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Treatment of severe mitral regurgitation with MitraClip system — a single-centre study

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ABSTRACT

Introduction. MitraClip (MC) is a catheter-based device to treat mitral regurgitation (MR). This method uses a transseptal approach and is based on the creation of a double orifice mitral valve by suturing of the middle scallops of the mitral valve's leaflets.

Aim. The aim of the study was to assess the effectiveness of MC method in treating patients with severe MR. We analysed MR severity, patient's clinical condition evaluated by New York Heart Association (NYHA) functional class, and the function of the left ventricle evaluated by Left Ventricle Ejection Fraction (LVEF).

Methods. A retrospective single-centre study with patients hospitalised at the Department of Cardiology and Internal Medicine in Bydgoszcz. All diagnosed with severe MR and treated by performing MC procedure in the time period from August 2010 to December 2014. The following data from medical history (NYHA class) and echocardiography examinations (MR severity and LVEF) were analysed in three time points: before, right after the procedure, and after the follow-up period (four weeks since discharge).

Results. The studied group consisted of 11 patients — 8 male, 3 female, aged 64.4 (± 10.2) years, treated with MC. All of the three analysed parameters improved relevantly as a result of the evaluated procedure. The percentage of patients classified as NYHA class III/IV presents as follows: 90% before the procedure, 55% after MC implantation (ns), and 44% after the follow-up period ($p = 0.01$). All patients suffered from severe-to-moderate (3+) and severe (4+) MR before the procedure. After implantation only 9% (ns) were still classified with 3+/4+ MR, and after the follow-up this percentage reached 18% ($p = 0.0005$). We observed relevant changes of LVEF. The average LVEF at baseline was 27.9 ± 2%, which increased to 29.6 ± 2% (ns) after the MC implantation and 34 ± 7% ($p = 0.02$) after the follow-up.

Conclusion. MC therapy is effective in patients with severe symptomatic MR with congestive heart failure and decreased LVEF. It reduces MR severity both acutely and after the follow-up period and improves NYHA class and LVEF.

Key words: mitral regurgitation, MitraClip

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Introduction

Mitral regurgitation (MR) is the second most common valvular heart disease requiring surgery in Europe after aortic stenosis [1]. We can single out two types of MR. The first one is degenerative MR, which is caused by changes of the valvular apparatus. The second one is called functional MR and develops in a result of remodelling of the left ventricle (LV) usually in the course of ischaemic heart disease [2]. MR incidence increases with age. It has become a serious clinical problem due to the ageing of the general population. Symptomatic severe MR or asymptomatic severe MR complicated by LV dysfunction requires surgical repair or replacement of the mitral valve (MV). Elderly patients with moderate-to-severe or severe MR are at high or prohibitive surgical risk caused by advanced age, the presence of comorbidities, or impaired LV function. Morbidity and mortality are directly related to MR severity among patients with heart failure and depressed left ventricular ejection fraction (LVEF).

MitraClip (MC) is a catheter-based device designed to perform edge-to-edge reconstruction of MV [3]. This method uses a transseptal approach and is based on

the creation of a mitral double orifice valve by suturing of the anterior and posterior MV leaflets. As a result the leaflets are closer during systole, thereby reducing the amount of regurgitation [1].

The EVEREST I (Endovascular Valve Edge-to-Edge Repair Study I) demonstrated the safety, feasibility, and significant haemodynamic improvement of the MC procedure [1]. In the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study II) study 279 patients with moderate to severe MR were randomised 2:1 either to MC implantation or open heart surgical valve repair [4]. At 12-month follow-up 55% of patients in the MC arm were free from death, surgery, or grade 3+ and 4+ MR as compared to 73% of patients in the surgery group [4]. Moreover, after the follow-up period 13% of surgical patients were in functional New York Heart Association (NYHA) class III or IV while in the MC group it was only 2% of patients [5]. Major adverse events assessed in the EVEREST II study were as follows: death, myocardial infarction (MI), reoperation for failed surgical repair or replacement, urgent or emergency cardiovascular surgery for adverse event, major stroke, renal failure, deep wound infection, mechanical ventilation for > 48 hours, gastrointestinal complication requiring surgery, new onset of permanent atrial fibrillation, septicaemia, and transfusion of ≥ 2 units of blood. Major adverse events occurred commonly in the surgery group (48% vs. 15%, $p < 0.001$) 30 days after the procedure [5]. The difference was mainly driven by the need for transfusion and prolonged mechanical ventilation. Therefore the MC technique has evolved into a therapeutic alternative for patients with significant MR of both degenerative and functional origin, whose surgical risk is considered prohibitive.

The aim of our study was to assess the reduction of MR severity in patients with severe symptomatic MR after performing the MC procedure. We also analysed the clinical condition of patients assessed by NYHA class and evaluated the function of LV with echocardiography by measuring LVEF.

Materials and methods

We conducted a retrospective single-centre study and enrolled patients hospitalised at the Department of Cardiology and Internal Medicine in Bydgoszcz, diagnosed with severe MR and treated by implantation of MC system in the time period from August 2010 to December 2014.

All patients included in the study had severe, symptomatic MR. The aetiology of MR was functional, associated with the remodelling and significant dysfunction of LV.

Patients with a history of recent MI, acute endocarditis, or rheumatic heart disease were excluded from the procedure. Other exclusion criteria were the anatomic contraindications evaluated by echocardiography such as coaptation length of MV leaflets < 2 mm, coaptation depth of MV leaflets > 11 mm, mitral valve area < 4 cm^2, flail gap > 10 mm, flail width > 15 mm, left ventricular end-systolic diameter (LVESd) > 55 mm, and massive calcifications of the valvular apparatus.

The heart team qualified all patients for the procedure. Both transthoracic and transoesophageal echocardiography examinations were performed before the procedure to assess the aetiology and mechanism of MR. Severity of MR was also graded by echocardiography. Severe MR was identified based on the criteria recommended by the European Association of Echocardiography [6]: vena contracta ≥ 7 mm, regurgitant volume ≥ 30 mL/beat (for functional MR), effective regurgitant orifice area ≥ 0.2 cm^2 (for functional MR), E wave dominant > 1.5 m/s, TVI mitral/TVI aortic (Time-Velocity Integral ratio) > 1.4, and systolic reversal in pulmonary veins. The biplane Simpson's method was used to measure volumes of LV and LVEF.

MC procedure was performed in an adapted haemodynamic lab using monitoring by transoesophageal echocardiography and fluoroscopy. The team should consist of a cardiologist, echocardiographer, anaesthesiologist, and cardiac surgeon.

Whole procedure included four stages. In the first stage the catheter was introduced through the femoral vein into the right atrium, and the septum was punctured. In the next stage, the catheter with the implant was positioned in the distal part of the left atrium, one centimetre above the MV. Subsequently, the opened implant was entered to the LV and it was positioned in the coaptation line. All corrections were made under the control of echocardiography. The implant was pulled into the left atrium and two leaflets of the MV were grabbed. Finally, the implant was closed and released, the catheter was removed. In the event of failure to obtain a satisfactory result, it was possible to use two or three implants [1]. The first successful implantation of four MC devices in Poland in a patient with severe, symptomatic MR was performed in Bydgoszcz [7].

Acute procedural success (APS) was defined as the reduction of MR severity to grade 2+ or lower after the clip implantation graded by echocardiography [9–16].

All data (collected from the medical history, discharge summary, and echocardiography examination) were analysed in three time points: before the procedure, right after the procedure, and after the follow-up period (four weeks after discharge). We used Statistica Soft version 12.5 software. Parametric values such as LVEF were compared using Student's t-test. Non-parametric values such as NYHA class were compared using Wilcoxon signed-rank test.

Table 1. Baseline characteristics of patients

	n = 11	%
Demographic		
Age (years)	64 ± 10	–
Sex		
Female	3	27
Male	8	73
Comorbidities		
Prior myocardial infarction	6	55
CABG	3	27
PCI		
Overall	5	45
LAD	2	18
RCA	1	9
LAD+Cx	1	9
LAD+RCA	1	9
Previous stroke	2	18
TIA	0	0
Arterial hypertension	4	36
Atrial fibrillation	2	18
Prior cardiac surgery	6	55
ICD/CRTD	5	45
Hypercholesterolaemia	2	18
DM	6	55
COPD	2	18
Chronic renal disease	3	27
Hypothyroidism	3	27
Gout	2	18
Cancer	0	0

Results

The analysed group consisted of 11 patients (8 male and 3 female) treated with MC system. The average age of the patients stood at 64.36 (± 10.2) years and ranged from 48 to 81 years. Before procedure 90% of patients were classified as III/IV NYHA class. Baseline characteristics of patients and their comorbidities are provided in Table 1.

The aetiology of MR was described as non-ischaemic in four patients (36%) and as ischaemic in seven of them (64%). MR severity in all of the studied cases was described as severe (4+) before procedure (Tab. 2). During the procedure five patients had one clip implanted and six of them had two clips. As the follow-up we defined control examination performed 43 ± 25 days after the procedure, i.e. approximately four weeks after discharge.

Table 2. Baseline characteristics of echocardiography parameters

	n = 11	%
LVEF ± SD (%)	29 ± 8	
LVEF < 40%	9	82
Aetiology of MRc		
Ischaemic	5	45
Non-ischaemic	6	55
Number of regurgitant jets (n = 9)		
1	3	33
2	6	67
Vena contracta ± SD [cm] (n = 9)	0.83 ± 0.12	–
MR severity 4+	11	100
RVSP (SPAP) ± SD [mm Hg] (n = 8)	57 ± 20	–

All of the patients suffered from severe (4+) MR. APS was achieved in 91% of the patients. At the follow up 82% had MR severity ≤+2. A comparison of MR severity before and after the procedure is presented below (Fig. 1).

Table 3 shows the changes of the most relevant echocardiography parameters observed before the procedure and after the follow-up.

Right after the MC implantation the percentage of patients classified as III/IV NYHA class reached 55%. After the follow-up patients with NYHA III/IV class made up only 44% of treated group (Fig. 2).

LVEF increased significantly from 27.9 ± 2 % before, to 29.6 ± 2% after the procedure. After the follow-up the average LVEF stood at 34 ± 7% (p = 0.022) (Fig. 3).

Discussion

To the best of our knowledge this is the first polish study revealing the effects of treatment with MC system in more than 10 patients. Other descriptions discussed up to three cases [2, 8]. In our study the follow-up period lasted 43 ± 25 days and we analysed the changes of three main parameters: NYHA class, MR severity, and LVEF. We compared our results with other registries (mainly European) which differed with the number of patients, the length of follow-up period, the average age, and the percentage of patients who suffered from prior MI, arterial hypertension, and DM. The compared registries included more patients (from 20 to 567) than in our study and the follow-up period lasted longer. The group in our study was younger (the average age was 64 years) than the groups from compared studies where the average age was between 70 and 78 years [9–16]. In our group 55% of patients suffered from prior MI,

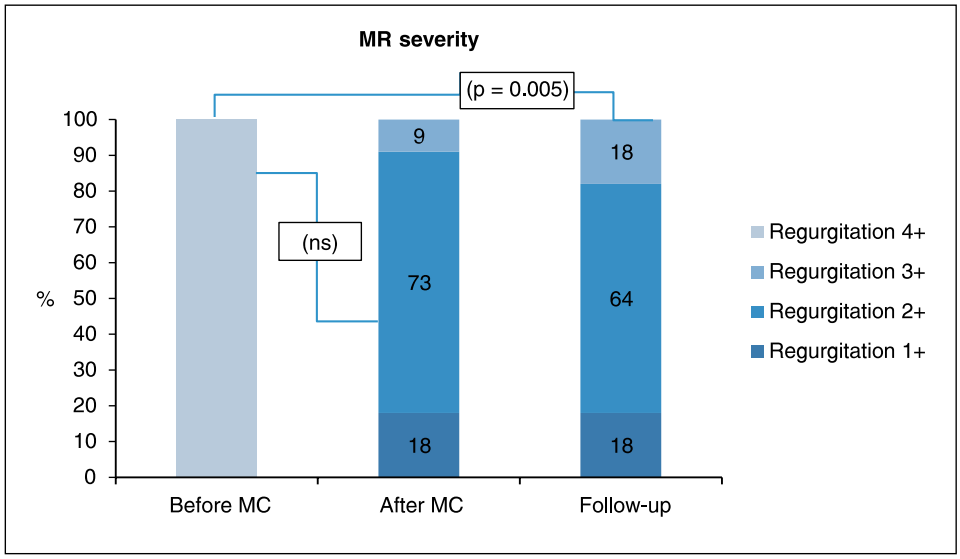

Figure 1. Comparison of MR severity before and after MC implantation, and after follow-up

Table 3. Comparison of echocardiography parameters before MC and after follow-up

	Before MC	After follow-up
LVEF ± SD (%)	29 ± 8	34 ± 7
Vena contracta ± SD [cm]	0.83 ± 0.12	0.48 ± 0.15
MR severity 1+ (% of patients)	0	18
MR severity 2+ (% of patients)	0	64
MR severity 3+ (% of patients)	0	18
MR severity 4+ (% of patients)	100	0

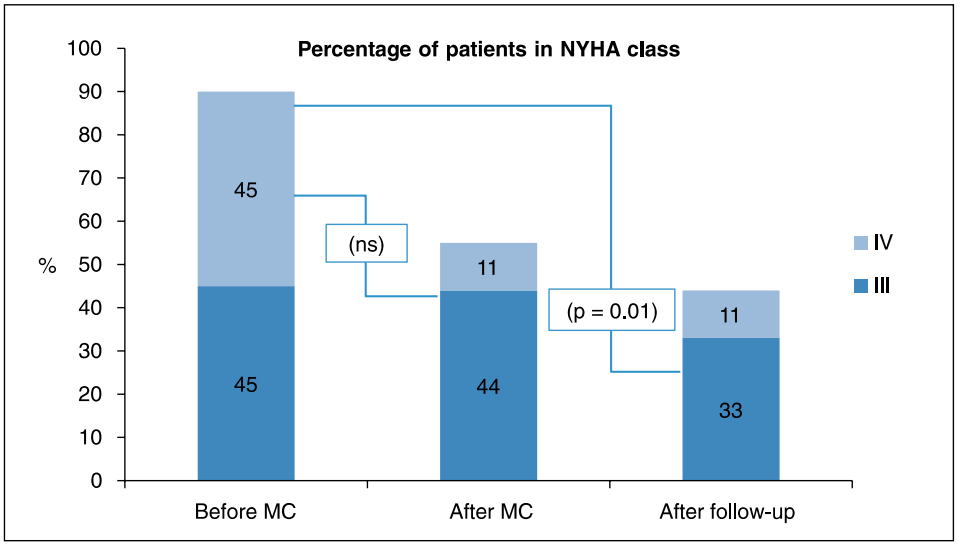

Figure 2. Comparison of percentage of patients in NYHA class before and after MC implantation, and after follow-up; III — NYHA III class; IV — NYHA IV class

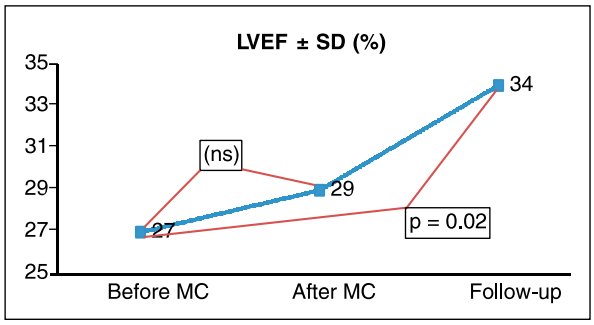

Figure 3. Comparison of LVEF (%) before and after MC implantation, and after follow-up

34.4% from arterial hypertension, and 55% from DM. In compared registries patients more often had arterial hypertension: from 64 to 85% [11, 13, 14, 16] of patients, but the percentage of prior MI and DM was lower — from 21 to 32% for MI [10, 11, 13] and 18 to 40% for DM [10, 11, 13, 14, 16]. The high percentage of patients who had undergone prior MI is connected with the aetiology of MR in our group. All our patients had functional MR and for the majority of them the aetiology was described as ischaemic. However, we confronted our results independently from the aetiology of MR. The majority of compared registries included patients mainly with functional MR except that from Feldman et al., who studied the group with mainly degenerative MR [16] and Gaemperli et al. [11] where the groups were similar: 45% with functional and 48% with degenerative MR.

MC therapy reduced MR severity. APS was achieved in 10 cases (91%). Other studies showed similar results: APS between 73 and 94% [9–16]. We confronted the percentage of patients with MR severity ≤ 2+ after the follow-up period (82% in our study) with other results and they were comparable to ours. Franzen et al. [9] and Gaemperli et al. [11] reported higher reduction of severity — 87% and 86%, while lower was recorded by Koifman et al. [14] — 64%, Feldman et al. [16] — 66%, the registry from Switzerland [15] — 58%, the registry from France [12] — 80%, and the ACCESS-EU registry [13] — 78.9%. All compared registries were characterised by longer follow-up periods, which lasted from 69 days to two years.

NYHA class significantly improved after the follow-up period; 44% of patients stayed in class III or IV. Compared to the other reports this percentage is higher. Koifman et al. [14] reported 90% of patients in class III or IV NYHA before the procedure, which reduced to 41% after 187 days, and Franzen et al. [9] showed reduction from 100% to 28% after six months of follow-up. In TRAMI registry [10] the follow-up period lasted 85 days and the same parameter decreased from 93% to 36%. In the registry from Switzerland [15] there were about 80% (no clear information) of patients in class III or IV NYHA before the implantation, and two years after the procedure there were 22%. The registry from France [12] and ACCESS-EU registry [13] reported as follows: the reduction from 77% to 9% and from 84.9% to 28.6% six months and 12 months after the procedure, respectively. Also the study by Feldman et al. [16] showed that at baseline there were 55% and only 8% of patients stayed in class III or IV NYHA after 12 months.

We observed that LVEF increased acutely after the procedure and after the follow-up period. The LVEF improved from the baseline value 27.9 ± 2% to 34 ± 7% after the follow-up period, which was statistically significant ($p = 0.02$). Interestingly, only one of the compared studies showed a similar effect. It was the study by Franzen et al. [9] where they analysed a group of patients with end-stage heart failure — all patients were in III or IV NYHA class and had LVEF ≤ 25%. The majority had severely dilated hearts (LVESd > 55 mm present in 78%). In this group LVEF increased from 20 ± 4% to 25 ± 9% ($p = 0.003$). All patients had functional MR in this study. Unfortunately, the study in which patients had mainly degenerative MR [16] did not reveal the changes of LVEF after the follow-up period. LVEF decreased or stayed stable at the follow-up in the rest of the compared registries. They presented a similar percentage of patients with functional MR (from 62 to 73,8%) but all of them differ from our study with higher baseline values of LVEF (from 36 to 47%) [12, 14, 15]. The highest baseline LVEF values were reported in the same study in which the percentage of patients with degenerative MR was the highest. However, Gaemperli et al. [11] indicate that even though LVEF was decreased in those cases, the LV contractility would be insignificantly affected due to load independent parameters.

As mentioned before, as many patients as presented in this study were not described in any other Polish publication. Two publications reported six cases of performing MC procedure in patients with severe MR. The first one, by Kalarus et al. [8], showed the results of implanting clips in three patients with severe (4+) ischaemic MR and high cardio surgical risk. All three patients were in class III or IV NYHA and had a history of prior MI and previous revascularisation procedures. Also, LVEF was impaired and ranged from 23 to 28%. On the fifth day after the procedure the researchers observed a reduction in MR severity and improvement of NYHA class and LVEF. The results five days after the procedure showed that MR severity decreased to ≤ 2+ in all three cases. All patients were in class II NYHA and their LVEF also increased and was between 25 and 33%. The second study, by Kübler et al. [2], presented results of performing MC procedure in three cases with a 90-day follow-up period. Also in this study all patients suffered from significant (3+/4+) ischaemic MR and were excluded from surgery due to high cardio surgical risk. Before the procedure two patients were in class III

NYHA and the third was in class III/IV. LVEF was 18%, 28%, and 25%, respectively. After 90 days of follow-up the MR severity reduced in two patients to ≤ +2 and in one patient quite severe (2+/3+) MR persisted. Exercise capacity assessed by NYHA class improved in all patients — two of them were in class II and the third one was in class II/III. Also, LVEF increased to 25% in one patient and to 30% in the other two. Due to the very small number of patients and the lack of statistical analysis comparison with our results is futile, although patients reported in those studies presented similar clinical condition and comorbidities to our patients.

The differences between our study and the other registries may be a result of the aetiology of MR. In our study all patients had functional MR, and 64% of patients in that group had ischaemic MR. It seems that the reduction of MR severity with MC procedure is independent of the aetiology of MR because both Franzen et al. [9] (100% with functional MR) and Gaemperli et al. [11] (only 45% with functional MR) reported similar reduction of severity — 87% and 86%, respectively. However, LVEF is strongly associated with the aetiology of MR — patients with functional MR usually had much lower LVEF than those with degenerative MR. Furthermore, both studies with only functional MR (ours and the study by Franzen et al. [9]) showed the same result — an improvement in LVEF after the follow-up period. Both groups had much lower baseline values of LVEF in comparison to other registries. We may assume that the improvement of LVEF after the follow-up period was a result of LV remodelling in patients with functional MR. Probably the fact that more patients had degenerative MR in other studies resulted in stable or even decreased LVEF after the follow-up period. The effect of remodelling in patients with degenerative MR is less noticeable because they had efficient LV. That is the reason why after reducing MR severity their LVEF stayed stable. LVEF could even decrease, especially in patients who were in the hyper-compensation phase of MR while the procedure took place.

The shorter follow-up period may also be a cause of differences between our study and the others. The longer follow-up period would probably not affect the reduction of MR, which was presented in the registry from Switzerland [15], where the percentage of patients with MR severity ≤ +2 was almost the same after one year and after two years of observation. MR severity worsened only in one patient during the second year. We may expect that the longer follow-up period would result in greater improvement of LVEF and NYHA class because patients with functional MR would have more time for beneficial remodelling of LV. However, improvement of NYHA could be inhibited by comorbidities, for example coronary artery disease, which is common in patients with functional MR.

The younger age of our patients should lead to greater improvement of clinical condition expressed by NYHA class based on the assumption that younger patient equals better overall condition. On the other hand, a higher percentage of patients in our group had history of prior MI and DM. It seems that those comorbidities could inhibited the improvement of NYHA class and led to differences between our study and the other registries.

Limitations of the study

In our opinion the main limitation of this study is the low number of patients and short follow-up period. Furthermore, the retrospective character inhibited us from gathering all essential data needed.

Conclusion

Patients suffering from severe symptomatic MR with heart failure and impaired LV function (decreased LVEF) can be successfully treated with the MC procedure. The MC procedure reduces the severity of MR in the majority of cases not only acutely after the procedure (APS in 91%) but also after the follow-up period (82%). It also led to the improvement of both NYHA class and LVEF. It proves that it can be an effective therapy for patients whose cardio surgical risk is considered prohibitive. Definitely further investigation, especially randomised, prospective trails, are needed.

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