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Original Article

The impact of cardiac resynchronization therapy with implantable cardioverter defibrillators on patients with moderate to severe chronic heart failure: A single-arm clinical trial

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Abstract

Background: Patients with moderate to severe chronic heart failure (CHF) are at high risk for cardiac mortality. Cardiac resynchronization therapy with defibrillators (CRT-D) as a potentially beneficial option can improve the clinical outcomes of such patients.

Methods: We conducted a single-arm clinical trial in which 48 patients with moderate to severe CHF were investigated regarding the beneficial outcome of CRT-D insertion. All participants were evaluated regarding different functional and echocardiographic factors including New York Heart Association (NYHA) functional class (FC), left ventricular ejection fraction (LVEF), mitral regurgitation (MR) as well as left ventricular end-systolic (LVESD) and end-diastolic (LVEDD) before and one month after the procedure. Furthermore, we investigated the influence of different variables including age, gender, and comorbidities on the aforementioned clinical and echocardiographic factors.

Results: Of the 48 CHF patients included in our study, 24 (50%) were males and 24 (50%) were females. The mean ± standard deviation (range) of the participants' age was 55.6±6.5 (40-69) years. CRT-D insertion significantly improved all functional and echocardiographic factors in CHF patients. The participants had a mean±standard deviation (range) LVEF of 22.1±5.8% (10-30%) before CRT-D insertion. A follow-up echocardiography performed one month after the implantation of CRT-D demonstrated a significant increase in LVEF to 27.1±5.5% (15-38%) (p<0.001). Additionally, echocardiography conducted one month after CRT-D insertion showed a reduction of LVESD from 6.8±0.5 cm (5.8-7.4 cm) to 6.2±0.5 cm (5.3-7.3 cm) (p<0.001).

Conclusion: There is prominent evidence for CRT-D insertion in reducing symptoms of heart failure as well as improving different echocardiography variables in patients with moderate to severe CHF.

Keywords: Cardiac resynchronization therapy, Implantable cardioverter defibrillator, Chronic heart failure.

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Chronic heart failure (CHF) is one of the main cardiac disorders characterized by structural and functional heart defects, resulting in increased pressure within the heart and reduced cardiac output. The prevalence of heart failure ranges from one to two percent in adults, with the prevalence increasing with age (1-5). Cardiac resynchronization therapy (CRT) is a potential management option for patients with CHF. It can improve the survival and quality of life of patients with reduced ejection fraction by synchronizing ventricular conduction and contraction and inducing reverse remodeling (6-8). CRT pacemakers are typically recommended for heart failure patients requiring pacing with reduced ejection fraction, as well as older CHF patients, or those with multiple comorbidities.

On the other hand, implantable cardioverter defibrillators (ICDs) are recommended for heart failure patients with a reduced ejection fraction or those remained symptomatic despite receiving optimal medical treatment. However, the implantation of an ICD for patients with reduced ejection fraction heart failure who are at high risk of sudden cardiac death and are eligible for CRT insertion remained controversial. CRT defibrillators (CRT-D) are generally recommended for heart failure patients with an ejection fraction of less than 35% despite receiving standard medical therapy. However, few clinical trials have evaluated both functional and echocardiographic outcomes of CRT-D in such patients (1, 9). According to mentioned elaborations, we aimed to conduct this study to investigate the clinical outcomes of CRT-D insertion, including functional variables and echocardiography findings, in patients with moderate to severe CHF in a single-arm clinical trial.

Methods

We conducted a single-arm clinical trial (ethical number: IR.MUBABOL.HRI.REC.1397.021) in which 48 patients with CHF who were referred to Omid Clinic and Ayatollah Rouhani Hospital of Babol from May 2018 to September 2018 were included. Patients were evaluated regarding the clinical outcomes of CRT-D insertion.

Subjects: All the participants meeting the following criteria were included in our study:

1. Left ventricular ejection fraction (LVEF) <35%, measured by echocardiography
2. Left bundle branch block (LBBB) with QRS > 120 msec
3. New York Heart Association (NYHA) functional class (FC) of above I despite receiving standard medical treatments.

Those individuals with atrial fibrillation (AF), a life expectancy of less than one year, and the potential to undergo revascularization therapy were excluded.

Study design: After history taking and physical examination, clinical and demographic data such as age, gender, and comorbidities such as diabetes mellitus (DM) and hypertension were collected. All participants then underwent transthoracic echocardiography (TTE) to measure the LVEF and mitral regurgitation (MR) as well as left ventricular end-systolic (LVESD) and end-diastolic (LVEDD) diameter, by Simpson and visual method, in two-chamber, four-chamber, and short axis views. Afterward, each participant was implanted with a CRT-D device, consisting of three leads placed into the coronary sinus, right atrium, and right ventricle, under local anesthesia. Subsequently, necessary supporting measures were carried out. Then, the participants were followed-up one month after the procedure, with a TTE and clinical examination performed at each follow-up session, and relevant data were collected (10). Different clinical variables including LVEF, LVESD, LVEDD, the severity of MR, and NYHA FC were investigated before and after the procedure. Subsequently, the impact of different baseline characteristic factors including age, gender, and comorbidity disorders on the abovementioned clinical variables was evaluated. This study was conducted by an approved ethical number of IR.MUBABOL.HRI.REC.1397.021 and approved Iranian Registry of Clinical Trials (IRCT) number IRCT20160926029976N3 of Babol University of Medical Sciences. Additionally, written informed consent was obtained from all the individuals who were included in our study.

Statistical analysis: To evaluate the impact of the intervention, the number of samples was obtained using the following formula:

$$n \geq \frac{(z_\alpha + z_\beta)^2 \sigma^2}{(\mu_1 - \mu_2)^2}$$

Therefore, the minimum sample size required was calculated as

$$n \geq (1.96 + 1.28)^2 (1/0.50)^2 = 42$$

Hence, including 10% sample loss, the final minimum number of suitable sample size was defined as 47. Data analysis was conducted using IBM SPSS Statistics for Windows, Version 23 (IBM Corp, Armonk, NY, USA). We used frequency and percentage to express qualitative data and mean±standard deviation (SD) to express the quantitative data. We used the Wilcoxon signed-rank test and Mann-Whitney U test to compare quantitative variables and chi-square to compare qualitative variables. In addition, we checked the assumption of normality by using the Kolmogorov-Simonov test. The p-value under 0.05 was considered statistically significant.

Results

A total of 48 participants with CHF who were referred to our hospital were investigated in our study. All individuals had an LVEF below 35% and a QRS duration above 120 msec in their ECG.

Demographic information of the patients: Out of the 48 participants, 24 (50%) were males and 24 (50%) were females. The mean ± SD (range) of the participants' age was 55.6±6.5 (40-69) years. The largest proportion of patients, accounting for 31 (63.33%) individuals, fell within the age group of 50 to 59 years. Regarding comorbidities, out of the

48 patients, 26 (54.2%) did not have any concurrent diseases. Among the remaining patients, 10 had only hypertension, 8 had only DM, and 4 had both conditions. The baseline characteristics of CHF patients who were involved in our study are demonstrated in table 1.

Clinical variables of the patients: In this study, several clinical variables, including LVEF, LVEDD, LVESD, NYHA FC, and MR severity were examined before and after the implantation of CRT-D (table 2). Before the procedure, the participants had a mean ± SD (range) LVEF of 22.1±5.8% (10-30%). However, a follow-up echocardiography conducted one month after the procedure revealed a significant increase in LVEF to 27.1 ±5.5% (15-38%) (p<0.001).

Regarding LVEDD, the patients had a mean±SD (range) diameter of 7.1±0.3 cm (6.4 -7.8 cm) before the procedure that decreased significantly to 6.7±0.4 cm (5.8 -7.8 cm) measured by echocardiography one month after CRT-D implantation. Additionally, the patients had a mean±SD (range) LVESD of 6.8±0.5 cm (5.8-7.4 cm) before CRT-D insertion.

An echocardiography performed one month after the procedure showed a decrement of LVESD to 6.2±0.5 cm (5.3-7.3 cm) that was statistically significant. (p<0.001). NYHA FC was another clinical variable that was examined before and after the procedure in our study. Out of the 48 patients who participated in the study, none were classified in NYHA FC 1. A total of 15 (31.3%) participants were classified as NYHA FC 2, and 33 (68.7%) participants were classified as NYHA FC 3. After the CRT-D implantation, a significant improvement in NYHA FC was reported (p< 0.001).

Table 1. The baseline characteristics of the CHF patients investigated in this study

Variables		Frequency (%)
Sex	Male	24 (50%)
	Female	24 (50%)
Age; years	40-49	7 (14.6%)
	50-59	31 (64.6%)
	60-69	10 (20.8%)
Comorbidities	None	26 (54.2%)
	HTN	10 (20.8)
	DM	8 (16.7%)
	DM + HTN	4 (8.3%)

All data are expressed as frequency and percentage for the baseline characteristics. CHF, chronic heart failure; DM, diabetes mellitus; HTN, hypertension

Table 2. Comparison of different clinical variables before and after CRT-D implantation

Variables		Before procedure	After procedure	P-value
LVEF, %		22.1±5.8	27.1±5.5	<0.001
LVEDD, cm		7.1±0.3	6.7±0.4	<0.001
LVESD, cm		6.8±0.5	6.2±0.5	<0.001
NYHA FC	**FC 1**	0 (0%)	14 (29.2%)	<0.001
	FC 2	15 (31.3%)	28 (58.3%)	
	FC 3	33 (68.7)	6 (12.5%)	
MR intensity	**None**	6 (12.5%)	10 (20.8%)	<0.001
	Mild	5 (10.4%)	20 (41.7%)	
	Moderate	19 (39.6%)	11 (22.9%)	
	Severe	18 (37.5%)	7 (14.6%)	

All data are expressed as frequency and percentage for qualitative variables or mean±SD for quantitative variables. CRT-D, cardiac resynchronization therapy with defibrillator; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MR, mitral regurgitation; NYHA FC, New York Heart Association function class.

Accordingly, 14 participants (29.2%) were classified as NYHA FC 1, 28 (58.3%) were classified as NYHA FC 2, and 6 (12.5%) were classified as NYHA FC 3. Furthermore, we investigated MR severity both before and after the CRT-D implantation using echocardiography. Initially, six (12.5%) participants did not have MR based on their echocardiography, while 5 (10.4%) patients had mild MR, 19 (39.6%) patients had moderate MR, and 18 (37.5%) patients had severe MR. One month after the procedure, a significant improvement was observed in MR severity (p<0.001). Specifically, 10 (20.8%) participants did not report MR, 20 (41.7%) participants had mild MR, 11 (22.9%) had moderate MR, and 7 (14.6%) participants had severe MR.

The relationship between the abovementioned clinical factors and baseline characteristics: The association between various baseline characteristics including age, gender, and comorbidity disorders (hypertension and DM) and aforementioned clinical variables consisting of LVEF, LVESD, LVEDD, NYHA FC, and MR intensity was investigated.

As can be seen in table 3, no significant impact of any baseline characteristics was reported based on our findings in this study.

Table 3. The association between different clinical factors and baseline characteristic

Variables			Age			Gender			Comorbidities		
			<56 years	>56 years	P-value	Male	Female	P-value	Negative	Positive	P-value
LVEF, %	Before procedure		23±5.4	21.1±6.2	0.35	21.5±6.3	22.6±5.4	0.50	23±5	21.0±6.6	0.42
	After procedure		28±5.3	26.2±5.6	0.29	26.3±6	27.9±4.9	0.37	27.8±4.5	26.2±6.5	0.28
LVEDD, cm	Before procedure		7.1±0.3	7±0.3	0.45	7.1±0.3	7±0.3	0.84	7±0.3	7.1±0.3	0.51
	After procedure		6.7±0.4	6.6±0.4	0.76	6.7±0.3	6.6±0.3	0.44	6.7±0.3	6.7±0.4	0.93
LVESD, cm	Before procedure		6.8±0.5	6.9±0.5	0.54	6.9±0.5	6.7±0.5	0.12	6.9±0.5	6.7±0.5	0.51
	After procedure		6.2±0.5	6.2±0.5	0.93	6.3±0.5	6.1±0.4	0.11	6.3±0.4	6.1±0.5	0.93
NYHA FC	Before procedure	FC 1	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	
		FC 2	9 (37.5%)	6 (25%)	0.35	7 (29.2%)	8 (33.3%)	0.76	11 (42.3%)	4 (18.2%)	0.07
		FC 3	15 (62.5%)	18 (75%)		17 (70.8%)	16 (66.7%)		15 (57.7%)	18 (81.8%)	
	After procedure	FC 1	8 (33.3%)	6 (25%)		7 (29.2%)	7 (29.2%)		9 (34.6%)	5 (22.7%)	
		FC 2	13 (54.2%)	15 (62.5%)	0.81	13 (54.2%)	15 (62.5%)	0.67	15 (57.7%)	13 (59.1%)	0.44
		FC 3	3 (12.5%)	3 (12.5%)		4 (16.7%)	2 (8.3%)		2 (7.7%)	4 (18.2%)	
MR Severity	Before procedure	None	3 (12.5%)	3 (12.5%)		3 (12.5%)	3 (12.5%)		3 (11.5%)	3 (13.6%)	
		Mild	4 (16.7%)	1 (4.2%)	0.34	4 (16.7%)	1 (4.2%)	0.52	4 (15.4%)	1 (4.5%)	0.63

Variables		Age			Gender			Comorbidities		
		<56 years	>56 years	P-value	Male	Female	P-value	Negative	Positive	P-value
After procedure	Moderate	7 (29.2%)	12 (50%)	0.84	8 (33.3%)	11 (45.8%)	0.80	9 (36.4%)	10 (45.5%)	0.21
	Severe	10 (41.7%)	8 (33.3%)		9 (37.5%)	9 (37.5%)		10 (38.5%)	8 (36.4%)	
	None	6 (25%)	4 (16.7%)		6 (25%)	4 (16.7%)		7 (26.9%)	3 (13.6%)	
	Mild	9 (37.5%)	11 (45.8%)		9 (37.5%)	11 (45.8%)		8 (30.8%)	12 (54.5%)	
	Moderate	6 (25%)	5 (20.8%)		5 (20.8%)	6 (25%)		8 (30.8%)	3 (13.6%)	
	Severe	3 (12.5%)	4 (16.7%)		4 (16.7%)	3 (12.5%)		3 (11.5%)	4 (18.2%)	

All data are expressed as frequency and percentage for qualitative variables or mean±SD for quantitative variables. LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MR, mitral regurgitation; NYHA FC, New York Heart Association function class; SD, standard deviation

Discussion

We aimed to assess the clinical outcomes of CRT-D insertion, including LVEF, LVEDD, LVESD, NYHA FC, and MR intensity in patients with CHF who were referred to Omid clinic and Ayatollah Rouhani Hospital of Babol. Regarding echocardiography findings, both LVEDD and LVESD significantly decreased following CRT-D implantation (p<0.001). LVEF significantly increased compared to pre-procedure levels (p<0.001). Additionally, MR severity significantly improved after CRT-D insertion (p<0.001). Furthermore, there was a significant decrease in NYHA FC (p<0.001). These findings indicate a positive and significant impact of CRT-D insertion on functional variables and echocardiography results. Subsequently, the association between different baseline features including gender, age, and comorbidities such as hypertension and diabetes mellitus, and functional outcomes was evaluated. No significant relationship was observed.

CHF is a major cardiac disorder involving structural and functional defects that lead to increased intracardial pressure and decreased cardiac output (1). The prevalence of CHF increases with age, affecting 1-2% of adults overall and over 10% of those over 70 years old (1-5). Despite recent advances, the prognosis for CHF patients has remained poor, with 20% annual mortality and 53% 5-year mortality (1, 11). Appropriate treatment modalities like CRT insertion with or without ICD implantation can reduce adverse events and improve the quality of life in high-risk CHF patients by improving heart function and preventing arrhythmias, leading to decreased mortality and improved symptom relief (12-15). Several studies investigated the clinical advantages of CRT insertion in such patients. In a randomized, double-blind clinical trial by Young et al. (16), a total of 369 participants with severe CHF were investigated regarding the clinical outcomes of CRT activation in addition to ICD. All patients received CRT-D, however, in 182 participants CRT was off (as a control group) and in the case group, both ICD and CRT were activated. Accordingly, based on their findings, NYHA FC and the quality of life of the patients whose CRT was on were significantly improved compared to the control group. Similarly, in our study, NYHA FC was significantly better after CRT-D insertion. Arshad et al. (17) conducted another clinical trial in which the beneficial outcomes of CRT-D insertion were investigated compared to those just underwent ICD. Their findings were similar to ours, as echocardiography factors including ejection fraction and echocardiography volumes significantly improved in CRT-D group compared to those just received ICD.

Furthermore, based on their results, echocardiographic evidence of reverse cardiac remodeling showed prominently greater improvement in women than in men. Conversely, no significant difference regarding echocardiography findings was observed between men and women in our study. In another study by Kanzaki et al. (18), the beneficial outcome of CRT implantation on MR was evaluated in heart failure patients. Subsequently, MR severity decreased significantly. A significant improvement

was also observed in our study regarding MR intensity after CRT-D insertion. Abraham et al. (19) conducted another clinical trial in which 186 patients with mild symptomatic heart failure were investigated regarding the clinical impact of CRT insertion. Similar to our article, a significant increase in LVEF and improvement in NYHA FC was reported subsequent to CRT implantation.

In another clinical trial conducted by De Marco et al. (20), they examined a total of 435 patients who had moderate to severe heart failure with NYHA FC 3 or 4. The objective of their study was to evaluate the impact of CRT, alongside medical treatment, on the exercise capacity and functional ability of the participants. The case group underwent CRT in addition to standard medications, while the control group just received routine standard medical therapy. Similar to our findings, a significant improvement in NYHA FC was reported in patients who received CRT compared to those were just under medical treatments. Furthermore, regarding exercise capacity variables, a significant beneficial outcome was revealed regarding six-minute walking distance in their study which was not evaluated in our manuscript. On the other hand, echocardiography variables such as LVESD, LVEDD, and MR severity were not investigated in that study unlike ours. Similar findings regarding the other variables investigated in our study were reported in the other studies conducted.

In a study by Cleland et al. (21), in which 813 patients with moderate to severe heart failure were studied, end systolic volume index was reduced in patients with CRT compared to the control group just taking conventional medical treatments. Furthermore, LVEF and MR severity were significantly better in CRT group. In addition, mortality beneficial of CRT insertion was also reported that was not evaluated in our article due to the short time follow-up in our study. In another study by Moss et el. (8), a total of 1820 participants with mild symptomatic heart failure were investigated regarding the clinical and echocardiography outcomes of CRT insertion in addition to ICD implantation. Echocardiography findings including LVEF, LVESD, and LVEDD were significantly better in the group underwent CRT along with ICD compared to the participants who received only ICD. All these findings were consistent to our results. Limitations of our study included small sample size, which was unavoidable due to the lack of facilities available in our hospital. Additionally, the follow-up period of our study could have been longer or divided into different sessions over time. However, our study had several strengths. Few studies have been conducted in our country regarding the impact of ICD or CRT insertion in patients with heart failure, and our study could be considered a pioneer in this research field. Moreover, we investigated different various clinical variables, including different echocardiography findings and functional variables, and explored the impact of demographic features and comorbidity disorders on these variables. Our findings suggest a positive and significant impact of CRT-D insertion on functional variables and echocardiography results. Specifically, LVESD, LVEDD, LVEF, MR severity, and NYHA FC significantly improved after CRT-D implantation. No significant influence of any demographic factors or comorbidities on different clinical variables investigated in our study was observed.

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Conflict of interest: This study was conducted without any financial or commercial relationships that would be construed as a conflict of interest.

Ethics approval: This study was conducted with an approved ethical number of IR.MUBABOL.HRI.REC.1397.021 and approved IRCT number of IRCT20160926029976N3 from Babol University of Medical Sciences. Additionally, written informed consent was obtained from all the individuals who were included in our study.

Authors' contribution: HSO: writing of the manuscript. AB: data gathering and data analysis. SD: writing of the manuscript. SA (Dr. Abrotan), MTSO, and MS: supervision and critical revision. SA (Mrs. Aboutalebzadeh): data analysis. MTHG: idea making, supervision, and critical revision.

Availability of data and materials: The data that support the findings of this study is available upon reasonable request from the corresponding author.

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