Long term clinical and echocardiographic results of mitral balloon valvotomy in children and adolescents

M E Fawzy, M A Stefadouros, H Hegazy, F El Shaer, M A Chaudhary, F Al Fadley

Aims: To assess the safety, efficacy, and long term results of mitral balloon valvotomy (MBV) for rheumatic mitral stenosis in children and adolescents in comparison to adults.

Methods: The results of 468 patients with mitral stenosis who underwent successful MBV and were followed up for 0.5–13 years were analysed. Patients were divided according to age at the time of MBV into group 1 consisting of 84 patients < 20 years of age (children and adolescents) and group 2 that included 384 patients, age > 20 (adults).

Results: Patients in group 1 had a lower mitral echo score (mean (SD) 7.5 (1.3) vs 8 (1.1), p < 0.001), smaller Doppler mitral valve area (MVA) (0.84 (0.17) vs 0.92 (0.18) cm², p < 0.001), and higher Doppler mitral valve gradient (15.0 (5.3) vs 12.7 (4.5) mm Hg, p < 0.001) than group 2. Immediately after MBV group 1 had larger MVA, whether measured by Doppler (2.0 (0.30) vs 1.96 (0.28) cm², p < 0.005) or by catheter (2.0 (0.59) vs 1.8 (0.52) cm², p < 0.001), and similar complication rates, compared to group 2. After a mean follow up of 5 (3.5) years there was no significant difference between groups 1 and 2 in the incidence of restenosis (14.3% vs 16.1%, NS). Event-free survival rates at 5, 10, and 12.5 years were 93%, 79%, and 79% for group 1 and 94%, 90%, and 84% for group 2 (p = 0.18).

Conclusions: MBV is safe and effective in children and adolescents with rheumatic mitral stenosis. It provides better immediate results than in adults and excellent long term results that are comparable to those seen in adults.

Mitrval balloon valvotomy (MBV) is an established non-surgical modality for the treatment of severe rheumatic mitral valve stenosis. Although in children and adolescents with rheumatic mitral stenosis the immediate haemodynamic effects of MBV have been adequately documented, there are few reports regarding the long term results of MBV in this age group. The purpose of this study was to evaluate the immediate and long term (up to 13 years) results of MBV in patients 20 years old or younger and compare these results to those obtained in the adult population.

METHODS

Study population

From 1989 to 2002, 521 consecutive patients underwent MBV in our hospital. On the basis of immediate results the procedure was successful in 501 (96.2%) patients and unsuccessful in the remaining 20 patients (severe mitral regurgitation in 10 patients; mitral valve area (MVA) < 1.5 cm² in 10 patients). These 20 patients were excluded from further analysis. Good immediate results were defined as a post-procedure MVA > 1.5 cm² as assessed by echocardiography and no mitral regurgitation of grade > 2/4 according to the Sellers classification. Thirty three patients who came from foreign countries were lost to follow up. The remaining 468 (93.4% of the 501 eligible patients) were followed up for 0.5–13 years (mean 5 (3.5) years) and constitute the study population. For the purposes of this study patients were divided according to age at the time of MBV into group 1, age ≤ 20 years (children and adolescents), and group 2 > 20 years of age (adults). Written informed consent was obtained from all patients or, in the case of patients under legal age, from their parents or guardians, before MBV.

Echocardiographic and Doppler examination

Two dimensional (2D echo) and Doppler echocardiographic studies were performed 1–2 weeks before the procedure using commercially available equipment (Hewlett-Packard Unit Sonos 1500 and 5500). In addition to the mean transmirtal valve gradient, the MVA was calculated from the Doppler study using the pressure half-time method and also by planimetry using the short axis 2D echo view. Pulmonary artery systolic pressure was estimated by continuous wave Doppler echocardiography using the modified Bernoulli equation (4 × [peak tricuspid regurgitant jet velocity]²) with 10 mm Hg added for the estimated right atrial pressure. The echo Doppler studies were repeated immediately after MBV, at six months, and annually thereafter for up to 13 years. The morphologic features of the mitral valve were categorised according to semiquantitated grading of leaflet thickening, mobility, calcification, and subvalvar involvement on a scale of 0 to 4 as described. The mitral valve morphology was considered favourable if the mitral echocardiographic score (MES) was ≤ 8.

Mitrval balloon valvotomy procedure

Mitrval balloon valvotomy was performed according to the stepwise Inoue technique as previously described. Standard haemodynamic measurements of the right and left heart included simultaneous measurement of left atrial and left ventricular pressures, mean mitral gradient, and MVA calculated using the Gorlin’s formula. Cardiac output was determined by the Fick or thermodilution method. All haemodynamic measurements were obtained before and immediately after MBV. A computer (Micro-Siemens

Abbreviations: MBV, mitral balloon valvotomy; MES, mitral echocardiographic score; MVA, mitral valve area; NYHA, New York Heart Association
Elema-AB, Solna, Sweden) was used for the calculation of haemodynamic parameters. Left ventriculography was performed before and immediately after valvotomy in order to assess the presence and severity of mitral regurgitation using the Sellers classification.11

Follow up
Clinical and echocardiographic assessments were carried out six months after MBV and annually thereafter for up to 13 years. The primary end point of follow up was mitral restenosis, defined as loss of ≥ 50% of the initial gain in MVA and MVA < 1.5 cm². The combined secondary end point included: (1) mitral restenosis (as defined above); (2) redo MBV; (3) mitral valve replacement; (4) New York Heart Association (NYHA) functional class III or IV; (5) cardiac death. Follow up evaluation at regular intervals consisted of direct interview with and physical examination of the patient, in addition to echocardiographic examination at each clinic visit. For prophylaxis against recurrence of rheumatic fever, patients were given either monthly intra-muscular injections of benzathine penicillin G 1.2 MU (or half this dose for children with body weight of < 27 kg) or oral penicillin V 250 mg twice daily. For patients allergic to penicillin, erythromycin (250 mg orally twice daily) was given instead. This prophylactic treatment was continued at least until age of 35 years.

Statistical analysis
Statistical analysis was performed using a commercially available software package (SAS v.8; Statistical Analysis System, SAS Institute Inc, Cary, North Carolina, USA). Invasive and echocardiographic data obtained before, immediately after, and long term after valvotomy in group 1 were compared with the corresponding data in group 2 using the non-paired Student’s t test (two tailed) or the χ² test (two tailed) or the Fisher’s exact test, as appropriate. The overtime change from baseline to follow up was evaluated separately for each age group by the paired Student’s t test. Univariate Cox regression analysis was used to identify predictors of restenosis. Kaplan-Meier analysis was used to determine (1) freedom from restenosis, and (2) event-free survival (survival with freedom from the predefined combined end points listed above) for patients in the two age groups. Comparison between groups was performed using the log rank test. Descriptive statistics for the continuous variables are reported as mean (SD). The level of significance was set at p < 0.05.

RESULTS
Demographic characteristics of both groups of patients are shown in table 1. The age in group 1 ranged from 10–20 years (mean (SD) 16.7 (3.3) years) and in group 2 from 21–61 years (mean (SD) 33.7 (9.5) years). Their weight range from 20–68 kg (mean 45 (10) kg for group 1 and 62 (18) kg for group 2, p < 0.001). The mean body surface area (BSA) was 1.4 (0.17) m² for group 1 and 1.6 (0.24) m² for group 2 (p < 0.01). Although male sex represented the minority in group 1 (29/84; 34.5%) and group 2 (99/384; 25.8%), there was no significant difference between the two groups in sex distribution (p = 0.104). The prevalence of atrial fibrillation was lower in the younger group 1 (6/84; 7.1%) than in the adult group 2 (58/384; 15.1%) (p = 0.05). The echocardiographic mitral valve score was slightly lower in group 1 than in group 2 (7.5 (1.3) v 8 (1.1); p < 0.001).

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (age &lt; 20) n = 84</th>
<th>Group 2 (age &gt; 20) n = 384</th>
<th>p Value (group 1 v II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>84</td>
<td>384</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>29 (34.5%)</td>
<td>99 (25.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.7 (3.3)</td>
<td>33.7 (9.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>10–20</td>
<td>21–61</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>45 (10)</td>
<td>62 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>20–68</td>
<td>46–85</td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.4 (0.17)</td>
<td>1.6 (0.24)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>6 (7.1%)</td>
<td>58 (15.1%)</td>
<td>0.05</td>
</tr>
<tr>
<td>NYHA class III/IW</td>
<td>76 (90.4%)</td>
<td>337 (87.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral echo score</td>
<td>7.5 (1.3)</td>
<td>8 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous surgical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>commissurotomy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mitral regurgitation (grade)</td>
<td>2 (2.4%)</td>
<td>17 (4.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Data presented as mean (SD) unless otherwise indicated. NYHA, New York Heart Association; NS, non-significant difference.</td>
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<td></td>
</tr>
</tbody>
</table>
Immediate haemodynamic results

Balloon valvotomy resulted in a significant, immediate increase in MVA with a corresponding significant decrease in transmirtal gradient, whether measured invasively (table 2) or by Doppler echocardiography (table 3), in both groups. In addition, a substantial fall in catheter measured mean left atrial pressure and systolic pulmonary arterial pressure, with an associated increase in cardiac index, were noted in both groups immediately after MBV. The statistical comparison of haemodynamic and echocardiographic data obtained before and immediately after valvotomy between the two groups is shown in tables 2 and 3. Although at baseline there was a small difference in Doppler MVA between group 1 and group 2 (0.84 (0.17) v 0.92 (0.18) cm², respectively; p < 0.001), both groups had the same MVA calculated by catheterisation (0.84 (0.24) v 0.83 (0.24) cm²; NS). Immediately after valvotomy the MVA was larger in group 1 than in group 2, measured by catheter (2.0 (0.59) v 1.8 (0.52) cm²; p < 0.001) or by Doppler (2.0 (0.30) v 1.96 (0.28) cm²; p < 0.05) (tables 2 and 3). There were no significant differences between the two groups in invasively determined mean left atrial pressure, systolic pulmonary arterial pressure, or pulmonary vascular resistance both before and immediately after and immediately after valvotomy (table 2).

Complications

The incidence of major adverse in-hospital events is shown in table 4. There were no in-hospital deaths. As noted above, severe post-valvotomy mitral regurgitation (grade ≥ 3) occurred in 10/521 patients (1.9%); all 10 patients were severe post-valvotomy mitral regurgitation (grade

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=84)</th>
<th>Group 2 (n=384)</th>
<th>p Value (group 1 v 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doppler MVA (cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.84 (0.17)</td>
<td>0.92 (0.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow up</td>
<td>0.56 (0.27)</td>
<td>0.72 (0.21)</td>
<td>NS</td>
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<tr>
<td>Systolic PAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17.5 (4.6)</td>
<td>20.9 (4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow up</td>
<td>17.9 (4.6)</td>
<td>21.4 (4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>LA dimension (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>46 (11.9)</td>
<td>48 (12.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow up</td>
<td>47 (11.7)</td>
<td>48.5 (12.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Restenosis</td>
<td>12 (14.3%)</td>
<td>16 (16.1%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*p<0.001; **p<0.0001; NS=all in comparison to baseline values in the same group.

Follow up results

Echocardiographic assessment performed after a follow up period of 0.5–13 years (mean 5 (3.5) years) demonstrated an MVA of 1.8 (0.34) m² and 1.7 (0.37) m² for group 1 and 2, respectively (NS). The mean diastolic mitral valve gradient remained at 5.4 (2.2) mm Hg and 5.8 (2.7) mm Hg, respectively (NS). Left atrial enlargement, as determined by the echocardiographic anteroposterior left atrial dimension, was present at baseline in both groups, although less pronounced in group 1 (46 (9) v 48.5 (6.9); p < 0.01). A significant reduction in left atrial dimension was observed at follow up in both groups (44 (6.5) mm v 44 (7.3) mm for groups 1 and 2, respectively; NS) (table 5).

Restenosis

Restenosis was encountered in 12 patients (14.3%) of group 1, nine of whom had successful redo MBV. Restenosis was also observed in 62 patients (16.1%) of group 2, 26 of whom underwent repeat MBV and 11 had mitral valve replacement. The remaining 28 patients with restenosis (three of group 1 and 25 of group 2) were either asymptomatic or mildly symptomatic and therefore did not require reintervention. No statistical difference was found in the incidence of restenosis between the two groups (table 5). Univariate Cox regression analysis identified mitral echocardiographic score as the only significant predictor of mitral valve restenosis (p < 0.0001). The estimated restenosis-free survival for the whole population and for patients with MES ≤ 8 and MES > 8 is depicted in fig 1. The restenosis rate is much higher in patients with MES > 8 (p < 0.0001) while fig 2 shows that freedom from restenosis was not different between the two age groups.

Follow up events

In group 1, no deaths occurred at follow up. Nine patients in this group (10.7%) had redo MBV because of restenosis associated with severe symptoms (NYHA class III/IV). The remaining 75 patients (89.3%) remained in functional class I/II.

In group 2, one patient with end stage renal failure died at follow up after mitral valve replacement for mitral restenosis. A total of 37/384 patients (9.6%) of this group were submitted to either redo MBV (26 patients; 6.8%) or mitral valve replacement (11 patients; 2.8%) because of severely symptomatic restenosis. The remaining 346 patients in this group were mildly symptomatic (NYHA class I/II) without further cardiac intervention. The probability of event-free survival at 5, 10, and 12.5 years were 93%, 79%, and 79% for group 1 versus 94%, 90%, and 84% for group 2, respectively (p = 0.18) (fig 3).

No patients in either group developed symptoms suggestive of recurrent rheumatic fever during follow up.

Regression of pulmonary hypertension

Comparison of values for systolic pulmonary arterial pressure obtained by Doppler before valvotomy to those seen at follow up demonstrated a significant regression of pulmonary hypertension over time in both groups. Thus, in group 1 the
systolic pulmonary artery pressure fell from 47.5 (16.2) mm Hg before MBV to 28 (4.7) mm Hg at follow up (p < 0.0001). The corresponding values for systolic pulmonary artery pressure in group 2 (before: 46.9 (18) mm Hg; follow up: 31 (9.9 mm Hg; p < 0.0001) were not significantly different from those observed in group 1. Most of this reduction in systolic pulmonary artery pressure occurred over time as demonstrated by Doppler echocardiography (table 5) following the initial modest drop observed by catheterisation recording immediately after the procedure (table 2).

Atrial septal defect
Immediately after MBV, iatrogenic atrial septal defect with small left to right shunt at the atrial level was detected by colour flow mapping in 17 patients in group 1 (20.2%) and 103 patients (26.8%) of group 2. The majority of these defects were closed at 4–12 months after valvotomy. At long term follow up, these defects were closed in all patients in group 1 and in all but nine patients in group 2.

DISCUSSION
Several studies have described the salutary immediate and mid term haemodynamic results of balloon valvotomy in children and adolescents with mitral valve stenosis. However, long term follow up studies of MBV in children are scarce. This study provides a longer follow up period compared to other studies. Pericardial tamponade, cerebral embolisation, and significant mitral regurgitation, are recognised complications of balloon mitral valvotomy. The rate of these complications in our series was lower than that previously reported by others.

Immediate results
The immediate results of MBV in our young age group were slightly better than those seen the adult group with a significantly larger immediate MVA in spite of a smaller BSA. This difference is probably related to the more favourable mitral valve morphology in the young as demonstrated by their lower mitral echocardiographic score. These findings are comparable to those reported by others.
Mitral balloon valvotomy in children

Long term results

Mitral restenosis

It has been hypothesised that children and adolescent patients may be more prone to developing restenosis because of the increased likelihood of smouldering rheumatic activity or recurrence of rheumatic fever in this age group. This hypothesis is not supported in our series where the restenosis rate was similar in the two age groups and no rheumatic fever recurrences were noted. The results of this study indicate that the valve morphology rather than the patient’s age is the main determinant of valve restenosis. These findings concur with reports of other investigators. Although no link was established between restenosis and recurrent rheumatic fever in our population, the absence of instances of recurrence of rheumatic fever confirms the effectiveness of long-term prophylactic antibiotic treatment.

Event-free survival

Although the difference in clinical events between the two groups failed to reach significance, there was a trend towards fewer events in the young population, most likely related to lower incidence of atrial fibrillation and more favourable mitral valve morphology in this young group. Kaplan-Meier analysis showed that 93% and 79% of the young population versus 94% and 84% of the adult population were alive and free from clinical events at 5 and 12.5 years of follow up, respectively, a finding corroborated by other investigators. This lack of intergroup difference in survival and adverse long term clinical events could possibly be attributed to the fact that our adult population was relatively young (mean age 33.7 (9.5) years), a finding similar to that reported by other investigators. 3

Regression of pulmonary hypertension

As previously reported by us and others, severe pulmonary hypertension is present in a large proportion of children with mitral valve stenosis. Immediately following valvotomy, pulmonary hypertension decreases slightly, with further substantial regression occurring at long term follow up, a finding consistent with the results of previously reported studies.

Atrial septal defect

The reported incidence of an atrial septal defect following MBV has ranged from 9–53%, with most defects closing after 3–12 months. The incidence of iatrogenic atrial septal defect in our population was within this range and its distribution was similar in both groups. At follow up, 92.5% (111/120) of such defects were closed.

Conclusions

Mitral balloon valvotomy is safe and effective in children and adolescents with rheumatic mitral stenosis. The immediate results of this procedure are slightly better in this young age group than in adults, with excellent long term results comparable to those seen in adult patients.

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REFERENCES


A 3 month old, asymptomatic infant with tuberous sclerosis and multiple intracardiac tumours that were diagnosed prenatally (panel A) underwent surgery for resection of a large tumour (1.3 x 0.8 x 0.7 cm) obstructing the right ventricular outflow tract (RVOT) (panel B). After birth the infant was followed expectantly given that the natural history of these tumours is often spontaneous regression. However, the peak gradient across the RVOT increased steadily from 40 mm Hg to 100 mm Hg, prompting surgery to relieve the obstruction and break the cycle of stenosis. The large size of the tumour necessitated a right ventriculotomy (panel C). Histology confirmed the diagnosis of rhabdomyoma (panel D). Recovery from surgery was uneventful. The RVOT remained patent with a residual gradient of 34 mm Hg as measured by echo Doppler.

(A) Fetal echocardiogram, four chamber view, demonstrating multiple rhabdomyomas in the left and right ventricles (arrows). (B) Transthoracic parasternal short axis view. There is a large rhabdomyoma (arrow) causing obstruction of the right ventricular outflow tract. The tumour is situated immediately proximal to the pulmonary valve. Additional tumours are seen proximally in the right ventricle. (C) Intraoperative photograph. The tumour (arrow) demonstrated in panel B is excised through a right ventriculotomy. (D) Histology confirming the diagnosis of rhabdomyoma. Haematoxylin & eosin staining.
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