Zagazig University Medical Journal
www.zumj.journals.ekb.eg
Volume29, Issue2, March 2023

Manuscript ID ZUMJ-2108-2309 (R1)

DOI **10.21608/zumj.2021.89415.2309**

ORIGINAL ARTICLE

Post-operative Management of Pulmonary Arterial Hypertension after Surgical Closure of Hypertensive Ventricular Septal Defect in Pediatrics.

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Submit Date 2021-08-06
Revise Date 2021-08-23
Accept Date 2021-08-24

ABSTRACT

Background: In spite of the great improvement in the intensive care management of cases of left to right shunt with pulmonary hypertension and understanding a lot about path physiology of pulmonary hypertension and the use of recent medications and methods to prevent and treat its hazards, it still has less satisfactory outcome after closure in comparison to cases with lower pulmonary artery pressure. Our objective was to evaluate the use of selective oral pulmonary vasodilators in the postoperative period in comparison to anti-failure measures alone.

Results: A retrospective study included 120 patients below two years who underwent surgical closure for hypertensive ventricular septal defect. Patients were divided into two groups each consists of 60 patients. In group I patients received anti-failure drugs only and in group II patients received selective pulmonary vasodilators in addition to anti-failure drugs. The preoperative patients data and echo pressure measurements where comparable among both groups with non-significant difference. The time of ventilation, ICU stay and hospital stay were significantly shorter in group II ($p < 0.05$). The rates of hypertensive crisis and 30-days mortality were higher in group I but without significant difference ($p > 0.05$).

Conclusions: Pulmonary antihypertensive drugs have an important role in lowering the pulmonary artery pressure and give better results after surgical closure of ventricular septal defect.

Keywords: Pulmonary arterial hypertension; Pulmonary hypertensive crisis; Selective pulmonary vasodilators.

INTRODUCTION

The morbidity and mortality of ventricular septal defect (VSD) closure in patients with pulmonary artery hypertension (PAH) is high. Pulmonary hypertensive crisis was the most common cause of postoperative mortality in such patients [1]. Patients with a large VSD and pulmonary hypertension are rarely seen in surgically advanced centers. However, they still account for a significant proportion of congenital heart disease cases in developing countries due to late referral. Severe PAH puts those patients at increased risk of morbidity and mortality after surgical closure of the VSD [2].

The closure of VSD before the age of six months is recommended to prevent the development of a pulmonary vascular disease (PVD) especially when it is large or non-restrictive. Cardiac catheterization is recommended to assess the pulmonary vasoreactivity when there is clinical or echo data alarming for irreversible elevation of pulmonary vascular resistance (PVR) [3].

METHODS

This is a retrospective study including 120 patients with hypertensive VSD who underwent primary surgical closure. The study was conducted from March 2019 to March 2021. Patients were classified into two groups; each one consists of 60 patients.

The first group received only routine anti-failure drugs (Captopril + Furosemide + Spironolactone).

The second group received selective pulmonary vasodilator in the form of tadalafil (1mg/kg/d) once daily or sildenafil (0.5mg/kg/ds) three times daily

immediately post-operative plus routine anti-failure drugs (Captopril + Furosemide + Spironolactone).

Preoperative diagnosis: Intracardiac shun, chamber dimensions and pressure measurements were detailed by echo. Few cases required cardiac catheterization to assess the pulmonary vasoreactivity where the shunt flow was bidirectional or the pulmonary artery pressure was systemic or near systemic.

Surgical technique: all patients of the two groups were operated under cardiopulmonary bypass. Myocardial protection was achieved by topical cooling and coronary perfusion with cold cardioplegic solution. The external morphology of different cardiac chambers and pulmonary artery were inspected, the type and size of the VSDs were identified in all cases. Cases with tricuspid valve incompetence were tested after closure of the VSD.

Ethics approval and consent to participate: the consent (written/verbal) was waived due to the retrospective nature of the study, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

STATISTICAL ANALYSIS

All statistical data were managed using Microsoft Excel program version 7 and SPSS statistical program version 23. Data were described using mean, standard deviation (± SD), frequencies and percentages. Means were compared using Student's test. The Chi-square ($\times^2$) test was performed for qualitative variables. A probability value (P-value) less than 0.05 was considered statistically significant.

RESULTS

The preoperative demographic data and echo pressure measurements where comparable among both groups with non-significant difference (P value > 0.05) as shown in table 1 and 2. Only Four patients in group I and three in group II underwent cardiac catheterization and all had improved PVR after 100% oxygen. Regarding the operative data, we have collected the total cardiopulmonary bypass (CPB) time and the cross-clamp time as shown in table 3. In addition, important events like failure of weaning from CPB or intraoperative development of pulmonary hypertensive crisis were investigated and none of our cases developed such complications.

In the early postoperative period, the need for inotropic support was compared between both groups with considering the type and doses of the drugs as detailed in table 4. We have used the vasoactive inotropic score (VIS) to **quantify the amount of cardiovascular support required by infants postoperatively** and included dopamine, dobutamine, epinephrine, milrinone, vasopressin, and norepinephrine.VIS = dopamine dose (ug/kg/min) + dobutamine (ug/kg/min) + 100×epinephrine dose (ug/kg/min) + 10×milrinone dose (ug/kg/min) + 10,000×vasopressin (ug/kg/min) + 100×norepinephrine dose (ug/kg/min).[4] The early postoperative outcome was compared including the rate of hypertensive crisis, time of mechanical ventilation, intensive care unit (ICU) and hospital stays, and the 30-day mortality as shown in table 5.

In the early postoperative echo (before hospital discharge), there was a highly significant difference in the mean pulmonary artery pressure ($p < 0.001$) and was reflected on RVEDA ($p = 0.007$), RVESA ($p < 0.001$) and TAPSE ($p < 0.001$). However, the left ventricular function and dimensions were not significantly different ($p > 0.05$) as shown in table 6. In the follow up period after 2-3 months, there was a highly significant difference in the mean pulmonary artery pressure ($p < 0.001$) and was reflected on RVEDA ($p = 0.007$), RVESA ($p < 0.001$) and TAPSE ($p < 0.001$). However, the left ventricular function and dimensions were not significantly different ($p > 0.05$) as shown in table 7.

Table (1): age, sex and weight of both groups

		Group I (n = 60)	Group II (n = 60)	p-value
Age (Month)	Range	5 – 20	5 – 24	0.394
	Mean	12.9 ± 5.69	12 ± 5.84	
Weight (kg)	Range	4 – 14	4.5 – 12	0.192
	Mean	8.56 ± 3.1	6.97 ± 1.6	
Sex	Male	38	32	0.267
	Female	22	28	

Table (2): Preoperative echo-cardiographic measurements of the two groups.

Echo measurements		Group I (n = 60)	Group II (n = 60)		p-value
Size of VSD, no (%)	< 0.5 cm	6.6	2	3.3	0.2
	0.5 - 1 cm	76.7	50	83.3	0.181
	> 1 cm	16.7	8	13.3	0.305
Pressure gradient across VSD, no (%)	>60 mmHg	0	0	0	0.999
	30– 60 mmHg	23.3	10	16.7	0.181
	<30 mmHg	76.7	50	83.3	0.181

Echo measurements	Group I (n = 60)	Group II (n = 60)	p-value
Systolic pulmonary artery pressure, mean, mmHg	59.2 ± 9.5	62.4 ± 9.1	0.071
LVEDD, mm	49.71±16.2	52.3±17.91	0.408
LVEF (m mode), (%)	61.05±7.12	62.88±6.52	0.381
RVESA, cm^2	4.37±1.72	4.17±1.05	0.747
RVEDA, cm^2	16.75±3.82	17.82±3.51	0.623
TAPSE, mm	17.12±3.45	18.52± 4.74	0.413

Table (3): Operative data of patients of the two groups

Operative data	Group I (n = 60)	Group II (n = 60)	P – value
Mean total bypass time,min	50.81 ± 8.51	53.26 ± 8.81	0.124
Mean cross clamp time, min	34.08 ± 5.3	35.24 ± 5.68	0.25

Table (4): The need for inotropic support using vasoactive inotropic score (VIS).

		Group I (n = 60)		Group II (n = 60)		P value
		No of patients	%	No of patients	%	
VIS/1st 24h	10	14	23.3	11	18.3	0.502
	10-15	29	48.3	27	45	0.711
	15-20	0	0	2	3.3	0.152
	20-25	13	21.7	11	18.3	0.645
	> 25	4	6.7	9	15	0.141
VIS/2nd 24h	10	12	20	20	33.3	0.098
	10-15	26	43.3	21	35	0.347
	15-20	8	13.3	4	6.7	0.222
	20-25	12	20	12	20	1
	> 25	2	3.3	3	5	0.645

Table (5): Comparison of postoperative outcome of both groups.

Variable	Group I (n = 60)	Group II (n = 60)	P value
Hypertensive crisis, n (%)	5 (8.3)	1 (1.7)	0.092
Time of ventilation, mean,hs	35.58±22.69	25.56±11.33	0.003
ICU stay, mean, days	3.89 ± 1.57	2.69 ± 1.1	0.004
Hospital stays, mean, days	8.95 ± 2.81	7.15 ± 3.88	< 0.001
30-day mortality, n(%)	5 (8.3)	2 (3.3)	0.242

Table (6): Early postoperative echo-cardiographic measurements of both groups

Echo measurements	Group I (n = 60)	Group II (n = 60)	p-value
Systolic pulmonary artery pressure, mean, mmHg	46.2 ± 8.5	39.4 ± 7.1	<0.001
LVEDD, mm	44.76±12.5	41.3±8.55	0.079
LVEF (m mode), (%)	71.05±7.13	69.88±9.52	0.762
RVESA, cm^2	4.37±1.72	4.17±1.05	0.443
RVEDA, cm^2	12.77±4.72	10.81±5.23	0.033
TAPSE, mm	12.18±2.35	10.62± 2.24	<0.001

Table (7): Late postoperative echo-cardio graphic measurements of the two groups.

Echo measurements	Group I (n = 60)	Group II (n = 60)	p-value
Systolic pulmonary artery pressure, mean, mmHg	36.2 ± 6.5	28.4 ± 4.1	<0.001
LVEDD, mm	37.51±14.2	35.3±11.41	0.349
LVEF (m mode), (%)	71.05±7.13	69.88±9.52	0.448
RVESA, cm^2	3.37±1.72	2.47±1.05	<0.001
RVEDA, cm^2	8.81±3.72	7.22±2.51	0.007
TAPSE, mm	14.18±2.35	12.62± 2.24	<0.001

DISCUSSION

It has been well known in the literature that oral sildenafil reduces pulmonary artery pressure and prevents severe pulmonary hypertension which causes hemodynamic instability and oxygen desaturation that accompany the abrupt increase in pulmonary artery pressure or central venous pressure [5].Persistent pulmonary hypertension has been one of the most significant causes of morbidity and mortality after surgical closure of ventricular septal defect [6]. In Egypt, the problem of pulmonary hypertension still represents one of the critical medical problems with congenital heart disease as we still encounter many cases referred late to cardiac surgical centers with significant pulmonary hypertension. This is due to lack of regular routine medical examination and sometimes delayed referral for surgery.

The age of our patients ranged between 5 – 24 months with mean age of 14 ± 5.2 months while, Aydemir et al studied 282 patients below one year old, divided them into 3 groups (< 3, 3-6, 6-12 months). Some patients (older than three months) had severe PH that did not drop after VSD closure despite medical therapy. These patients required prolonged mechanical ventilation that contributed to ventilator associated pneumonia leading to death [7]. Furthermore, when authors like Sharma et al studied older age group (mean 3.2 ± 3 years), they reported significant better outcome in the sildenafil group regarding ventilation time and ICU stay [8]. In the study of Schulze-Neick and coworkers, they studied the effect of pulmonary hypertension on CPB-related inflammation and subsequently the outcome. They found that the median ventilatory time was 1.75 versus 2 days in patients with the lowest pulmonary vascular resistance versus patients significantly higher pulmonary vascular resistance. Furthermore, there was a significant difference regarding cardiopulmonary bypass time and mechanical ventilation time (P <.05) [9].

Similar to our results, Peiravian F and colleagues investigated **42 patients and divided them into 2 groups,** the mean age was higher than ours (5.25 ± 4.70and 3.97 ± 3.20 years in the sildenafil and control groups respectively (p = 0.308**)).** They found significant decrease in the postoperative pulmonary pressure in sildenafil group. Moreover, the rate of pulmonary hypertensive crisis was significantly less compared to the control group (p = 0.02). The time of ventilation was less in sildenafil group (p = 0.013) [10]. Furthermore, Lindberg et al, reported that children with severe PH needed longer ventilation and ICU stay times, and had more circulatory and renal complications than did the other children [11].

In the contrary,Hofer A et al studied 65 patients divided into two groups and found that there is no difference between both groups regarding the

development of hypertensive crisis, the ventilation time, ICU stay or v//x/x/votpnhl[p[he hospital stay[12]. Many series reported that pulmonary hypertensive crisis is a major risk factor for postoperative mortality after surgical closure in hypertensive VSD patients with different percentage reported in the literature [6,11,13].

In our series, we reported 8.3% incidence of pulmonary hypertensive crisis among the first group and 1.7% in the second group which wasless than other reports by Peirvian et al [10] who reported 9.5% an incidence of 9.5% and Ingram and coworkers who reported an incidence of 20% [9]. In our series the mortality was 5(8.3%) in group I versus 2(3.3%) in group II (p = 0.242).Among patients who developed pulmonary hypertensive crisis postoperatively the mortality was high as 3/5 (60%) of group I cases.Hopkins and colleagues prospectively investigated the effect of pulmonary hypertensive crisis on postoperative outcome and observed 54.5% mortality among patients with severe pulmonary hypertension [5] .Similarly, Lindberg and colleagues reported 22.2% mortality after pulmonary hypertensive crisis in their patients [11].

CONCLUSION

Oral selective pulmonary vasodilators are effective therapy for reducing postoperative complications related to pulmonary hypertension. They are safe, easily applied and inexpensive.

STUDY LIMITATIONS: This study is a retrospective study with its drawbacks. The short-term follow-up was not sufficient for drug evaluation. The effect of pulmonary hypertension should be investigated also in older children to differentiate the pulmonary overflow from persistent changes in the PVR.

Competing interests: No conflict

Funding: No external source of funding.

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To Cite:

Rezk, M., Kasab, I., Aglan, B., Saleh, M., Elshafie, E., Post-operative Management of Pulmonary Arterial Hypertension after Surgical Closure of Hypertensive Ventricular Septal Defect in Pediatrics. *Zagazig University Medical Journal*, 2023; (464-468): -.doi: 10.21608/zumj.2021.89415.2309.