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Effect of Percutaneous Transvenous Mitral Commissurotomy on Plasma Apelin Level in Mitral Stenosis Patients

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Abstract

Background: Apelin is an endogenous peptide with positive inotropic property secreted by the heart besides other tissues. Plasma apelin levels are altered in chronic heart failure with left ventricular dysfunction. However, the effect of left atrial hemodynamic overload on plasma apelin levels in mitral stenosis (MS) is unknown. In this observational study, we estimated plasma apelin level in MS patients, before and twelve weeks after percutaneous transvenous mitral commissurotomy (PTMC) and compared with plasma brain natriuretic peptide (BNP) levels, mitral valvular pressure gradient and quality of life measure.

Methods: Venous blood samples were drawn from 10 MS patients and 10 age-matched controls, with informed consent. Apelin was estimated by competitive ELISA and BNP using an auto-analyzer. PTMC was done by atrial septal puncture and Inoue balloon. Self-administered Kansas City cardiomyopathy questionnaire (KCCQ) was used to assess quality of life. Variables distributed normally were expressed as mean ± S.D. and others as median (interquartile range) and analyzed using appropriate statistical tests. A p-value<0.05 was considered statistically significant.

Results: MS patients belonged to NYHA class II & III, had pulmonary artery hypertension but left ventricular ejection fraction>50%. Plasma apelin was lower [320 (167, 515) vs. 570 (415, 680) pg/ml; p=0.028] and BNP level higher [44 (15, 117) vs. 6 (5, 10) pg/ml; p=0.001] in MS patients compared to controls, respectively. PTMC decreased mitral valvular pressure gradient [6.7 (5.0, 8.7) vs. 20.5 (12.4, 27.2) mm of Hg; p=0.012] and improved KCCQ score (84 ± 7 vs. 54 ± 10%; p<0.001) but did not change plasma apelin and BNP levels [330 (192, 465) and 42 (19, 86) pg/ml, respectively].

Conclusion: Plasma apelin is depressed and BNP level raised in MS patients. Changes in plasma apelin level may occur slower compared to hemodynamic and functional improvement post PTMC.

Keywords: Mitral stenosis; PTMC; BNP; Apelin; KCCQ

Abbreviations: MS: Mitral Stenosis; PTMC: Percutaneous Transvenous Mitral Commissurotomy; BNP: Brain Natriuretic Peptide; LVEF: Left Ventricular Ejection Fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; CTRI: Clinical Trials Registry of India; IESC: Institutional Ethics Sub-Committee; ECG: Electrocardiography; EDTA: Ethylene Diamine Tetraacetic Acid; SPSS: Statistical Package for the Social Sciences; NYHA: New York Heart Association; BMI: Body Mass Index

Introduction

Mitral stenosis (MS) is the commonest sequel of rheumatic heart disease most prevalent in developing countries including India and is associated with significant morbidity [1]. Long-standing MS leads to progressive dilatation of left atrium altering the hemodynamic and endocrine functions of the heart [1,2]. Pulmonary hypertension is also a frequent complication of long standing MS [1]. The surgical therapy of choice for MS in symptomatic patients with optimum valve morphology is percutaneous transvenous mitral commissurotomy (PTMC) which provides immediate hemodynamic improvement and relieves congestive symptoms [3]. However, there is dearth of information whether PTMC improves the endocrine function of the heart too. Cardiac endocrine function has been known for the last two decades [4]. Among the several hormones, Brain natriuretic peptide (BNP) secreted by ventricular cardiomyocytes has established an important role in the diagnosis and risk stratification of cardiovascular disorders [5]. Apelin has been recently identified as a novel endocrine peptide released from the heart [6]. Besides heart, apelin is also secreted by other organs such as lungs, vascular endothelium, placenta, kidney and adipose tissue [7]. Apelin binds to and activates the G-protein coupled APJ receptor which is mostly co-expressed on the same cells *viz.* cardiomyocytes, vascular smooth muscle cell and endothelial cells [8,9]. It is the most potent endogenous cardiac inotrope known to date [8]. Apelin is constitutively expressed in tissues and causes endothelium-dependent vasodilatation of both arterial and venous blood vessels and improves ventricular contractility thereby augmenting cardiovascular efficiency [10-12]. Alterations in plasma apelin levels have been reported in heart failure [7]. Plasma apelin levels have been shown to be raised in early and lowered in late stages of chronic heart failure, respectively [13,14]. Rise in plasma apelin is thought to be a compensatory mechanism which sustains cardiac function in early stages of heart failure but somehow becomes exhausted heralding the

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development of decompensated heart failure [15]. A clinical trial of short term apelin intravenous infusion in chronic heart failure patients demonstrated encouraging results [16]. Plasma apelin levels have been reported to be strongly correlated with atrial apelin content in healthy hearts implying predominant secretion from atria in healthy individuals [17]. However, information about change in plasma apelin levels in mitral valvular or atrial pathology is scanty except for studies in atrial fibrillation. Reduced plasma apelin levels have been reported in patients of lone atrial fibrillation and has been proposed as a predisposing factor for this condition [18]. It is not known whether hemodynamic overload of the left atrium in MS can cause alterations in plasma apelin levels and whether successful unloading of the left atrium by PTMC can reverse such alterations with the concomitant hemodynamic and functional improvement. Such alterations may help in diagnosis and/or predicting prognosis of mitral stenosis patients. To address these lacunae, we investigated plasma apelin levels in mitral stenosis patients undergoing elective PTMC.

Materials and Methods

The study was approved by the Institutional Ethics Sub-Committee (IESC/T-18/04.12.09) of the All India Institute of Medical Sciences, New Delhi and registered with the clinical trials registry of India (CTRI 2009/091/000935). This investigation conformed to the principles outlined in the Declaration of Helsinki. Signed written informed consent was obtained from all subjects before their participation in the study. This observational study consecutively recruited 10 MS patients of either gender, aged between 12 to 80 years, with severe valvular stenosis (echocardiographically determined mitral valvular area<1.5 cm^2), undergoing elective PTMC. Ten healthy age-matched subjects with an unremarkable clinical examination, normal routine laboratory investigations and a normal echocardiographic study were recruited from relatives of the patients to serve as control group. MS patients were excluded if they had history of acute coronary syndrome within the previous one month, diabetes mellitus, obesity, hypercholesterolemia, stage 2 or uncontrolled hypertension, hepatic or renal failure or were pregnant or lactating women. All study participants underwent a clinical evaluation including medical history, physical examination, routine laboratory investigations, 12-lead electrocardiography (ECG) and transthoracic two-dimensional echocardiography at their recruitment into the study. The primary outcome measure was the change in baseline plasma apelin levels in MS patients at a follow-up 12 weeks post PTMC. The secondary outcome measures were (a) compare plasma apelin levels in MS patients with that of control group and (b) find correlations between plasma apelin levels, plasma BNP levels, mitral valvular pressure gradient and quality of life measures in MS patients. Venous blood samples collected into sterile EDTA containing vacutainers from the median antecubital vein of either arm of subjects were immediately placed on ice and centrifuged within 1 hour at 3000 rpm at 4°C for 10 minutes. Plasma was extracted and stored in aliquots at -80°C until analysis. Plasma apelin levels were determined using a commercially available apelin-C terminus competitive enzyme-linked immunoassay (Ray Biotech Inc., USA) according to the manufacturer's instructions mentioned in user manual 1.1. Plasma BNP was estimated using a commercially available auto-analyzer device (Triage, Biosite Inc, USA) according to the manufacturer's protocol. This device has been used and validated previously in clinical trials [19]. Transthoracic two-dimensional echocardiography was performed in all participants using Philips GE11X echocardiography machine and adult transducer probe. Left ventricular ejection fraction (LVEF) was obtained by Simpson's method using images obtained in an apical four-chamber view [20]. Quality of life was assessed using the overall summary score obtained on the self-administered Kansas City Cardiomyopathy Questionnaire (KCCQ) which has been validated in clinical trials of heart failure patients [21]. MS patients underwent trans-esophageal echocardiography within 24 hours prior to PTMC to exclude the presence of left atrial thrombus and to assess mitral valve morphology. PTMC was done through the transvenous route with atrial septal puncture and an Inoue balloon [3]. Statistical analysis was done using SPSS software version 16.0 (SPSS Inc., Chicago, Illinois). Qualitative variables were compared between groups at baseline using Chi-square test. All quantitative variables found to be normally distributed were expressed as mean ± S.D. and those found to be asymmetrically distributed were expressed as median (interquartile range). Comparison of quantitative variables between the two groups at baseline was done using Student's *t* test for parametric variables and using Mann-Whitney U test for non-parametric variables, respectively. Comparison of quantitative variables between follow-up and baseline within each group was done using Student's paired t-test for parametric variables and Wilcoxon sign-rank test for nonparametric variables, respectively. A p-value less than 0.05 was considered statistically significant.

Results

A total of 10 MS patients and 10 healthy controls were recruited with informed consent between February 2010 and October 2011. The median time since diagnosis of MS was 5.5 (3.5, 10.5) months. There were no significant differences in the age, gender distribution, body mass index, systolic and diastolic blood pressures between the MS and control group (Table 1). MS patients had a lower left ventricular ejection fraction than controls (58 ± 3 vs. 64 ± 3%; p=0.005). New York Heart Association (NYHA) functional status was class II for 3 and class III for 7 MS patients. All MS patients had moderate to severe pulmonary hypertension (pulmonary artery pressure>25 mm of Hg). The plasma BNP and apelin levels were significantly altered in MS patients compared to controls. Specifically, the plasma BNP was higher and plasma apelin levels lower in MS patients compared to controls (Table 1). All MS patients underwent successful PTMC as evidenced by significant immediate increase in mitral valvular area [1.7(1.4, 2.0) vs. 0.9(0.6, 1.0) cm^2; p=0.012] compared to baseline value (Table 2). The pulmonary artery pressure (42 ± 20 vs. 64 ± 21 mm of Hg; p=0.001), left atrial pressure (14 ± 3 vs. 29 ± 6 mm of Hg; p<0.001) and mitral valve pressure gradient [6.7 (5.0, 8.7) vs. 20.5 (12.4, 27.2) mm of Hg; p=0.012] decreased significantly immediately after PTMC compared to baseline values. No complications occurred in patients during or post PTMC. At a follow-up 12 weeks after PTMC, the left ventricular

Baseline Characteristic	Normal Control (n=10)	Mitral Stenosis patients (n=10)
Age (years)	34 ± 10	26 ± 6
Sex (male:female)	7:3	4:6
BMI (kg/m^2)	22.8 ± 2.9	22.2 ± 3.6
NYHA Class (n)	Not applicable	II (3), III (7)
Systolic BP (mm of Hg)	115 ± 14	110 ± 8
Diastolic BP (mm of Hg)	74 ± 8	74 ± 9
AF prevalence (%)	Nil	2/10 (20%)
Prevalence of pulmonary artery hypertension (%)	Nil	10/10 (100%)
Plasma BNP (pg/ml)	6 (5,10)	44(15,117)**
Plasma apelin (pg/ml)	570 (415,680)	320 (167,515)*

*p<0.05 compared to control, **p<0.01 compared to control. All values are expressed as mean ± S.D. except plasma apelin and BNP expressed as median (25^{th}, 75^{th} percentile).

Table 1: Baseline characteristics of study participants.

Parameters	Baseline (n=10)	Post-PTMC (n=10)
LVEF (%)	58 ± 3	58 ± 4
KCCQ OS score	54 ± 10	84 ± 7**
Mitral valve area (cm^2)	0.9 (0.6,1.0)	1.7 (1.4,2.0)*
Left Atrial pressure (mm of Hg)	29 ± 6	14 ± 3**
Pulmonary artery pressure (mm of Hg)	64 ± 21	42 ± 20**
Plasma BNP (pg/ml)	44 (15,117)	42 (19,86)
Plasma apelin (pg/ml)	320 (167,515)	330 (192,465)

*p<0.05 vs. baseline value; **p<0.01 vs. baseline value. All values are expressed as mean ± S.D. except mitral valve area, plasma apelin and BNP expressed as median (25^{th}, 75^{th} percentile).
LVEF: Left ventricular ejection fraction, KCCQ OS: Kansas City Cardiomyopathy Questionnaire overall summary, PTMC: Percutaneous transvenous mitral commissurotomy.

Table 2: Post PTMC follow-up versus baseline parameters in patients of Mitral stenosis.

ejection fraction of MS patients did not change compared to baseline value (58 ± 4 vs. 58 ± 3%; p=1.0). The KCCQ overall summary score of MS patients increased significantly (84 ± 7 vs. 54 ± 10; p<0.001) compared to baseline values. However, there was no significant change in post PTMC plasma BNP [42 (19, 86) pg/ml] and plasma apelin [330 (192, 465) pg/ml] levels compared to baseline values 12 weeks after PTMC (Table 2).

Discussion

In the present study, patients of MS had elevated plasma BNP and depressed plasma apelin levels compared to age-matched healthy controls. Elevated plasma BNP level is documented in MS patients [2,22]. However, our study is the first to report that plasma apelin levels are depressed in MS patients. This implies that perturbation of cardiac endocrine function in MS involves alterations in apelin physiology in addition to that of BNP. As pointed out earlier, reduced plasma apelin level has been reported in patients of lone atrial fibrillation [18]. The prevalence of atrial fibrillation ranges from 40 to 75% in symptomatic mitral stenosis patients [1]. Two of the 10 mitral stenosis patients in our study had atrial fibrillation. This may partly account for the depressed plasma apelin level in MS patients. However, recruitment of MS patients with atrial fibrillation could not be avoided in our study due to high prevalence of atrial fibrillation in mitral stenosis patients visiting our tertiary care institution. Other factors may also contribute to reduced plasma apelin levels in mitral stenosis patients. We put forth three hypotheses to explain the reduced plasma apelin levels in MS patients. Firstly, circulating apelin is predominantly synthesized from the atria in healthy individuals [17]. Left atrial remodeling in response to chronic hemodynamic overload is observed in MS and involves structural, functional, electrical, metabolic and neuro hormonal alterations [23]. Atrial dilatation with stretching of atrial myocytes is the hallmark of structural remodeling [23]. Increases in plasma levels of atrial natriuretic peptide and BNP are associated with left atrial dilatation [23]. Mechanical stretch has been shown to down regulate apelin gene expression in cultured neonatal rat ventricular myocytes in an *in vitro* study [8]. It may be postulated that stretching of atrial myocytes may analogously decrease atrial apelin synthesis and lead to reduced plasma apelin levels in MS patients. Secondly, it is evident from both animal and human studies that increased synthesis of apelin accompanies compensatory cardiomyocyte hypertrophy in response to hemodynamic stress and that exhaustion of apelin synthetic machinery or its excessive degradation heralds cardiovascular decompensation and depression of plasma apelin levels [15]. For example, a study in hypertensive rats has reported increased synthesis of apelin from ventricular myocytes in compensatory left ventricular hypertrophy and subsequent downregulation of apelin mRNA in overt heart failure [24]. Further, clinical studies have shown that plasma apelin levels are elevated in early stages of heart failure with left ventricular dysfunction and are subsequently depressed with progression of systolic dysfunction and deterioration of functional status of patients [13,14]. However, the left ventricles in MS patients are not subject to excessive hemodynamic load unlike chronic heart failure patients and thus do not undergo hypertrophy thereby limiting any up regulation of apelin synthesis. Thirdly, pulmonary hypertension has been reported to be associated with low serum apelin levels for less understood reasons [25]. Patients with pulmonary artery hypertension have decreased apelin expression in pulmonary endothelial cells [26]. However, it is not clear whether depression of plasma apelin levels is a cause or consequence of pulmonary hypertension. All MS patients in our study had pulmonary hypertension. The development of pulmonary hypertension in MS patients is an indicator of long-standing natural history and severity of disease. The prevalence of pulmonary artery hypertension is high in mitral stenosis patients taken up for elective PTMC in our tertiary care institution. This is due to several factors including low socio-economic and educational status of the patients in conjunction with nonspecific symptoms of mitral stenosis which delays their presentation to healthcare institutions thereby prolonging accurate diagnosis and intervention before development of pulmonary artery hypertension. PTMC in MS patients was successful with increase in mitral valve area and KCCQ score along with reductions in mitral valve gradient, pulmonary artery pressure and left atrial pressure compared to baseline values. However, plasma apelin and BNP levels in MS patients did not change significantly from baseline twelve weeks after PTMC in our study. Plasma BNP levels have been shown to decrease after PTMC within 24 hours in MS patients in sinus rhythm [27]. Another study from our institution has shown depression of elevated NT-pro BNP levels after successful PTMC in MS patients [28]. It should be noted that our study had a longer follow-up period of 12 weeks unlike the early post-operative blood sampling in previous studies. It is possible that the BNP levels which are reduced immediately post PTMC may increase over time due to currently unexplored reasons. The time-period of twelve weeks was selected in our study because plasma apelin levels apparently took longer to change in contrast to plasma BNP levels in previous studies [29-31]. Our results suggest that change in plasma apelin may occur slower compared to the hemodynamic and functional improvement following PTMC in MS patients. Reduction in elevated plasma NT-proBNP levels has been shown to correlate with the reduction in pulmonary artery pressures post PTMC in MS patients [32]. In our study, though immediate postoperative pulmonary artery pressures were significantly reduced, they were not normalized. It is possible that the significant albeit non-restorative reduction in pulmonary artery pressures was insufficient to normalize plasma BNP and apelin levels. Therefore, it can be presumed that low plasma apelin levels in our patients were contributed by pathophysiological changes in both left atrium and pulmonary vasculature. Further studies with longer follow-up period and direct tissue sampling are required to clarify the site of apelin synthesis in the setting of MS and pulmonary hypertension. Some limitations should be taken into account while interpreting the results of our study. Firstly, the small sample size and relatively short follow-up period prevented us from making major conclusions. Secondly, the hemodynamic data was obtained immediately prior to and post PTMC while the quality of life scores and plasma peptide levels immediately before and 12 weeks post PTMC, respectively. The hemodynamic parameters at 12 weeks

post PTMC could not be assessed due to ethical concerns. Thirdly, the drugs (diuretics) taken by the patients could have affected the plasma concentrations of the evaluated peptides.

Conclusion

Plasma apelin level was depressed and plasma BNP level raised in mitral stenosis patients. Plasma BNP level may increase over time after early postoperative reduction post PTMC. Plasma apelin level was not restored to normal at least twelve weeks after PTMC. Thus, endocrine heart function with respect to plasma BNP and apelin level is altered in patients of mitral stenosis and restoration of plasma apelin level seems to be slower compared to the rapid improvement in hemodynamic and functional status post PTMC. Larger prospective studies with direct tissue sampling and longer follow-up are required to explore the site of apelin secretion in mitral stenosis and pulmonary hypertension.

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Conflict of Interest

There are no conflicts of interest to declare.

Disclosure

Part of this paper was presented as oral presentation in 63rd annual conference of Cardiological Society of India 2011 at Mumbai and as poster presentation in Annual Conference of Association of Physiologists and Pharmacologists of India 2011 at New Delhi.

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