ORIGINAL ARTICLE

Balloon Valvuloplasty in Dysplastic Pulmonary Valve Stenosis: Immediate and Intermediate Outcomes

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ABSTRACT

Objective: To determine the immediate and intermediate outcome in dysplastic and doming pulmonary valve stenosis in children and to determine various factors associated with unsuccessful outcome.

Study Design: An interventional study.

Place and Duration of Study: The Children's Hospital, Lahore, Pakistan, from June 2006 to December 2012.

Methodology: All patients presenting with severe pulmonary valve stenosis were enrolled in the study. Balloon valvuloplasty was performed on all patients. Successful outcome (residual gradient < 36 mmHg) was compared with matched doming pulmonary valve stenosis control group valvuloplasty. Difference in various quantitative variables was calculated using independent t-test and Mann Whitney U test. Categorical variables were compared using Chi square and Kruskal-Wallis test. Multivariate analysis was performed to determine various factors associated with outcome. Kaplan-Meier survival table was used to determine freedom from re-intervention proportions.

Results: One hundred and fifty two patients (Dysplastic group A, n=73; Doming group B, n=79) with median age of 24 months (range 3 - 192 months) and M:F; 2:1 were included in the study. Mean gradient decreased from 96 ± 33 mmHg to 29 ± 20 mmHg. Group A had significantly higher number of patients with unsuccessful outcome (9.6%, p=0.02). Pre-procedure gradient > 75 mmHg was the most significant factor associated with unsuccessful outcome (p < 0.001). Median follow-up duration was 3 years (range 1 - 6 years). Freedom from re-intervention proportion at 1, 3 and 6 years was 91.3%, 86.7% and 78.9% respectively in group A compared to 100%, 96.5% and 96.5% respectively in group B. Immediate post-procedure gradient > 60 mmHg was the only significant factor associated with re-intervention in group A (p=0.001).

Conclusion: The results from balloon valvuloplasty in dysplastic pulmonary valve were suboptimal when compared to doming valves. However, it provides a high freedom from re-intervention rate in intermediate follow-up. Intervention at moderate severity can result in better outcome.

Key Words: *Balloon valvuloplasty. Pulmonary valve stenosis. Follow-up. Children.*

INTRODUCTION

Isolated pulmonary valve stenosis is a common congenital heart defect occurring in 5 - 9% of all congenital heart defects. Since the earliest reports on balloon valvuloplasty in 1982 by Kan, transcatheter intervention has been established as the treatment of choice for such lesions.[1] Stenotic pulmonary valve has characteristically fused commissures with central opening giving it its doming appearance.[2] A subgroup of this condition is associated with significant valve leaflet thickening and no definite commissural fusion lines termed as dysplastic pulmonary valve.[3] Dysplastic pulmonary valve stenosis comprises of 7 - 10% of all isolated valvular pulmonary stenosis patients. These patients with dysplastic pulmonary valve stenosis have somewhat different hemodynamics as the valve annulus and right ventricular outflow tract are also narrow.[4,5] The response of this subgroup to balloon valvuloplasty has been considered variable with limited follow-up studies concentrating on this form of valvular stenosis.[6,7]

As a result, controversies exist about percutaneous vs. surgical management approach. In this study, the aim was to compare the immediate and intermediate outcomes of dysplastic pulmonary valvuloplasty with age, gender, severity and right ventricular function matched doming pulmonary valvuloplasty, and determine various factors associated with unsuccessful outcome and requirement of re-intervention in these patients.

METHODOLOGY

The interventional study was conducted at a single tertiary paediatric cardiac care facility at The Children's Hospital, Lahore, from June 2006 to December 2012; following ethical approval from hospital ethical committee. All patients with congenital heart defect underwent diagnostic transthoracic echocardiography. All patients with dysplastic pulmonary valve and severe valvular stenosis were selected. Dysplastic valve was defined as pulmonary valve with irregular thickened leaflets and no definite commissural fusion lines while

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doming valve was defined as a pulmonary valve with smooth thin contour leaflets, having definite commissural fusion lines and dome formation during ejection phase of cardiac cycle.[3] Any patient with associated subvalvular or supravalvular stenosis were excluded from the study. Patients with critical pulmonary stenosis associated with borderline right ventricle dimension or age less than 3 months were also excluded from the study to minimize confounding factors.

Seventy three patients were identified with dysplastic pulmonary valve based on thickened morphology of pulmonary valve leaflets, having severe valvular stenosis (instantaneous pressure gradient > 60 mmHg; peak to peak gradient > 50 mmHg).[8] Seventy nine age, gender, weight, severity of valvular stenosis and right ventricular function matched patients with doming pulmonary valve and normal valve leaflet thickness were selected. Both the groups were included in the study after informed consent from parents of individual patients.

After careful history and clinical examination, all the patients enrolled in the study underwent cardiac catheterization through femoral venous access. Right ventriculogram in full lateral projection was performed to confirm the valvular stenosis and pulmonary valve morphology and annulus. Peak to peak gradient across pulmonary valve was documented in all cases. Low pressure balloon (Tyshak II, Cordis or Z-Med Balloon), 20 - 50% greater than valve annulus, was selected and inflated across pulmonary valve over extra stiff exchange length guide wire. Post-procedure right ventriculogram was performed to document adequate valve opening. Post-procedure pulmonary artery to right ventricular outflow tract pull back gradient was measured using an end hole catheter, carefully excluding any right ventricular outflow obstruction gradient. Peak to peak pressure gradient across pulmonary valve was recorded. The procedure outcome was termed successful with good opening of pulmonary valve and peak to peak pressure gradient < 35 mmHg. Outcome was termed as partially successful if residual gradient was between 36 - 63 mmHg. Procedure was termed unsuccessful if residual gradient > 64 mmHg along with a fall in gradient less than 50%.[8] Immediate follow-up at 24 hours post-procedure was performed through transthoracic echo-cardiography documenting residual instantaneous pressure gradient across pulmonary valve, pulmonary regurgitation (mild, moderate, severe), tricuspid regurgitation (mild, moderate, severe) and RV function. Follow-up echocardiography was performed at 1, 3 and 6-months, 1 year and subsequently yearly documenting the same parameters and any evidence of restenosis.

Data were tabulated and analyzed using SPSS version 17 (Chicago IL. Inc.). Demographic profile was recorded. Complications during procedure were also recorded. Kolmogrov-Smirnov test was applied to check for normality assumption. Mean ± SD were calculated for all quantitative variables with normal distribution including valve annulus size, valve Z-score, balloon to annulus ratio, pressure gradient across pulmonary valve, fall in gradient following balloon valvuloplasty and residual gradient at follow-up. Median with range was calculated for non-normal distribution variables including age,[9] weight and follow-up duration. Frequencies were calculated for categorical variables including gender, complications, restenosis (gradient > 50 mmHg) and intervention free patients at various follow-up durations.[10] Independent t-test was used to determine any significant difference between various quantitative variable in either group. Mann Whitney U test was used to compare non-normal distribution variables. Chi-square test was used to determine any significant difference in categorical variables between the two groups. Kruskal Wallis test was used to determine any significant difference between nonparametric variables in patients with various outcomes. Spearman's correlation Rho was calculated where applicable to find any significant correlation between various variables and outcome. Multivariate analysis was performed to find various factor associated with outcome and re-intervention. Kaplan Meier survival table was used to estimate proportions of freedom from re-intervention in either group at various follow-up periods. p-value < 0.05 was considered as significant.

RESULTS

One hundred and fifty two patients (dysplastic Group A, n=73; doming Group B, n=79) were included in the study (Table I). Median age at the time of intervention was 24 months (range 3 - 192 months) with male: female ratio of 2:1. Pre-procedure Right Ventricle (RV) systolic dysfunction based on tricuspid annular plane systolic excursion (TAPSE < 2 SD for age) was found in 31/152 (20.4%) patients with no significant difference between the two groups (group A 18 vs. group B 13, p=0.21). Mean pulmonary valve annulus was 10.9 ± 3.5 mm (range 5.0 - 20.8 mm) with no significant difference between the two groups, p=0.058). Mean Z-score for pulmonary valve annulus was -1.53 ± 1.2 (range -5.0 to ±1.5). Mean Z-score for group A (range -1.8 ± 1.3) was significantly less than group B (range -1.3 ± 1.2, p=0.04). Mean peak to peak gradient across pulmonary valve was 96 ± 33 mmHg with no significant difference between both groups (p=0.76). Mean balloon size used was 14 ± 4 mm (range 8 - 25 mm). Mean balloon to annulus ratio was 1.3 ± 0.2. Significantly larger balloon were used in group A (balloon-to-annulus ratio = 1.35 ± 0.2, range 1 - 1.8 vs. mean 1.27 ± 0.1, range 0.8 - 1.5 in group B, p=0.003). Balloon stabilization was significantly more difficult in group A (n=8/73, 11.0%) than group B (n=2/79, 2.5%, p=0.04). One patient had a pre-ballooning cardiac arrest and procedure was abandoned. Procedure was successful in 101 patients (66.4%) and partially successful in 43 patients (28.3%). The procedure was unsuccessful in 7 patients (4.6%).

Using multivariate analysis, dysplastic pulmonary valve (p=0.017) and pre-procedure peak to peak gradient >75 mmHg (p < 0.001) were found to be the significant factors associated with unsuccessful outcome (Table II). Group A had significantly higher number of patients with unsuccessful outcome (9.6%, p=0.02). Though there was significant association between pulmonary valve annular diameter Z-score and balloon to annulus diameter ratio in multivariate analysis, no significant correlation was found between either variables (rho 0.18, p=0.14 and rho -0.21, p=0.07 respectively) and successful outcome in group A. In group A, patients having pre-procedure gradient < 75 mmHg had 88% (22/25) successful outcome while it was 48.9% in patients with > 75 mmHg gradient, remaining having unsuccessful or partially successful outcome. Similarly, in group B, 96.7% (29/30) had a successful outcome when pre-procedure gradient was < 75 mmHg. In patients with higher gradient, successful outcome was achieved in only 55.1% (27/49), remaining having partially successful outcome only.

Table I: Demographic profile of patients with dysplastic and doming pulmonary valve .

	Group A (dysplastic) n=73	Group B (doming) n=79	p-value
Age	Median 18 months (Range 3-156 months)	Median 24 months (Range 3-192 months)	0.376*
Male	48 (65.8%)	54 (68.4%)	0.73*
Weight	Median 9 kg (Range 3.5-42 kg)	Median 10 kg (Range 3.5-56 kg)	0.21*
Pulmonary valve annulus diameter	10.3 ± 3.5 mm	11.4 ± 3.5 mm	0.058*
RV dysfunction	18 (24.7%)	13 (16.5%)	0.21*
Peak to peak gradient across pulmonary valve	97 ± 33 mmHg	95 ± 34 mmHg	0.76*

p-value > 0.05 (non-significant).

Table II: Multivariate analysis showing dysplastic pulmonary valve and pre-procedure peak to peak gradient across PV associated with successful outcome. Z-score and balloon to annulus ratio, though having significant association, did not have significant correlation with successful outcome.

Variable	Mean square	F	Significant
Age in months	105.473	0.042	0.958
Gender	.213	0.955	0.387
Weight in kg	17.642	0.168	0.846
BSA	.030	0.343	0.710
PV annulus on fluoroscopy (mm)	18.561	1.494	0.228
PV annulus Z-score	6.153	4.162	0.017
Dysplastic pulmonary valve	1.010	4.195	0.017
RV dysfunction	.041	0.255	0.776
Balloon size (mm)	23.995	1.273	0.283
Balloon to annulus ratio	.157	6.046	0.003
Balloon size index	8.014	0.213	0.808
Balloon stabilization	.042	0.735	0.481
Pre-procedure gradient across pulmonary valve (mmHg)	9633.975	9.720	< 0.001
Pre-procedure gradient > 75 mmHg across pulmonary valve	3.046	15.611	< 0.001

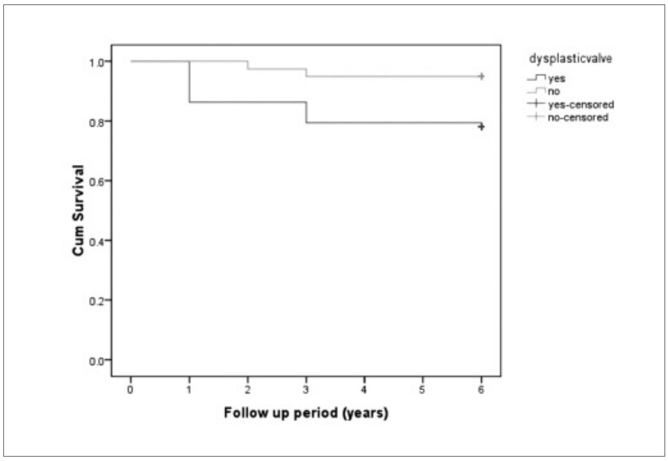

Figure 2: Kaplan-Meier Survival Curve showing Freedom from re-intervention in Doming (96.5%) and Dysplastic (78.9%) pulmonary valve groups at 6 years follow-up.

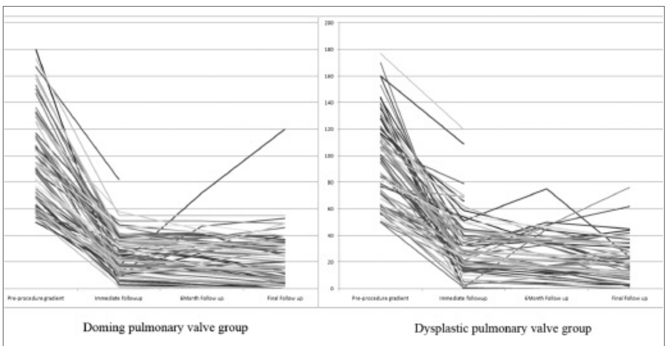

Figure 1: Comparison of fall in gradient (mmHg) across pulmonary valve at immediate and intermediate follow-up between Doming and Dysplastic pulmonary valve groups (Individual cases).

Post-procedure gradient was significantly lower in group B (26 ± 15 mmHg) than group A (33 ± 23 mmHg) despite a smaller balloon size, p=0.02. Residual RV muscle bundles were found in 13 patients (8.6%) with no significant difference between both groups (p= 0.66). Hemodynamically significant arrhythmias occurred in 5 patients (3.3%; SVT 3, sinus bradycardia 2). Arrhythmias were significantly higher in patients with pre-procedure RV dysfunction (p=0.006). Severe pulmonary regurgitation developed in 1 patient. Pericardial effusion occurred in 1 patient (0.7%) and cardiac arrest during balloon inflation requiring resuscitation occurred in 1 patient (0.7%). There was no mortality associated with the procedure.

All the patients were followed up at 1 month, 3-month, 6-month and then yearly intervals for any clinical symptoms and re-stenosis through transthoracic echocardiography. Median follow-up duration was 3 years (range 1 - 6 years). Residual pressure gradient decreased significantly in group A at final follow-up (mean 23 ± 17 mmHg, p=0.001). There was a slight decrease in gradient in group B, however, it did not reach significant level (mean 22 ± 19 mmHg, p=0.16). None of the patients with partially successful valvuloplasty showed any hemodynamically significant increase in gradient during the follow-up (Figure 1).

Re-intervention rate was significantly higher in group A (9/73, 12.3%) than group B (2/79, 2.5%, p=0.03). Severe valvular re-stenosis occurred in 2 patients from group A during the follow-up period requiring re-ballooning. Surgical re-intervention was required in 7 patients (9.6%) from group A (6 with narrow valve annulus, RV outflow tract and unsuccessful valvulopasty, 1 with significant RV muscle bundles) and 2 patient (2.5%) from group B (RV muscle bundles). Freedom from reintervention cumulative proportion using Kaplan Meier survival table at 1, 3 and 6 years was 91.3%, 86.7% and 78.9% respectively in group A while it was 100%, 96.5% and 96.5% respectively in group B (Figure 2). Immediate post-procedure gradient above 60 mmHg was the only significant factor associated with re-intervention in group A (p=0.001).

DISCUSSION

Dysplastic pulmonary valve differs significantly from the commonly occurring doming pulmonary valve variety in isolated pulmonary valvular stenosis. These valves have a myxomatous morphology with poorly delineated lines of commissural fusion. As a result, the balloon valvuloplasty hemodynamics do not hold true as they do in typical form.[11] Post-ballooning valve opening is unpredictable due to inherent morphology. Moreover, the valve annulus is smaller than doming valve variety. These variations make the final outcome relatively less consistent.[12]

In this study, successful outcome was achieved in 61.6% in group A which was significantly lower than group B. This result was comparable with previous studies showing 65% success rate in dysplastic valve balloon valvuloplasty.[13] A significant number of patients had a partially successful outcome (27.1%) that did not require any subsequent intervention in the intermediate follow-up for upto 6 years. Considering the outcome in these patients as favorable, the cumulative acceptable outcome was 88.7%. These results were much better than previous reports.[14]

Smaller annular size has been documented in previous studies as a major factor in suboptimal results. Pulmonary valve annulus was significantly smaller on Z-scoring in group A in this study. However, annular size did not have any significant effect on the final outcome. Patients already with small tricuspid valve annulus and borderline RV were already excluded as the critical pulmonary stenosis patients. This might be the reason for this difference in observation from previous studies.[5,10]

The optimal balloon-to-annulus ratio though well-established in doming valve, is still debatable in dysplastic valves. It has been advocated that the abnormal nature of the valve requires higher than usual balloon sizes.[5] The increased size has its own drawbacks with risk of damaging RV outflow tract and even tricuspid valve.[15,16] In this study, balloon to annulus ratio was significantly higher in group A. However, there was no correlation between larger balloon size and better outcome.

Balloon stabilization was significantly difficult in dysplastic valve than group B. Smaller annular size and abnormal morphology explain this technical difficulty. However, the final outcome was not affected. Double balloon technique was not required in any of the cases included. The frequency of complications was not significantly different in either group. Complication rate is known to be higher especially in neonates and young infants.[17] In this comparative study, only patients older than 3 months were included resulting in much lower incidence of complications. Arrhythmias were significantly higher in children with RV dysfunction. These arrhythmias were mainly due to sensitive RV myocardium not tolerating catheter manipulation. Severe pulmonary regurgitation developed in one patient. Patient has remained asymptomatic without any medical therapy. These patients tend to develop RV failure at 20 - 30 years follow-up as documented previously. Unlike previous data, degree of pulmonary regurgitation did not increase in this study during intermediate follow-up.[6] However, life long follow-up is required for these patients with severe pulmonary regurgitation.[18] Pericardial effusion and cardiac arrest were mainly procedural complications not associated with dysplastic nature of the valve.

Pre-procedure pressure gradient was a significant factor determining the outcome. In patients with pre-procedure gradient < 75 mmHg, the successful outcome was as high as 88% while it was only 48.9% in patients with higher gradient. This finding was in agreement with previously conducted studies and favors early balloon valvuloplasty in patients even with dysplastic valves.[19] Pre-ballooning gradient has been documented as the most significant predictor of immediate outcome and residual gradient for long-term outcome even in animal models.[20] With increasing severity of stenosis, the infundibular hypertrophy progressively worsens and results in suboptimal outcome following ballooning. This infundibular hypertrophy was mainly the reason for partially successful valvuloplasty in dysplastic group causing dynamic RV outflow tract obstruction. It has been reported previously to be associated with reactive RV outflow tract stenosis.[21] It appears to regress with time as was demonstrated in this study. This finding has been documented in long-term follow-up studies of upto 17 - 23 years.[22,23] A few patients may require short-term beta-blocking agents for its resolution. Sympathetic overactivity may be one of the major factors in these patients with dynamic RV outflow tract obstruction decreasing after valvuloplasty.[24]

Re-intervention rate was significantly higher in patients with dysplastic valve. It mainly included the unsuccessful patients where immediate relief was not achieved. This was in accordance with previous studies showing immediate high post-ballooning gradient as a major predictor of restenosis.[10] Patients with partially successful outcome did not show any worsening in their gradient over the intermediate follow-up. Freedom from intervention was significantly lower than group B. However, this group still had a significant number of patients who did not require re-intervention during 6 years of follow-up. These findings were supported by reports of normal exercise tolerance in children post pulmonary balloon valvuloplasty at 6 years mean follow-up despite having mild to moderate residual stenosis.[25] Freedom from intervention at 6 years follow-up was 78.9% which supports early balloon intervention in dysplastic valves rather than initial surgical approach. Freedom from re-intervention has been documented from 70 to 95% though dysplastic valves and critical pulmonary valve were not taken into consideration in most studies.[11] Restenosis was uncommon (2.7%). The frequency of restenosis was much lower than previously documented figures (10%).[10] It was an intermediate duration follow-up study and may have an increase in frequency at long-term follow-up. The response to repeat balloon valvuloplasty was very good as documented in previous studies.

CONCLUSION

Dysplastic pulmonary valve stenosis represents a distinct form of isolated pulmonary valvular stenosis. The results from balloon valvuloplasty are suboptimal when compared to doming valves. Pre-procedure gradient < 75 mmHg across pulmonary valve was the only significant factor associated with successful outcome. Immediate post-procedure gradient < 60 mmHg was significantly associated with higher freedom from re-intervention rate. Larger balloon relative to annular size did not affect the final outcome. Despite a suboptimal result, balloon valvuloplasty should be considered as the first mode of intervention as it provides a fairly high freedom from re-intervention rate in intermediate follow-up.

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