PREDICTORS OF RESTENOSIS AFTER PERCUTANEOUS BALLOON MITRAL VALVULOPLASTY

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ABSTRACT

INTRODUCTION: Restenosis has been an anticipated occurrence after percutaneous transmitral commissurotomy (PTMC). Factors such as sub-optimal valve area after the procedure and the presence of chronic atrial fibrillation predict a likelihood of restenosis. This study therefore aims to identify the clinical factors that contribute to the development of restenosis, as local studies on adult Filipinos are sparse.

METHODS: This is a 10-year retrospective chart review of patients who underwent PTMC undertaken in a specialized tertiary hospital in the Philippines. A chi-square and t-test were applied to the data to determine the association of each individual factors and multiple logistic regression was applied to determine the independent effect of each factor.

RESULTS: Five Hundred Thirty Five (535) charts were reviewed for 10 years. Of 535 charts, 206 were included in the study. Restenosis rate was computed at 19.42% in 10 years. Among the clinical characteristics, diabetes mellitus was linked with restenosis ($p = 0.021$). Further, the following were linked to restenosis: Wilkins score of >8 ($p = 0.017$), pulmonary hypertension prior to PTMC ($p = 0.017$ for mild, 0.018 for moderate, and 0.029 for severe), heart failure symptoms under NYHA functional class II classification ($p = 0.026$), prior AF ($p = 0.019$), and fusion of the anterolateral commissure ($p = 0.003$). Multiple logistic regression analysis showed relationship with restenosis with age [Odds ratio 1.04, $p = 0.016$ [95% CI (1.00-1.07)] and fusion of the anterolateral commissure [Odds ratio of 3.49 and a $p = 0.012$ [95% CI (1.31-9.24)].

CONCLUSION: There is a high likelihood of restenosis for patients after PTMC if the following are present: increasing age, diabetes mellitus, pulmonary hypertension, high Wilkins score, NYHA functional classification II, atrial fibrillation and fusion of the anterolateral commissures.

KEYWORDS: [Mitral restenosis] [PTMC] [Balloon valvotomy] [Mitral stenosis] [Predictors of Restenosis] [Restenosis rate]

INTRODUCTION

Rheumatic heart disease confers a concurrent disease in the mitral valve[1]. The disease occurs in around 19% of Filipino children with the prevalence increasing with repeated attacks of Rheumatic fever[2]. In 1984, Inuoe introduced the percutaneous mitral balloon valvuloplasty and has recently been considered as the procedure of choice for favorable cases of mitral stenosis.

Restenosis is defined as a loss of > 50% of the initial gain in MVA[3]. The incidence of re-stenosis after a successful mitral valvulopalsty is in the range of 10% and 20% in foreign literatures[4]. In contrast, a local study done by Ang et al showed that the re-stenosis rate after percutaneous mitral balloon valvotomy was at 2.3% after 3 years, 11.3% after 5 years and 26.4% after 8 years[5]. Mainly, re-stenosis is related to the presence of chronic atrial fibrillation at baseline and a suboptimal percutaneous mitral balloon valvotomy[6]. Wilkins score was also an independent risk factor in the development of re-stenosis [7] [8] [9]. Likewise, fluoroscopic Ca $^{++}$[10], presence of Pulmonary Congestion and functional class would likely predict re-stenosis [11].

Unfortunately, there is no available local data that looks on the factors that predispose adult Filipino patients who underwent valvuloplasty to re-stenose hence, the formulation of the study. Therefore, the study aims to determine factors associated with re-stenosis after percutaneous mitral balloon valvuloplasty.

METHODOLOGY

The Institutional Review Board of the Philippine Heart Center approved the conduct of this paper and waiver of informed consent was granted.

Study Design

This study was a 10-year Retrospective Cohort trial from 1998-2008 conducted at the Philippine Heart Center.

Study Population

Inclusion Criteria:

1. Patients 18 years old and above who have Rheumatic Mitral Stenosis who underwent percutaneous mitral balloon valvotomy

Exclusion Criteria:

1. Patients who develop complications immediately after the percutaneous mitral balloon valvotomy that required mitral valve surgery such as the following:
    a. Presence of severe MR
    b. Cardiac perforation

2. Absence of follow-up 2 dimensional echocardiogram within 6 months after the valvuloplasty

Sample Size Determination:

Sample size was computed at n=133 at 95% confidence level, relative error of 10% assumed re-stenosis rate of 26.4% at 8 years follow-up as presented in the paper of Ang et al [5].

Identification of Variables

Patients who had percutaneous mitral balloon valvotomy were included in the study. Baseline demographic characteristics such as the age, sex and the presence of co-morbidities were compiled prior to the start of the study. Further, baseline clinical characteristics such as the presence of atrial fibrillation, mitral valve area post percutaneous mitral balloon valvotomy, pulmonary hypertension, presence of Mitral valve regurgitation, Wilkins score and NYHA Functional classification were also be recorded.

Outcome Measures

The primary outcome measure was re-stenosis after the percutaneous mitral balloon valvotomy.

Study Maneuver

The primary investigator reviewed the medical charts of patients who underwent percutaneous mitral balloon valvotomy at the Philippine Heart Center from 1998-2008. The demographic characteristics of patients and clinical characteristics that underwent percutaneous balloon valvotomy were obtained. These are as follows: age, sex, and presence of co-morbities (eg. hypertension & diabetes). Smoking, Wilkins score, presence of pulmonary hypertension, mitral valve regurgitation post procedure, heart rhythm (atrial fibrillation or sinus rhythm), NYHA classification, and valve area post procedure and commissural opening will also be recorded.

Statistical Analysis

Quantitative data was presented as mean standard deviation (sd) and qualitative in frequency and percent distribution. To determine association of different factor with re-stenosis, Fisher's exact test for categorical variables and t-test for continuous variables were applied. To determine the independent effect of each factor to re-stenosis, multiple logistic regression analysis were applied to the data. A p value 0.050 was considered significant.

RESULTS

Five Hundred Thirty Five charts were reviewed from the year 1998-2008. Of the 535 charts, 206 were included in the study. The rest were excluded due to the following reasons: (1) no follow-up 2D echocardiography within 6 months after PTMC and (2) presence of severe MR. In the reviewed charts, 40 out of 206 were noted to have a loss of ≥ 50% in the initial MVA gain after PTMC. Restenos is rate was computed at 19.42% in 10 years.

Table 1: Demographic Profile of Patients Mitral Stenosis post Percutaneous Balloon Valvuloplasty

	MEAN	Standard Deviation
Age	36.99	11.18
	Frequency	**Percent**
Sex		
Male	36	17.48%
Female	170	82.52%
Hypertension	6	2.91%
Diabetes Mellitus	10	4.85%
Smoking	17	8.25%

The study population had a mean age of 36.99 omprising 17.48% males and 82.52% females. 2.91% were hypertensives, 4.85% were diabetics and 8.25% were smokers.

Table 2. Clinical Characteristics of Patients with Restenosis

	Re-stenosis		P-Value
	(+) n = 40 (%)	(-) n = 166 (%)	
Hypertension	1 (0.006%)	5 (12.5%)	0.863
Diabetes	5 (12.5%)	5 (0.03%)	0.021
Smoking	5 (0.03%)	12 (0.008%)	0.283
Wilkins Score			
>8	10 (25%)	17 (10.24%)	0.017
Pulmonary Hypertension			
Normal	6 (15%)	63 (39%)	
Mild	16 (40%)	49 (30%)	0.017
Moderate	9 (23%)	24 (15%)	0.018
Severe	9 (23%)	27 (17%)	0.029
Mitral Regurgitation post procedure			
None	3 (9%)	35 (21%)	
Trivial	12 (35%)	41 (25%)	0.073
Mild	9 (26%)	56 (34%)	0.370
Moderate	10 (29%)	31 (19%)	0.059
NYHA Functional Class			
I	1 (2.5%)	33 (20%)	
II	38 (95%)	126 (76%)	0.026
III	1 (2.5%)	6 (4%)	0.250
IV	—	—	—
Atrial Fibrillation pre procedure	18 (45%)	43 (26%)	0.019
Valve Area post procedure			
<50% from the initial valve area	14 (40%)	63 (40%)	0.967
≥ 50% of the initial valve area	21 (60%)	96 (60%)	
Commissural Opening post procedure			
Anterolateral Commissure			
Fully open	12 (34%)	78 (49%)	
Partially fused	11 (31%)	63 (39%)	0.779
Fused	12 (34%)	19 (12%)	0.003
Posteromedial Commissure			
Fully open	15 (44%)	90 (56%)	
Partially fused	10 (29%)	49 (31%)	0.649
Fused	9 (26%)	21 (13%)	0.052

For the clinical characteristics, hypertension and smoking were not associated with restenosis having a P value of 0.863 and 0.283 respectively. The presence of diabetes mellitus however, was associated with restenosis compelling a P value of 0.021. Possessing a Wilkins score of >8 were correlated with restenosis with a P value of 0.017. Moreover, pulmonary hypertension prior to PTMC confers the association with restenosis with the following p values: 0.017, 0.018, and 0.029 respectively for mild, moderate and severe pulmonary hypertension. The existence of Mitral regurgitation after the valvuloplasty with any grade (trivial, mild and moderate), were not coupled with restenosis evidenced by a non-statistically significant P value of 0.073, 0.370 and 0.059 respectively. There were no patients who were in NYHA functional class IV. Likewise, the presence of heart failure symptoms classified under the NYHA functional class II classification was somehow linked with restenosis with a P value 0.026.

Existence of prior AF was associated with restenosis having a statistically significant P value of 0.019. The valve area after PTMC was neither associated with the occurrence of the outcome with a non-significant P value of 0.967.

Opening of the commissures matters most for the anterolateral commissure. Non-opening or fusion of this commissure was related with restenosis having a significant P value of 0.003. Partial fusion was not related with the outcome with a P value of 0.779. On the other hand, opening of the posteromedial mitral commissure has no relation with restenosis with the following p values 0.649 and 0.052.

The table with the subcategory of commissural opening post procedure was changed during the course of the study period. This is because the description that was used in the echocardiographic report made the classification in the original protocol difficult to sort-out. Echocardiography detailed the commissural opening as follows: (1) Open; (2) Partially fused and (3) Fused. While, the original protocol described the commissural opening as: Anterolateral commissure open, Posteromedial commissure open and Both commissures open. To coincide with the echocardiographic report, the classification was changed as follows: Open; partially fused and fused.

Multiple logistic regression analysis of all the variables were also done to determine the independent effect of each factor to restenosis. Results showed a significant likelihood of restenosis with age having an odds ratio of 1.04 p = 0.016 [95% CI (1.00-1.07)] and fusion of the anterolateral commissure with a possibility of 3.49 p = 0.012 [95% CI (1.31-9.24)].

DISCUSSION:

The results showed that the patients who underwent PTMC were mostly females and was in accordance with the overall incidence of rheumatic mitral stenosis having a ratio of 2:1 compared to males [20]. Restenosis rate for this study was 19.42% over a 10-year

agreeing with international reports. However, this rate is lower compared to a local study done by Ang et al. In the study, the mean age was 36.99, which was also consistent with the occurrence of mitral stenosis in the Asian population being more frequent in the less than 40-year-old population[20].

The presence of hypertension and smoking seems not to be associated with the occurrence of mitral stenosis. But, the presence of diabetes confers a risk for restenosis. One of the mechanisms involved in the pathophysiology of diabetes involves inflammation leading to impairment of insulin secretion[15]. On the other hand, it was initially thought that a persistent and recurrent rheumatic process was involved in restenosis. However, restenosis occurrence was not found to be so[15]. A plausible explanation between the occurrence of both diabetes and mitral restenosis is likely the involvement of inflammation in both cases. Nevertheless, the specific mechanism has not been completely elucidated. A Wilkin's score of <8 is an indication for PTMC. However, there are patient subsets where a score of >8 had to undergo the procedure with a higher risk for restenosis. As was seen in this study, the likelihood of having restenosis for a score of >8 is high which also coincided with internationally published literatures [7] [8] [9]. Further, the presence of commissural calcification seen by 2D echocardiography is a useful predictor of outcome in patients with otherwise "good" valves (echo score <8). Calcification of one commissure or more predicts a less than 50% probability of achieving a valve area above 1.50 cm^2 [21]. Immediately after a PTMC, PA pressures fell together with reduction in mitral valve gradient. And, the pulmonary arterial pressure taken after the procedure is a factor for the occurrence of restenosis with higher rate if the pressures are [22]. In this study, in contrast to other published reports, the pulmonary artery pressures were measured before PTMC. As the results would show, every grade of pulmonary hypertension from mild, moderate to severe was associated with restenosis achieving a statistically significant connection. A plausible explanation for the occurrence of restenosis in relation to pulmonary hypertension after a PTMC could be related to the vascular changes that occur in the pulmonary tree specially in long standing mitral stenosis. Atrial fibrillation at baseline is associated with a two-fold occurrence of restenosis [25]. In this study, the presence of atrial fibrillation was linked with restenosis that is in parallel with other studies [12] [25].

NYHA class before percutaneous mitral balloon valvotomy was associated with restenosis [23]. This study further illustrates the role of the NYHA classification in restenosis. In particular, having a functional class II confers a likelihood of having restenosis. However, the populations on this study were mostly in the class II category with only sparse distribution on class III and no class IV. Hence, this study is not powered to predict the contribution of each classification to restenosis. Mitral regurgitation was linked also with restenosis [26]. In this paper, the presence of any degree of mitral regurgitation was not linked with restenosis.

Mitral valve area after percutaneous mitral balloon valvotomy predicted the occurrence of restenosis [24]. However on this paper, the valve area was not associated with restenosis. The mechanism for increase in the mitral valve area after a PTMC involves the splitting of the commissures both for the anterior and posterior. A successful splitting can be achieved depending on the subvalvar apparatus and the presence of commissural calcification whereby the less subvalvar and commissural calcification provided the best result for efficacious commissural splitting [27].

It was studied in this paper the independent association of the anterior and the posterior commissural opening in relation to the occurrence of restenosis. Published studies were limited only on describing the occurrence of restenosis in association of splitting of the commissures in general. It was shown interestingly on this study that the fusion of the anterolateral mitral commissure was associated with restenosis having a P value of 0.003.

A multiple regression analysis of all the variables showed that age and fusion of the anterolateral commissures were significantly associated with restenosis. Age confers a 1.04 likelihood of restenosis per year in that an aging patient will eventually have restenosis over time and fusion of the anterolateral commissure confers a 3.49 likelihood of restenosis.

LIMITATIONS OF THE STUDY:

The study was done in a retrospective manner involving review of patients chart admitted with rheumatic mitral stenosis undergoing PTMC. Further, records of patient's data were sometimes incomplete because of losses through time.

RECOMMENDATION

A better study design that involves patient follow-up should be done to determine the magnitude of each characteristic in the development of clinical restenosis.

CONCLUSION

Based on this study, factors such as age, diabetes mellitus, pulmonary hypertension, NYHA functional classification II, high Wilkins score, atrial fibrillation and fusion of the anterolateral commissures were significantly associated with restenosis. However, the presence of an ageing mitral stenosis patient and with fusion of the anterolateral commissure was independently found to have the highest risk for restenosis.

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