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ORIGINAL RESEARCH

Effectiveness of Metoprolol in Improving Cardiac and Motor Functions in Patients with Chronic Heart Failure: A Prospective Study

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Purpose: To assess gender-, age-, and the dose-related influence of metoprolol on cardiac function, motor function, quality-of-life (QoL), and mental status in Chinese chronic heart failure (CHF) patients.

Patients and Methods: This single-center, prospective study enrolled CHF patients with resting heart rate (HR) >80 bpm and used metoprolol continuous release tablets. Patients were initiated with 12.5-mg metoprolol. All patients were assessed for change in cardiac function, motor function, QoL, and mental status according to gender (men vs women), age (<60 vs ≥60 years), and metoprolol dose administered (47.5 mg [n=37], 71.25 mg [n=7], 118.75 [n=74], and 142.5 mg [n=19]).

Results: Overall, 154 CHF patients (101 men and 53 women), with median age 66.39 years, were enrolled. In total, 116 and 38 patients were aged ≥60 and <60 years, respectively. We observed a slight decrease in systolic blood pressure (SBP) in women compared with men. HR had increased with an increase in ejection fraction (EF) from baseline to 1 month (35.24 ±6.15 and 34.79±6.25) and increased to 50.00±4.45 and 50.72±4.09 among both the genders. Cardiac index (CI) and motor function had improved along with better QoL after metoprolol treatment in both the genders. In both age groups (<60 and ≥60 years), improvement in cardiac function, motor function, and QoL was observed; however, there was a difference in mental status. The dose effect of metoprolol on cardiac function, motor function, QoL, and mental status showed a gradual decrease in EF with dose increments, with no change in CI. Motor function, QoL, and mental status did not show much difference with uptitration of metoprolol dose.

Conclusion: Psychological responses to metoprolol treatment differ with gender, with no age-related changes in terms of cardiac function, motor function, QoL, or mental status, except increases in depression, burnout, and anxiety.

Keywords: metoprolol, chronic heart failure, quality-of-life, heart rate, psychological responses

Plain Language Summary

Chronic heart failure (CHF) is a global concern. The main choice of drug for treating CHF is a beta-blocker. Metoprolol is a beta-blocker that reduces the mortality rate and enhances the quality-of-life (QoL) of patients with CHF; however, it is reported to have central nervous system (CNS) side-effects including depression and anxiety. We conducted a study to observe the effect of metoprolol treatment on cardiac function, motor function, QoL, and mental status according to gender, age, and dose of metoprolol among Chinese patients with CHF. Our study enrolled 154 patients with CHF, including 101 men and 53 women, with

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a median age of 66.39 years. With metoprolol treatment, we observed a slight decrease in systolic blood pressure in women compared with men. However, an increase in heart rate and ejection fraction was observed in both the genders. In addition, Improvement was noted in motor function and QoL. Irrespective of age, cardiac function, motor function, and QoL had improved, but an increase in depression and burnout was also noted. There was no significant difference in cardiac function, motor function, QoL, or mental status with an increase in metoprolol dose.

Introduction

Chronic heart failure (CHF) is emerging as a major global health problem associated with structural or functional alterations of the myocardium involving adrenergic receptor stimulation and adrenergic system activation, leading to myocardial fibrosis and remodeling.[1,2] Despite advancements in the management of CHF, the risk of morbidity and mortality remains substantially high, with a prevalence of approximately 5.7 million in the US and is expected to increase to 8 million by 2030[3] and over 4.2 million in China.[4] Moreover, it puts a huge economic burden on the healthcare system as this chronic condition of CHF leads to poor quality-of-life (QoL)[5,6] and loss of work productivity.[7]

Beta-blockers remain the mainstay of treatment for patients with CHF because of their inherent property to counteract the sympathetic over-activity associated with left ventricular dysfunction, in addition to lowering the heart rate (HR), contractility, and blood pressure, thus lowering the mortality of CHF.[2,8,9] The beneficial effects of beta-blockers are further supported by a meta-analysis of randomized control trials (RCTs) showing total reduction of mortality and heart failure-related sudden death in patients with CHF.[10–14]

Metoprolol, a cardio-selective beta-blocker, has shown reduction in CHF mortality[2] and improved QoL and mobility.[12,15,16] However, this well-established beneficial effect of beta-blocker is associated with CNS side-effects such as depression[17–19] and anxiety,[20] which are ultimately responsible for decreased QoL and increased risk of mortality among patients with CHF.[21] However, some studies show contrasting results, with no increase in depressive symptoms.[22]

In addition, it is unknown whether the neuropsychiatric adverse effects and increase in depression and anxiety in CHF are associated with metoprolol or are pre-existing but remain unnoticed during the initiation of the therapy, which places beta-blockers in a controversial position despite their well-established benefits. Furthermore, reduction in spontaneous motor activity was observed with the use of beta-blockers, and preclinical studies have shown that psychological states such as depression and anxiety are known to alter the motor function.[23] We conducted the present study to add to the current knowledge on the effect of metoprolol treatment on cardiac function, motor function, QoL, and mental status considering gender-, age-, and dose-related impact of metoprolol on Chinese patients with CHF.

Patients and Methods

Study Design and Patient Population

This is a single-center, prospective study. The complete study design and patient inclusion criteria have been described elsewhere.[16] In brief, all the enrolled CHF patients had a resting HR of >80 bpm, were with or without neuropsychiatric disorders such as depression and anxiety, and were treated at the Second Affiliated Hospital of Kunming Medical University between February 2013 and April 2016. Patients were excluded if they had a resting HR <60 bpm, SBP <90 mm Hg, metoprolol usage in the past 3 months, contraindications for beta-blockers, administration of class I or class III antiarrhythmic agents, <6 months' expected survival, a pacemaker, a history of coronary bypass surgery, or a recent heart attack.

Ethical Approval

The Second Affiliated Hospital of Kunming Medical College University approved the study protocols and complied with Good Clinical Practices, the Declaration of Helsinki, and its subsequent revisions. All the included patients provided written informed consent prior to their enrollment.

Treatment Intervention and Follow-Up

We collected baseline patient data before treatment with an initial daily dose of 23.75- or 47.5-mg metoprolol continuous release tablets (Betaloc® ZOK, AstraZeneca, Sweden), and the dose was escalated by 23.75 mg every 7 days until the target HR level (60–70 bpm) was achieved during the follow-up. The average dose used to reach the target goal was 99.75 mg (47.5–142.5 mg). All the patients were followed up at 1, 3, 6, and 12 months from intervention for final outcome measurement.

Study Outcomes and Measurement

The study outcome was to compare change in cardiac function, motor function, QoL, and mental status at 1, 3, 6, and 12 months from baseline according to gender (men

vs women), patients age (≥60 years vs <60 years), and metoprolol dose (47.5, 71.5, 95, 118.75, and 142.5 mg). Change in all the study outcomes was also evaluated within the groups.

Cardiac function was measured in terms of EF (%) and cardiac index (CI [L/min/m^2]). We measured motor function using a standard 6-minute walk test (6MWT) and Veterans Specific Activity Questionnaire (VSAQ). QoL was measured by an 8-item short form questionnaire (SF-8), in which the higher score denotes improved QoL, and the Minnesota Living with Heart Failure Questionnaire (MLHFQ), in which the highest score denotes worst QoL.

Mental and burnout status was assessed using the Hospital Anxiety and Depression Scale (HADS) and Copenhagen Burnout Inventory (CBI) questionnaire, respectively.

Statistical Analysis

The statistical software R (version 3.6.2, R core team, R Foundation for Statistical Computing, Vienna, Austria) was used to perform all the analyses. Descriptive statistics were used to present the baseline characteristics as mean ±standard deviation (SD), median (range), numbers, and percentages. We used Student's *t*-test to compare the mean values for all the parameters between the two groups. Change in values for EF, CI, 6MWT, VSAQ, SF-8, MLHFQ, HADS, and CBI scores at the various follow-up periods were compared with baseline values using repeated measure one-way analysis of variance (ANOVA), followed by post hoc Bonferroni correction analysis. $P<0.05$ was considered to be statistically significant for all the analyses.

Results

Sociodemographic Characteristic

A total of 169 patients were included in the study, of which 11 were excluded owing to intolerance to metoprolol dose increments and four patients were lost to follow-up. The remaining 154 patients were included for the final data analysis (median age= 66.39 years; men, n=101; women, n=53). Baseline sociodemographic characteristics and other comorbidities of the included patients are presented in Table 1.

Table 1 Baseline Sociodemographic Characteristics of Patients

Patient Characteristics (n=154)	N (%)
Age, median, years	66.39
Men	101 (65.58)
Women	53 (34.41)
Comorbidities	
Hypertension	115 (74.67)
Diabetes mellitus	101 (65.58)
Coronary artery disease	99 (64.28)
Stroke	137 (88.96)
Cardiac disease family history	54 (35.06)
Smoking	111 (72.07)
Alcohol	86 (55.84)
History of MI	59 (38.31)
BMI, kg/m^2	23.85±3.62
GFR, mL/min/1.73 m^2	73.9±26.8
NYHA class III–IV	145 (94.15)
Concomitant medications at baseline	
ACEIs/ARBs	150 (97.40)
Diuretics	145 (94.15)
Digoxin	114 (74.02)
Antithrombotic agents	146 (94.80)

Abbreviations: MI, myocardial infarction; GFR, glomerular filtration rate; NHYA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Gender-Related Changes in Post-Metoprolol Treatment

An average metoprolol dose of 99.75 mg was required to reach the target HR. EF in both men and women increased from baseline (37.60±5.91 and 37.64±6.10) to 1 month (35.24±6.15 and 34.79±6.25) and increased to 50.00±4.45 and 50.72±4.09, respectively, at the end of 12 months with no statistically significant between-gender difference ($P>0.05$; Table 2). However, across the different time points, a statistically significant difference was observed in EF between men and women ($P<0.05$). CI increased from baseline (1.78±0.22 and 1.79±0.21) to 12 months (2.70±0.25 and 2.78±0.23) with no statistically significant difference between men and women, respectively. However, a statistically significant difference was observed across different time points, except from baseline to 1 month ($P<0.05$).

A decrease in HR was observed in both the genders with no statistically significant between-gender difference. However, across the time points, change in HR was statistically significant ($P<0.05$). SBP slightly increased from baseline to 12 months in men and decreased in women, with statistically significant between-gender difference from baseline to 12 months (Table 2). Across the time points, SBP showed a statistically significant difference from baseline to 12 months.

With respect to motor function, distance walked in 6MWT increased in both men and women, and this

Table 2 Change in Cardiac Function, Motor Function, and QoL Post-Metoprolol Treatment with Respect to Gender

Time	Cardiac Function					
	Ejection Fraction, %			Cardiac Index, L/min/m^2		
	Male	Female	P-value	Male	Female	P-value
Baseline	37.60±5.91	37.64±6.10	0.9708	1.78±0.22	1.79±0.21	0.7955
Month 1	35.24±6.15	34.79±6.24	0.6733	1.71±0.29	1.75±0.24	0.2815
Month 3	35.90±5.27	35.36±4.75	0.5184	2.26±0.21	2.26±0.18	0.9797
Month 6	48.13±4.56	47.32±4.36	0.2846	2.61±0.19	2.60±0.18	0.749
Month 12	50.00±4.45	50.72±4.09	0.3182	2.70±0.25	2.78±0.23	0.0668
	Heart Rate, bpm			Systemic Blood Pressure, mm Hg		
Baseline	83.16±6.47	81.89±7.21	0.2844	121.39±14.09	136.92±2.17	<0.001
Month 1	82.72±6.74	82.73±6.77	0.1934	126.73±13.65	126.74±13.72	0.1402
Month 3	82.72±6.74	82.73±6.77	0.1934	126.73±13.65	126.74±13.72	0.1402
Month 6	82.72±6.74	82.73±6.77	0.1934	126.73±13.65	126.74±13.72	0.1402
Month 12	64.59±3.13	65.38±3.32	0.1597	122.28±6.76	125.47±6.67	<0.05
	Motor Function					
	6MWT, m			VSAQ Score		
Baseline	368.42±33.82	369.57±34.51	0.8435	6.41±1.03	6.73±1.15	0.0963
Month 1	341.58±32.45	340.94±33.09	0.9087	4.86±0.87	5.95±0.92	0.2141
Month 3	349.71±34.04	352.74±31.46	0.5830	5.48±0.97	5.62±1.15	0.4424
Month 6	398.40±21.18	398.72±22.52	0.9318	7.89±1.07	7.79±1.00	0.5713
Month 12	414.41±20.84	420.34±20.35	0.0911	8.16±0.98	8.47±0.89	0.0473
	QoL Score					
	SF-8 Score			MLHFQ Score		
Baseline	44.00±2.59	44.06±2.95	0.9064	74.36±3.68	73.77±3.95	0.3759
Month 1	39.22±1.69	39.70±1.55	0.0795	88.67±4.36	89.06±4.40	0.6076
Month 3	42.26±2.51	42.57±3.07	0.5301	86.55±5.00	87.58±5.14	0.2357
Month 6	48.83±1.18	48.94±1.28	0.5982	64.36±3.48	64.79±4.52	0.5413
Month 12	52.05±1.94	52.19±2.58	0.7309	53.74±8.00	53.85±8.42	0.9397

Abbreviations: 6MWT, 6-minute walk test; MLHFQ, Minnesota Living with Heart Failure Questionnaire; bpm, beats per minute; VSAQ, Veterans Specific Activity Questionnaire.

association across the different time points was found to be statistically significant. VSAQ scores increased from baseline (6.41±1.03 and 6.73±1.15 in men and women, respectively) to 12 months, with statistically significant between-gender difference only at 12 months and showed $P<0.05$ across the different time points (Table 2).

Increase in SF-8 scores, denoting improvement in QoL, was observed from baseline to 12 months in men and women (Table 2). Moreover, a decrease in MLHFQ scores, denoting better QoL between men and women, was observed with a statistically significant difference across the different time points for both SF-8 and MLHFQ scores ($P<0.05$).

HADS scores for depression gradually increased from baseline (9.32±2.95 and 7.87±2.15) to 12 months, with a statistically significant difference between men and women, respectively (Table 3), and across the time points ($P<0.05$). HADS anxiety scores also increased from baseline to 12 months, with statistically significant between-gender differences only at 1 and 12 months and $P<0.05$ across all the time points except from baseline to 1 month. CBI scores increased from baseline to 12 months among men and decreased in women, with no statistically significant between-gender difference ($P>0.05$).

Age-Related Changes

A non-significant increase in EF and CI was observed in both patients aged <60 and ≥60 years ($P>0.05$). In comparison with different time points, a statistically significant

Table 3 Change in Mental Status Post-Metoprolol Treatment with Respect to Gender

Time	HADS_Depression			HADS_Anxiety		
	Male	Female	P-value	Male	Female	P-value
Baseline	9.32 (2.95)	7.87 (2.15)	0.001	8.45 (2.03)	7.79 (2.01)	0.056
Month 1	10.27 (2.82)	8.83 (2.67)	0.002	8.34 (1.97)	7.72 (1.95)	0.043
Month 3	10.37 (2.81)	8.96 (2.71)	0.003	7.19 (1.17)	6.91 (0.90)	0.099
Month 6	10.37 (2.76)	9.05 (2.60)	0.004	7.14 (1.09)	6.92 (0.87)	0.189
Month 12	10.31 (2.65)	9.22 (2.54)	0.015	7.19 (0.99)	6.89 (0.78)	0.039
	CBI Scores					
Baseline	60.19 (6.50)	59.75 (6.59)	0.691			
Month 1	60.80 (7.10)	60.53 (7.78)	0.83			
Month 3	62.58 (8.92)	61.40 (9.07)	0.44			
Month 6	62.62 (8.89)	61.55 (9.23)	0.49			
Month 12	62.43 (9.22)	61.90 (8.74)	0.725			

Abbreviations: HADS, Hospital Anxiety and Depression Scale; CBI, Copenhagen Burnout Inventory.

difference was observed for both EF and CI ($P<0.05$). HR and SBP showed a non-significant reduction in both the age groups, with the changes being constant at baseline and month 1, 3, and 6 and drastic reduction at the end of 12 months (Table 4). In comparison with different time points, a statistically significant difference was observed only from baseline to 12 months for HR and SBP.

Motor function assessed by 6MWT showed a gradual non-significant increase among both patients aged <60 and ≥60 years, except at the end of 1 month ($P<0.05$). VSAQ scores also increased among both the age groups from baseline to 12 months (Table 4).

With regard to QoL, a sudden decrease in SF-8 scores from baseline (44.10±2.60 and 43.97±2.75) to 1 month (39.42±1.64 and 39.37±1.67 in patients aged <60 and ≥60 years, respectively) and gradual increase in scores at 3, 6, and 12 months were observed between both the age groups, with a statistically significant difference at 12 months ($P<0.05$). MLHFQ scores also showed a sudden increase from baseline to 1 and 3 months and gradually decreased at 6 and 12 months between both the age groups, with a statistically significant difference at the end of 3 months ($P<0.05$; Table 4). Change in scores in comparison with outcomes of motor function and QoL at different time points from baseline to 12 months has shown a statistically significant difference.

With regard to mental status, a gradual increase in HADS depression scores was observed in both the age groups, with no statistically significant difference between the age groups. However, HADS anxiety scores decreased from baseline to 12 months, and CBI scores showed an increasing trend among both the age groups (Table 5), with a statistically significant difference between different time points, except from baseline to 1 month, for both HADS depression and CBI scores.

Metoprolol Dose-Related Changes at the End of 12 Months

EF gradually decreased from 51.41±3.75 to 48.63±5.13 with an increase in the dose of metoprolol from 47.5 to 142.5 mg. CI did not show much change with increase in the dose of metoprolol. Motor function and QoL showed statistically non-significant differences with respect to different doses of metoprolol (Table 6). Mental status scores evaluated by HADS depression, HADS anxiety, and CBI scores also showed no statistically significant difference ($P>0.05$) with respect to different doses of metoprolol (Table 7).

Repeated measure ANOVA with Bonferroni correction was used to establish significant differences at different time points (Supplementary Tables 1 and 2).

Discussion

In this study, we explored the effect of metoprolol on change in cardiac function, motor function, QoL, and mental status of CHF patients with respect to gender, age, and different metoprolol doses. Our findings highlight that metoprolol treatment with respect to gender showed improved cardiac and motor function, better QoL, and increased depression but decreased anxiety scores. With regard to age, metoprolol treatment had shown improved cardiac and motor function and improved QoL with higher

Table 4 Change in Cardiac Function, Motor Function, and QoL Post-Metoprolol Treatment with Respect to Age

Time	Cardiac Function					
	Ejection Fraction, %			Cardiac Index, L/min/m^2		
	<60 years	≥60 years	*P*-value	<60 years	≥60 years	*P*-value
Baseline	37.08 (6.18)	37.79 (5.89)	0.534	1.76 (0.23)	1.79 (0.21)	539
Month 1	34.50 (6.45)	35.28 (6.08)	0.516	1.77 (0.24)	1.71 (0.28)	0.196
Month 3	36.47 (5.57)	35.47 (4.92)	0.323	2.31 (0.19)	2.24 (0.20)	0.077
Month 6	47.55 (4.95)	47.95 (4.36)	0.661	2.61 (0.18)	2.61 (0.18)	0.856
Month 12	49.66 (4.26)	50.44 (4.35)	0.332	2.72 (0.23)	2.73 (0.25)	0.867
	Heart Rate, bpm			Systemic Blood Pressure, mm Hg		
Baseline	87.03 (4.54)	81.31 (6.76)	5.372	132.82 (6.55)	124.74 (14.76)	7.427
Month 1	87.03 (4.54)	81.31 (6.76)	5.372	132.82 (6.55)	124.74 (14.76)	7.427
Month 3	87.03 (4.54)	81.31 (6.76)	5.372	132.82 (6.55)	124.74 (14.76)	7.427
Month 6	87.03 (4.54)	81.31 (6.76)	5.372	132.82 (6.55)	124.74 (14.76)	7.427
Month 12	65.58 (3.09)	64.63 (3.23)	0.109	124.74 (7.53)	122.93 (6.63)	0.19
	Motor Function					
	6MWT, m			VSAQ Score		
Baseline	367.11 (34.69)	369.37 (33.84)	0.726	6.64 (1.18)	6.48 (1.05)	0.441
Month 1	331.74 (32.09)	344.52 (32.23)	0.037	4.79 (0.89)	4.97 (0.88)	0.293
Month 3	345.55 (29.91)	352.46 (34.035)	0.237	5.79 (1.14)	5.44 (0.98)	0.1
Month 6	395.74 (21.43)	399.41 (21.64)	0.363	7.80 (1.08)	7.88 (1.04)	0.717
Month 12	416.82 (19.26)	416.33 (21.36)	0.895	8.21 (1.04)	8.28 (0.93)	0.698
	QoL Scores					
Baseline	44.18 (2.60)	43.97 (2.75)	0.658	74.03 (4.00)	74.20 (3.72)	0.815
Month 1	39.42 (1.64)	39.37 (1.67)	0.870	89.53 (4.14)	88.57 (4.42)	0.228
Month 3	42.37 (3.11)	42.36 (2.58)	0.99	88.55 (4.64)	86.37 (5.09)	0.017*
Month 6	49.05 (1.18)	48.81 (1.22)	0.281	65.18 (4.71)	64.28 (3.53)	0.284
Month 12	52.90 (1.67)	51.84 (2.26)	0.003*	53.39 (7.21)	53.90 (8.42)	0.717

Abbreviations: 6MWT, 6-minute walk test; bpm, beats per minute; QoL, quality-of-life; VSAQ, Veterans Specific Activity Questionnaire.

Table 5 Change in Mental Status Post-Metoprolol Treatment with Respect to Age

Time	HADS_Depression			HADS_Anxiety		
	<60 years	≥60 years	P-value	<60 years	≥60 years	P-value
Baseline	8.71 (2.54)	8.85 (2.87)	0.771	8.34 (2.13)	8.19 (2.03)	0.70
Month 1	9.58 (2.78)	9.84 (2.88)	0.62	8.18 (2.01)	8.16 (1.99)	0.938
Month 3	9.68 (2.77)	9.95 (2.88)	0.61	7.18 (1.11)	7.06 (1.09)	0.551
Month 6	9.76 (2.69)	9.97 (2.81)	0.69	7.11 (1.01)	7.05 (1.04)	0.778
Month 12	9.84 (2.66)	9.97 (2.67)	0.80	6.90 (0.92)	7.15 (0.93)	0.149
	CBI Scores					
Baseline	60.64 (6.48)	59.84 (6.54)	0.515			
Month 1	60.97 (6.88)	60.63 (7.48)	0.80			
Month 3	62.72 (8.77)	62.00 (9.05)	0.664			
Month 6	62.94 (8.97)	62.03 (9.03)	0.59			
Month 12	62.28 (9.39)	62.24 (8.95)	0.98			

Abbreviations: HADS, Hospital Anxiety and Depression Scale; CBI, Copenhagen Burnout Inventory.

Table 6 Impact of Metoprolol Dose on Cardiac Function, Motor Function, and QoL at the End of 12 Months

	Cardiac Function				Motor Function				QoL			
	EF, %		CI, L/min/m^2		6MWT, m		VSAQ		SF-8		MLHFQ	
Dose 47.5 mg	51.41 (3.75)	0.223	2.76 (0.23)	0.234	420.65 (19.97)	0.263	8.49 (0.96)	0.407	51.97 (1.88)	0.061	53.51 (10.67)	0.946
Dose 71.25 mg	51.00 (4.83)		2.7 (0.31)		408.86 (24.43)		8.57 (0.79)		52.43 (2.82)		54 (3.06)	
Dose 95 mg	49.94 (3.98)		2.8 (0.20)		411.24 (20.24)		8.06 (0.97)		50.71 (2.93)		54.88 (4.28)	
Dose 118.75 mg	50.08 (4.36)		2.68 (0.27)		417.74 (20.69)		8.19 (0.95)		52.34 (2.06)		53.41 (7.35)	
Dose 142.5 mg	48.63 (5.13)		2.78 (0.20)		410.68 (21.30)		8.21 (1.03)		52.53 (1.81)		54.68 (9.55)	

Abbreviations: EF, ejection fraction; CI, cardiac index; 6MWT, 6-minute walk test; MLHFQ, Minnesota Living with Heart Failure Questionnaire; QoL, quality-of-life; VSAQ, Veterans Specific Activity Questionnaire; SF-8, 8-item short form questionnaire.

Table 7 Impact of Metoprolol Dose on Mental Status at the End of 12 Months

	Mental Status					
	HADS_Depression		HADS_Anxiety		CBI_Equally	
Dose 47.5 mg	10 (2.55)	0.635	6.97 (1.01)	0.87	61.15 (9.42)	0.216
Dose 71.25 mg	9.29 (3.04)		7 (1.15)		67.86 (9.53)	
Dose 95 mg	10.71 (3.00)		7.18 (0.73)		64.80 (8.81)	
Dose 118.75 mg	9.92 (2.49)		7.15 (0.95)		61.34 (9.14)	
Dose 142.5 mg	9.42 (3.15)		7 (0.82)		63.60 (7.19)	

Abbreviations: HADS, Hospital Anxiety and Depression Scale; CBI, Copenhagen Burnout Inventory.

depression and decreased anxiety scores. Furthermore, there were no significant differences with different doses of metoprolol in cardiac, motor, QoL, and mental status in patients with CHF.

Gender-related differences in the pharmacokinetics of metoprolol are well established.[24] In our study, a reduction in HR from baseline to 12 months was observed in both the genders. SBP was higher in women at all time points, and reduction in SBP was observed at 12 months. A similar pattern of responses was also reported in previous studies.[16,25] Moreover, in our study, both EF and CI were similar between men and women. Motor function was evaluated using 6MWT and VSAQ scores, which are reliable tools to evaluate functional capacity and prognosis.[26,27] In our study, metoprolol also improved the motor function of male and female patients with CHF. In both men and women, improvement in the QoL was observed as a biphasic response with both SF-8 and MLHFQ scales after metoprolol treatment. Previous studies using various questionnaires have also demonstrated improvement in QoL with metoprolol usage among patients with CHF.[16,28,29]

Neurohormonal dysfunction due to pathophysiological modifications caused by prolonged anxiety and depression can lead to cardiac abnormalities.[30,31] In addition, symptoms of depression and anxiety are often unrecognized,[32] which results in disease progression.[33] Our study results demonstrated that metoprolol treatment increased the HADS depression scores and decreased the anxiety scores among both men and women.

In our study, in patients aged <60 and ≥60 years, significant and expected reductions in HR and SBP were observed; however, the reductions were observed only at 12 months of metoprolol treatment, and no changes were observed at baseline and 1, 3, and 6 months in both the age groups.

Cardiac function post-metoprolol treatment evaluated by EF and CI showed a biphasic response, with an initial decrease at 1 month and significant improvement of both EF and CI by 12 months in both the age groups (<60 and ≥60 years). This further confirms that the beta-blocker action of metoprolol on both EF and CI is independent of age.[34] A study conducted by Neto et al[35] also reported similar findings. Motor function evaluated by 6MWT and VSAQ also showed an initial decrease at 1 month and improvement by 12 months post-metoprolol treatment. This finding correlates with the decrease in cardiac function at 1 month as patients with CHF encounter myopathy of both cardiac and skeletal muscles,[36] which further validated the deterioration of motor function in these patients.[37,38]

QoL after metoprolol treatment has also shown a similar trend as cardiac and motor function in patients with CHF, with an initial decline in QoL at the end of 1 month and subsequent improvement by 12 months. Patients with CHF are prone to anxiety and depression due to neurohormonal dysregulation,[32] and evidence suggests that elders are more susceptible to depression and anxiety, which impact their QoL.[39,40] Our study showed higher HADS depression scores, indicating improvement in depression, but lower HADS anxiety scores, denoting that patients with CHF express more anxiety, and higher CBI scores with better burn out status in both the age groups (<60 and ≥60 years).

In our study, we also examined the dose-mediated effect of metoprolol on cardiac, motor, QoL, and mental status of patients with CHF. A slight decrease in EF and no change in CI were observed with an increase in the dose of metoprolol. A study conducted by Zhang et al[41] also showed no significant changes in the cardiac function with different doses of metoprolol. No dose-dependent changes with metoprolol were observed in motor function and QoL. However, a good correlation between QoL and clinical outcomes was reported by other studies.[42,43] Metoprolol use in the treatment of CHF could worsen pre-existing depression or lead to depression.[31] In our study, mental status measured with HADS depression, HADS anxiety, and CBI scores did not show much difference with dose increment of metoprolol.

The strength of our study was that we have provided comprehensive evidence involving the effect of gender, age, and metoprolol dose on cardiac, motor, QoL, and mental status of patients with CHF at baseline and 1, 3, 6, and 12 months. Our study also had certain limitations. First, we did not include a control group or use placebo to compare the outcomes with the treatment groups. Second, most of the questionnaires were self-administered instead of an interview-based method, which might have resulted in variances in responses. Third, we followed patients with CHF for 1 year, and thus, long-term mortality and metoprolol influence on different outcomes could not be captured. Finally, other confounding factors including age, sample size, and comorbidity medications taken could have influenced the study findings.

Conclusion

Gender-related differences were mostly observed in mental status after metoprolol treatment, suggesting that psychological response to metoprolol differs between men and women. Metoprolol has demonstrated age-independent improvement in cardiac function, motor function, and QoL, whereas an increase in depression and burnout as well as improvement in anxiety scores were observed. Uptitration of metoprolol to target dose showed no significant difference in clinical outcomes.

Disclosure

The authors declare that they have no conflicts of interest for this work.

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