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ORIGINAL ARTICLE
Valvular Heart Disease

Real-World Experience of MitraClip for Treatment of Severe Mitral Regurgitation

– Compromise Between Mitral Regurgitation Reduction and Maintenance of Adequate Opening Area –

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Background: Percutaneous edge-to-edge mitral valve repair with the MitraClip® was shown to be a safe and feasible alternative compared to conventional surgical mitral valve repair. Herein is reported our experience on MitraClip® for high-risk surgical candidates with severe mitral regurgitation (MR).

Methods and Results: Patients with severe MR (3 or 4+) and high operative risk were considered for MitraClip® implantation. Device success was defined as placement of 1 or more MitraClips® with reduction of MR to ≤2+. Patients were followed up clinically and with echocardiography at 1 year. A total of 27 patients with severe MR (age, 74±12 years; 17 male; logistic EuroSCORE, 27±12; left ventricular ejection fraction, 40±17%) were treated. Fifty-six percent of MR was degenerative and 44% was functional. Device success was 93% with 14 patients receiving 2 clips. MR severity was reduced from 3.5±0.5 to 1.7±0.8 (P<0.001); New York Heart Association class improved from 3.1±0.4 to 2.0±0.8 (P<0.001). In 45% of functional and in 29% of degenerative MR patients, to avoid mitral stenosis, additional MitraClip® implantation was not attempted, with resultant transmitral mean gradient of 4.9±1.6 mmHg vs. 3.1±1.4 mmHg, respectively (P=0.01).

Conclusions: MitraClip® was shown to be an effective and safe treatment for patients with both functional and degenerative MR. Inability to obtain a greater reduction of MR was the consequence of borderline transmitral gradient requiring a compromise to avoid mitral stenosis, particularly in the functional MR patients. (*Circ J* 2012; **76:** 2488–2493)

Key Words: Degenerative mitral regurgitation; Functional mitral regurgitation; MitraClip; Mitral regurgitation; Mitral valve area

Conventional surgical repair or replacement has been the standard of care for symptomatic severe mitral regurgitation (MR). Before the emergence of transcatheter valve therapies, however, optimal medical therapy and cardiac resynchronization therapy in selected candidates have been the only treatment for patients deemed too high risk for conventional surgery. Percutaneous edge-to-edge mitral valve repair with the MitraClip® system was demonstrated to be a safe and feasible alternative to surgical treatment for severe MR, although it was less effective at reducing MR than conventional surgery.[1] Adverse valve morphology and severe left ventricular dysfunction have been the 2 major challenges in treatment with the MitraClip® system.[2,3] We report our experience with the MitraClip® for patients with severe symptomatic MR who are high risk for conventional surgery.

Methods

Patient Selection and Preoperative Assessment

Consecutive patients who underwent elective edge-to-edge MitraClip® implantation for symptomatic severe chronic MR (grade 3+ or 4+) with high operative risk were prospectively collected within the hospital database. Surgical risk assessment was defined according to Logistic EuroSCORE ≥20% and Society of Thoracic Surgeons-predicted risk of mortality (STS-PROM) ≥10% or by the presence of specific surgical risk fac-

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tors not covered by the EuroSCORE and STS-PROM. The decision for proceeding with MitraClip® implantation was based on multidisciplinary team assessment of surgical risk and valve anatomy as to the suitability for MitraClip® implantation. The exclusion criteria used were different from the commonly applied EVEREST criteria.[4] For degenerative MR, patients were considered unsuitable if (1) flail width was >25 mm and gap was >12 mm; (2) flail leaflets did not have secondary chordae support; (3) baseline mitral valve area (MVA) was <3.5 cm^2 and (4) there was excessive Barlow disease with multiple jets. For those with functional MR who had a central jet, patients were considered contraindicated for the procedure if (1) the gap between 2 leaflets was >3 mm; (2) there was a posterior-oriented posterior mitral leaflet (PML) in a posterior wall aneurysm; and (3) there was a small baseline MVA <3.5 cm^2 with restrictive anterior mitral leaflet (AML). Active endocarditis and poor life expectancy were also considered as absolute exclusion criteria. All patients underwent preoperative transthoracic and transesophageal echocardiography (TEE) prior to intervention to assess the mitral valve morphology, severity of MR and anatomical suitability for MitraClip® implantation. Clinical assessment included identification of symptoms, New York Heart Association (NYHA) functional class and lung function test in those with a history of pulmonary disease.

Procedures

Procedure was performed under general anesthesia in a catheterization laboratory at Royal Brompton Hospital, London. Both fluoroscopic and 3D-TEE guidance were utilized. The right femoral vein was used as the primary vascular access with concomitant placement of a 5-Fr arterial sheath in the contralateral femoral artery to monitor the arterial blood pressure during the procedure. An 18-Fr sheath was placed in the right femoral vein with a transseptal puncture performed under TEE real-time guidance as previously described.[5] After use of i.v. heparin to achieve an activated clotting time of >250 s, a 22-Fr steerable sheath was advanced 1–2 cm in the left atrium. The MitraClip® device is mounted on a steerable catheter allowing correction of the medial/lateral and antero-posterior orientation in order to safely navigate within the left atrium under TEE guidance. Once the device was positioned central in the mitral valve orifice, the 2 arms of the MitraClip® were opened and oriented perpendicular to the mitral closure line using 3D-TEE. The MitraClip® was then retracted to capture the 2 leaflets, aiming at the source of maximal regurgitation. Reduction of MR was assessed immediately using TEE and on day 4 post-operatively using transthoracic echocardiography.

The patients were extubated on the same day after the procedure in the recovery room where the hemodynamic status was monitored overnight. They would be transferred to the step-down high-dependency unit the next morning and then to the cardiology ward where they would start to mobilize and receive further medication titration.

Medication and Follow-up

Anticoagulation or anti-platelet therapy was individualized based on the presence of atrial fibrillation, concomitant coronary artery disease, previous coronary stent implantation and bleeding risk. All patients received aspirin 75 mg daily for at least 3 months and clopidogrel for 4 weeks unless they were receiving warfarin, in which case the warfarin would be continued post-procedurally with international normalized ratio targeted at 2–3.

Echocardiographic assessments before and after the procedure or at follow-up were based on American Society of Echocardiography guidelines.[6] In particular, severity of MR was assessed according to the technique previously described by Foster et al.[7] Clinical and echocardiographic follow-up were scheduled at 6 weeks, 3 months, 6 months and 1 year thereafter.

Outcome Measures

Procedural success was defined as successful and stable MitraClip® placement with residual MR ≤2+ upon discharge. Major adverse events at 12 months were defined as a composite of cardiovascular mortality, myocardial infarction, unplanned cardiac surgery, transfusion >2 units and heart failure requiring hospitalization. Clinical assessment and echocardiogram were carried out at pre-defined period as aforementioned. Quality of life assessment was carried out prior to MitraClip® implantation and at 12 months after the procedure utilizing the Medical Outcomes Study Short-form Health Survey (SF-36 version 2), which consists of 36 health-related questions providing both a physical component summary (PCS) and a mental component summary (MCS).[8–10]

Statistical Analysis

Continuous variables are expressed as mean±SD when normally distributed and as medians with interquartile ranges when not normally distributed. Paired Student t-tests were utilized to assess the differences in the means of continuous variables before and after procedures. P<0.05 was considered statistically significant. Analyses were performed with SPSS version 17.0 (SPSS, Chicago, IL, USA).

Results

Twenty-seven patients with a mean age of 74±12 years were identified (17 male, 10 female). Twelve patients had functional MR (44%) while 15 patients suffered from degenerative MR (56%). Six patients (22%) had left ventricular ejection fraction (LVEF) ≤25% and 5 of them belonged to a functional MR sub-group. A total of 52% of patients did not meet the EVEREST valve criteria. Among all 27 patients, MitraClip® was successfully implanted in 25 patients (overall procedural success, 93%) with 11 patients receiving 1 clip and 14 patients receiving 2 clips. Mean logistic EuroSCORE was 27±12%; Society of Thoracic Surgeons (STS) risk score was 14±9%. LVEF was 40±17%. Severity of MR was reduced from 3.5±0.5 to 1.8±0.7 (P<0.001), resulting in an improvement in NYHA from class 3.1±0.4 to 2.0±0.8 (P<0.001). The improvement in LVEF at follow-up was from 40±17% to 46±18% (P<0.001). At 1 year, 93% of patients had reduction of MR to ≤2+, with 32% of these patients having MR reduction to ≤1+. Mean follow-up was 332±140 days (range, 96–642 days) without inpatient or 30-day mortality. Major adverse events occurred in 2 patients (7.4%) with functional MR and successful MitraClip® implantation who died at 90 and 297 days after the procedure, respectively, due to further deterioration in left ventricular function presenting with heart failure. Compared between the functional MR and degenerative MR subgroups, clinical outcome in terms of reduction of MR and improvement in NYHA was not significantly different (1.6±0.9 vs. 1.8±0.9, P=0.53 and 1.1±0.9 vs. 1.0±0.7, P=0.79; **Table 1**).

In the present series there was a predominance of degenerative MR patients undergoing MitraClip® implantation, which is different from other reported series in Europe.[11] Of note, 6 (45%) of the functional MR patients with clips implanted required a compromise between perfect reduction of MR by implanting new clip, and avoidance of significant mitral valve opening area reduction. In the degenerative MR patients, only

Table 1. Effect of MitraClip Implantation

	Functional MR	Degenerative MR	P value
No. patients	12	15	–
Male	9 (75)	8 (53)	0.58
Age (years)	71±14	77±10	0.21
Logistic EuroSCORE	27±16	27±9	0.98
STS score	13±6	12±7	0.91
MR severity			
3+ (moderate-to-severe)	8	5	0.09
4+ (severe)	4	10	
Before MitraClip			
MR severity	3.3±0.5	3.6±0.5	0.09
NYHA class	3.1±0.5	3.0±0.3	0.92
LVEF (%)	32±17	46±14	0.03
LVEDD (mm)	6.4±0.9	5.7±0.9	0.04
LVESD (mm)	5.0±1.3	3.5±0.7	0.01
LVEDV (mm^3)	228±123	156±32	0.23
LVESV (mm^3)	173±96	86±3	0.12
Systolic pulmonary pressure (mmHg)	48±15	51±16	0.71
Transmitral gradient (mmHg)	2.2±1.3	1.4±0.4	0.03
After MitraClip (at 12 months)			
MR severity	1.8±0.6	1.9±0.7	0.66
NYHA class	2.0±1.0	2.1±0.6	0.84
LVEF (%)	36±21	53±12	0.02
LVEDD (mm)	6.0±1.2	5.1±0.5	0.01
LVESD (mm)	4.5±1.4	3.2±0.7	0.01
LVEDV (mm^3)	206±101	121±35	0.16
LVESV (mm^3)	146±78	54±26	0.09
Systolic pulmonary pressure (mmHg)	40±12	45±16	0.36
Mean transmitral gradient (mmHg)	4.9±1.6	3.1±1.4	0.01
Successful implantation	11 (92)	14 (93)	0.88
No. clips implanted	1.3±0.7	1.5±0.6	0.43
Major procedural complications	0 (0)	0 (0)	1.0

Data given as n (%) or mean±SD.
LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Table 2. Strategies to Avoid Mitral Valve Opening Area Reduction

	Functional MR	Degenerative MR	P value
Meeting EVEREST valve criteria	6 (50)	9 (60)	0.62
Before MitraClip			
MR severity	3.3±0.5	3.6±0.5	0.09
Mean transmitral gradient (mmHg)	2.2±1.3	1.4±0.4	0.03
Mitral valve area (cm^2)	3.6±0.6	4.1±0.4	0.03
After MitraClip (at 12 months)			
MR severity	1.8±0.6	1.9±0.7	0.66
Mean transmitral gradient (mmHg)	4.9±1.6	3.1±1.4	0.01
Mitral valve area (cm^2)	1.5±0.4	1.8±0.5	0.07
Compromise in initial planned strategy to avoid mitral stenosis	6 (45)	4 (29)	0.12
No. clips implanted	1.3±0.7	1.5±0.6	0.43
Deployment of >1 clip	5 (42)	9 (60)	0.36

Data given as n (%) or mean±SD.
MR, mitral regurgitation.

Table 3. Quality of Life Scores (SF-36v2)

	Functional MR	Degenerative MR	P value
Before MitraClip			
PCS	35.0±3.5	36.5±4.3	0.20
MCS	37.0±3.3	37.4±3.1	0.69
After MitraClip			
PCS	48.5±9.7	53.3±8.0	0.36
MCS	50.2±7.5	55.6±7.1	0.85
Improvement in PCS	13.5±8.5	16.7±8.6	0.69
Improvement in MCS	12.7±6.9	18.2±7.8	0.59

Data given as mean±SD.
MCS, mental scoring components; PCS, physical scoring components; MR, mitral regurgitation; SF-36v2, Medical Outcomes Study Short-form Health Survey.

4 patients required such a compromise. Most of these patients who received MitraClip® had restrictive AMLs or presence of calcified valve leaflets, which precluded implantation of further clips to achieve perfect MR reduction. Comparing the degenerative and functional MR groups, the mean gradient across the mitral valve differed before implantation (1.4±0.4 mmHg vs. 2.2±1.3 mmHg respectively, P=0.03) and after implantation (3.1±1.4 mmHg vs. 4.9±1.6 mmHg respectively, P=0.03). A mean transmitral gradient ≥5 mmHg was taken as a contraindication for further clip implantation, and post-implantation mitral valve mean gradient of 4.9 mmHg in the functional group supported the rationale of compromising further MR reduction to avoid risk of significant reduction in MVA (Table 2).

Concerning the quality of life assessment utilizing SF-36v2 questionnaire, baseline physical (PCS) and mental scoring components (MCS) showed significant impairment (Table 3). Both functional and degenerative MR patients showed improvement in quality of life in physical (functional MR PCS increase 13.5±8.5 vs. degenerative MR PCS increase 16.7±8.6, P=0.36) and mental aspects (functional MR PCS increase 12.7±6.9 vs. degenerative MR PCS increase 18.2±7.8, P=0.08).

Discussion

The present report on MitraClip® implantation in a predominant (56%) degenerative MR patient group, expands the result of the EVEREST II trial, in which 73% of patients had MR of degenerative etiology.[1] At 1 year, reduction of MR to ≤2+ was achieved in 93% of the present patients (ie, 100% in all patients with clip implanted), which is similar to the results in the published series.[12,13] In the present study MitraClip® was shown to be a safe procedure in that there were no major adverse events peri-procedurally or 30-day mortality. Two patients died because of heart failure related to dilated cardiomyopathy in the functional MR group, and they had significant LV dysfunction at baseline. For those patients with successful MitraClip® implantation, clinical benefits were demonstrated in terms of reduction of MR severity, improvement in NYHA class and improvement in LV size. In the present study, the functional MR patients had less LVEF improvement than the degenerative MR patients. This may be due to progressive worsening of LV systolic function in the presence of dilated cardiomyopathy despite successful reduction of MR by MitraClip®.

In the present study, all patients who had MitraClip® implanted could achieve reduction of MR to ≤2+, which is a promising result. In this technically demanding procedure, the cooperation and communication between the interventional operators and the cardiologist who performs the TEE is of great importance, not only during the positioning of the clips and assessment of MR reduction but also in determining the site of optimal transseptal punctures. Therefore, the effect of the learning curve of the whole heart team, not only the primary operators, would impact on the clinical outcome in terms of MR reduction and complication rates.[14]

Despite the absence of complete reduction of MR in both the functional and degenerative subgroups, together with the lack of significant improvement in LVEF and reduction in pulmonary arterial pressure, significant improvement in symptoms, in terms of reduction in NYHA class, was observed in patients with successful procedure. This phenomenon was also observed in other similar studies.[1,12,13] In addition, comparing the quality of life in patients who received the MitraClip® therapy before and after the procedure, patients usually had an equal or larger perceived improvement in quality for both physical and mental status.[15] Such an improvement could also be demonstrated in previous studies including the landmark EVEREST II study. Comparing the degenerative and functional MR subgroups, there was no significant difference in terms of degree of improvement despite the difference in baseline LV function between the 2 groups. This showed that a reduction of MR compared with baseline would lead to a meaningful symptomatic improvement as well as perceived general health these patients, who often had multiple comorbidites.[16]

Of note, during the implantation of the MitraClip®, there is very often a compromise between complete reduction of MR and resultant significant reduction in mitral valve opening area due to placement of further clips.[17] In these patients, significant improvement in symptoms could still be achieved despite the lack of completion of MR. This is evidenced by the fact that despite MR severity of 1.7±0.8 at 12 months after MitraClip® implantation, patients still perceived improvement in symptoms.

After placement of the first clip at the optimal position, usually at or close to the center in between the commissures, meticulous TEE assessments should be performed to assess the residual regurgitation and transmitral mean gradient to give feedback to the operator as to whether a second clip is needed or feasible without significantly reducing the mitral valve opening area. Restrictive AML movement is an infrequent finding in functional MR patients. Due to the annular dilatation and presence of restrictive PML,[18] if AML excursion is also reduced, there will be a higher resultant transmitral gradient and more reduction in MVA if more than 1 clip is placed. When the MitraClip® procedure was initially planned, the AML excursion (Figure) was assessed on TEE in the left ventricular

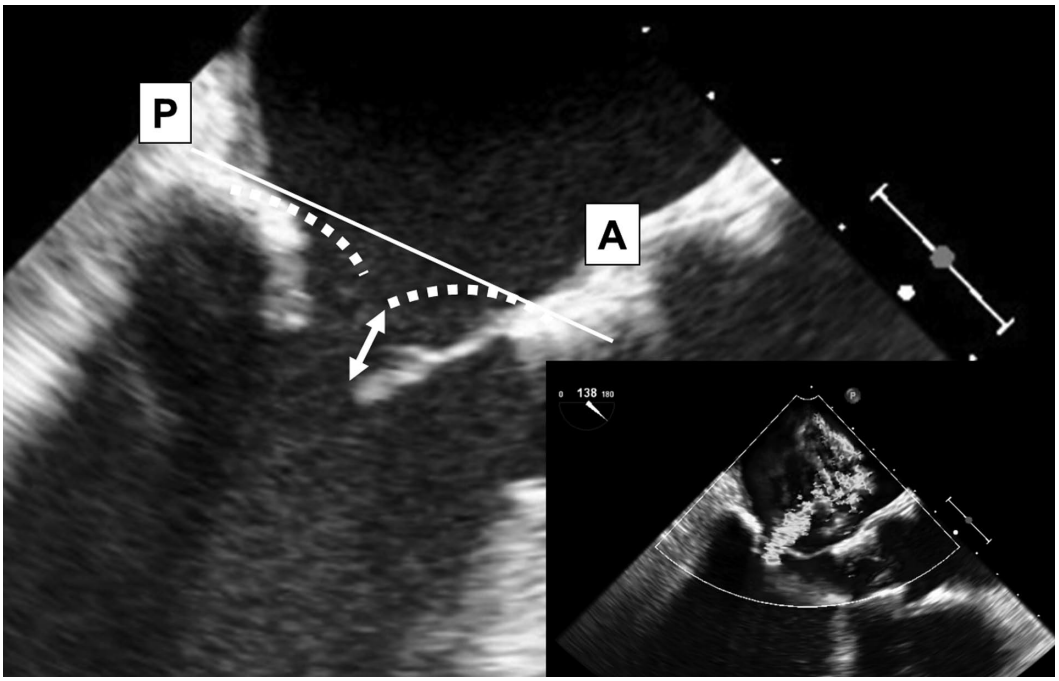

Figure. Anterior mitral leaflet (AML) excursion. White line, plane of mitral annulus; dotted lines, position of both mitral leaflets during ventricular systole; 2-headed arrow, AML excursion (measured perpendicularly to the plane of the mitral annulus). (**Inset**) Severe mitral regurgitation in the same patient. A, anterior; P, posterior.

outflow tract (LVOT) view, and it was observed that for those with baseline reduced AML excursion <1.4 cm in the background of restrictive PML, there was higher chance of resultant transmitral gradient ≥5 mmHg if more than 1 clip was placed, and therefore such a strategy aiming at perfect MR reduction was very often abandoned. A higher proportion of patients in the functional MR group (45% vs. 29%, P=0.12) required such a compromise in achieving perfect MR reduction to avoid significant reduction in opening area. Comparing those patients with or without a compromise in additional clip implantation, the AML excursion was 1.2±0.2 vs. 1.8±0.3 (P<0.001) respectively. Therefore, reduced AML excursion is identified as one of the predictors for a higher chance of significant MVA reduction if more than 1 clip is placed. In addition, baseline small MVA, small thickened annulus, thickened mitral leaflets and uncertainty of the contribution of MR to the resultant transmitral gradient are the factors that might compromise the strategy in implanting additional clip(s) to achieve perfect MR reduction. Larger studies, however, are required to allow identification of predictors of significant MVA reduction in the 2-clip strategy. Fortunately, despite the modest reduction of MR, the resultant symptom improvements were often meaningful to these patients who were very high-risk surgical candidates.

At Royal Brompton Hospital, the exclusion criteria for MitraClip® implantation were different from the commonly applied EVEREST valve suitability criteria, and a more liberal approach in treating patients with adverse valve morphology was adopted. In particular, partial calcification of leaflets, length and depth of coaptation, width and maximal gap of the flailed leaflet, absolute valve area <4.0 cm^2, poor ejection fraction, and non-central location of jet origin were not absolute contraindications. In particular, in some patients, the short coaptation length (ie, <2 mm) and slightly excessive coaptation gap (>10 mm) and width (>15 mm) could be overcome with adenosine-induced asystole to facilitate the grasping of both leaflets by the clip arms.[2] Therefore, patients were considered unsuitable only when there was reasonable concern that the MitraClip® would fail to grasp both leaflets, or when they had heavily calcified mitral leaflets or rheumatic mitral disease, in which there is a high likelihood of resultant mitral stenosis after clip(s) placement.

In terms of background risk, poor LV function is not an absolute contraindication to clip implantation, particularly when all medical and device therapies have already been optimized. In those with extremely poor LV function with EF <15%, it should be seriously considered as to whether clip implantation should be offered to these patients, who are also considered to have poor long-term prognosis. Successful reduction of MR in these patients, however, often resulted in meaningful improvement in quality of life and symptoms.

Conclusion

MitraClip® was shown to be an effective and safe treatment for patients with severe functional and degenerative MR, with no major procedural-related complications in this series. In some patients, particularly those with functional MR with restrictive AMLs in the presence of restrictive PMLs, there were often compromises between perfect MR reduction and the risk of creating mitral stenosis by placement of an extra clip. The majority of these high-surgical-risk patients who had a successful MitraClip® implantation could benefit from symptom and quality of life improvement.

Study Limitation

Owing to the relatively small number of recruited patients, further studies evaluating MitraClip® therapy and the compromise between MR reduction and resultant significant mitral valve opening area reduction, are needed to draw a more meaningful conclusion.

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