

Efficacy and safety of propranolol in infants with heart failure due to moderate-to-large ventricular septal defect (VSD-PHF study) – A prospective randomized trial

Sivasubramanian Ramakrishnan¹, Nirmal Ghati², Ramandeep Singh Ahuja³, Kinjal Niranjan Bhatt⁴, Hem Chandra Sati⁵, Anita Saxena¹, Shyam Sunder Kothari¹

¹Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India, ²Department of Cardiology, Jai Prakash Narayan Apex Trauma Centre, All India Institute of Medical Sciences, New Delhi, India, ³Department of Cardiology, Krishna Hospital and Research Centre, Haldwani, Uttarakhand, India, ⁴Department of Cardiology, Synergy Super Specialty Hospital, Rajkot, Gujrat, India, ⁵Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

- Aims** : The utility of beta-blocker therapy in infants with heart failure (HF) due to significant left-to-right shunt lesions is not known. The study aimed to assess the efficacy and safety of propranolol in infants with HF due to moderate-to-large ventricular septal defect (VSD).
- Methods** : The prospective randomized trial included 80 infants with HF and moderate-to-large VSD, randomly allocated to receive either conventional therapy alone ($n = 40$) or propranolol plus conventional therapy ($n = 40$). The primary endpoint was a composite of all-cause mortality, hospitalization for HF and/or chest infection, and referral for surgery. The secondary clinical outcomes were the individual components of the composite endpoint. In addition, the patients were followed up to detect safety outcomes, for example, bronchospasm, bradyarrhythmia, and worsening HF symptoms.
- Results** : The addition of propranolol therapy to the conventional medications did not result in significant improvement in the primary composite endpoint (32.50% vs. 52.50%; $P = 0.07$). There was a trend toward improvement, but the study is underpowered for this important question. However, propranolol therapy significantly decreased the risk of hospitalization (12.50% vs. 32.50%; $P = 0.03$) and worsening of Ross HF class (5.41% vs. 28.21%; $P = 0.01$) as compared to conventional therapy (estimated number needed to treat = 5). Propranolol did not result in any significant safety concerns in these infants except bronchospasm in an infant.
- Conclusions** : Propranolol therapy in infants with significant left-to-right shunt may prevent worsening in HF symptoms and hospitalization and is well tolerated. However, it does not reduce mortality or need for surgery.
- Keywords** : Beta-blocker, left-to-right shunt, pediatric heart failure, propranolol, ventricular septal defect

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Address for correspondence: Dr. Shyam Sunder Kothari, Department of Cardiology, Cardio-Thoracic Centre, All India Institute of Medical Sciences, West AIIMS Campus, Ansari Nagar East, New Delhi - 110 029, India. E-mail: kothariss100@gmail.com

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INTRODUCTION

Infants with ventricular septal defects (VSDs) often present with heart failure (HF) requiring hospitalization for medical stabilization and, in severe cases, even early surgical closure. These infants with moderate-to-large VSDs need to undergo early surgery because of recurrent HF, lower respiratory tract infections (LRTIs), and failure to thrive before spontaneous closure occurs.^[1] Limited medical therapy options are available for the treatment of infants with systolic dysfunction, including diuretics, digoxin, and angiotensin-converting enzyme (ACE) inhibitors.^[2-4] However, the efficacy of these drugs is not proven in infants with moderate-to-large VSD causing significant left-to-right shunt and pulmonary over circulation. Furthermore, there is a risk of renal failure with the use of ACE inhibitors in infants.^[5]

There is a scarcity of data supporting the use of beta-blockers in pediatric HF. Few nonrandomized studies have shown that treatment with beta-blocker improves functional class and prognosis in pediatric patients with HF.^[6-8] However, a large randomized controlled trial (RCT) of carvedilol in pediatric HF failed to demonstrate improvements in outcomes.^[9] All these trials included patients with left ventricular (LV) systolic dysfunction. Infants with VSD and HF have increased pulmonary blood flow and have seemingly normal LV systolic function. Studies have shown enhanced neurohumoral activation, including the sympathetic system in these infants.^[10,11] Hence, beta-blockers might have salutary effects in these infants with seemingly normal LV function and HF.

Even though left-to-right shunts are the most common cause of HF in infants and young children, only a few small studies have examined the effects of beta-blockers in this setting.^[12-14] Propranolol resulted in improvement in Ross class, serum renin level, and mean heart rate in these studies. However, none of these studies assessed the effects of propranolol on hard clinical endpoints, for example, mortality, HF hospitalization, and referral for surgery.

General anesthesia and cardiopulmonary bypass during corrective surgery for congenital heart disease in infancy are not free of potential complications. Intraoperative embolic stroke, hypoxic-ischemic injury, and resulting developmental, cognitive delays are among the most notable complications.^[15] Hence, a strategy to postpone surgery so that the infant grows and tolerates surgery better may be desirable. Besides, nearly 30%–40% of VSDs are likely to close spontaneously. Furthermore, some VSDs may become small enough with time to obviate the need for surgery. Hence, we sought to study the efficacy of propranolol in the clinical course of infants with moderate-to-large VSD and HF, especially whether

the therapy can have any impact on HF symptoms, hospitalization, mortality, and referral for surgery.

METHODS

Study design

The study was a single-center, prospective, parallel, open-label RCT conducted in a tertiary care referral hospital in India. The clinical study was conducted in accordance with the Helsinki Declaration. The institutional ethical committee approved the study protocol, and the trial was prospectively registered in Clinical Trials Registry – India (<http://ctri.nic.in>; Registration Number: CTRI/2009/091/000525). The patient recruitment started on June 2010, and enrollment was completed on August, 2014. Written consent was taken from parents or legally authorized guardians.

Study population

Infants (age <1 year) with VSD were recruited from the cardiology outpatient department and screened for eligibility. Infants having a moderate VSD and selected infants with large VSD with a history of congestive HF (CHF) were included in the trial. Echocardiographic criteria for moderate VSD were – (i) VSD diameter more than one-third, but less than the size of the aortic orifice, (ii) right ventricular, and pulmonary artery pressure ranging from normal to two-thirds of systemic pressure, and (iii) dilated left-sided cardiac chambers.^[16] Large VSD was defined as VSD with the diameter of the defect equal to or more than the size of the aortic orifice. CHF was defined as episodes of tachypnea, grunting, chest retraction, and diaphoresis during exertion like feeding or at rest in infants with moderate-to-large VSD and pulmonary over circulation. Patients with urgent indications for VSD closure (i.e., significant pulmonary artery hypertension [PAH], uncontrolled severe CHF, significant failure to thrive, hospitalization for CHF, and/or LRTI) were excluded from the trial and referred for early surgical correction. Infants were classified to have “uncontrolled HF” if the HF symptoms were not relieved even after optimal medical therapy (furosemide/spironolactone ± digoxin). Infants with severe HF requiring endotracheal intubation and mechanical ventilation or having hemodynamic instability were also considered as “uncontrolled HF” patients. Large unrestricted VSD with right ventricular and pulmonary artery systolic pressures equal or near (gradient across the defect <10 mmHg) to systemic pressure was considered to have “significant PAH.” Significant failure to thrive was defined as weight <3rd percentile for age, or weight deceleration crossing two percentile lines, or weight <80% of the ideal weight for age.^[17] The exclusion criteria were – prior hospitalization for CHF and/or LRTI, associated congenital cardiac defects

requiring intervention (e.g., coarctation of the aorta and patent ductus arteriosus), asymptomatic status, Down's syndrome and other syndromic disorders, associated major anomalies (e.g., tracheoesophageal fistula) predisposing to chest infection, severe anemia (hemoglobin <9 g%), renal or hepatic dysfunction, and hypersensitivity or contraindication to propranolol usage. Patients whose parents or legal guardians refused to give consent were also excluded from the study.

All the participants underwent a thorough clinical evaluation (including Ross HF class^[18] assessment) and basic laboratory investigations, including electrocardiography (ECG), chest X-ray, hemogram, liver function tests, and renal function tests. The patients also had a detailed echocardiographic examination at the beginning of the study.

All the patients were kept on fixed doses of diuretics (furosemide) and digoxin for a run-in phase of at least 15 days before randomization. The dose of furosemide was 1 mg/kg every 12 h in commercially available oral syrup formulation. The dose of oral digoxin was 10 mcg/kg/24 h. After treatment allocation, the dose of digoxin and diuretics was increased on follow-up as the weight of the child increased, without breaching the maximum dose.

Patient randomization and intervention

A computer-generated table of random numbers was used to randomize the participants in a 1:1 ratio to the "control arm" – continuing conventional treatment alone or the "propranolol arm" receiving propranolol in addition to the conventional medications. Propranolol was started at a dose of 1 mg/kg/day in divided doses and was escalated at weekly intervals to a maximum dose of 4 mg/kg/day. If any patient achieved a mean heart rate of 100/min below the maximum dose, they were continued on the same regimen. However, none of our patients achieved the heart rate target below 2 mg/kg/day dose of propranolol. The heart rate was monitored as a part of general physical examination during visits. Until the infants achieved the maximum target dose of propranolol, they were assessed at a weekly interval for dose escalation.

Follow-up

All the patients were assessed at 2-monthly intervals for 1 year. During each visit, clinical examination, Ross HF class assessments, and ECG were done. All patients were assessed for HF symptoms, LRTI, PAH, and side effects of propranolol – bradycardia and bronchospasm. Echocardiography was performed at baseline, 3rd month, 6th month, and the end of 1-year follow-up. It was done earlier if the primary endpoint was met (e.g., the patient referred for surgery). The treating physician had the authority to send the child for surgery at any moment

during the trial if there were uncontrolled HF and severe PAH. The treating physician also had the ability to stop or modify study intervention in case of any adverse effects. However, there was no significant alteration of HF treatment other than the study drug in both groups that could have affected the outcomes. The study follow-up was considered complete if the subject met the endpoint of referral for surgery.

Outcomes

The primary outcome was a composite endpoint of all-cause mortality, hospitalization for HF and/or LRTI, and referral for VSD closure surgery. Lower respiratory tract infection (LRTI) was defined using the previous version of the World Health Organization criteria.^[19] The secondary clinical outcomes were the individual components of the composite endpoint, i.e., all-cause mortality, hospitalization for HF and/or LRTI, and referral for VSD closure surgery. The safety outcomes were bradyarrhythmia, bronchospastic episodes, and worsening of HF (i.e., increase in Ross HF class by at least one class from baseline). Bradyarrhythmia has been defined as a heart rate <60/min in the presence or absence of any conduction block (sinus pause and atrioventricular block). Bronchospasm was diagnosed by the presence of shortness of breath, cough, and tachypnea with wheezing in chest auscultation.

Statistical analysis

The study involved a group of patients with moderate-to-large VSD and recurrent CHF. Hence, an estimated 75% of patients would require surgery over a 1-year time frame. Since nearly 30%–40% of VSDs reduce in size over time and almost 25% of moderate VSDs spontaneously close,^[1] we assumed that the beta-blocker would reduce the event rate by one-third. Based on the above assumptions, with an alpha error level of 5% (95% confidence interval) and 90% power, the estimated sample size was 62 in each group.

All analyses were performed using the statistical software Stata 14.0 (StataCorp, Texas, USA). Categorical variables were expressed as frequency and percentage. Quantitative variables were expressed as mean ± standard deviation (SD) or median (range). Chi-square/Fisher's exact test was used to compare the proportion of categorical variables between the two groups. Independent *t*-test was used to compare the mean between the two study groups. The mean differences between the baseline and the final value of the LV dimensions (LV end-diastolic inner-dimension [LVEDD] and LV end-systolic inner-dimension [LVESD]) and VSD pressure gradient were calculated and compared between the two study groups using Wilcoxon rank-sum test. Intention-to-treat analysis was carried out using the analysis of worst-case scenarios so that the lost to follow-up patients were assumed to suffer the composite

adverse outcome. A per-protocol analysis was also carried out to validate the result and reported in Supplementary Material. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

A total of 189 infants were screened for eligibility, and among them, 80 patients were included in the trial. Among the excluded patients, 53 patients had an indication of early surgery (9 patients had severe PAH and 44 patients had uncontrolled HF), and 56 patients did not give consent [Figure 1]. Children with associated heart defects were not screened for further eligibility. Although the calculated sample size was 124 (62 in each group), we could recruit 80 patients (40 in each group) due to poor participation in the study over a 4-year period. Two patients in the propranolol group and one patient in the control group lost to follow-up. In addition, one patient discontinued propranolol therapy in the intervention group due to bronchospasm.

Baseline characteristics

The baseline characteristics were similar in the two study groups [Table 1 and Supplementary Table S1]. The mean (\pm SD) age of the patients was 5.12 (\pm 2.64) months and 5.60 (\pm 3.17) months in the control group and propranolol group, respectively. Overall, 16.25% of the study population (8 out of 40 in the conventional group and 5 out of 40 in the propranolol group; $P = 0.55$) at enrollment had a large VSD. However, they were not in need of an immediate surgery. The propranolol

group had more patients in Ross HF Class III compared to the control group at the beginning of the study (35% versus 22.50%; $P = 0.19$). However, the only patient with Ross HF Class IV was in the control group. The use of various drugs, including diuretics, digoxin, and multivitamin supplements, was comparable in both groups. Baseline echo parameters – peak gradient across the VSD, LVESD, and LVEDD – were also comparable. Approximately two-thirds of the VSDs were located in the perimembranous region in both groups. The median follow-up duration was 7 months, with the longest follow-up of up to 32 months. This is because the follow-up was considered to be completed at the time of outcomes such as mortality and heart surgery referrals. Patients who were lost to follow-up (two patients in the propranolol group and one patient in the control group) also contributed to this finding.

Outcomes

The primary composite endpoint occurred in 21 (52.50%) patients of the control group and 13 (32.50%) patients of the propranolol group [Table 2]. This difference did not reach statistical significance despite a trend toward improvement in the propranolol arm ($P = 0.07$). Although an intention-to-treat analysis was done assuming the worse outcome in lost to follow-up patients (two in the propranolol group and one in the control group), the difference remained insignificant even with per-protocol analysis (control = 20 [51.28%] vs. propranolol = 11 [29.73%]; $P = 0.06$) [Supplementary Table S2].

Table 1: Baseline characteristics of the study population

Parameters	Control group (n=40) ^a	Propranolol group (n=40) ^a	P
Age (months)	5.12 \pm 2.64	5.60 \pm 3.17	0.47
Sex			
Male	30 (75)	26 (65)	0.33
Female	10 (25)	14 (35)	
Weight (kg)	4.78 \pm 1.08	4.70 \pm 1.44	0.79
Ross HF class			
I	9 (22.50)	13 (32.50)	0.19 ^b
II	21 (52.50)	13 (32.50)	
III	9 (22.50)	14 (35.00)	
IV	1 (2.50)	0	
History of LRTI	24 (60)	20 (50)	0.37
Hemoglobin (g/dl)	10.50 \pm 1.42	10.53 \pm 1.19	0.89
Furosemide dose (mg/day)	6.05 \pm 2.26	6.01 \pm 2.22	0.94
Furosemide dose (mg/kg/day)	1.29 \pm 0.48	1.28 \pm 0.50	0.89
VSD pressure gradient (mmHg)	38.67 \pm 15.92	41.87 \pm 15.28	0.39
LVESD (mm)	15.18 \pm 3.15	14.48 \pm 2.89	0.33
LVEDD (mm)	25.78 \pm 3.76	25.48 \pm 3.83	0.74
VSD sites			
Perimembranous	24 (60)	24 (60)	0.61 ^b
Subaortic	4 (10)	6 (15)	
Muscular	6 (15)	7 (17.50)	
Subaortic + perimembranous	3 (7.50)	2 (5)	
Inlet	3 (7.50)	0	
Outlet	0 (0)	1 (2.50)	
Follow-up duration (months)	7.57 \pm 6.56	6.89 \pm 2.61	0.55

^aValues are mean \pm SD or frequency (%), ^bFisher's exact test. HF: Heart failure, LRTI: Lower respiratory tract infection, VSD: Ventricular septal defect, LVEDD: Left ventricular end-diastolic dimension, LVESD: Left ventricular end-systolic dimension, SD: Standard deviation

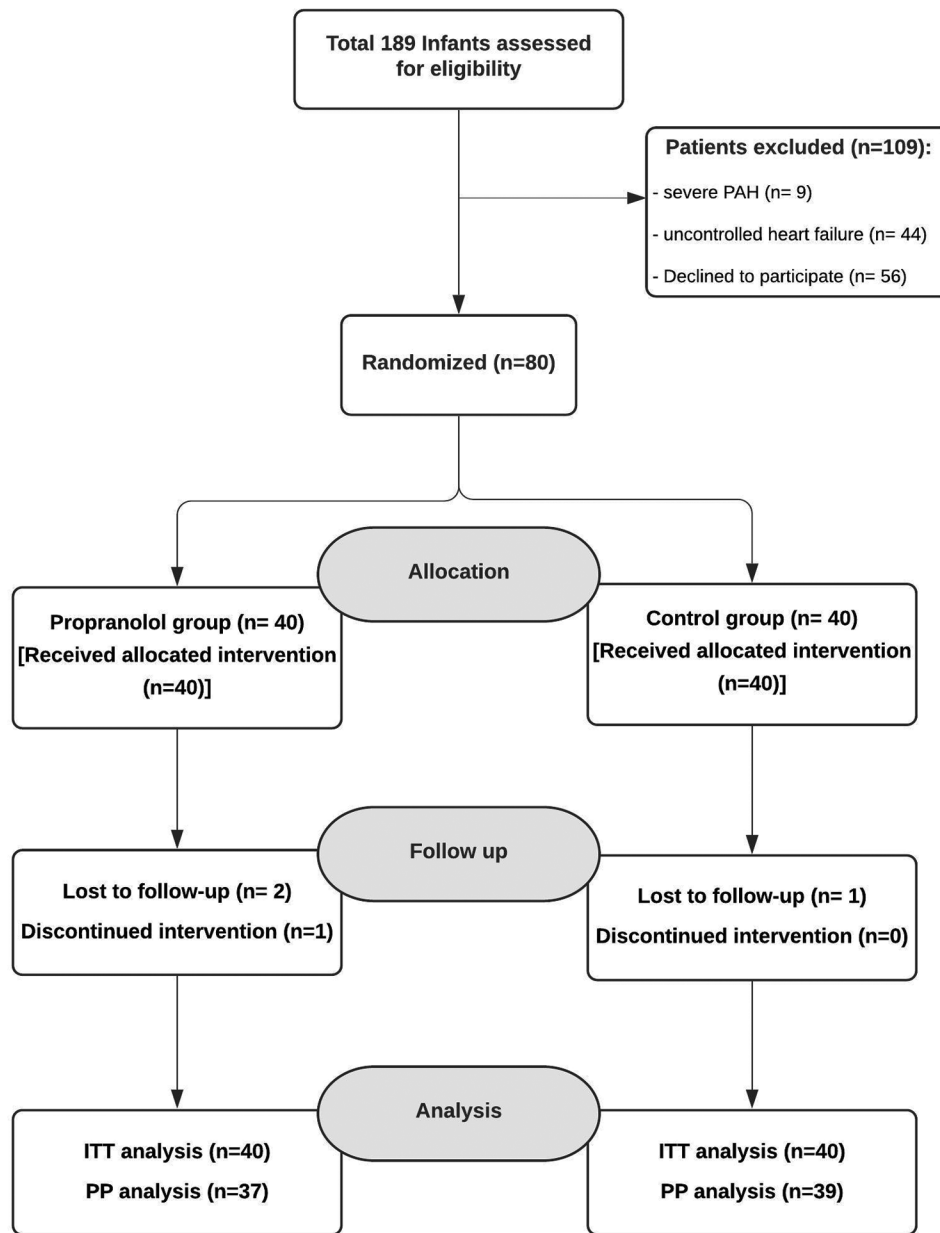


Figure 1: Trial consort diagram showing recruitment, randomization, and analysis of the study population. PAH: Pulmonary artery hypertension, ITT: Intention-to-treat, PP: Per-protocol

Table 2: Frequency of primary and secondary endpoints in the study groups

Adverse outcomes	Intention-to-treat analysis ^a		P
	Control group, n (%)	Propranolol group, n (%)	
Primary composite endpoint ^b	21 (52.50)	13 (32.50)	0.07
Secondary endpoints			
All-cause mortality	3 (7.50)	3 (7.50)	1.00 ^d
Total hospitalization (either HF or LRTI) ^c	13 (32.50)	5 (12.50)	0.03
Hospitalization for HF	11 (27.50)	4 (10.00)	0.08 ^d
Hospitalization for LRTI	4 (10.00)	4 (10.00)	1.00 ^d
Referrals for surgery	11 (27.50)	11 (27.50)	1.00

^aIntention-to-treat analysis (n=40 in both groups); worst outcome assumed in lost to follow-up patient (1 patient in the control group, 2 patients in the propranolol group), ^bPrimary composite endpoint: Composite endpoint of all-cause mortality, hospitalization for HF and/or chest infection, and referral for VSD closure surgery, ^cTotal hospitalization: Hospitalization due to either HF or LRTI, ^dFisher's exact test. Bold values are significant (P<0.05). HF: Heart failure, LRTI: Lower respiratory tract infection, VSD: Ventricular septal defect

Regarding the per-protocol analysis of secondary endpoints, two patients (5.13%) in the control group and one patient (2.70%) in the propranolol group expired ($P = 1.00$). All three had been referred for surgery and were awaiting the same [Supplementary Table S2]. A significantly lower number of infants in the propranolol group needed hospitalization for worsening of HF and/or LRTI than in the control group (8.11% vs. 30.77%; $P = 0.02$). This difference is mainly due to a significantly lower number of HF hospitalization in the propranolol group (5.41% vs. 25.64%; $P = 0.02$). There was no significant difference in the referral for surgery: 10 patients in the control arm (25.64%) as compared to 9 patients in the beta-blocker arm (24.32%; $P = 0.89$). The intention-to-treat analysis of secondary endpoints also showed similar results, except the HF hospitalization rate, which did not differ significantly [Table 2]. However, there was a trend toward a lower HF hospitalization rate in the propranolol group in comparison to the control group ($P = 0.08$).

Safety endpoints

In one patient, propranolol was stopped by her pediatrician due to severe bronchospasm [Table 3]. This occurred about 3 months after starting the drug. The treating pediatrician withheld propranolol and managed her with a bronchodilator (salbutamol). The child did not require hospitalization, and the problem resolved within a few days. Propranolol was discontinued, and during follow-up, the child did well without any compelling need for surgery or progression in HF symptoms. There was one episode of bradycardia in a patient in the control arm. The electrocardiogram revealed sinus pauses. This patient was on digoxin, which was then discontinued. The child was then managed conservatively during the rest of the follow-up period without any worsening of HF symptoms or LRTI. Worsening of HF (worsening of Ross HF class by at least one class from baseline) occurred more frequently in the conventional treatment arm (11 patients; 28.21%) than the propranolol arm (2 patients; 5.41%), and this was statistically significant ($P = 0.01$).

Echocardiographic parameters

In both groups, there was a significant increase in the final VSD pressure gradient from the baseline ($P < 0.01$

for both arms). Total 7 out of 24 patients (29.17%) who did not achieve the primary endpoint/lost to follow-up in the control arm and total 7 out of 17 patients (41.18%) who did not achieve the primary endpoint/lost to follow-up in the propranolol arm reached a VSD pressure gradient >70 mmHg at the end of the study ($P = 0.51$). In addition, three patients (7.5%) in the propranolol group achieved spontaneous closure of VSD. However, at the end of the study, there was no significant intergroup difference in any echocardiographic parameters [Table 4]. Of special note, one child in the control arm developed infundibular obstruction (Gasul’s phenomenon)^[20] with a right ventricular outflow tract gradient of 60 mmHg. It occurred within 7–8 months of age, and the child underwent successful surgery at 1.5 years of age.

DISCUSSION

In this randomized controlled, open-labeled, single-center trial, the addition of propranolol to conventional therapy did not result in a significant reduction in the composite primary endpoint even though there was a trend toward improvement. However, propranolol significantly reduced hospitalizations (due to HF ± LRTI) and prevented worsening of HF symptoms in infants with VSD and HF. The therapy was well tolerated, and the reduction in hospitalization or worsening of symptoms was impressive, with a number needed to treat only five infants.

The mechanisms of HF in VSD are not fully understood and cannot be explained by the established paradigms of HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction.^[21-23] Infants with HF due to left-to-right shunt lesions do not suffer from LV systolic dysfunction. A large left-to-right shunt at the ventricular level increases pressure in the pulmonary vascular bed, and intravascular volume increases as a compensatory mechanism. Consequently, there are significant LV volume overload and raised LV filling pressure, especially during exertion. Recent reviews have suggested that HF in VSD is a complex phenomenon with hemodynamic alterations and neurohumoral responses that are further influenced by genetic and epigenetic factors.^[23]

The augmented adrenergic system and catecholamine surge shown in infants with VSD^[10,11] help to maintain the cardiac output in the initial stages by increasing the heart rate, myocardial contractility, and peripheral vasoconstriction.^[24,25] However, studies in adults with HF have shown that the augmented adrenergic system leads to desensitization and alteration of β -1: β -2 adrenergic receptor ratio in the failing heart in the chronic phase. This ultimately results in maladaptive cellular remodeling (e.g., fibrosis and apoptosis) and myocardial injury.^[25-27] Limited studies have shown similar changes

Table 3: Frequency of safety endpoints in the study groups

Side effects	Control group (n=39) ^a	Propranolol group (n=37) ^a	P
Worsening HF class ^c	11 (28.21)	2 (5.41)	0.01^b
Bronchospasm	0	1 (2.70)	0.99
Bradycardia	1 (2.56)	0	0.99

^aValues are frequency (%), ^bFisher’s exact test, ^cIncrease in ross HF class by at least one class from the baseline value. Bold values are significant ($P < 0.05$). HF: Heart failure

Table 4: Difference between the baseline and final values of the echocardiographic parameters of the study populations

Echocardiographic parameters	Mean±SD		P
	Propranolol group (n=37)	Control group (n=39)	
LVEDD (mm)			
Baseline	25.3±3.8	25.8±3.8	0.62
Final	27.4±4.1	27.1±4.3	0.79
Mean change	1.8±5.3	0.5±4.9	0.36
LVESD (mm)			
Baseline	14.4±3	15.1±3.2	0.32
Final	16.2±3.2	15.9±3.3	0.80
Mean change	1.9±2.7	0.3±3.3	0.14
VSD pressure gradient (mmHg)			
Baseline	41.6±15.4	38.5±16.1	0.41
Final	64.5±25.8	58.25±19.4	0.38
Mean change	20.5±25.9	18.1±16.7	0.67

SD: Standard deviation, VSD: Ventricular septal defect, LVEDD: Left ventricular end-diastolic dimension, LVESD: Left ventricular end-systolic dimension

in pediatric HF.^[24,28] Beta-blockers not only suppress the adverse effects of chronic adrenergic activation but also may reduce left-to-right shunt by systemic vasodilatation, contribute to sodium and water avidity by inhibiting renal sympathetic activation,^[29] decrease the rise in serum creatinine with ACE inhibitors,^[30] and modulate the excess neurohumoral activation associated with diuretic use. Another hypothesis is that congenital heart disease may result in cytokinesis failure leading to decreased cardiomyocyte proliferation in infants' hearts mediated by activation of the Hippo tumor suppressor pathway.^[31] The Hippo tumor pathway is activated by β -adrenergic receptors.^[32] A recent study has shown that β -adrenergic blockage by propranolol can rescue cytokinesis failure and increase cardiomyocyte division in neonatal mice and human cardiomyocytes *in vitro*.^[31] However, this needs to be verified in prospective human trials.

While beta-blockers are established agents for HFrEF in adults,^[33-35] their role in pediatric HF failure is not as well established. Several small nonrandomized studies have reported a beneficial effect of beta-blockers in pediatric HF of diverse etiologies.^[6-8] However, in a large prospective randomized trial, carvedilol did not result in significant improvement in the HF outcomes in children with HF and ventricular dysfunction.^[9] There might be several reasons for the apparent lack of benefit of beta-blockers in that trial.^[36] The study population in that trial was quite different from our study. Only 14% of patients were suffering from CHD and a dysfunctional systemic LV. The median age range was 1.8–3.6 years in the different treatment arms. In comparison, our study included only infants (age <1 year) with moderate-to-large VSD and significant left-to-right shunt. In a subgroup analysis, the authors reported a trend toward benefit in those with systemic LV compared to the systemic right ventricle, supporting our finding. Some translational and clinical studies in pediatric HF have also identified important differences in the pathogenesis and molecular mechanisms as compared to adult HF.^[21]

Pediatric HF trials are generally difficult to conduct, and most trials suffer from heterogeneous patient groups or lack of power due to small numbers.

Limited studies have tested the effects of beta-blockers exclusively in infants with VSD. A prospective, randomized study of propranolol in infants with CHD and left-to-right shunt included a total of 20 patients with 10 infants (age <3 months) treated with digoxin and diuretics alone.^[12] After 17 days of propranolol treatment, the infants showed significant improvement in Ross HF score, lower renin levels, and lower heart rate on Holter monitoring, suggesting that the addition of propranolol can effectively reduce neurohormonal activation. Another retrospective study included a total of 22 infants with a left-to-right shunt. Half of the infants were treated with propranolol and half with captopril. Propranolol was more effective than captopril in reducing Ross HF score, shortening hospital stay, and lowering plasma renin activities.^[13] Both these studies included a smaller number of patients and were of shorter duration. An observational study that evaluated six infants with significant left-to-right shunt and refractory HF reported a significant decrease in HF score and neurohumoral activity with propranolol therapy.^[14] However, the study population had complex congenital heart disease with VSD as a part of other structural defects. A recent systematic review^[37] that included a total of 420 participants from seven prospective randomized trials (including the conference abstract from our group based on this study^[38] and another unpublished RCT^[39]) suggested that beta-blocker therapy may improve CHF symptoms in the pediatric population. However, the evidence supporting its regular use as a measure to reduce mortality is still very weak. However, this systematic review included children with both shunt lesions and LV systolic dysfunction.

We have treated all patients with diuretics and digoxin as conventional medical therapy. We have decided to use propranolol as it is one of the well-studied beta-blockers

in VSD with HF and because of its familiarity of use (especially in decreased pulmonary blood flow physiologies) and low cost. Contrary to popular belief, the evidence base for ACE inhibitors in VSD with HF is limited. Furthermore, our national guidelines on drug therapy do not recommend the regular use of ACE inhibitors in HF secondary to left-to-right shunt.^[40] We do not use ACE inhibitors in our institute, because of its lack of proven efficacy and associated harm, especially in infants.^[2,5]

Our study had several limitations. Although the sample size was larger than the previous trials of VSD with HF, the study was still underpowered to detect the effects of propranolol in reducing mortality and the need for early surgery. One of 40 infants needed discontinuation of propranolol, and the safety also needs to be confirmed with larger sample size. The calculated sample size was 62 in each group, but we could enroll only 40 patients in each group. Furthermore, contrary to the plan at the start of the trial, we could enroll only 16.25% with large VSD, which significantly reduced the event rates and the power of the study. There were logistic constraints of an investigator-initiated nonfunded study in continuing the trial till complete enrollment. As such, the power of the study for primary endpoint is only 43.9%, but the effects on hospitalization were remarkable. With the current observed rates of the primary outcome, 95 patients are needed to be recruited in either group for an adequately powered (80%) trial. Further, we excluded sicker infants with uncontrolled HF needing immediate surgery, which decreases the event rates and the power of the study. However, denying early surgical repair in these infants may be unethical.

Most of the hospitalizations were in the local hospitals, and as a result, there was a lack of standardized criteria for hospitalization. However, various physicians involved in the decision-making about hospitalization of the study participants were unaware of the study endpoints. This, in fact, could be an advantage for the adjudication of endpoints of the study. Furthermore, the open-label design could introduce bias in the family's reporting of symptoms and the assessment of study endpoints. However, the need for surgery was not significantly different between the two arms. Blinded assessment of clinical outcomes, growth parameters, echocardiographic measures, and use of additional biomarkers could have added value to the trial. Age-based Ross HF score and the New York University Pediatric HF Index could have been used instead of the traditional Ross score.^[41]

Management of large VSD should be surgical and medical management at best is a temporizing measure. Hence, it may seem unethical that the infants who were included in the trial had moderate-to-large VSD and a history of HF, but surgery was not done. Although, patients having

uncontrolled HF and severe PAH requiring early surgery were excluded. In a real-world scenario, in many parts of the world, this patient population constitutes a large segment of infants with VSD due to the nonavailability or saturated surgical units. Hence, the results of this study are relevant to this patient population who are awaiting surgery while being medically managed for HF.

Although our study did not show any statistically significant benefit of propranolol therapy in the reduction of mortality, it showed a favorable trend by preventing worsening of HF symptoms and hospitalization. The result of our study may encourage future prospective trials to assess the unexplored utility of beta-blocker therapy in modifying the natural course of patients with moderate-to-large VSD.

CONCLUSIONS

The addition of a beta-blocker to the conventional treatment prevented worsening of HF symptoms and hospitalization in infants with moderate-to-large VSD and was well tolerated. However, there was no statistically significant difference in mortality and need for surgery as the study design was underpowered for this important question. Overall, beta-blockers may be clinically useful for the management of infants with VSD and HF. Larger studies are required to clarify further the role of beta-blockers in this subgroup of patients.

Consent to participate

Informed consent was obtained from legal guardians.

Consent for publication

Legal guardians of patients signed informed consent regarding publishing their data.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL

**“Efficacy and Safety of Propranolol in Infants with Hear
Failure due to Moderate to Large Ventricular Septal
Defect (VSD-PHF study) - A Prospective Randomized
Trial”**

Supplementary materials

Supplementary table S1: Baseline characteristics of the study population (Per-protocol analysis)

Parameters	Control group* (n=39)	Propranolol group* (n=37)	P-value
Age (months)	5.10 ± 2.67	5.54 ± 3.27	0.52
Sex			
<i>Male</i>	29 (74.4)	24 (64.9)	0.36
<i>Female</i>	10 (25.6)	13 (35.1)	
Weight (Kg)	4.77 ± 1.09	4.76 ± 1.48	0.96
Ross HF class			
<i>I</i>	9 (23.08)	13 (35.14)	0.25 [#]
<i>II</i>	20 (51.28)	12 (32.43)	
<i>III</i>	9 (23.08)	12 (32.43)	
<i>IV</i>	1 (2.50)	0 (0)	
History of LRTI	23 (58.97)	18 (48.65)	0.36
Hemoglobin (g/dl)	10.51 ± 1.44	10.44 ± 1.19	0.81
Furosemide dose (mg/day)	6.10 ± 2.26	6.01 ± 2.16	0.86
Furosemide dose (mg/kg/day)	1.30 ± 0.48	1.26 ± 0.49	0.72
VSD pressure gradient (mmHg)	38.50 ± 16.11	41.62 ± 15.45	0.42
LVESD (mm)	15.13 ± 3.18	14.40 ± 2.83	0.32
LVEDD (mm)	25.80 ± 3.81	25.34 ± 3.80	0.62

VSD sites			
<i>Perimembranous</i>	23 (58.97)	21 (56.76)	
<i>Subaortic</i>	4 (10.26)	6 (16.22)	
<i>Muscular</i>	6 (15.38)	7 (18.92)	
<i>Subaortic + perimembranous</i>	3 (7.69)	2 (5.40)	0.81 [#]
<i>Inlet</i>	3 (7.69)	0	
<i>Outlet</i>	0 (0)	1 (2.70)	
Follow up duration (months)	7.64 ± 6.63	6.97 ± 2.60	0.57

* Values are mean ± SD or frequency (%), # Fischer exact test

HF- heart failure, LRTI- lower respiratory tract infection, VSD- ventricular septal defect, LVEDD- left ventricular end-diastolic dimension, LVESD- left ventricular end-systolic dimension; SI units: mm - millimeter, kg - kilogram, g - gram, dl – deciliter

Supplementary table S2: Frequency of primary and secondary endpoints in the study groups (Per-protocol Analysis)

Adverse outcomes	Per-protocol Analysis [‡]		
	Control group	Propranolol group	P-value
	<i>n (%)</i>	<i>n (%)</i>	
Primary composite endpoint [*]	20 (51.28)	11 (29.73)	0.06
Secondary endpoints			
<i>Cardiovascular death</i>	2 (5.13)	1 (2.70)	1.00 [#]
<i>Total Hospitalization (HF ± LRTI)</i>	12 (30.77)	3 (8.11)	0.02[#]
<i>Hospitalization for HF</i>	10 (25.64)	2 (5.41)	0.02[#]
<i>Hospitalization for LRTI</i>	3 (7.69)	2 (5.41)	1.00 [#]
<i>Referrals for surgery</i>	10 (25.64)	9 (24.32)	0.90

^{*}Primary composite endpoint: composite endpoint of all-cause mortality, hospitalization for HF and/or chest infection, and referral for VSD closure surgery.

[‡]Per protocol analysis (control group, n= 39; propranolol group, n= 37); [#] Fischer exact test

Bold values are significant (P < 0.05)

HF- heart failure, LRTI- lower respiratory tract infection