Impact of the Learning Curve in Device Time, Echocardiographic Outcome and Clinical Outcome in Patients Treated with MitraClip®

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ABSTRACT

Background

Contradictory findings are published with respect to a learning curve for echocardiographic and clinical outcome of mitral valve (MV) repair with the MitraClip® system.

Methods

The study included 39 patients with heart failure symptoms and at least moderate mitral regurgitation (MR) who underwent MitraClip® implantation. The learning curve was analyzed after creating three subgroups of 13 patients each according to the treatment period . A patient was defined as echocardiographic responder when MR severity decreased by at least 1 class considering the 6-scale MR classification to maximally moderate, and as clinical responder when the patient was alive and NYHA class improved to class 1 or 2 without a hospitalization for heart failure.

Results

Mean device time decreased continuously from 122±57 to 75±39 to 51±17 minutes in periods 1 to 3 ($P < 0.05$). There were no differences in number of patients with a complication between the different time periods. After 3 to 6 months the percentage of echocardiographic responders increased from 18% to 62% to 69% ($P < 0.05$). In the cardiomyopathy subgroup the percentage of echocardiographic responders also increased from 18% to 67% to 80% ($P < 0.05$). The number of clinical responders however did not significantly increase , in particular in the cardiomyopathic subgroup: 33% to 33% to 40%. Mortality in the cardiomyopathy cohort was 24% compared to 0% in the non-functional MR group.

Conclusion

Despite an increase in echocardiographic responders after MitraClip® in time the number of clinical responders did, in particular in patients with functional MR, not increase.

INTRODUCTION

Mitral regurgitation (MR) is a common disorder[1] and mitral valve (MV) surgery is worldwide an established therapy to cure the disease.[2] More recently, percutaneous edge-to-edge mitral valve repair using the MitraClip® (Abbott, Abbott Park, IL, USA) has been shown to be a reasonable alternative, in particular for older patients with multiple co-morbidities and high operative risk.[3,4] In fact, the number of MitraClip® implantations is currently exponentially increasing and numerous new centers will introduce this technique for MR treatment in the future. Being a rather complicated technique, experience of the treating team (in particular the imaging and interventional cardiologist) seems crucial and an important learning curve is expected. Unfortunately, only sparse data are available in the literature with conflicting results.[5,6] In the German Mitral Valve Registry it was claimed that the training and proctor system leads to already high initial procedure success and relatively short procedure time without a learning curve. However, in a study by Schillinger *et al.* procedural times steadily decreased and durability and completeness of MV repair increased as a function of the learning curve although mortality and hospitalization up to 6 months were not significantly influenced by the learning curve. The current study therefore assessed the echocardiographic and clinical outcome of MV repair with the MitraClip® according to our experience in time with the procedure.

METHODS

Study design and patients

The study included 39 patients with heart failure symptoms and at least moderate MR (Table 1). Patients were assigned to MitraClip® therapy following the decision of a Heart Team in consideration of current guidelines,[7] surgical risk, anatomical aspects, and eligibility for percutaneous treatment. Enrollment and treatments were performed from May 2012 until July 2015. The learning curve was analyzed after creating three subgroups of 13 patients each according to treatment period (period 1: patients 1–13; period 2: patients 14–26; period 3: patients 27–39). The study was approved by the institutional review board and consent was obtained in all patients for anonymised prospective data collection for research purposes.

Procedure

The MitraClip® and implantation procedure have been described in detail previously.[8] The MitraClip® system consists of a 24 F-guiding catheter and a cobalt chromium clip, which is mounted on the tip of a delivery system. Under fluoroscopy and echocardiography guidance, the device is introduced through the femoral vein into the right atrium. After trans-

septal puncture, the MitraClip® is advanced through the left atrium into the left ventricle to grasp the mitral leaflets. Finally, both arms of the clip are closed and the free edges of the leaflets are connected together creating a double orifice. All procedures were performed by the same interventional team. Device time was defined as time from insertion of the steerable MitraClip® guiding catheter until removal of the clip delivery system.

Echocardiographic measurements

Left ventricular ejection fraction (EF) was measured with a triplane method, with use of TomTec software (TomTec, Unterschleissheim, Germany). All other variables were measured at baseline and follow-up according to standard guidelines.[9-11] MR severity was scored according to 6 scales: none/trivial, mild, mild-to-moderate, moderate, moderate-to-severe, severe).[10]

Complications

All complications were reported according to the Mitral Valve Academic Research Consortium (MVARC) consensus document.[12]

Follow-up

Clinical and transthoracic echocardiographic examinations were performed at baseline, pre-discharge and after 3 to 6 months. The following major adverse events were documented: death (cardiac or non-cardiac), hospitalization due to congestive heart failure and New York Heart Association (NYHA) functional class. Echocardiography was performed according to current recommendations.[11] A patient was defined as echocardiographic responder when MR severity was moderate or less. In case a patient died before 6 months the latest available echo before death but after MitraClip® was considered as echocardiographic end-point. A patient was defined as clinical responder when the patient was alive and NYHA class improved to class 1 or 2 without a hospitalization for heart failure.

Statistical analyses

Categorical data are presented as numbers and percentages. Normality of continuous variables was evaluated by Shapiro-Wilk tests and data were then presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Differences in treatment periods were tested by one-way ANOVA followed by unpaired t-test with Bonferroni adjustment or by Kruskall–Wallis ANOVA followed by Dunn-Bonferroni test. Differences in the percentage, classes, or grades were tested by chi-square test or Fisher's exact test where appropriate. Mann-Whitney U test was used for testing within groups of echoresponders and nonresponders. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS version 21.0.0.1 (SPSS, IBM, Armonk, NY).

RESULTS

Baseline characteristics

Total cohort

Baseline characteristics are given in Table 1. The etiology of MR was functional due to ischemic (n = 21) or non-ischemic (n = 9) cardiomyopathy in 30 (77%), isolated annular dilatation in 5 (13%) and prolapse in 4 (10%) of patients. Mean age was 72.0 ± 9.9 years. All patients presented with relevant general or specific (e.g. porcelain aorta) co-morbidities, which is reflected by a high mean logistic EuroSCORE of 20.9 ± 15.9 %.

Patients stratified by treatment period

The number of patients with functional MR due to a cardiomyopathy decreases from 13 (100%) in period 1 to 12 (92%) in period 2 and 5 (38%) in period 3 ($P < 0.001$). Later included patients were older ($P < 0.05$) with smaller left ventricular end-diastolic dimensions ($P < 0.005$) and higher left ventricular ejection fractions ($P < 0.005$)

Procedural data

Mean device time was 85 ± 51 minutes and decreased continuously from 122 ± 57 to 75 ± 39 to 51 ± 17 minutes in periods 1 to 3 ($P < 0.05$). The mean numbers of implanted clips in periods 1, 2, and 3 were 1.33 ± 0.65, 1.38 ± 0.65, and 1.33 ± 0.49, respectively, with no significant differences between the periods (P = NS). Mean resultant transmitral gradients were 3.1 ± 1.3, 4.2 ± 2.1 , and 3.8 ± 2.2 in the respective periods (P = NS).

Complications

All major and minor complications are reported in Table 2. There were no differences in the number of patients with a complication between the different time periods.

Echocardiographic outcome

Total cohort

Six-months echocardiographic outcome was not available in 2 patients from period 1 because of lost to follow-up in one patients and death in one other patient. In 3 other patients who died during the first 6 months the latest available echo after MitraClip® was incorporated into analyses. One patient with failed clip insertion (period 1) and one with left atrial perforation (period 3) send for emergent surgery (without percutaneous or surgical repair of the MV done) were analysed according to an intention-to-treat approach. In none of the patients clip detachment occurred during follow-up. In total 19 patients of the 37 considered for analysis (51%) were echocardiographic responders. The number of

echocardiographic responders increased from period 1 to 3 from 2 (18%) to 8 (62%) to 9 (69%). (P <0.05). Left ventricular EF did not change significantly, both in responders (-4% ± 7%) and non-responders (+1% ± 9%). Indexed LA volumes did also not change significantly both in echocardiographic responders (-1 ± 18 ml/m^2) and non-responders (+7 ± 11 ml/m^2).

Temporal changes in MR response after Mitraclip implantation between pre-discharge and the follow-up

As can be seen in Figure 1, in the 37 patients available for analysis 9 were at discharge MR non-responders, all these patients remained non-MR responders at 3-6 months follow-up. Twenty-eight patients were at discharge MR responders, of whom 19 remained MR responders and 9 deteriorated to MR non-responders. The total number of MR non-responders thus increased from 9 (24%) to 18 (49%) during short-term follow-up.

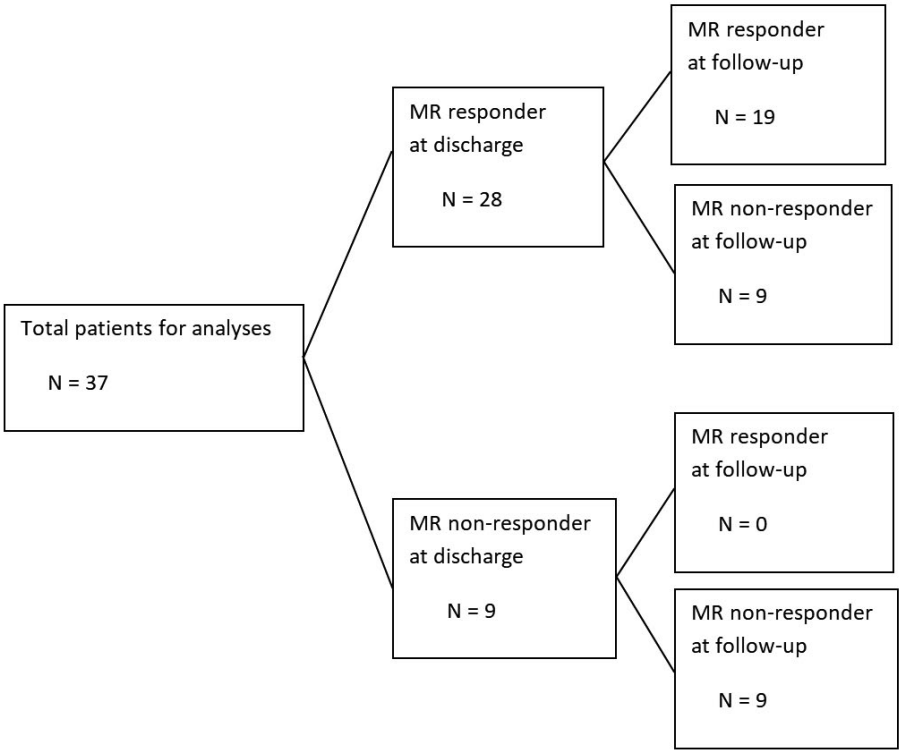

Figure 1
Temporal changes in MR response after Mitraclip implantation between predischarge and the follow-up.

Cardiomyopathy cohort

As mentioned before functional MR due to cardiomyopathy was present in 30 (77%) of patients and decreased significantly from period 1 to 3 (P <0.001). Echocardiographic outcome could be assessed in 28 from the 30 patients, due to the aforementioned reasons. Fourteen patients (50%) were echocardiographic responders (period 1: 18%; period 2: 67%; period 3: 80%, P <0.05). No differences were seen in echocardiographic responders in patients with functional MR versus non-functional MR (50% vs. 56%). In the patients with MR secondary to cardiomyopathy left ventricular EF did not change significantly in both responders and non-responders (respectively, -4% ± 7% and +1% ± 9%). Although overall LA volumes remained unchanged (0 ± 16 ml/m^2), LA volumes decreased non-significantly by 5 ± 17 ml/m^2 in responders compared to a non-significantly increase of 6 ± 13 ml/m^2 in non-responders.

Clinical outcome

Total cohort

The clinical end-point mortality was seen in seven out of 38 analysable patients (18%), five patients died because of heart failure, one patient died because of bleeding complications after MitraClip® implantation (period 2) and one patient had non-cardiac death. Mortality and/or hospitalization for heart failure was seen in 14 patients (37%) and mortality and/or hospitalization for heart failure and/or NYHA class ≥3 in 22 patients (58%).

Patients stratified by treatment period

The number of clinical responders did not significantly increase from period 1 (4 patients, 33%) to period 2 (4 patients, 31%) to period 3 (8 patients, 62%) (P= 0.22). Three patients died in period 1, 4 in period 2, and in period 3 there was no mortality in the first 6 months.

Cardiomyopathy cohort

In the subgroup of patients with secondary MR due to heart failure 10 patients (35%) were clinical responders. No differences were seen in the different periods (period 1: 4 out of 12 patients, 33%, period 2: 4 out of 12 patients, 33%, and period 3: 2 out of 5 patients, 40%). The number of clinical responders tended to be lower in the group of patients with functional MR compared to the non-functional MR group (35% vs. 67%, P <0.10). Mortality in the cardiomyopathy cohort was 24% (7/29). Mortality tended to be higher in the group of patients with functional MR compared to the non-functional MR group (24% vs. 0%, P =0.12).

DISCUSSION

This study investigated the learning curve of percutaneous MV repair with the MitraClip® in a single center. The main findings are that 1) procedural times steadily decreased, 2) indications shifted from functional MR to a mix of functional MR and non-functional MR, 3) echocardiographic responders steadily increased both in functional MR and non-functional MR and 4) the number of clinical responders in patients with functional MR was lower and did not increase in time.

The learning process in MitraClip® repair of the MV involves several factors, including patient selection by an interdisciplinary heart team discussing the risk of surgery and the probability of having a successful MitraClip® repair, experience of the interventional team (technical skills, defining the best strategy, and interaction with the echocardiographer during the procedure. Data on the impact of the learning curve are sparse and contradictory.[5,6]

Learning curve effects on device time

In most studies a reduction in device implantation or procedural time was reported in time[6,8,13,14] even despite a higher number of clips implanted per patient in later periods in some studies.[14] In the present study, mean procedural times steadily decreased from 122 ± 57 minutes to 51 ± 17 minutes, unrelated to the number of clips implanted in the different periods and despite inclusion of patients with degenerative MR in the later cohorts, by some reported associated with longer device time.[13,15]

Learning curve effects on MR outcome

Only sparse data on learning curve effects on MR outcome are available in the literature with conflicting results.[5,6] Schillinger *et al.* were the first to describe a rather quick learning curve in 3 consecutive cohorts of 25 patients that underwent MitraClip® implantation. Procedural times steadily decreased and durability and completeness of MV repair increased as a function of the learning curve. In contrast, in the large German mitral valve registry by Ledwoch *et al.* a learning curve in procedural time or MR reduction was absent in 2 consecutive cohorts of approximately 25 patients per center (totaling to 250 patients per cohort for the total of 10 centers). Explanations for the absent learning curve were 1) the learning curve may take more time to show, 2) guidance by the proctor of the operator through the procedure may be very effective, and 3) the learning curve may be masked by the inclusion of more complex cases over time (more difficult prolapse in terms of location or extent or gap of the prolapsing segment(s) or cardiomyopathic patients with greater coaptation depth). Unfortunately, these variables were not registered in the registry. With respect to the first explanation it should be noted that results were already excellent in the first cohort with 95% of patients having maximally moderate MR (under anesthesia). In the present study the number of echocardiographic responders significantly increased both

in the overall cohort as well as the functional MR subgroup in accordance to the study of Schillinger *et al.*.[6] It should be noticed that in our study included patients became progressively older and pathology shifted from MR secondary to cardiomyopathy (functional MR, in fact in the first period only such patients were included) to a more heterogeneous group of patients with different pathologies including also mitral annulus dilatation and MV prolapse (degenerative MR).[16] Because in most studies trends have been described in degenerative etiology towards less improvement and more deterioration in MR our results are remarkable.[13,15,17,18]

Learning curve effects on clinical outcome

Clinical outcome according to the learning curve was only reported by Schillinger *et al.*.[6] Despite the above described increased durability and completeness of MV repair as a function of the learning curve mortality and hospitalization up to 6 months were not significantly influenced by the learning curve. In particular in the functional MR group the number of clinical responders was low (31%) and clinical outcome was poor (mortality was 24%). Although it is clear that chronic secondary MR adds to the burden of HF by imposing volume overload on an already compromised LV and worsens prognosis, there is according to the present guidelines remarkably little evidence that correcting chronic severe secondary MR prolongs life or even improves symptoms for a prolonged period.[19] This paradox may result from the fact that mitral interventions in ischemic MR do not prevent coronary artery disease from progressing, nor does it prevent the continued idiopathic myocardial deterioration in non-ischemic chronic secondary MR. Importantly, the in our study included patients with functional MR were often end-stage disease patients with a median LV end-diastolic diameter of 73mm. In the randomized MITRA-FR trial percutaneous clipping of the mitral valve for severe secondary MR in symptomatic heart failure had also no impact on mortality and unplanned hospitalization.[20] In contrast, in the recently published randomized COAPT (Clinical Outcomes Assessment of the MitraClip® Therapy Percutaneous Therapy for High Surgical Risk Patients) trial an impressive reduction in mortality was seen. [21] The ongoing RESHAPE-HF (A Randomized Study of the MitraClip® Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) in patients with functional MR associated with congestive heart failure (NYHA class III or IV and $15\% \geq EF \leq 40\%$) will certainly contribute further to better elucidation of the role of MitraClip® therapy in high surgical risk patients with functional MR.

CONCLUSIONS

Despite an increase in echocardiographic responders after MitraClip® in time the number of clinical responders did, in particular in patients with functional MR, not increase.

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