perfusion improved and their Glenn pressures decreased, they were classified as iNO respondents. After a while of stabilization, the responsive patients were weaned off of the iNO in accordance with the institutional weaning protocol.

Combination of milrinone infusion and sildenafil ingestion were started **for group (B)** patients. The two most frequently used intravenous and oral medications for pulmonary vasodilatation in children are milrinone and sildenafil. Milrinone is a phosphodiesterase inhibitor type 3 (PDEI III) and is commonly used to recover heart function after cardiopulmonary bypass. Moreover, this drug has been particularly useful in patients with concomitant pulmonary hypertension (PHTN) (12). The oral phosphodiesterase inhibitor type 5 (PDEI V), sildenafil, has shown to reduce pulmonary vascular resistance (PVR) in patients with chronic PHTN (13). Similarly, the preliminary use of intravenous sildenafil has been effective in reducing postoperative PHTN in children after heart surgery (14). Single ventricle physiology patients display to have endothelial nitric oxide pathway, and it has been postulated that the absence of pulsatile blood flow results in accumulation of endothelin-1 (15–16). In order to lower pulmonary vascular resistance in patients with single ventricle physiology, efforts have been made to achieve these goals. Patients with superior and total cavopulmonary circulation have been shown to have improved exercise tolerance after taking sildenafil (17). Additionally, researches have demonstrated that pulmonary vasodilators reduce vascular resistance and mean pulmonary arterial pressure (18, 19). Patients with single ventricle have been registered to be treated with sildenafil for up to two years without experiencing any significant adverse effects. Therapeutic dose of sildenafil was 2–8 mg/kg/day (20) and of intravenous milrinone was 0.3-0.75 μg /kg/min (20). Milrinone was tapered off slowly over 24–72 h. Because of the potential risk of systemic hypotension, an initial infusion was started at 0.33 μg/kg/min and increase the dose according to clinical condition to a maximum of 0.75 μg/kg/min (21). The patients were kept on oral sildenafil and aspirin after stopping milrinone, and they continued taking these medications for long time after they were discharged from the hospital. After initial stabilization and improvement in systemic perfusion, patients were quickly weaned and extubated to promote spontaneous ventilation. Epinephrine, milrinone and dobutamine were continuously infused for inotrope support, and crystalloid solutions were used for fluid volume resuscitation when needed. PaO2 levels, base deficit, heart rate and blood pressure were used to determine the indication for inotrope use and fluid volume support in order to maintain appropriate systemic perfusion.

The heart rate, systemic blood pressure, inotrope score (22), fluid volume resuscitation and base deficit of every patient in both groups were examined in order to assess systemic perfusion. Samples of arterial blood gas were recorded in order to examine the impact of pulmonary vasodilators on ventilator parameters. The proportion of partial pressure of oxygen to fraction of inspired oxygen (Pao2/Fio2) was computed using the previously mentioned parameters. All patients with high Glenn pressures had their pulmonary vasodilator effects assessed following the start of their treatment.

The statistical program SPSS (SPSS Inc, Chicago, IL) was used to analyze the data.

Mean ± standard deviation is used to express all continuous results.

Categorical comparisons were conducted using Fisher's exact test. The 2-tailed paired t test or the Wilcoxon signed rank tests were used to compare the response to pulmonary vasodilators therapy in both groups after it began with the baseline values prior to the start of pulmonary vasodilators therapy.

Result

A bidirectional Glenn anastomosis with higher Glenn pressure were found in 25 infants over a period of 18 years and were distributed in 2 groups **(Table 1).** Group A included 12 patients that

received NO therapy in the postoperative time for highly elevated Glenn pressures. Group B contained 13 cases that were treated by combination therapy of intravenous milrinone and oral sildenafil for the same reason. The NO was initiated within 4 hours of surgery in pediatric cardiac surgery intensive care unit (PCSICU) or even in the operative room (OR) after surgery. Milrinone was started mostly in operating room and the first doses of oral sildenafil were initiated usually after first 3-6 hours of PCSICU admission via nasogastric tube. There is no significant difference in preoperative oxygen saturation, demographic data or weight between both groups **(Table 2)**. No significant difference was observed in the intraoperative data of patients requiring NO therapy in group A or combined therapy in group B for elevated Glenn pressures **(Table 4)**. Ten of 12 patients in group A underwent additional cardiac procedures: 4 patients underwent atrial septal defect (ASD) enlargement, 3 patients had Pulmonary artery (PA), 2 patients had Patent ductus arteriosus (PDA) ligation and 1 patient had bilateral bidirectional Glenn shunt **(Table 3)**. Six only of 13 patients in group B did additional procedures: 4 patients underwent atrial septal defect (ASD) enlargement, 1 patient had Pulmonary artery (PA) and 1 patient underwent Patent ductus arteriosus (PDA) ligation (Table 3)**.** Two patients (16.7%) had a negative response to NO therapy in group A and 3 patients (23.1%) with milrinone and sildenafil therapy in group B (Table 6). Significant reduction in the Glenn pressures were noticed in both groups after receiving their treatment (P-value=0.00001 in group A and 0.00001 in group B). The Inotrope Score is a tool used to quantify the level of support a patient is receiving from inotropic support, typically used in critical care settings (23).

We used this equation to calculate the score "dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 100 × epinephrine (μg/kg/min) + 100 × norepinephrine (μg/kg/min) + 10 × milrinone (μg/kg/min) + 10,000 × vasopressin (units/kg/min) + 50 × levosimendan (μg/kg/min)". Inotrope score became higher with elevated Glenn pressure to support to maintain systemic perfusion and was associated with a more negative base deficit (p _ 0.019) (Table 5). After starting of therapy, there was an insignificant lowering in inotrope score (P value 0.30 in groups A, 0.684 in group B). But a marginal improvement in the base deficit were noticed in group A (P value *0.070*) and a significant improvement in the base deficit were noticed in group B (P value 0.029) (Table 5). PaO2/FiO2 ratio (P/F ratio) is the ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2 expressed as a fraction, not a percentage). A lower P/F ratio generally indicates poorer oxygenation and more severe lung dysfunction (24). A significant improvement in the P/F ratio (p=0.0094 in group A and p=0.0093 in group B) was recorded in both groups (table 5).

The non-responders to the pulmonary vasodilators therapy were 2 patient in NO group (16.7%) and 3 patients in milrinone-sildenafil group (23.1%) (Table 6). No significant lowering of higher Glenn pressures was observed in those cases. Follow up studies were done and we discovered that the reasons were attributed to surgical problems. So, those group underwent 2nd operative look to fix the complication e.g. Glenn shunt re-anastomosis and Pulmonary artery band. Only one case underwent MAPCAs coiling in cardiac catheterization lab (Table 7).

Discussion

In this study NO and milrinone/sildenafil therapy made a significant decrease in Glenn pressures. It improved the postoperative blood pressure. Glenn pressures reduced from 23.4 mm Hg to 18.2 mm Hg in NO therapy group and from 25.1 mm Hg to 17.9 mm Hg in milrinone/sildenafil therapy group.

The rest of patients with persistent high Glenn pressure (16.7% in NO group and 23.1% in milrinone-sildenafil group) were referred to surgical complications. We know that continuous diffusion of endogenous NO from the pulmonary endothelium induces pulmonary vasodilation and lower pulmonary arterial pressures. Those patients probably have originally poor endogenous nitric oxide giving higher pulmonary vascular resistance and could be aggravated by cardiopulmonary bypass (25). Both factors mostly prompted the significant higher Glenn pressures. Milrinone is an inhibitor of phosphodiesterase III and is usually used to improve cardiac function after

cardiopulmonary bypass plus its effect on associated pulmonary hypertension (26). The sildenafil (oral phosphodiesterase type 5 inhibitor) is known to reduce pulmonary vascular resistance (PVR) especially in patients with chronic PHTN (27).

Response to NO therapy in group A was against some former studies that didn't make a change in postoperative higher Glenn pressure [6, 8]. In those studies, the postoperative Glenn pressures were slightly high (17±2 mm Hg), not significant high like in our study (23.4±2.3 mmHg). The benefit of NO is to induce vasodilatation and lowering the pulmonary pressure even in the use of pulmonary vasoconstriction. So, NO needs significant elevated pulmonary vascular resistance to make its effect (28, 29).

Bidirectional Glenn shunt physiology needs a pressure gradient to secure the flow between the superior vena cava and the pulmonary vasculature. Only slight increases in superior vena caval pressure are enough to overcome a low pressure circuit and any elevation of pulmonary artery resistance in BDG. So, more fluid volume and inotrope support is needed at first to overcome the elevated Glenn pressures and to preserve systemic perfusion (29). Following NO therapy, a noticeable decrease in inotrope score was correlated with a drop in Glenn pressures, which allowed forward flow from the superior vena cava to the pulmonary circulation, improving the single ventricle's stroke volume and systemic perfusion. There is no significant decrease in inotrope score with Milrinone/sildenafil therapy. It may be attributed to the systemic vasodilator effect of milrinone which enhance the rate of vasopressor to counteract the effect of milrinone (30).

An assessment of PaO2/FiO2 ratio (P/F ratio) was used as a tool in our study to evaluate the pulmonary function. The P/F ratio is usually used as a parameter of oxygen gas exchange (31, 32). Accuracy of this index in single ventricle patients is still questionable. But, at least, we can use it to follow the improvement or regression in pulmonary function at different conditions. There are no noticeable improvements in the PaO2 after initiation of pulmonary vasodilators in both groups. But assessment of P/F ratio showed a significant upgrading in the responders patients of both groups. The NO most likely caused this improvement in pulmonary gas exchange by increasing the local alveolar hypoxic response (33) and lowering Glenn pressures, which in turn caused blood flow to be redistributed to lung regions with a better ventilation to perfusion ratio (34). It is known for a cardiopulmonary bypass to impair the intrapulmonary distribution of blood flow and ventilation (V/Q distribution), which regulates pulmonary gas exchange (35). Milrinone and sildenafil mainly enhances pulmonary gas exchange by lowering pulmonary vascular resistance, increasing cardiac output, and reducing pulmonary congestion, which improves ventilation-perfusion matching and oxygenation. However, because of the possibility of systemic hemodynamic effects, its use needs to be closely monitored (36, 37).

We have five patients in this study didn't respond to the pulmonary vasodilators in both group. There are no differences in Glenn pressures, inotrope score and P/F ratio. We discovered surgical lesions in 2 patients of NO group and 3 patients of milrinone-sildenafil group. All 5 patients underwent second surgical look and fixed the reason of Glenn failure. A lack of significant response to pulmonary vasodilators can be Useful to distinguish reversible elevated Glenn pressure from other residual surgical lesions (38).

According to many studies, a preoperative pulmonary artery pressure of less than 15 mm Hg is ideal for performing Bidirectional Glenn shunt (3, 39–42), and operations carried out on patients who have high pulmonary artery pressures are more likely to have a worse outcome (4, 43, 44). BDG patients with high preoperative pulmonary artery pressures and pulmonary vascular resistance could gain benefit from the pulmonary vasodilators. The lack of a 3rd control group, full arterial and venous blood gases follow up, cardiac output data, and pulmonary function tests were among the limitations of our study.

Conclusion

We conclude that in a subgroup of patients with noticeable increases in Glenn pressures following BDG, NO therapy alone or milrinone-sildenafil combination therapy significantly lowers Glenn

pressures and enhances systemic perfusion and pulmonary gas exchange. Patients undergoing BDG who have high preoperative pulmonary artery pressures and pulmonary vascular resistance may benefit from those pulmonary vasodilators. Milrinone-Sildenafil combination therapy proved that can give similar effect of NO therapy. So, it can be used as effective pulmonary vasodilators in hospitals that cannot provide NO gas due to lack of equipment. Surgical lesions should be assessed in patients who do not respond to the pulmonary vasodilators effect.

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Table 1. Cardiac diagnosis:

Cardiac diagnosis	**Group A**	**Group B**
Tricuspid atresia	6	8
Mitral atresia	1	-
Hypoplastic left heart syndrome (HLHS)	1	-
Unbalanced atrio-ventricular septal defect (AVSD)	2	3
Double outlet right ventricle (DORV)	1	1
Double inlet right ventricle (DILV)	1	1

Table 2. Preoperative data of study's patients:

Preoperative data	**Group A**	**Group B**
Patients numbers (No.)	12	13
Age (months)	5.9±2.3	7.3±3.5
Sex (Male/Female)	7/5	8/5
Weight (kg)	5.1±2.1	5.9±2.5
Preoperative oxygen saturation (O2 sat. %)	72.5±2.3	74.5±4.1

Table 3. Intraoperative additional cardiac procedures:

Additional cardiac procedures	**Group A**	**Group B**
Atrial septal defect (ASD) enlargement	4	4
Patent ductus arteriosus (PDA) ligation	2	1
Pulmonary artery (PA) band	3	1
Bilateral bidirectional Glenn shunt	1	-

Table 4. Intraoperative and immediate postoperative data of patients:

Intraoperative data	**Group A**	**Group B**	**P-value**
Operation (OR) time, min.	158.3±35.1	169.4±44.3	0.493
Cardiopulmonary bypass (CPB) time, min.	85.1±27.2	90.3±29.7	0.652

Table 5. Postoperative data of patients:

Postoperative data	Group A (Pre-therapy)	Group A (Post-therapy)	P value	Group B (Pre-therapy)	Group B (Post-therapy)	P value
Glenn pressure, mmHg	23.4±2.3	18.2±2.4	0.00001	25.1±3.1	17.9±2.8	0.00001
Mean blood pressure (MBP), mmHg	57±9.3	60 ± 7.7	0.40	55.9± 8.8	59 ± 6.8	0.34
Heart rate (HR)	159.4±16.7	151.5 ± 16.6	0.26	160.5 ± 14.5	149.5 ± 14.9	0.081
Inotrope score	14.5±8.2	11.2 ± 7.1	0.30	15.1 ± 7.9	13.9 ± 6.9	0.684
PaO2	47.1±15.9	49.2 ± 9.1	0.70	45.9 ± 13.8	48.9 ± 11.1	0.56
PaO2/FiO2 ratio (P/F ratio)	49.7±16.9	72.4 ± 21.6	0.0094	50.2 ± 17.1	74.3 ± 23.4	0.0093
Base deficit	-1.3±2.5	0.6±2.4	0.070	-1.55±2.1	0.7 ±2.6	0.029

Table 6. Pulmonary vasodilators effect on hemodynamics of non-responders:

Postoperative data	Group A (2/12) (Pre-therapy)	Group A (Post-therapy)	Group B (3/13) (Pre-therapy)	Group B (Post-therapy)
Number of patients	2, 16.7%	-	3, 23.1%	-
Glenn pressure, mmHg	21.3±3.8	23.2±4.4	22.1±3.1	24.9±2.6
Mean blood pressure (MBP), mmHg	63.2±11.2	62 ± 6.7	59.9± 7.8	58 ± 7.4
Heart rate (HR)	156.4±12.3	159 ± 14.3	158.5 ± 11.5	161.2 ± 9.9
Inotrope score	14.2±6.2	14.7 ± 6.9	15.3 ± 8.8	15.5 ± 6.4
PaO2	40.2±10	39.1 ± 9	42.2 ± 12	41.1 ± 11
PaO2/FiO2 ratio (P/F ratio)	69.7±16.2	61.2 ± 31.2	67.3 ± 13.4	60.9 ± 16.2
Base deficit	-2±2.9	-2.9±2.3	-2.1±3.3	-3 ±2.9

Table 7. Causes of early failure of Glenn shunt:

Causes of early failure of Glenn shunt	Group A	Group B
Glenn shunt stenosis	1	2
High pulmonary flow (antegrade pulmonary flow)	-	1
Missed Major aortopulmonary collateral arteries (MAPCAs)	1	-
Total	**2/12, 16.7%**	**3/13, 23.1%**