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ScienceDirect

Journal of the Chinese Medical Association 81 (2018) 305−310

www.jcma-online.com

Original Article

Initial experience with percutaneous edge-to-edge transcatheter mitral valve repair in a tertiary medical center in Taiwan

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Received August 8, 2017; accepted September 25, 2017

Abstract

Background: The transcatheter edge-to-edge mitral valve repair, using MitraClip, has been a safe and effective treatment for severe mitral regurgitation (SMR) in the westerners. However, the therapeutic results of the MitralClip in Taiwan remained elucidated.
Methods: Patients with symptomatic SMR were evaluated by the heart team. For those with high or prohibitive surgical risks, transcatheter mitral valve repair was performed in hybrid operation room. During procedure, continuous hemodynamic monitoring was conducted. Transthoracic echocardiography (TTE), blood tests, and six-minute walk test (6MWT) were performed before and 1-month after surgery.
Results: A total of 20 patients (73.4 ± 11.1 years, 85% male) with a mean Euroscore II of 13.2 ± 17.7% and a mean STS score of 8.7 ± 9.0% for mortality were enrolled. After a mean procedural time of 239 ± 95 min, an average of 1.8 ± 0.7 clips were used in each procedure. The procedural successful rate was 95% to achieve mild residual mitral regurgitation. Cardiac output was increased from 3.6 ± 0.9 to 4.6 ± 1.4 ($p = 0.008$) and V-wave of left atrial pressure declined from 24.4 ± 9.8 to 19.3 ± 7.1 ($p = 0.030$) immediately during the index procedure. There was no peri-procedural death, myocardial infarction, stroke or any events requiring emergent cardiac surgery. All patients experienced significant improvement in heart failure symptoms. The 6-min walk distance increased from 219.6 ± 118.4 m to 279.1 ± 111.6 ($p = 0.04$) at 1 month. The echocardiogram further showed significant improvements of mitral regurgitation, pulmonary artery systolic pressure, and the left ventricular end-diastolic volume.
Conclusion: Trans-catheter edge-to-edge mitral valve repairs are safe and effective in Asians with symptomatic SMR, regarding the improvements of clinical symptoms and exercise capacities. MitraClips is also associated with reverse remodeling of pulmonary hypertension and left ventricular size in patients with SMR.

Keywords: Mitral regurgitation; Transcatheter mitral valve repair

1. Introduction

More than 10% of the subjects, aged≥ 75 years have moderate to severe mitral regurgitation,[1] resulted from prolapsing leaflets or rupture chordae (degenerative mitral regurgitation, DMR), or as a consequence of annulus dilatation or abnormal left ventricular function (functional mitral regurgitation, FMR). Patients with symptomatic mitral regurgitation, if left untreated, would experience progressive heart

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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https://doi.org/10.1016/j.jcma.2017.11.006

failure, and the 5-year mortality rate could be as high as 50%.[2] Although mitral valve repair or replacement is the standard treatment for DMR, only 49% of them have received surgery in European heart survey.[3] For those with DMR and advanced age or FMR, the mitral valve surgery may carry high or even prohibitive risks.

The transcatheter edge-to-edge mitral valve repair, using MitraClip (Abbott Vascular, Menlo Park, CA, USA), has been suggested as an alternative of mitral valve therapy for patients with moderate to severe symptomatic DMR in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II).[4,5] Moreover, MitraClip has also been proposed the survival advantages over medical treatment in the inoperable patients.[6,7] Given one of the major determinants for the procedural success of MitraClip is the mitral valve area, the use of MitraClip to treat mitral regurgitation in Asians may be with challenges when Asian's hearts are smaller than the Western's.[8,9]

In the present study, we reported the initial experience of using MitraClip in Taiwan to demonstrate the feasibility of trans-catheter mitral valve repair for severe mitral regurgitation (SMR). We also showed the hemodynamic and echocardiographic influences of MitraClip in these patients.

2. Methods

2.1. Study participants

Subjects with heart failure and SMR were eligible for this study. All patients would undergo a standard diagnostic workup, including history taking, physical examinations, functional capacity assessments by the New York Heart Association (NYHA) classification and 6-min walk test, transthoracic and transesophageal echocardiogram, diagnostic coronary angiography, and right heart catheterizations for preoperative evaluation. The heart team would disclose the surgical risks and discuss with the patients for the treatments for SMR. Patients undergone trans-catheter mitral valve repair were enrolled in this analysis. The investigation conformed to the principles outlined in the Declaration of Helsinki. A written informed consent approved by our institutional review board was obtained from each subject before enrollment.

2.2. Study protocol

In addition to the pre-operative evaluations, patients would undergo repeated assessments for functional capacity and cardiac performance by transthoracic echocardiogram at 1, 3, 6, and 12 months after the index procedure. Blood tests at fasting were also obtained for the measures of hemoglobin, serum creatinine, and N-terminal pro-B type natriuretic peptide (NT-proBNP) levels. All participants were followed in the clinics or by telephone contact every month for a year.

2.3. Echocardiographic measurements

All patients received a comprehensive Doppler and M-mode transthoracic echocardiography according to the recommendations of American Society of Echocardiography.[8,10] Left ventricular end diastolic and systolic volume (LVEDV and LVESV), and left ventricular ejection fraction were measured by biplane Simpson's method. The regurgitant volume, vena contracta and effective regurgitant orifice of mitral regurgitation were also calculated.[11] The left and right atrial length and transverse major and minor axis were measured from the apical four-chamber view.[8] The severity of mitral regurgitation was then graded as mild (grade 1), mild-to moderate (grade 2), moderate- to severe (grade 3), or severe (grade 4) accordingly. The measurements of mitral valve area (MVA), the flail gap, flail width, coaptation length and coaptation height were obtained by transesophageal echocardiogram (TEE).[4]

2.4. Transcatheter mitral valve repair

The procedure was conducted under general anesthesia with the guidances of fluoroscopy and TEE in a hybrid operative room. During the procedure, pulmonary artery pressure and cardiac output were continuously recorded by Swan–Ganz catheter. In brief, MitraClip was introduced into left atrium after the transseptal puncture to grasp the leaflets and minimize the regurgitation.

Procedural success was defined as a successful implantation of one or more clips to immediately reduce mitral regurgitation of less than grade 2.[12] Procedure related complications of myocardial infarction, stroke, transient ischemic attack, major bleeding and major vascular complications were recorded according to Valve Academic Research Consortium (VARC) and VARC-2 definitions.[13]

2.5. Statistical analysis

Means, standard deviations, and percentages were used to describe the characteristics of the study population. Paired t-test was used for the comparison of pre- and post-procedure hemodynamic and echocardiographic changes. Because of the skewed distribution, NT-proBNP was taken log transformation prior to the statistical analysis. Non-parametric independent t-test was used to compare the baseline characteristics between groups. Statistical significances were set at $P < 0.05$ and all statistical analyses were carried out using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

A total of consecutive 20 patients (73.4 ± 11.1 years, 17 men) treated with MitraClip were included in this analysis. The baseline characteristics were displayed in Table 1. The patients were characterized by high surgical risk (median Euroscore II of 13.2% and median STS score of 8.7% for mortality), and multiple morbidities. The surgeon declined to conduct surgical repair or replacement due to prior open-heart surgery (4 patients), severe lung disease (4 patients), disabled

Table 1
Baseline characteristics of the study population.

	n = 20 (%)
Age (years)	73.4 ± 11.1
Male	17 (85)
Height (cm)	161.3 ± 10.3
Weight (Kg)	62.3 ± 13.5
Morbidities, n (%)	
Diabetes mellitus	6 (30)
Hypertension	15 (75)
Severe chronic pulmonary disease	4 (20)
Coronary artery disease	9 (45)
Prior stroke	4 (20)
Chronic kidney disease (eGFR < 60 mL/min)	15 (75)
Peripheral vascular disease	2 (10)
Chronic atrial fibrillation	13 (65)
Prior open heart surgery	4 (20)
Serum creatinine (mg/dL)	1.9 ± 1.5
EuroScore II	13.2 ± 17.7
STS score	8.7 ± 9.0
HF hospitalization within a year	16 (80)
Echocardiographic parameters	
Degenerative MR	11 (55)
Functional MR	8 (40)
Mixed etiology	1 (5)
MR volume (ml)	113.6 ± 67.4
Vena contracta width (cm)	0.7 ± 0.2
Mitral valve area (cm^2)	4.3 ± 0.6

HF = heart failure.

cerebral vascular accidents (4 patients), and severely depressed LVEF of <30% (3 patients). All of the participants had SMR with a mean regurgitation volume of 113.6 ± 67.4 ml and were with NYHA Fc III to IV symptoms. The mean baseline MVA is 4.3 ± 0.6 cm^2. In addition, 8 patients (40%) have FMR. The flail gap is 8 ± 5 mm and the flail width is 13 ± 3 mm in patients with DMR. Among the FMR patients, the tethered height is 10 ± 3 mm and coaptation width is 1 ± 2 mm (see Table 2).

3.2. Procedure outcomes

Among the 20 procedures, 4 were done emergently while they had been put on mechanical hemodynamic support or inotropic agents. MitraClip was implanted successfully in all of patients, when 11 patients received 2 clips and 3 patients received 3 clips. The mean number of clips used in each procedure was 1.8 ± 0.7. The mean duration of the procedure, defined as the start time of femoral venous puncture to the time vascular is closed, was 239 ± 95 min. The average post-procedure stay in hospital is 6.2 ± 3.8 days. The procedures success rate was 95%. There was no peri-procedure death, myocardial infarction, stroke or any adverse events requiring emergent cardiac surgery. One patient, who had undergone catheter ablation for incessant ventricular tachycardia 2 days before the index procedure, experienced significant pericardial effusion after heparinization. After pericardiocentesis and blood transfusion, the MitraClip procedure was conducted successfully.

Table 2
Characteristics of the index procedure.

	n = 20 (%)
Procedure success	19 (95)
Procedure death	0 (0)
Device embolization	0 (0)
Single leaflet detachment	0 (0)
Cardiac tamponade/significant effusion	1 (5)
Conversion to surgery	0 (0)
Stroke (embolic/hemorrhagic)	0 (0)
Myocardial infarction	0 (0)
Acute kidney injury	0 (0)
Vascular access complications	0 (0)
Transfusion ≥ 2 units	1 (5)
Ventilation > 48 h	1 (5)
Numbers of clip	1.8 ± 0.7
Use of vascular closure device	17 (85)
Procedure duration (minutes)	239.2 ± 95.0
Post-procedure hospital stay (days)	6.2 ± 3.8
30-day mortality	1 (5)

An 86 years-old lady with mitral cleft and previous coronary bypass surgery presented with biventricular failure, characterized by hyperbilirubinemia before the index procedure. She experienced deteriorating hyperbilirubinemia and died within 30 days when mitral regurgitation hasn't been successfully abolished.

With regard to the acute hemodynamic improvement, the cardiac output increased from 3.6 ± 0.9 to 4.6 ± 1.4 L/min ($p = 0.008$) and V-wave of left atrial pressure declined from 24.4 ± 9.8 to 19.3 ± 7.1 ($p = 0.030$) immediately after the procedure, while the pulmonary artery pressure and mean left atrium pressure remained unchanged (Table 3). The femoral venous access was successfully closed by Proglide (Abbott Vascular) in 17 patients and by temporary subcutaneous "Figure-of-Eight" sutures in 3 patients.[14] None of the patients experienced vascular access complications.

3.3. Clinical improvements and echocardiographic changes

One month after the index procedure, the clinical symptoms were significantly improved that the patients were all with NYHA Fc I or II symptoms (Fig. 1). The 6-min walk distance was increased from 219.6 ± 118.4 m to

Table 3
Peri-procedural hemodynamic changes.

	Pre	Post	*p*
sPAP (mmHg)	45.7 ± 15.6	49.5 ± 12.4	0.093
dPAP (mmHg)	23.4 ± 6.9	24.6 ± 6.9	0.202
mPAP (mmHg)	33.2 ± 10.4	35.6 ± 8.5	0.108
mLAP (mmHg)	16.2 ± 7.7	16.8 ± 6.6	0.571
v-wave LAP (mmHg)	24.4 ± 9.8	19.3 ± 7.1	0.030
Cardiac output (L/min)	3.59 ± 0.93	4.58 ± 1.42	0.008
Trans-mitral MPG (mmHg)	2.3 ± 0.9	3.6 ± 1.3	0.002

sPAP = pulmonary artery systolic pressure; dPAP = pulmonary artery diastolic pressure; mPAP = mean pulmonary artery pressure; mLAP = mean left atrial pressure; MPG = mean pressure gradient.

279.1 ± 111.6 m ($p = 0.04$). In addition to the grade of mitral regurgitation, pulmonary artery systolic pressure decreased from 63.7 ± 22.9 to 49.6 ± 14.4 mmHg ($p = 0.007$) (Table 4). The left ventricular end-diastolic volume was also reduced significantly from 125.4 ± 47.5 to 107.6 ± 37.9 ml ($p = 0.018$). Meanwhile, the left ventricular end-systolic volume, LVEF, and the sizes of left and right atria were not changed.

4. Discussion

The present study has demonstrated the efficacy and safety of transcatheter mitral valve repair with MitraClip to treat patients with SMR and high or prohibitive surgical risks. In the preliminary experience in Taiwan, there was a 95% procedural successful rate and no requirement for emergent cardiac surgery. In addition, we illustrated the hemodynamic improvement of cardiac output and V wave declined immediately after the procedure. The patients may thereafter have better functional capacity and reverse remodeling of left ventricle.

To date, the EVEREST criteria have been acknowledged as the basic of an anatomical selection process. In EVEREST study, the anatomical eligible for MitraClip procedure comprised that a primary regurgitation originating from central A2/P2 region, coaptation length greater than 2 mm and coaptation depth less than 11 mm in FMR, and flail gap less than 10 mm and width less than 15 mm in DMR.[23] However, there were only limited cases to fulfill the strict echocardiographic criteria for MitraClip procedure. In fact, Attizzani GF et al. have shown with reasonable expanded echocardiographic features, the safety and efficacy are comparable to EVEREST eligible patients.[24] In this study, only 35% of our patients fulfilled the EVEREST criteria. For compassion reason, two of our patients with mitral cleft underwent MitraClip procedure and the procedural success rate was 50%. Even mitral cleft is not suitable for MitraClip, there were several case reports describing how to fix the SMR with cleft.[25–27] Our unfavorable experience discouraged using MitraClip to treat mitral cleft, especially in the early stage of the transcatheter mitral valve repair program.

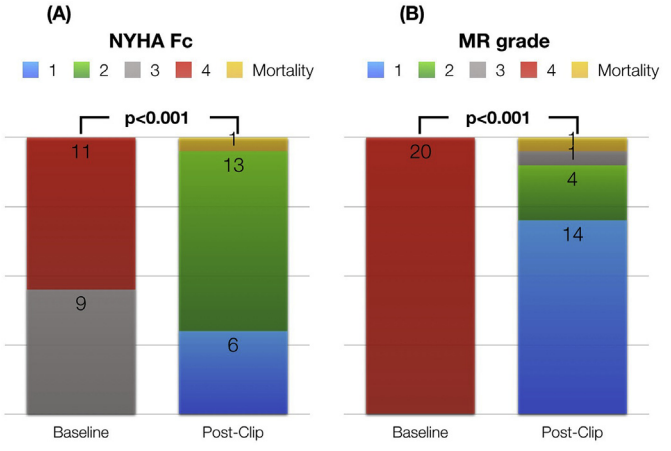

Fig. 1. (A) Results for NYHA class improvement before and 1 month after clip implantation. (B) Results for MR reduction before and 1 month after clip implantation.

Table 4
Clinical and echocardiographic parameters before and after MitraClip.

	Pre	Post	p
LVIDd (mm)	60.3 ± 9.1	58.9 ± 9.1	0.057
LVIDs (mm)	40.7 ± 12.2	40.0 ± 11.5	0.288
LVEDV (ml)	125.4 ± 47.5	107.6 ± 37.9	0.018
LVESV (ml)	60.7 ± 37.6	57.8 ± 35.1	0.409
LA major axis length (mm)	60.8 ± 15.9	61.4 ± 6.2	0.860
LA minor axis length (mm)	52.2 ± 16.2	51.5 ± 8.6	0.812
RA major axis length (mm)	56.8 ± 7.8	54.5 ± 10.1	0.167
RA minor axis length (mm)	39.3 ± 13.1	42.9 ± 9.7	0.199
PASP (mmHg)	63.7 ± 22.9	49.6 ± 14.4	0.007
TAPSE	16.9 ± 4.0	19.44 ± 4.6	0.052
MPG of MV	2.5 ± 1.0	3.5 ± 0.9	0.002
LVEF (%)	52.9 ± 15.0	48.9 ± 15.6	0.057
Log NT-proBNP (pg/ml)	3.24 ± 0.52	3.11 ± 0.50	0.132
6MWT distance (meters)	219.6 ± 118.4	279.1 ± 111.6	0.040

LVIDd = left ventricular internal diameter at end-diastolic phase; LVIDs = left ventricular internal diameter at end-systolic phase; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; LA = left atrial; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion; LVEF = left ventricular ejection fraction; MPG = mean pressure gradient; MV = mitral valve; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; 6MWT = 6 min walk test.

Another important limitation of MitraClip is the residual MVA after edge-to-edge repair. Since the residual mitral regurgitation after MitraClip procedure was related to the clinical outcomes,[28] it has been suggested to eliminate all the residual regurgitation with more clips if the trans-mitral valve mean pressure gradient is less than 5 mmHg. In the German TRAnscatheter Mitral Valve Interventions (TRAMI) registry, an average of 1.5 clips was implanted in a single procedure.[29] In the study population, the baseline MVA was 4.3 ± 0.6 cm^2 and 8 patients (40%) had MVA of <4 cm^2, which was beyond the EVEREST criteria. However, the study population has received an average of 1.8 clips to minimize the residual regurgitation. The MitraClip Asia-Pacific Registry (MARS) also showed that 52% patients have received ≥2 clips.[21] The study result and MARS registry supported the clipping strategy should be similar in Westerners and Asians in spite of the anatomical differences.

Given the Asian patients are reluctant to undergo open-heart surgery and the observed mortality is higher than the surgical risk prediction model,[30,31] there is an unmet need to ameliorate the disease awareness and the therapeutic adherence in Asians. The study results may support the transcatheter approach as an alternative therapy for SMR in Asia. In addition to patients with DMR in EVEREST II trial, the efficacy and safety of trans-catheter mitral valve repair also have been established in patients with advanced age,[32] LV systolic dysfunction,[33,32] and extreme surgical risk, when surgery was usually declined.[29] In this study, 3 patients had LVEF of <30% and the experienced similar improvements of cardiac output and functional capacity to the others after successful trans-catheter procedures. One patient went through severe afterload mismatch and warranted transit mechanical hemodynamic

support when the mitral regurgitation was completely fixed.Peri-procedural inotropics might be indicated to ameliorate the afterload mismatch in patients with severely depressed LVEF undergoing MitraClip procedures.[34−36]

The study demonstrated an acute increase of cardiac output after MitraClip. The V-wave declined after fixing SMR in our study, is also recognized as an important indicator for procedure success and has positive correlation to patient's functional capacity after MitraClip.[37] Although the pulmonary artery systolic pressure (PASP) did not change immediately, the echocardiogram showed a significant decrease of PASP at 1 month. The results may support the reversibility of pulmonary hypertension in patients with SMR, which may further ameliorated tricuspid regurgitation in some of the patients.[38] In addition, we also observed a significant reduction of LVEDV but not LVESV at 1 month, which was in line with what Glower et al. have reported a greater reduction of LVEDV than LVESV in EVEREST II trial.[39] In MARS registry, a significant reduction of left ventricular end-diastolic dimension was also observed as early as 30 days after the index procedure.[21] Furthermore, we demonstrated a significant increase in 6-min walk distance after the procedure to provide an objective support for MitraClip. With superior procedural safety, trans-catheter mitral edge-to-edge repair is an encouraging therapy in patients with either FMR or DMR and high or prohibitive surgical risks.

Nowadays, the American and European guidelines have recommended the transcatheter mitral valve repair is a reasonable treatment option in patients with severe DMR and prohibitive surgical risks.[15,16] Given the growing evidences have illustrated the clinical and hemodynamic improvement after transcatheter correction of severe FMR,[17−19] MitraClip is recommended in the European guideline for patients with severe FMR who are not indicated for revasculization and remain symptomatic after optimal medical treatment.[15] While 40% of the study population was FMR, we may have demonstrated the feasibility and safety of MitraClip in treating FMR as in DMR patients. The results were similar in 46% subjects in Japan pivotal study of FMR[20] and 54% patients in Asia-pacific registry of FMR.[21] However, its efficacy and long-term outcome could only be concluded when the results of the randomized-controlled trial (COAPT trial NCT01626079) is available.

Even the preliminary data may have encouraged the clinical application of MitraClip, the case number is limited and the follow-up period is short. The long-term impacts of MitraClip on hemodynamics, clinical outcomes and ventricular remodeling should be further evaluated. According to the guideline, we believe MitraClip should be reserved for patients with high or prohibitive surgical risks.

In conclusion, trans-catheter edge-to-edge mitral valve repairs are feasible to treat patients with symptomatic SMR and high or prohibitive surgical risks in Asians to improve clinical symptoms and exercise capacities. For those with eligible valvular anatomy, MitraClips may also be related to a reverse remodeling of pulmonary hypertension and left ventricular volumes. The preliminary experience in Taiwan may encourage the percutaneous therapy for patients with SMR when mitral valve surgery is not a choice.

Acknowledgments

This work was supported by a grant from the Taipei Veterans General Hospital, Taiwan, R.O.C. (V106B-019).

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