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ARYA Atherosclerosis

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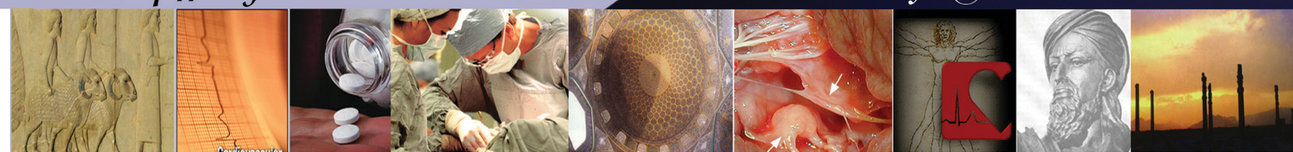

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Postal Code: 8166173414 Tel: + 98 31 36115206 Fax: +98 31 36115311
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Effect of an educational intervention based on BASNEF model on treatment adherence after coronary artery bypass surgery: A randomized clinical trial

Atefeh Torknejad[1], Sima Babaei[2], Mohsen Mirmohammadsadeghi[3]

Original Article

Abstract

BACKGROUND: Coronary artery bypass graft (CABG) surgery is the most effective treatment for cardiovascular disease (CVD). Adherence to treatment after CABG surgery is very important. One of the educational models used in this regard is the BASNEF (Belief, Attitudes, Subjective Norms, and Enabling Factors) model. The present study aimed to assess the effect of an educational intervention based on BASNEF model on adherence to treatment in patients after CABG surgery.

METHODS: The present study was a randomized clinical trial. In this study, 72 patients who had undergone CABG surgery participated in the two intervention and control groups. Patients in the intervention group took part in 4 40-minute educational sessions based on BASNEF model after discharge. The patients in both groups completed the Modanloo Adherence to Treatment Questionnaire (MATQ) and a researcher-made BASNEF model questionnaire before the intervention, after the educational intervention, and at the 3-month follow-up. Data were analyzed using independent t-test, chi-square test, Man-Whitney test, and repeated measures analysis of variance (ANOVA). Mauchly's sphericity test was used for testing sphericity and the Greenhouse-Geisser correction was used in the case of lack of sphericity. All P-values of less than 0.05 were considered significant.

RESULTS: The total score of the MATQ and its subscales had significantly improved in the intervention group after the intervention compared with the control group ($P < 0.050$). In addition, the mean scores of the model constructs (knowledge, attitude, behavior intention, subjective norms, and enabling factors) had significantly improved after the intervention in the intervention group in comparison with the control group ($P < 0.050$).

CONCLUSION: The educational intervention based on BASNEF model improved adherence to treatment in patients after CABG surgery. Moreover, the model constructs improved in the intervention group in comparison with the control group after the intervention.

Keywords: Treatment Adherence; Coronary Artery Bypass Graft Surgery; Educational Models

Date of submission: 22 Aug. 2019, *Date of acceptance:* 17 Feb. 2020

Introduction

Cardiovascular disease (CVD) has become widespread due to the development of urban life and changes in human habits.[1] Coronary artery disease (CAD) is one of the most common CVDs, causing various complications such as myocardial infarction (MI), angina pectoris, and heart failure.[2] Moreover, according to the most recent report of the World Health Organization (WHO), the prevalence of CVDs and the need for coronary artery bypass graft (CABG) surgery will reach 14.7% by 2020.[3] A large number of patients with CAD who do not respond to drug therapies are candidate for CABG surgery.[4] After CABG surgery, the patients may be at risk of angina pectoris, MI, or even stroke. Therefore, adherence to

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1- MSc Student, Faculty of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran
2- Assistant Professor, Nursing and Midwifery Care Research Center, Faculty of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran
3- Associate Professor, Chamran Medical and Research Heart Center AND Department of Cardiac Surgery, Isfahan University of Medical Sciences, Isfahan, Iran
Address for correspondence: Sima Babaei; Assistant Professor, Nursing and Midwifery Care Research Center, Faculty of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran; Email: babaee@nm.mui.ac.ir

treatment and follow-up after surgery is very important.[5] Due to poor adherence to the treatment and rehabilitation plan, the physical health and quality of life (QOL) of some patients worsens after surgery. Thus, adherence to treatment is a major contributor to overall health and post-surgical treatment.[6] Adherence to treatment and management of risk factors were found to be weak at 1 year after CABG surgery.[7] In some chronic diseases, nearly 50% of people do not adhere to therapeutic activities.[8] Non-adherent patients are important for health delivery systems, because they need more care and attention, and symptoms of their disease may lead to increased rate of hospitalization.[9] Furthermore, a significant part of the success of surgery in the long term depends on adherence to treatment, which is essential to prevent the recurrence of CAD.[10] Adherence to treatment is also the result of an interactive relationship between the patient, the social environment, and the caregiver.[11] Thus, the provision of sufficient information to patients is a basic responsibility of health professionals. A systematic and scientific health education program needs an appropriate model.[12] Nurses have a key role in educating cardiovascular surgical patients regarding the management of their post-surgical care after discharge.[13] Training in different ways and in different people in appropriate conditions can have significant impact on modifying awareness and attitude as well as enhancing individuals' behavior and performance.[14] One of these educational models is the BASNEF (Belief, Attitude, Subjective Norm, and Enabling Factors) model. In this model, in addition to knowledge and attitudes, some factors such as enabling factors and subjective norms are also important in behavioral change processes (Figure 1).

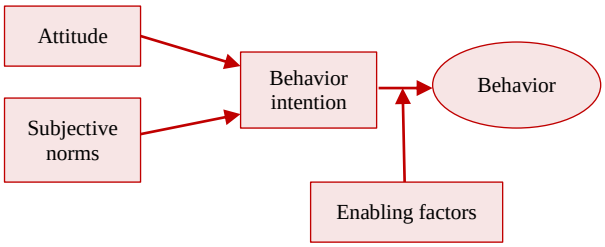

Figure 1. BASNEF model structure

This model is based on behavioral changes through some factors such as attitude (relatively systematic organization of beliefs about an object or position which prepares a person to react in a particular direction, enabling factors such as facilities, money, and skills that are necessary for realizing a behavior), behavioral beliefs (visible performance), and subjective norms (perceived social pressure based on which an individual follows the wishes of those who are more important to him/her than others).[15] The effectiveness of the BASNEF educational model has been confirmed in several studies.[16,17] Patients who undergo CABG surgery have a long history of CVD. Thus, it has significant effects on their lives and they should be adherent to a particular treatment plan. Post-operation adherence to treatment after CABG surgery is poor. In addition, lack of adherence to treatment leads to complications such as atherosclerosis, MI and angina pectoris, and eventually, heart failure.

It is argued that adherence to treatment after CABG surgery is very important. In patients with chronic CAD, lack of adherence to cardio protective medications (β-blockers, statins, and/or angiotensin-converting enzyme inhibitors) was associated with a 10% to 40% relative increase in risk of cardiovascular hospitalizations and a 50% to 80% relative increase in risk of mortality. Thus, adherence to medication or to a treatment plan is very important.[18] Therefore, the role of post-surgical education is significant. In this regard, education in the right framework and under suitable conditions can be effective. Some studies suggest that the use of appropriate and scientific training models by healthcare staff can be effective in empowering patients and their families. However, in addition to the patient's need for education, the presence of the patient's family is also important.[19] Furthermore, different variables affect adherence to treatment; researchers have categorized these variables into patient's personal characteristics, cognitive factors, and patient's interpersonal relationship with the medical team or his/her family.[20] According to studies and the importance of adherence to treatment in patients after CABG surgery, this study was performed to investigate the effect of an educational intervention based on the BASNEF model on adherence to post-surgical recommendations in these patients.

Materials and Methods

A randomized, controlled, clinical trial with parallel groups was conducted with two groups of intervention and control. The study group participants were selected from among patients undergoing CABG surgery. First, the purpose of the study was explained to all patients during discharge. Those who were willing to take part in the study were asked to provide a written consent form. The participants were chosen based on the inclusion criteria and through convenience

sampling. Next, each participant received a random numbered card and based on the number, whether it was odd or even, they were assigned to either the control or experimental groups. Sample allocation continued until the sample size reached the predetermined number (36 patients in the intervention group and 36 patients in the control group). The researcher, referring to the surgical ward in Chamran Hospital, Isfahan, Iran, selected the participants daily from 9 am to 6 pm, depending on the number of patients discharged. The protocol of this study was approved by the ethical committee of Isfahan University of Medical Sciences, Iran (IRCT20180729040629N1).

The inclusion criteria included the ability to communicate and speak Persian, lack of attendance in previous training sessions (any other studies relevant to this study), lack of history of heart surgery (first time surgery), and attendance of one family member in the training sessions. The exclusion criteria included lack of collaboration in training sessions, lack of attendance of a family member in the study sessions, and incidence of acute physical or psychological problems during training. Therefore, 2 patients in the experimental group were excluded from the study (1 patients did not attend classes, and 1 patients did not complete the questionnaires); thus, 34 patients were analyzed in the intervention group. In control group, 1 patient was excluded from the study (the patient did not complete the questionnaires before discharge); thus, 35 patients were analyzed in the control group. First, the purpose of the study was explained for the experimental and control groups, then, the training sessions were held for the experimental group. In order to observe ethical principles, the control group received only hospital discharge education and a post-operative care education booklet. The experimental and control groups completed the Modanloo Adherence to Treatment Questionnaire (MATQ) and a researcher-made questionnaire based on the BASNEF model before the educational intervention. Then, the 4, 40-minute educational sessions were conducted for patients in the intervention group during 4 weeks after discharge. The 36 patients were divided into groups of 4 patients (Figure 2). The educational sessions were performed each day of the week for a different group of patients. The first session was immediately after discharge. In the subsequent weeks, 3 other sessions were held.

The educational sessions based on BASNEF model consist of 6 phases. Phase 0 includes the initial assessment, familiarity with group members, brief statements of subjects for the intervention group (preliminary meeting).

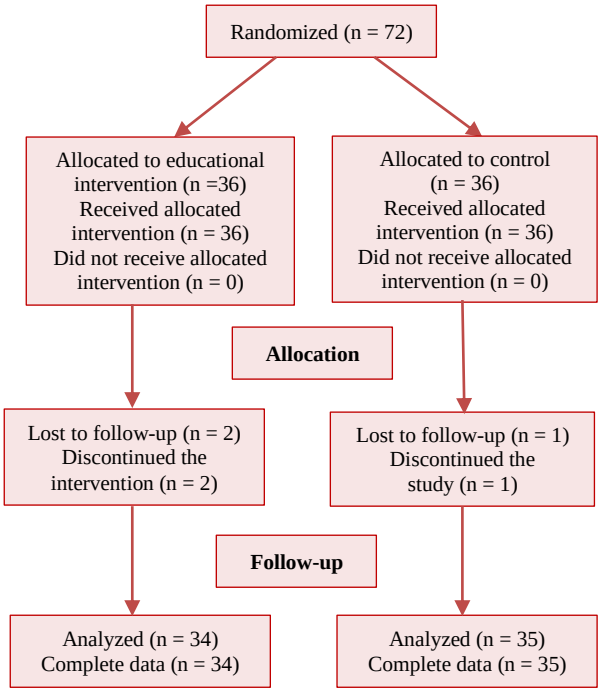

Figure 2. Patients flow in the control and intervention group

Phase I consists of increasing knowledge and changing the beliefs, attitudes, and behaviors of patients based on the educational model (Knowledge and attitude). Phase II includes the formation of behavioral intention based on the educational model (Behavioral intention). In phase III, the formation of subjective norms is addressed based on the educational model (Subjective Norms). In phase IV, the enabling factors based on the educational model and their impact on performance are explained (Enabling Factors), and phase V consists of the reviewing of the content of the previous sessions. In the educational sessions, recommendations about post-operative care were presented using PowerPoint, educational pamphlets, booklets, and videos. Furthermore, lectures, question and answer, group discussions, and problem-solving method were employed in the sessions for patients who had undergone CABG surgery to teach them self-care and management of post-surgery complications (Table 1). An educational package about post-surgical care recommendations and the researcher's telephone number were provided for patients so that they could contact the researcher if they had any problems during the intervention with regard to post-operative care.

Table 1. The content of the educational sessions in the intervention group for patients after coronary artery bypass graft surgery

Phase	Session number	Content of sessions
Phase 0: Initial assessment, familiarity with group members, brief statements of subjects for the intervention group (introduction)	Initial meeting	Greetings, introducing educators to patients and patients to each other, explaining the number of sessions and their structure for patients, completing of the consent form by patients, and completing of the questionnaires in the first stage before the intervention
Phase I: Increasing knowledge and changing the beliefs, attitudes, and behaviors of patients based on the educational model (Knowledge and attitude)	Session 1	A short speech about heart disease and explaining CABG surgery, Talking about the post-operative lifestyle to change the attitudes and beliefs of patients and encourage them to learn more about heart disease and heart surgery, and providing a definition of healthy nutrition after CABG surgery and a list of foods with a high salt content
Phase II: The formation of behavioral intention based on the educational model (Behavioral intention)	Session 2	Educating patients about healthy behavior after surgery and what is exactly expected of them, explaining the necessity of the cessation of high-risk behaviors such as smoking cigarettes and tobacco products, alcohol consumption, and use of canned foods, ready-made foods, and fast food due to their high fat and high salt content, explaining how drugs are used and the importance of adherence to regular drug use, explaining the side effects of the medications used by patients, educating them about the importance of blood pressure control and how to measure and record it, educating them on relaxation techniques in order to avoid stress and anxiety, and explaining correct exercise and its levels for post-operative patients based on consultation with the physician
Phase III: Formation of subjective norms based on the educational model (Subjective Norms)	Session 3	A meeting with a family member of the patient who has the greatest impact on the patient in managing their living conditions, talking about its role in improving the patient's healthy behavior and adherence to treatment after surgery
Phase IV : Explanation of enabling factors based on the educational model and their impact on performance (Enabling Factors)	Session 4 (in this sessions and all meetings)	Providing patients with a pamphlet and a booklet in order to continue education during the study, introducing patients to therapeutic centers where they can go if they need medical care, and providing them with the researcher's phone number in case they have a question during the study
Phase V: Evaluation	After 4 weeks of intervention	Reviewing the content of past sessions, and completing of the questionnaires on the last session by patients

CABG: Coronary artery bypass graft

Data were collected at 3 stages, before the intervention, after 4 weeks of educational intervention, and after 12 weeks for follow-up. Patients in both groups were contacted in order to collect data 12 weeks after the intervention and were asked to complete the MATQ and a researcher-made BASNEF model questionnaire.

The data collection tools used were the MATQ and a researcher-made BASNEF model questionnaire. The BASNEF model questionnaire includes 2 main sections, a demographic characteristics form and questions related to the educational model. The second section comprises (49 questions) the 4 subscales of knowledge (11 items; e.g., Do you know how CABG surgery is performed?), attitude (9 items; e.g., adherence to post-surgical care), behavioral intention (7 items; e.g., Had you earnestly decided to continue the treatment after CABG surgery?), subjective norms (5 items; e.g., To what extent will your family help you in post-surgical care?), and enabling factors (8 items; e.g., educational sessions about post-surgical care are available to me). All items are scored based on a 3-point Likert scale (yes = 3; I do not know = 2; no = 3). The validity of the BASNEF model questionnaire was confirmed by 10 experts in cardiac surgery, cardiac nursing, and health education of the School of Nursing and School of Health in Isfahan University of Medical Sciences. After the announcement of the results by the

professors, the necessary corrections were made. The content validity ratio (CVR) values of most of the items were higher than 0.70. Cronbach's alpha was used to determine the reliability of the questionnaire; the Cronbach's alpha of the constructs of knowledge, attitude, behavioral intention, subjective norms, and enabling factors was 0.80, 0.85, 0.82, 0.93, and 0.83, respectively. The Cronbach's alpha of the model constructs ranged from 0.75 to 0.83. Because the calculated Cronbach's alpha for each studied construct was higher than 0.70, it can be said that this tool's consistency is acceptable.

The MATQ consists of the 7 subscales (40 items) of focus on treatment (9 items; e.g., many treatments have become a part of my daily life; total score: 0-45), willingness to participate in treatment (6 items; e.g., I'm looking forward to the advice of the medical team; total score: 0-35), ability to adapt (7 items; e.g., before doing anything, I think about its impact on my illness; total score: 0-35), adapting the treatment with life plan (5 items; e.g., the more complex the treatment recommendations, the more difficult it will be to adapt it to the life plan; total score: 0-25), adherence to treatment (4 items; e.g., having different responsibilities does not keep me from continuing treatment; total score: 0-20), commitment to treatment (5 items; e.g., I maintain hope in the treatment by thinking about its positive aspects; total score: 0-25), and doubt in the implementation of treatment (3 items; e.g., contradictory recommendations from the treatment team prevent me from continuing treatment; total score: 0-15). The total score of adherence to treatment ranges from 0 to 200. The validity of the MATQ was 0.914, with a Cronbach's alpha of 0.921, and the reliability of the questionnaire was approved through test-retest reliability estimation for a 2-week interval (r = 0.858).[21]

The statistical analysis was conducted in SPSS statistical software (version 16; SPSS Inc., Chicago, IL, USA). The normality distribution of the quantitative data was determined using Kolmogorov-Smirnov test. Continuous and categorical variables were presented as mean ± standard deviation (SD) and absolute number (percentage), respectively. Independent t-test or Mann-Whitney U test were used for comparing normal and non-normal variables between groups. Chi-square test (or Fisher's exact test) was used for comparing categorical variables in groups. Repeated measures analysis of variance (ANOVA) was used to evaluate the intervention effect in time. Mauchly's sphericity test was used for testing sphericity and the Greenhouse-Geisser correction was used in the case of lack of sphericity. A P-value of less than 0.05 was considered significant.

Results

We enrolled 69 CABG patients in the study, 34 individuals in the intervention group and 35 in the control group. No significant difference was observe between the groups regarding age (P = 0.880), gender (P = 0.520), level of education (P = 0.150), occupation (P = 0.190), marital status (P = 0.990), and duration of the disease (P = 0.320), and cardiac risk factors such as diabetes (P = 0.730), hypertension (HTN) (P = 0.390), hyperlipidemia (P = 0.730), and smoking (P = 0.300). The average age of the participants in the intervention and control group was 62.06 ± 9.53 and 62.43 ± 8.39 years, respectively. All of the participants in the intervention (n = 34; 100%) and control group (n = 35; 100%) were married. In the intervention group, 17 (50%), 10 (24.9%), 7 (20.6%), and 0 (0%) participants were self-employed, retired, housewives, and employed, respectively. In the control group, 13 (37.1%), 7 (20%), 14 (20%), and 1 (2.9%) participants were, respectively, self-employed, retired, housewives, and employed. In the intervention group and control group, 12 (35.3%) and 15 (42.9%) participants were women, respectively. In the intervention group, 3 (8.8%), 21 (61.8%), 8 (23.5%), and 2 (5.9) participants were illiterate, and had a primary school education, high school diploma, and academic degree, respectively. In the control group, 7 (20%), 21 (60%), 7 (20%), and 0 (0%) participants were illiterate, and had a primary school education, high school diploma, and academic degree, respectively (Table 2).

At baseline, before the intervention, there were no significant differences in total score of the MATQ and its subscales between the two groups (P > 0.050) (Table 3).

Table 3 shows that after the intervention and at the 3-month follow-up, the mean score of the MATQ and the scores of focus on treatment, willingness to participate in treatment, ability to adapt, combining treatment with life, commitment to treatment, doubt in the implementation of treatment, and adherence to treatment increased in the intervention group compared to the control group (P < 0.001).

The results of within group analysis showed that the mean score of the MATQ and the scores of focus on treatment, willingness to participate in treatment, ability to adapt, combining treatment with life, commitment to treatment, doubt in the implementation of treatment, and adherence to treatment increased in the intervention group after the intervention compared to baseline (P < 0.050).

Table 2. Demographic characteristics and some clinical history variables in the intervention and control groups

Variables	Level	Intervention group (n = 34)		Control group (n = 35)		P*
		n (%)		n (%)		
Gender	Female	12	35.3	15	42.9	0.520
	Male	22	64.7	20	57.1	
Occupation	Employed	0		1	2.9	0.190
	Self-Employed	17	50.0	13	37.1	
	Retired	10	24.9	7	20.0	
	Housewives	7	20.6	14	40.0	
Education	Illiterate	3	8.8	7	20.0	0.150
	Primary school education	21	61.8	21	60.0	
	High school diploma	8	23.5	7	20.0	
	Academic degree	2	5.9	0	0.0	
Disease duration	Less than 1 month	11	32.4	5	14.3	0.320
	1 month to 11 months	11	32.4	16	45.7	
	1 year	2	5.8	4	11.4	
	More than 1 year	10	29.4	10	28.6	
Marital status	Married	34	100	100	35.0	0.990
	Single	0	0	0	0	
Diabetic disease (yes)	-	16	47.1	15	42.9	0.730
HTN (yes)	-	21	61.8	25	71.4	0.390
Hyperlipidemia (yes)	-	16	47.1	15	42.9	0.730
Smoking (yes)	-	7	20.6	4	11.4	0.300
Age (Mean ± SD)	-	62.06 ± 9.53		62.43 ± 8.39		0.880**

* Chi-square test (or fisher's exact test if needed), ** Independent t-test
SD: Standard deviation

According to the Bonferroni multiple comparison test, the mean total score of the MATQ at baseline was significantly lower than immediately after the intervention and 3 months after the intervention.

Table 3. Comparison of the mean score of adherence to treatment and its dimensions between the two groups

Variables	Groups	Before the intervention	After the intervention	3-month follow-up	P**
Total score	Intervention	122.20 ± 55.39$^{\lambda}$	163.19 ± 68.61$^{\epsilon}$	167.14 ± 59.17$^{\epsilon}$	< 0.001
	Control	128.36 ± 26.06	127.20 ± 65.80	127.13 ± 69.22	0.970
	P*	0.420	< 0.001	<0.001	< 0.001¥
Focus on treatment	Intervention	26.60 ± 99.30$^{\lambda}$	37.60 ± 3.35$^{\epsilon}$	37.30 ± 15.75$^{\epsilon}$	< 0.001
	Control	30.90 ± 47.65	30.60 ± 59.77	30.30 ± 54.78	0.980
	P	0.080	< 0.001	< 0.001	< 0.001¥
Willingness to participate in treatment	Intervention	24.05 ± 6.01$^{\lambda}$	31.40 ± 68.27$^{\epsilon}$	32.30 ± 41.35$^{\epsilon}$	< 0.001
	Control	22.70 ± 74.69	21.50 ± 49.23	21.30 ± 43.30	0.110
	P*	0.400	< 0.001	< 0.001	< 0.001¥
Ability to adapt	Intervention	22.40 ± 6.76$^{\lambda}$	29.40 ± 71.06$^{\epsilon}$	30.30 ± 00.82$^{\epsilon}$	< 0.001
	Control	24.70 ± 7.01	23.40 ± 57.23	22.20 ± 89.49	0.660
	P*	0.170	< 0.001	< 0.001	< 0.001¥
Combining treatment with life	Intervention	13.20 ± 76.59$^{\lambda}$	17.20 ± 35.72$^{\epsilon}$	16.10 ± 65.53$^{\epsilon}$	< 0.001
	Control	14.30 ± 41.83	14.20 ± 83.19	14.10 ± 97.27	0.710
	P*	0.410	< 0.001	< 0.001	< 0.001¥
Adherence to treatment	Intervention	12.30 ± 59.12$^{\lambda}$	16.30 ± 21.36$^{\epsilon}$	16.20 ± 91.15$^{\epsilon}$	< 0.001
	Control	13.50 ± 73.37	14.30 ± 03.18	14.20 ± 97.02	0.370
	P*	0.280	0.007	< 0.001	0.002¥
Commitment to treatment	Intervention	13.10 ± 74.88$^{\lambda}$	19.30 ± 47.24$^{\epsilon}$	20.30 ± 47.04$^{\epsilon}$	< 0.001
	Control	13.40 ± 11.18	13.20 ± 83.33	13.10 ± 31.94	0.220
	P*	0.430	< 0.001	< 0.001	< 0.001¥
Doubt in the implementation of treatment	Intervention	9.10 ± 35.76$^{\lambda}$	12.10 ± 24.84$^{\epsilon}$	14.10 ± 00.48‡	< 0.001
	Control	9.30 ± 73.47	9.20 ± 31.03	9.10 ± 57.87	0.570
	P*	0.570	< 0.001	< 0.001	< 0.001¥

Data are reported as mean ± Standard deviation (SD).
* P-value of between group comparisons obtained from two-sample t-test (or Mann-Whitney U where appropriate); ** P-value of within group comparisons; ¥ P-value for time group obtained from repeated measures analysis of variance; $^{\lambda, \epsilon, \ddagger}$ The results of Bonferroni multiple comparison test
The use of the same letter is illustrative of lack of statistical difference between the groups.

Moreover, the mean scores of focus on treatment, willingness to participate in treatment, ability to adapt, combining treatment with life, commitment to treatment, and adherence to treatment at baseline were significantly lower than after the intervention and 3 months after the intervention. The mean score of doubt in the implementation of treatment was significantly different between the intervention and control groups within all study ($P < 0.050$). There were no significant differences in the control group at different stages of the study ($P > 0.050$).

Furthermore, there were significant trend effect as interaction of time, and the group were statistically significant for score of total adherence to treatment and all subscales ($P < 0.050$). The scores increased in the intervention group, while little change was observed in the control group (Table 3).

According to the results presented in table 4, at baseline, there were no significant differences in BASNEF model constructs between the two groups ($P > 0.050$). An increase was observed in the mean score of knowledge, attitude, subjective norms, enabling factors, and behavioral intention after the intervention and at the 3-month follow-up in the intervention group compared to the control group ($P < 0.001$).

Moreover, there was an increase in the mean score of knowledge, attitude, subjective norms, enabling factors, and behavioral intention in the intervention group as a result of the intervention ($P < 0.050$); however, there were no significant differences in the mean scores of these constructs in the control group ($P > 0.050$).

The Bonferroni multiple comparison test showed that in the intervention group the mean scores of knowledge, attitude, subjective norms, enabling factors, and behavioral intention were significantly higher immediately after the intervention and 3 months after the intervention compared to before the intervention. Nevertheless, there was no significant difference in the scores of these constructs 3 months after the intervention compared to immediately after the intervention (Table 4).

Discussion

The results of the study indicated that the age range of patients in the intervention and control group was 40-83 years and 45-80 years, respectively. Therefore, there was no significant difference between the intervention and control groups in terms of mean age. This finding was in line with that of the study by Meng et al.[22] They also found no significant difference between the experimental and control groups in terms of gender, occupation, and education; all the participants in their study were also married.[22]

***Knowledge and Attitude*:** The mean score of knowledge of the patients was significantly higher immediately and 3 months after the intervention in intervention group compared to the control group. This means that an educational intervention with the appropriate model can increase patients' level of knowledge. This finding was in line with that of previous studies. Tol et al. found that patients' knowledge and attitude regarding blood pressure increased after the educational intervention.[23]

Table 4. Comparison of the mean scores of BASNEF model constructs between the two groups

Variables	Groups	Before the intervention	After the intervention	3-month follow-up	P**
Knowledge	Intervention	52.11 ± 27.19$^{\epsilon}$	95.17 ±45.23$^{\lambda}$	99.2 ± 47.17$^{\lambda}$	< 0.001
	Control	54.22 ± 55.59	55.14 ± 58.75	54.19 ± 75.21	0.970
	P*	0.600	< 0.001	< 0.001	< 0.001¥
Attitude	Intervention	89.70 ± 19.95$^{\epsilon}$	99.00 ± 83.97$^{\lambda}$	99.00 ± 83.97$^{\lambda}$	< 0.001
	Control	93.90 ± 12.38	94.50 ± 61.38	93.30 ±20.55	0.460
	P	0.060	< 0.001	< 0.001	0.002¥
Behavioral intention	Intervention	73.10 ± 87.69$^{\epsilon}$	88.19 ± 65.51$^{\lambda}$	89.13 ± 92.86$^{\lambda}$	< 0.001
	Control	76.17 ± 73.70	73.21 ± 15.76	73.18 ± 06.91	0.700
	P*	0.420	0.003	< 0.001	< 0.001¥
Subjective norms	Intervention	48.17 ± 24.14$^{\epsilon}$	91.19 ± 76.14$^{\lambda}$	94.10 ± 71.22$^{\lambda}$	< 0.001
	Control	46.24 ± 86.71	45.22 ± 14.93	45.40 ± 34.53	0.930
	P*	0.790	< 0.001	< 0.001	< 0.001¥
Enabling factors	Intervention	40.10 ± 29.06$^{\epsilon}$	95.70 ± 59.46$^{\lambda}$	93.60 ± 57.92$^{\lambda}$	< 0.001
	Control	39.23 ± 10.56	37.21 ± 14.42	38.14 ± 10.22	0.920
	P*	0.780	< 0.001	< 0.001	< 0.001¥

Data are reported as mean ± Standard deviation (SD).

* P-value of between group comparison obtained from two-sample t-test (or Mann-Whitney U where appropriate); ** P-value of within group comparison; ¥ P-value for time group obtained from repeated-measure analysis of variance; $^{\epsilon, \lambda}$ The results of Bonferroni multiple comparison test

The use of the same letter is illustrative of lack of statistical difference between groups.

In a study on education in relation to cardiac rehabilitation and patients' level of knowledge, it was found that patients' level of knowledge about heart disease had increased after the intervention,[24] which is in line with the current study findings. In the present study, the attitude of the patients had improved immediately and 3 months after the intervention. This indicates that this educational intervention can improve the knowledge and attitude of patients about surgery and conditions of care after CABG surgery.

Behavior intention, subjective norms, and enabling factors: The educational intervention was effective on behavioral intention in patients participating in the study; the mean scores of behavioral intention in the experimental group were higher immediately and 3 months after the intervention, but they did no differ in the control group. In the study by Sarayloo et al., the educational program based on BASNEF model increased the scores of knowledge, attitude, behavior intention, and performance in the experimental group.[25] As a result of the present study, subjective norms had increased in the patients in the intervention group after 4 weeks of educational intervention and at the 12-week follow-up. These findings are in accordance with that of other studies. Poshtchaman et al. reported an increase in the mean score of subjective norms in the intervention group after 4 weeks of intervention and at the 12-week follow-up in comparison with pre-intervention.[26] The mean score of the enabling factors increased in the intervention group in comparison with the control group after 4 weeks of educational intervention and at the 12-week follow-up. This illustrates that social protection of the family and friends and the adaptation of the treatment to the individual's living conditions will increase adherence to treatment after surgery.

Modanloo Adherence to Treatment Questionnaire and its subscales: The data indicated a significant difference in the mean score of the adherence to treatment subscale of the MATQ after 4 weeks of educational intervention and at the 12-week follow-up in the intervention group compared to the control group. In this regard, the results of the study by Wu et al. on heart failure patients also suggested that oral and written education along with the facilitation of education are effective in improving adherence to drug regimen,[27] which is in line with the findings of this study. Moreover, Aggarwal et al. and Gance-Cleveland also confirmed the importance of the presence of family members with the patient in receive training education.[28,29] In the present study, the mean score of the focus on treatment subscale of the MATQ increased immediately and 12 weeks after the intervention compared to pre-intervention in the intervention group. Moreover, the mean score of the willingness to participate in treatment subscale also improved immediately and 3 months after the intervention compared to pre-intervention. This finding suggests that patients' willingness to participate in the treatment adherence and drug therapeutic recommendation education course after the intervention had increased. The study of Lin et al. on risk factors after CABG confirmed this finding.[30] In this regard, the findings of the present study showed that the mean score of the ability to adapt subscale in the experimental group increased immediately and 3 months after the intervention compared to the control group. Similarly, the study by French et al. showed that the individual's ability to control him/herself in relation to these recommendations and to understand his/her condition are important factors in the patient's commitment to medical recommendations.[31]

The mean score of the doubt in the implementation of treatment subscale changed after the intervention and at the 3-month follow-up compared to pre-intervention. Furthermore, this score was higher 3 months after the intervention compared to immediately after the intervention. It can be concluded that the educational intervention based on the BASNEF model has influenced the subscale of doubt in the implementation of treatment in CABG patients immediately after the intervention, while this effect has not been constant after 3 months of follow-up in the intervention group.

This suggests that in addition to influencing the level of knowledge and attitude of patients, the educational intervention affected their level of performance in postoperative care which augmented their level of trust in the medical team. In this regard, a study on the factors related to non-adherence to medication has shown that adherence to treatment is affected by several factors and has various barriers.[32] These include socioeconomic factors (treatment costs), health system factors, disease characteristics, and patient-related factors (level of knowledge, attitude, and behavior intention). Therefore, in order to increase adherence to treatment, it is necessary to consider each of these problems and to resolve them. As in this study, the educational model was used to educate patients on various factors influencing treatment adherence, its results confirm the present study findings.[32]

The present study data indicate that the educational sessions in the framework of the

educational model for patients after CABG surgery also increased the total score of the MATQ and its subscales. In addition, the level of knowledge, attitude, behavioral intention, subjective norms, and enabling factors that include socioeconomic status increased in patients in the intervention group after the intervention. However, Chien et al. found that the need-based training of the patient and family in the intensive care unit led to increased knowledge and awareness, but did not have a significant impact on the level of dietary adherence.[33] The data of this study indicated that education based on the needs of patients and their family has a significant effect on various aspects of adherence to treatment. It seems that consideration of other aspects of adherence to treatment, in addition to adherence to diet, can also elevate the total score of adherence to treatment in patients after CABG surgery.

Conclusion

The purpose of this study was to implement an education program based on the BASNEF model and evaluate its effect on adherence to post-surgical treatment based on the MATQ. The results were obtained with the consideration of all the factors influencing the study period and the participants. The results of this study suggested that an educational intervention based on the framework of an appropriate model can increase the total score of adherence to treatment and the scores of focus on treatment, willingness to participate in treatment, ability to adapt, combining treatment with life, adherence to treatment, commitment to treatment, and doubt in the implementation of treatment. Moreover, it can increase the patients' scores in the model constructs (knowledge, behavioral intention, subjective norms, and enabling factors). After CABG surgery, patients need training and follow-up for postoperative care, which is the task of the medical team, especially nurses. Therefore, it is recommended that this educational model be used to improve care after CABG surgery, reduce postoperative complications, and improve adherence to treatment. Patients who have undergone CABG surgery experience changes in different aspects of their life, so the medical team, especially nurses, should know these factors and educate them based on their needs. This study shows that identifying the needs of patients and educating them after surgery based on an appropriate education model can affect patient's knowledge, behavior intention, attitude, subjective norms, and enabling factors. Thus, patients' adherence to treatment will improve after CABG surgery.

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Conflict of Interests

Authors have no conflict of interests.

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The factors related to hospitalization period in patients with acute myocardial infarction treated after primary percutaneous coronary intervention

Fardin Mirbolouk[(1)], Arsalan Salari[(1)], Mahboobeh Gholipour[(2)], Salman Nikfarjam[(2)], Reza Pourbahador[(2)], Hamideh Mohamadnia[(3)], Niloufar Akbari-Parsa[(2)]

Original Article

Abstract

BACKGROUND: Decreasing the hospital length of stay (LOS) in ST-segment elevation myocardial infarction (STEMI) after primary percutaneous coronary intervention (PPCI) is an issue which is related to reducing hospital costs. This study was aimed to determine the average number of hospital LOS among patients with STEMI treated by PPCI and predictors of longer LOS.

METHODS: This cross-sectional study was performed on 561 patients with STEMI who referred to Heshmat Hospital, Rasht, north of Iran, within 2015-2018. As soon as STEMI was detected, patients were transferred to the catheterization laboratory (cath lab) in the shortest possible time and underwent PPCI. A questionnaire including characteristics of patients, procedures, and in-hospital adverse events was completed. Data were analyzed with SPSS software.

RESULTS: The mean age of patients was 59.36 ± 11.90 years. 74.2% (n = 416) of subjects were men and 25.8% (n = 145) were women. The hospital LOS of 3 to 6 days had the highest prevalence up to 47%. The results of the multiple logistic regression showed that risk of hospital LOS > 6 days in unsuccessful percutaneous coronary intervention (PCI) was 33.2 versus 66.8 in successful PCI (P = 0.001). Moreover, the risk of hospital LOS > 6 days in subjects who had post-procedure complication, problems at admission, and primary comorbidities was 9.13 (7.22-11.53)-fold, 4.09 (2.86-5.85)-fold, and 1.75 (1.35-2.27)-fold more than those who had not, respectively

CONCLUSION: By identifying controllable predictive factors associated with prolonged hospitalization after PPCI, the length of hospitalization can be decreased; also, the patient remission can be enhanced and hospital costs reduced.

Keywords: Myocardial Infarction; Percutaneous Coronary Intervention; Length of Stay

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Introduction

ST-elevation myocardial infraction (STEMI) is the worst manifestation of acute coronary syndrome (ACS) after sudden cardiac death. In addition, the incidence of ischemic heart disease (IHD) in developing countries is rising.[1,2] Cardiovascular disease (CVD) is the first cause of death in Iran with a massive burden[3] which needs special clinical services that can be very costly.[4] IHD in Iran over the age of 40 is 14 in 100, and the rate of myocardial infraction (MI) in both sexes remains high.[5] We have beds deficiency about 30% to 40%, and this deficiency is high in some areas. Reduction in the number of inpatient days increases hospital profit with more efficient bed management. Therefore, determination of the factors associated with reducing hospitalization period is vital. Recently, primary percutaneous coronary intervention (PPCI) is the preferred therapeutic strategy in patients with STEMI that improves short and long-term results and can decrease

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1- Associate Professor, Cardiovascular Diseases Research Center AND Heshmat Hospital, Department of Cardiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
2- Assistant Professor, Cardiovascular Diseases Research Center AND Heshmat Hospital, Department of Cardiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
3- Cardiovascular Diseases Research Center AND Heshmat Hospital, Department of Cardiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
Address for correspondence: Niloufar Akbari-Parsa; Assistant Professor, Cardiovascular Diseases Research Center AND Heshmat Hospital, Department of Cardiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran; Email: niloufarakbariparsa@gmail.com

hospital length of stay (LOS).[6,7] This method has been associated with minimized risks of recurrent MI (reMI), intracranial hemorrhage (ICH), infarction-associated artery reocclusion, and myocardial ischemia.[8-10] In the current context, despite the rising cost of medical care, proper use of limited medical resources is important, and the hospital LOS is a determinable indicator for both the patient and the health care system. Identifying the predictors of long-term admissions can provide an opportunity to reduce the hospital LOS.[11] Long-term predictors include recurrent infarction, pulmonary edema, continuous hypotension, sustained ventricular tachycardia (VT), high-grade atrioventricular block (AV block), acute ventricular septal defect (VSD), frequent ischemia requiring emergency coronary artery bypass graft (CABG), ejection fraction (EF), insulin-dependent diabetes, transient ischemic attack (TIA) or cerebrovascular accident (CVA), sex, thrombolysis in myocardial infarction (TIMI) flow after PPCI, history of arrest during treatment, creatinine during admission, requiring anti-coagulant therapy or requiring intra-aortic balloon pump (IABP), and distance from the hospital.[10,12-14] Besides, geographic and hospital-dependent variables are important.[12] We aimed to determine the average number of hospital LOS among patients with STEMI treated by PPCI and evaluate the most important predictors of longer LOS in Heshmat Hospital, Rasht, north of Iran. Hence, by controlling the factors associated with the long-term admission of patients after PPCI, the length of hospitalization and subsequently contributing costs, manpower, and time in the health care system can be reduced.

Materials and Methods

This cross-sectional study was conducted on 561 patients with STEMI who were either referred to Heshmat Hospital or sent from other hospitals and were treated by PPCI after approval of Ethical Committee of Guilan University of Medical Sciences, Rasht (IR.GUMS.REC.1396.292). Sampling began in 2017 and continued until 2018. This paper was extracted from a specialty thesis (No.: 96072207) in Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences.

Also, considering the fact that patients were in 3 groups of short, intermediate, and long-term admission, the sample size of each of these subgroups is estimated at 187 people. Sample size was obtained by considering the error rate of 5% and the test power of 90% based on the performance curve for each group of about 186. Samples were collected in each group as available. The STEMI was diagnosed based on clinical symptoms including typical cardiac chest pain for more than 30 minutes and electrocardiographic (ECG) alterations with ST elevation of more than 1 mm in at least 2 continuous leads and more than 2 mm in 2 precordial leads or new left bundle branch block (LBBB). Patients with symptoms during the last 12 hours or sustained chest pain with ECG evidence of STEMI were included. As soon as STEMI was detected, patients were transferred to the catheterization laboratory (cath lab) and underwent PPCI. The LOS duration was calculated based on hours from moment of admission until the discharge order, divided on 24.

Patients with previous fibrinolytic therapy, death events during hospitalization, life expectancy lower than 1 year, those who needed IABP or required an emergent revascularization of non-infarct related artery [CABG or staged percutaneous coronary intervention (PCI)], as well as those who left the hospital before discharge with their own consent or transferred to another hospital for any reason were excluded.

A five-sectioned questionnaire including characteristics of the patient such as age and body mass index (BMI), comorbidities and past medical history, status and problems at admission, procedure success and complications, and post-PCI in-hospital events and complications was completed for each patient after signing the informed consent form.

Frequency and percentage were used to describe the qualitative data and mean and standard deviation (SD) were used to describe the quantitative data. Kolmogorov-Smirnov test (K-S test) was used for normality of groups. Chi-square test (for qualitative variables) and analysis of variance (ANOVA) test (for quantitative variables) were used to examine the relationship between groups. Multiple logistic regression test was performed to detect relationships between the independent variables in the presence of the other independent variables. Dependent variable in this model (length of hospital stay) was divided in two groups of less than 6 days and more than 6 days. The SPSS software (version 16, SPSS Inc., Chicago, IL, USA) was applied to perform statistical analysis. $P < 0.050$ was considered as statistically significant.

Results

The mean age of patients in the study was 59.36 ± 11.90 years. According to the age group classification, 25.7% of subjects (n = 144) were in the group of less than 50 years old, and 29.1% (n = 163), 28.5% (n = 160), and 16.8% (n = 94) of subjects were in the age groups of 51 to 60, 61 to 70, and above 70 years, respectively. 74.2% (n = 416) of subjects were men and 25.8% (n = 145) were women. Patient characteristics and procedure/in-hospital adverse events based on LOS groups are shown in table 1.

Table 1. Patient characteristics and procedure/in-hospital adverse events

Patient characteristics		LOS ≤ 3 days [n (%)]	LOS 3-6 days [n (%)]	LOS > 6 days [n (%)]	P*
Gender	Men	144 (77.0)	138 (73.8)	134 (71.7)	0.493
	Women	43 (23.0)	49 (26.2)	53 (28.3)	
Age (year)	< 50	53 (28.3)	59 (31.6)	32 (17.1)	0.003
	51-60	63 (33.7)	48 (25.7)	52 (27.8)	
	61-70	50 (26.7)	50 (26.7)	60 (32.1)	
	> 70	21 (11.2)	30 (16.0)	43 (23.0)	
BMI (kg/m^2)	< 19	0 (0)	1 (0.5)	0 (0)	< 0.001
	19-25	53 (28.3)	49 (26.2)	74 (39.6)	0.008
	25-30	120 (64.2)	109 (58.3)	96 (51.3)	
	> 30	14 (7.5)	28 (15.0)	17 (9.1)	
Education	Illiterate	38 (20.3)	49 (26.2)	72 (38.5)	0.017
	Primary	78 (71.7)	65 (34.8)	62 (23.2)	0.002
	Diploma	61 (32.6)	60 (32.1)	50 (26.7)	
	Higher	10 (5.3)	13 (7.0)	3 (1.6)	
Refer weekdays	Saturday-Wednesday	150 (80.2)	143 (76.5)	164 (87.7)	0.017
	Thursday-Friday	37 (19.8)	44 (23.5)	23 (12.3)	
Distance to the hospital	Saturday-Wednesday	150 (80.2)	143 (76.5)	164 (87.7)	0.840
	Thursday-Friday	37 (19.8)	44 (23.5)	23 (12.3)	
	< 30 minutes	98 (52.7)	96 (51.3)	88 (47.3)	
	30 minutes-2 hours	80 (43.0)	81 (43.3)	87 (46.8)	
	> 2 hours	8 (4.3)	10 (5.3)	11 (5.9)	
Refer season	Spring	49 (26.2)	39 (20.9)	48 (25.7)	0.024
	Summer	56 (29.9)	62 (33.2)	40 (21.4)	
	Autumn	45 (24.1)	54 (28.9)	44 (23.5)	
	Winter	37 (19.8)	32 (17.1)	55 (29.4)	
Admission time	6 AM-12 PM	33 (17.6)	45 (24.1)	40 (21.4)	0.332
	12 PM-6 PM	86 (46.0)	69 (36.9)	71 (38.0)	
	6 PM-6 AM	68 (36.4)	73 (39.0)	76 (40.6)	
DM		33 (17.6)	49 (26.2)	57 (30.5)	0.014
HTN		65 (34.8)	72 (38.5)	100 (53.5)	0.001
HLP		36 (19.3)	55 (29.4)	52 (27.8)	0.053
CVA/TIA		2 (1.1)	4 (2.1)	9 (4.8)	0.069
CKD		5 (2.7)	11 (5.9)	34 (18.2)	< 0.001
PD		2 (1.2)	5 (2.7)	4 (2.1)	0.523
PCI history		0 (0)	8 (4.3)	9 (4.8)	0.012
CABG history		5 (2.7)	2 (1.1)	7 (3.7)	0.249
IHD familial history		7 (3.7)	21 (11.2)	13 (7.0)	0.020
Smoking		65 (34.8)	77 (41.2)	73 (39.0)	0.430
Procedure/in-hospital adverse events					
Cardiogenic shock		0 (0)	0 (0)	8 (4.3)	< 0.001
Need to intubation		0 (0)	1 (0.5)	8 (4.3)	0.002
Heart arrest		0 (0)	0 (0)	5 (2.7)	0.006
Arrhythmia		0 (0)	9 (4.8)	13 (7.0)	0.002
Pulmonary edema		3 (1.6)	10 (5.3)	29 (15.5)	< 0.001
Kilip class	1	1 (33.3)	0 (0)	0 (0)	0.028
	2	0 (0)	9 (90.0)	20 (69.0)	
	3	2 (66.7)	1 (10.0)	7 (24.1)	
	4	0 (0)	0 (0)	2 (6.9)	
Heart rhythm during admission	Sinusoid	187 (100)	175 (93.6)	163 (87.2)	< 0.001
	VT	0 (0)	2 (1.1)	2 (1.1)	
	VF	0 (0)	7 (3.7)	11 (5.9)	
	AV block	0 (0)	3 (1.6)	11 (5.9)	
		Mean ± SD	Mean ± SD	Mean ± SD	
BMI (kg/m^2)		57.48 ± 10.91	58.12 ± 34.49	62.27 ± 11.74	
Education		26.71 ± 2.48	27.15 ± 3.16	26.28 ± 3.06	

* Chi-square test

LOS: Length of stay; BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipoproteinemia; CVA: Cerebrovascular accident; TIA: Transient ischemic attack; CKD: Chronic kidney disease; PD: Pulmonary disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; IHD: Ischemic heart disease; VT: Ventricular tachycardia; VF: Ventricular fibrillation; AV block: Atrioventricular block; SD: Standard deviation

As shown in table 1, patients with longer LOS were older and more frequently had prior diabetes (P = 0.014), hypertension (HTN) (P = 0.001), and chronic kidney disease (CKD) (P < 0.001). In addition, there was significant differences between LOS groups in terms of BMI (P = 0.008), education (P = 0.002), refer days (P = 0.017), and season (P = 0.024). There were also differences in procedural characteristics and in-hospital adverse events. Patients in the long LOS group were more likely to have cardiogenic shock (P < 0.001), heart arrest (P = 0.006), arrhythmia (P = 0.002), pulmonary edema (P < 0.001), or need intubation (P = 0.002). The frequency of AV block and ventricular fibrillation (VF) was higher among patients with long LOS versus sinus heart rhythm in short LOS group (P < 0.001) (Table 1).

The results of the study of infarct frequency distribution in patients with MI treated with primary angioplasty in LOS groups are shown in figure 1. The frequency of anterior MI was significantly higher in longer LOS group (P = 0.021).

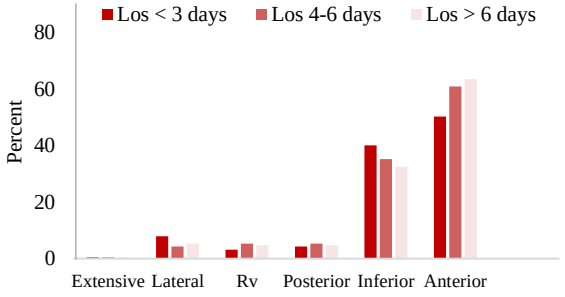

Figure 1. Length of stay (LOS) based on myocardial infarction (MI) anatomic location

Patients' admission variables based on LOS groups are shown in table 2. There was a statistically significant difference between the values of the variables of systolic blood pressure (SBP) (P < 0.001), diastolic blood pressure (DBP) (P < 0.001), EF (P = 0.001), creatinine (P < 0.001), glomerular filteration rate (GFR) (P < 0.001), and symptom onset (minutes) (P < 0.001) in LOS groups. SBP, DBP, EF, and GFR were lower in longer LOS group; creatinine and symptom onset were higher in longer LOS group.

The PCI findings among the three LOS groups are shown in table 3. There was a statistically significant difference between the frequency of the variables of post-PCI TIMI (P < 0.001), glycoprotein IIb/IIIa (GPIIb/IIIa) (P < 0.001), and involved arteries (P < 0.001) in LOS groups. Post-PCI TIMI among short, intermediate, and long LOS groups was 90.4%, 86.1%, and 67.4%, respectively. Also, for most of the patients with longer LOS, GPIIb/IIIa inhibitor had been used (67.6%).

The results of the study of frequency distribution of culprit artery types in patients with MI treated with primary angioplasty in LOS groups are shown in figure 2. The LOS status was statistically related to culprit artery type. Left anterior descending (LAD) and left circumflex (LCX) had higher frequencies in longer LOS groups.

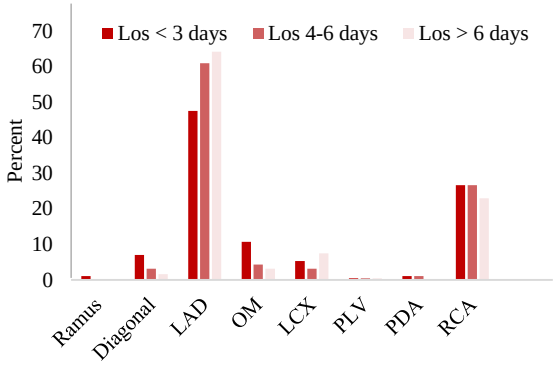

Figure 2. Length of stay (LOS) based on infarct-related artery

LAD: Left anterior descending; OM: Obtuse marginal; LCX: Left circumflex; PLV: Posterior left ventricular; PDA: Posterior descending artery; RCA: Right coronary artery

Table 2. Patients' admission variables based on length of study (LOS) groups

Variable	LOS < 3 days	LOS 3-6 days	LOS > 6 days	P*
	Mean ± SD	Mean ± SD	Mean ± SD	
SBP (mmHg)	138.17 ± 27.84	134.75 ± 26.95	126.63 ± 28.92	< 0.001
DBP (mmHg)	85.41 ± 13.80	82.51 ± 14.95	78.68 ± 17.03	< 0.001
Heart rate (bpm)	80.74 ± 12.91	81.57 ± 16.29	82.87 ± 20.10	0.461
LVEF (%)	39.79 ± 10.05	38.34 ± 9.30	35.99 ± 9.54	0.001
Creatinine (mg/dl)	0.98 ± 0.19	1.05 ± 0.24	1.14 ± 0.30	< 0.001
GFR (ml/min)	80.10 ± 9.21	76.85 ± 12.24	71.05 ± 14.80	< 0.001
Symptom onset (minute)	179.90 ± 157.90	179.10 ± 137.01	280.60 ± 382.50	< 0.001

* Analysis of variance (ANOVA)

LOS: Length of stay; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVEF: Left ventricular ejection fraction; GFR: Glomerular filteration rate; SD: Standard deviation

Table 3. Percutaneous coronary intervention (PCI) findings among the three lenght of study (LOS) groups

Variable		LOS < 3 days [n (%)]	LOS 3-6 days [n (%)]	LOS > 6 days [n (%)]	P*
Pre-PCI TIMI	0	137 (73.3)	129 (69.0)	131 (70.1)	0.527
	1	33 (17.6)	30 (16.0)	35 (18.7)	
	2	17 (9.1)	27 (14.4)	19 (10.2)	
	3	0 (0)	1 (0.5)	2 (1.1)	
Post-PCI TIMI	0	0 (0)	0 (0)	2 (1.1)	< 0.001
	1	1 (0.5)	4 (2.1)	4 (2.1)	
	2	17 (9.1)	22 (11.8)	55 (29.4)	
	3	169 (90.4)	161 (86.1)	126 (67.4)	
Collaterals	+	46 (24.6)	52 (27.8)	41 (21.9)	0.419
	-	141 (75.4)	135 (72.2)	146 (78.1)	
GPIIb/IIIa	+	91 (48.7)	97 (51.9)	125 (67.6)	< 0.001
	-	96 (51.3)	90 (48.1)	60 (32.4)	
Involved arteries	1	64 (34.2)	56 (29.9)	39 (20.9)	< 0.001
	2	89 (47.6)	67 (35.8)	69 (36.9)	
	3	34 (18.2)	64 (34.2)	79 (42.2)	

* Chi-square test

LOS: Length of stay; TIMI: Thrombolysis in myocardial infarction; PCI: Percutaneous coronary intervention; GPIIb/IIIa: Glycoprotein IIb/IIIa

The results of the multiple logistic regression are shown in table 4. The risk of length of hospital stay more than 6 days in unsuccessful PCI was 3.029 (2.31-3.97)-fold more than successful PCI. Also, the risk of length of hospital stay more than 6 days in subjects who had post-procedure complication, problems at admission, and primary comorbidities were 9.13 (7.22-11.53)-fold, 4.09 (2.86-5.85)-fold, and 1.75 (1.35-2.27)-fold more than those who had not, respectively. Furthermore, BMI had a significant role in the LOS in hospital. With increased BMI, LOS also increased.

Table 4. Variables in the equation of regression model

Variable	OR	95% CI	P*
Primary comorbidities	1.75	1.35-2.27	0.031
Successful PCI	3.02	2.31-3.97	< 0.001
Post-procedure complications	9.12	7.22-11.53	< 0.001
Problems at admission	4.09	2.86-5.85	< 0.001
Age group	0.90	0.81-1.00	0.359
BMI	1.56	1.28-1.89	0.016
Constant	0.23		0.110

* Multiple binary logistic regression

PCI: Percutaneous coronary intervention; BMI: Body mass index; OR: Odds ratio; CI: Confidence interval

The results of the study of frequency distribution of the number of coronary arteries involved in patients with MI treated with primary angioplasty in LOS groups are shown in figure 3. The three-vessel involvement was more frequent in the longer LOS group.

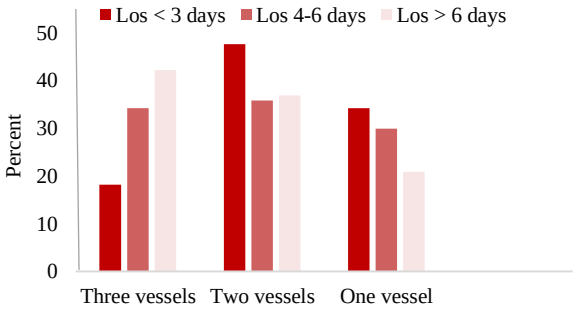

Figure 3. Length of stay (LOS) based on number of diseased coronary arteries

Discussion

The LOS of 3-6 days had the highest prevalence up to 47%, which was in accordance with the previous studies. Amazingly, the prevalence of other two groups was the same (26.5%). There are controversial studies about this issue that whether age is related to LOS periods.[15,16] In the current paper, the mean age of patients with LOS higher than 6 days was 62.27 ± 11.74. About 64.2% of patients with BMI of 25-30 kg/m^2 had the LOS > 6. In assessing the correlation between education and LOS, most of the illiterate patients had the highest LOS while the medium group had bachelor and higher education. In Germany, 19.1% of the patients who died due to MI had a low education and 13.1% had high education.[17] In the study by Ahmadi et al., the values were 34.0% and

11.0%, respectively.[18]

The distance between the place of residence and the hospital, as well as the time of admission throughout the day did not have a significant correlation with LOS. It seems that the admission in winter has a significant relation with long hospitalization. In our study, 30.5% of people with diabetes had a LOS of more than 6 days. In one study, there was a significant correlation between increased duration of hospitalization and diabetes.[19] Similarly, in another research, there was a correlation between the incidence of diabetes and LOS more than 5 days.[20] Also, 53.5% of people with HTN had LOS more than 6 days; whereas, Karabulut et al. reported that 73.0% of patients with HTN had a LOS longer than 72 hours.[19] Although we realized that just 29.4% of patients with hyperlipoproteinemia (HLP) had an average duration of admission, previous study showed that more than half of the people with HLP had an admission period of 72 hours.[19] In the study by Swaminathan et al., 65.3% of people with HLP had LOS less than 3 days, and this relationship was significant.[20] Only 9.1% of patients had a history of PCI. No patient who had discharged less than 3 days had a history of previous PCI. In the study by Isik et al., 15.4% of the people had a history of previous PCI, of which 7.8% had LOS less than 6 days and 6.6% had LOS of more than 6 days.[16] Only 7.5% of the patients had a history of CABG, of which 3.7% had LOS more than 6 days. Although 41.2% of our patients with a history of smoking had an average LOS, it does not seem a significant relation. In the study of Isik et al., 6% of smokers had LOS of less than 6 days.[16]

Regarding the incidence of complications at the time of admission and during PCI, pulmonary edema was the most frequent while cardiogenic shock and the need for intubation were the least frequent complications. In terms of infarction site, we found a significant correlation with the LOS, since more than half of the patients with anterior infarction had LOS more than 6 days. In Melberg et al.'s study, 43.0% of the patients had anterior infarction.[21] Similar to our findings, patients with anterior infarction had LOS more than 6 days which was significantly related.[16] The results of the data in terms of characteristics at the time of admission showed that the relation of all variables including SBP and DBP, heart rate per minute, left ventricular EF (LVEF), creatinine, GFR, and duration of onset of symptoms with LOS was significantly consistent with other researches.[16,19] The results showed that most of the patients who had only sinus heart rhythm had LOS less than 3 days. Patients with VT, VF, and AV block heart rhythms had an increased LOS. TIMI before PCI had no effect on LOS before angioplasty. However, TIMI after PCI was related to LOS. In culprit artery, the LAD was the most common involved vessel, and 64.0% of patients with LAD infarction had LOS more than 6 days. The right coronary artery (RCA) item also had the second highest incidence among patients in this study but did not directly affect the increase in LOS. In the study of Isik et al., the LAD item was the most common involved vessel and patients had LOS more than 6 days. Also, RCA did not have an effect on the LOS.[16]

Most of our patients with LOS more than 6 days required GP IIb/IIIa inhibitors and this relationship was significant. In the study of Melberg et al., the use of GP IIb/IIIa was associated with an increase in LOS, but this was not significant.[21] Patients with successful angioplasty in 90% of cases had LOS less than 3 days. In this study, increasing the duration of PCI increased the duration of hospitalization. Door-to-balloon duration and contrast volume did not have an effect on the increase in admission days. The most common complication was slow flow during PCI which had a direct relationship with LOS more than 6 days. The distribution of complications during hospitalization revealed that 94.7% of uncomplicated patients had short LOS during admission. In contrast, 39.0% of patients with kidney failure had long LOS. After that, vascular complications, anemia and the need for blood transfusion, and VT were the most frequent complications in our patients. Complications such as VF, thrombocytopenia, reocclusion, pericardial effusion, and reMI were less frequent, but there was a relationship between the incidence of these complications and the duration of admission. There was no relationship between other complications and hospitalization time.

Therefore, it is suggested that this study be carried out in a great sample size in other provinces so that better studies could be found in Iran. The impossibility of comparing the results of our study with other hospitals and examining the variables of the hospital such as scientific level, financing, and annual PPCI were the limitations of this study.

Conclusion

It seems that the proper use of medical facilities and resources in the current situation is a priority. The LOS, bed occupancy rate (BOR), and average patient's stay are the main economic indicators for reducing health care costs in the country. Also, identifying

related factors such as comorbidities, BMI, PCI failure, having post-treatment complications, and clinical symptoms and problems during admission can lead to minimizing overuse of medical resources and maximizing the patient's remission.

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Conflict of Interests

Authors have no conflict of interests.

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The comparison of procedural and clinical outcomes of thrombolytic-facilitated and primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction (STEMI): Findings from PROVE/ACS study

Maryam Soleimani[1], Azam Soleimani[2], Hamidreza Roohafza[1], Nizal Sarrafzadegan[1], Marzieh Taheri[1], Ghasem Yadegarfar[3], Maedeh Azarm[1], Neda Dorostkar[4], Hajar Vakili[1], Masoumeh Sadeghi[2]

Original Article

Abstract

BACKGROUND: There is still a controversy in the preferred method of reperfusion in acute ST-segment elevation myocardial infarction (STEMI), when the achievement of well-defined "golden time" is difficult. We sought to evaluate the procedural and in-hospital outcomes of the strategy of "thrombolytic administration and rescue or routine percutaneous coronary intervention (PCI)" versus "primary PCI (PPCI)" strategy in acute STEMI.

METHODS: In this observational prospective study, the data of 237 patients with acute STEMI presented or referred to Chamran Cardiovascular Research Center in Isfahan, Iran, were collected (PROVE/ACS study). Baseline characteristics, thrombolysis in myocardial infarction (TIMI) flow grade of infarct-related artery (IRA), left ventricular ejection fraction (LVEF), and in-hospital outcomes were evaluated.

RESULTS: The mean age of patients was 61.4 ± 13.0 years, 86.9% were men, 13.1% were diabetic, and 67.9% had anterior STEMI. Patients in the "thrombolytic then PCI" group were younger, more smoker, more often male with higher body weight and lower systolic blood pressure (SBP). The pre-PCI TIMI flow grade 3 was more often seen in the "thrombolytic then PCI" group (39.4% vs. 21.0%, P < 0.001) and less thrombectomy was performed in this group of patients (12.9% vs. 26.7%, P = 0.011). Time to reperfusion was significantly longer in PPCI group (182.4 ± 233.7 minutes vs. 44.6 ± 93.4 minutes, respectively, P < 0.001). No difference in mortality, mean of LVEF, and incidence of atrial fibrillation (AF) was observed in two groups.

CONCLUSION: If the PPCI strategy could not be performed in the golden time, the strategy of thrombolytic administration and rescue or routine PCI leads to more initial IRA patency and less thrombectomy with similar clinical outcomes.

Keywords: ST Segment Elevation Myocardial Infarction; Percutaneous Coronary Intervention; Thrombolytic Therapy; Treatment Outcome; Reperfusion

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Introduction

ST-segment elevation myocardial infarction (STEMI) is the most serious type of acute coronary syndromes (ACS). Primary percutaneous coronary intervention (PPCI) is the treatment of choice according to the recent guidelines on the management of STEMI if it could be accomplished in the golden time (less than 120 minutes from symptom onset) and in an experienced center.[1,2]

Decision on the type of reperfusion is made based on many factors such as the presence of well-defined local STEMI management strategy,

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1- Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Interventional Cardiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Address for correspondence: Azam Soleimani; Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; Email: asoleimanii@gmail.com

individual patient factors, team experience, and hospital facilities but "the time elapsed from symptom onset and the time delay to reperfusion" are the main factors for choosing between thrombolytic therapy and PPCI as the preferred reperfusion strategy.[2-4] Some studies have proposed that very early thrombolysis works as PPCI in efficacy and outcomes.[5-7] Fibrinolytic-based facilitated percutaneous coronary intervention (PCI) (immediate transfer to PCI after early fibrinolysis) was associated with more patent infarct-related artery (IRA) and better pre-PCI thrombolysis in myocardial infarction (TIMI) flow in most trials.[7-9] In the Alliance for Myocardial Infarction Care Optimization (AMICO) registry, this strategy reduced the mortality and combined endpoints.[9] More recent studies showed increased infarct size and event rates with fibrinolytic-based facilitated PCI compared to PPCI, in spite of better pre-PCI TIMI flow.[8] The comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial demonstrated lower 5-year mortality in patients with STEMI who received thrombolytic therapy within 2 hours of symptom onset compared with PPCI.[10] In the Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial, fibrinolysis during 3 hours of symptom onset in patients who could not be transferred for PPCI within 1 hour of first medical contact (FMC) was associated with slightly better primary endpoints in spite of increased intracranial hemorrhage (ICH).[5]

Regarding the available data, evaluation of the outcome of each reperfusion strategy in the regions with long distance to PCI-capable hospital is necessary. There is a lack of evidence about the time delay to both reperfusion treatments, procedural (angiographic), clinical, and in-hospital outcomes of acute STEMI in Middle East region, especially in Iran. In this study, we aimed to compare the outcomes of patients with acute STEMI who were managed with thrombolytic therapy then rescue or routine PCI versus PPCI strategy in a referral high-volume PCI-capable hospital in Iran. The findings of such study can provide the valid data to provide local guidelines in the management of acute STEMI.

Materials and Methods

The data of this observational prospective study was derived from "Persian Registry Of cardioVascular disease/Acute Coronary Syndrome (PROVE/ACS)".[11] In the STEMI registry, an observational prospective study from October 2015 to October 2016, the demographic, clinical, laboratory, electrocardiographic (ECG), echocardiographic, and angiographic data and in-hospital course of all patients with acute STEMI presented or referred to the three main hospitals of Isfahan, Iran, were consecutively collected. Follow-up was done until hospital discharge. Medical interview, physical examination, and laboratory assays were performed by trained health personnel, using a validated questionnaire, calibrated instruments, and a standard protocol.[11] An external auditor team evaluated the data periodically and randomly. The study protocol was approved by the Research Ethical Committee of Isfahan University of Medical Sciences, Isfahan, and all patients provided written informed consent.

In this study, the data of 237 patients with acute STEMI presented or referred to Chamran Cardiovascular Medical and Research Center in Isfahan, Iran, were used. The acute STEMI diagnosis was made based on the third universal definition of myocardial infarction (MI). Acute STEMI was diagnosed if ST-segment elevation at the J point ≥ 0.1 mv was seen in two contiguous leads. The cut points in V2-V3 leads were defined as ≥ 0.25 mv in men < 40 years, ≥ 0.2 mv in men ≥ 40 years, and ≥ 0.15 mv in women.[12] Patients with glomerular filtration rate (GFR) < 30 and patients who refused coronary angiography were excluded. All demographic, past medical history, physical examination, and ECG data [heart rate, rhythm abnormalities such as atrial fibrillation (AF) and location of STEMI] of the patients were recorded at presentation. History of diabetes mellitus (DM) was defined as fasting plasma glucose (FPG) ≥ 126 mg/dl or already taking anti-diabetic medications. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dl, total cholesterol (TC) ≥ 200 mg/dl, triglyceride (TG) ≥ 150 mg/dl, high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dl in men or < 50 mg/dl in women, or receiving its medications.[13] The body mass index (BMI) was calculated with this formula: body weight (kg) divided by height (meter) to the power of two.

Participants who used at least one cigarette per day were considered as current smokers**.** History of heart failure (HF) was defined as left ventricular ejection fraction (LVEF) ≤ 40% or history of admission due to HF symptoms. The presence of left main (LM) stenosis (stenosis > 50%), the number of diseased vessels (stenosis > 75% diameter), TIMI

flow grade before and after PCI, and procedural outcomes were assessed by two blinded interventional cardiologists. Echocardiography during the first 24 hours of admission was performed with an expert echocardiographer.

Patients with acute STEMI in the study were placed in two groups:

1- Thrombolytic then PCI strategy group (lytic then PCI group): these patients were admitted in a non-PCI-capable hospital at first. In the first hospital, the patients without contraindication to thrombolysis [such as active bleeding, recent ischemic stroke, history of ICH, history of major trauma or surgery within 30 days, uncontrolled hypertension (HTN), chronic oral anticoagulation, active malignancy, and pregnancy] had received loading dose of chewable aspirin (325 mg), clopidogrel (300 mg in patients < 75 years, 75 mg in patients ≥ 75 years), and standard dose of thrombolytic agent [either reteplase (10 units + 10 units intravenous (IV) boluses given 30 minutes apart) or streptokinase (1500000 units during 90 minutes) based on local availability] and then had been transferred to the Chamran Cardiovascular Medical and Research Center (a referral high-volume PCI-capable hospital) with an equipped ambulance. In this center, the patients underwent emergent catheterization if the chest pain and ST-segment elevation was not resolved. If there was no residual chest pain and ST-segment resolution of ≥ 75% was achieved, the routine PCI strategy, preferably but not exclusively, within 24 hours of symptom onset was performed.

2- PPCI strategy group (PPCI group): these patients were presented to Chamran Cardiovascular Medical and Research Center [by themselves or Emergency Medical System (EMS)] and were transferred for primary PCI, after loading dose of chewable aspirin (325 mg) and clopidogrel (600 mg). At the catheterization laboratory, 5000 units of unfractionated heparin (UFH) was administered in IV form and PCI of the IRA was performed if the culprit lesion in IRA had ≥ 75% stenosis or TIMI flow < grade 3. Administration of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, performance of thrombectomy, and type of stent were on the decision of the expert interventional cardiologist team that performed the procedure.

Data entry was done using EPI Info (version 6). Data were analyzed by SPSS software (version 15, SPSS Inc., Chicago, IL, USA). Statistical significance was assessed at a level of 0.05 (two-tailed). Quantitative variables were represented as mean ± standard deviation (SD) and compared by independent samples t-test or Mann-Whitney U test where normality assumption did not exist. Normality assumption was checked using Kolmogrov-Smirnov test (K-S test). The Wilcoxon signed-rank test was used to compare changes in TIMI flow before and after PCI in patients with STEMI. Qualitative variables were represented as frequency (percentage) and chi-square test or Fisher's exact test was used whenever appropriate.

Results

The data of 237 patients with acute STEMI were analyzed in two groups of lytic versus PPCI. The mean age of patients was 61.4 ± 13.0 years. Two hundred and six patients (86.9%) were men and 31 patients (13.1%) were diabetic. History of HF and previous MI was observed in 34 (14.7%) and 35 (15.5%) patients, respectively. Of 237 patients, 161 patients (67.9%) had anterior STEMI and in the remaining (76 patients, 32.1%), STEMI occurred in other locations (inferior, lateral, posterior). Baseline characteristics and data of initial presentations of the patients in both groups are presented in table 1. Patients in the thrombolytic group were younger, more smokers, more often men with higher body weight (without difference in BMI) and lower systolic blood pressure (SBP). A trend to more history of HF was observed in PPCI group (18.8% vs. 10.4%, P = 0.072) that were more often in killip class of one or two (Table 1).

Table 2 represents comparison of clinical and angiographic outcomes of patients with STEMI in both groups. The time to reperfusion was significantly longer in the PPCI group compared with lytic group (182.4 ± 233.7 minutes vs. 44.6 ± 93.4 minutes, respectively, P < 0.001). The prevalence of one, two, and three-vessel disease in the patients with acute STEMI was 107 (45.1%), 80 (33.8%), and 47 (19.8%), respectively. LM stenosis was observed in 3 patients, one had no involved vessels, and 2 (0.8%) were unknown. Thrombectomy was performed in 45 (19.0%) patients [22 (14.9%) of anterior MI vs. 23 (31.5%) of other MI, P = 0.004], significantly less often in thrombolythic then PCI group [odds ratio (OR): 0.40, 95% confidence interval (CI): 0.20-0.83]. After adjustment for age and sex, the difference remained significant (OR: 0.37, 95% CI: 0.18-0.77). Mean LVEF of the patients was 37 ± 12% (32 ± 10% in anterior vs. 46 ± 9% in other MI, P < 0.001).

Table 1. Baseline characteristics of patients with ST-elevation myocardial infarction (STEMI)

Baseline variables	Primary PCI (n = 121)	Thrombolytic then PCI (n = 116)	P
Sex (male)	100 (82.6)	106 (91.4)	0.040*
Killip class > 3	1 (4.5)	2 (16.7)	0.270**
DM	35 (32.7)	27 (27.6)	0.420*
Dyslipidemia	34 (37.8)	35 (37.2)	0.930*
Smoking	42 (35.0)	60 (51.7)	0.010*
History of previous MI	21 (18.4)	14 (12.5)	0.210*
HF	22 (18.8)	12 (10.4)	0.070*
AF at entrance	3 (2.5)	2 (1.7)	> 0.999**
History of CABG	2 (1.7)	2 (1.8)	> 0.999**
Location of current MI (anterior)	78 (64.5)	83 (71.6)	0.240*
Weight (kg)	73.5 ± 12.7	78.8 ± 13.3	0.010††
BMI (kg/m^2)	26.3 ± 4.4	26.6 ± 3.9	0.210††
Age (year)	64.8 ± 13.6	57.9 ± 11.4	< 0.001††
Baseline heart rate	79.9 ± 23.7	77.4 ± 21.1	0.470††
Baseline SBP	135.5 ± 27.8	122.7 ± 22.3	< 0.001††
Earliest Hb	14.6 ± 1.9	14.5 ± 1.7	0.620†

Data are presented as mean ± standard deviation (SD) or frequency and percentage

* Chi-square test was used; ** Fisher's exact test was used; † Independent samples t-test was used; †† Mann-Whitney test was used

PCI: Percutaneous coronary intervention; DM: Diabetes mellitus; MI: Myocardial infarction; HF: Heart failure; AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; BMI: Body mass index; SBP: Systolic blood pressure; Hb: Hemoglobin

Table 3 shows the TIMI flow before and after PCI in the study population. The TIMI flow grades after PCI were significantly improved in both groups with more than 95% of all patients with STEMI reaching the TIMI flow grade 2 and 3 after PCI. The pre-PCI TIMI flow grade was significantly better in the group of "thrombolytic then PCI" (TIMI flow grade 3, 39.4% vs. 21.0%, P < 0.001).

Three patients died during hospitalization, two of them had anterior MI, and all of them were in the "thrombolytic then PCI" group. There were no reports of significant vascular access site complication and ICH or extracranial hemorrhage.

Discussion

This observational prospective study was a well quality controlled registry with validated data of patients with acute STEMI presented in Chamran Cardiovascular Medical and Research Center in Isfahan. In this study, patients who received thrombolytic therapy then transferred for PCI were younger, mostly men, more smokers, with higher body weight, lower SBP, and a trend to less history of HF compared with PPCI patients. In this group, pre-PCI TIMI flow was better and less thrombectomy was performed. Time to reperfusion was significantly longer in PPCI group. No difference in final LVEF, incidence of arrhythmia, HF, and in-hospital mortality was seen.

Table 2. Clinical and procedural outcome of patients with ST-elevation myocardial infarction (STEMI)

Clinical and procedural variables		Primary PCI	Thrombolytic then PCI	P
Number of diseased vessels	0	0 (0)	1 (0.9)	0.400*
	1	60 (49.6)	47 (41.2)	
	2	37 (30.6)	43 (37.7)	
	3	24 (19.8)	23 (20.1)	
	LM	0 (0)	3 (2.7)	
Identifiable culprit lesion		121 (100)	108 (95.6)	0.030*
Thrombectomy		32 (26.7)	13 (12.9)	0.010**
AF during admission		2 (1.7)	3 (2.8)	0.670*
Any hemodynamic support		2 (1.7)	4 (3.9)	0.420*
Mortality		0 (0)	3 (2.6)	0.120*
Mean time delay to reperfusion (minutes)		182.4 ± 233.7	44.6 ± 93.4	< 0.001††
LVEF		36.0 ± 13.0	37.0 ± 10.0	0.210††

Data are presented as mean ± standard deviation (SD) or frequency and percentage

* Fisher's exact test was used; ** Chi-square test was used; †† Mann-Whitney test was used

PCI: Percutaneous coronary intervention; LM: Left main; AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction

Table 3. Thrombolysis in myocardial infarction (TIMI) flow before and after percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI)

TIMI flow		Primary PCI	Thrombolytic then PCI	P
Before PCI	0	60 (50.4)	27 (27.3)	< 0.001*
	1	18 (15.1)	5 (5.1)	
	2	16 (13.4)	28 (28.3)	
	3	25 (21.0)	39 (39.4)	
After PCI	0	0 (0)	1 (1.0)	0.371**
	1	5 (4.2)	3 (3.0)	
	2	26 (22.0)	29 (29.3)	
	3	87 (73.7)	66 (66.7)	
P		< 0.001††	< 0.001††	-

Data are presented as frequency and percentage
* Chi-square test was used; ** Fisher's exact test was used; †† Wilcoxon signed-rank test was used
PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction

PPCI is the preferred method of reperfusion if it could be accomplished in a timely fashion.[1,2] Performing reperfusion in the "golden time" is essential, regarding the flat curve of mortality benefit with reperfusion after the first 3-4 hours of symptom onset.[14] Achievement of reperfusion via PPCI with an experienced operator in the "golden time" in many countries is a problematic issue.

In this observational study, patients in the lytic group had higher baseline risk profile, except for the younger (mean of 6.9 years) age at presentation.

In the Leipzig Immediate Prehospital Facilitated Angioplasty in STEMI (LIPSIA-STEMI) trial, patients with STEMI presented < 3 hours from symptom onset were randomized and compared in two groups: lytic-facilitated PCI (pre-hospital lytic) versus PPCI.[8] In line with our results, pre-PCI TIMI flow was better in the lytic-facilitated PCI group, but contradictory with our study, the trial showed a trend to worse infarct size, more early and late microvascular obstruction (MVO) in cardiovascular magnetic resonance (CMR), and 30 days event rate in the lytic-facilitated PCI group. The thrombolytic agent that was used in the LIPSIA-STEMI trial was tenecteplase that was not available in our country.

In the STREAM trial, patients within 3 hours of symptom onset who could not underwent PPCI during 1 hour of FMC, were candidate for lytic therapy (tenecteplase) and rescue or routine PCI in 24 hours.[5] The primary end points of death, shock, congestive HF (CHF), and reinfarction at 30 days in this group were similar with patients in the PPCI group. The increased incidence of ICH in older age was disappeared after the dose reduction of tenecteplase.[5] Higher IRA patency, lower time to reperfusion, and similar 12-month outcomes with this pharmaco-invasive strategy was achieved in a Korean study.[15] The results of STEPP-AMI trial (a prospective, observational, multicenter study comparing tenecteplase facilitated PCI versus primary PCI in Indian patients with STEMI) were matched with our study in more IRA patency, less thrombus with similar 30 days and 2 years clinical end points, and major bleeding in lytic-facilitated PCI compared with primary PCI.[7,16]

In a meta-analysis of lytic-facilitated PCI in comparison with PPCI, lower incidence of cardiogenic shock, higher stroke rates, and similar mortality rates was observed.[17] There are multiple trials and expert opinions that proposed similar outcomes using lytic-facilitated PCI compared with PPCI in patients with acute STEMI for whom PPCI could not be performed in the golden time even in the elderly.[6,18-20]

This study was a prospective observational report of patients with acute STEMI presented to Chamran Cardiovascular Medical and Research Center with delicate protocols for data collection and external evaluation. In this study, the strategy of "lytic then PCI" had similar clinical outcomes with less performance of thrombectomy and better pre-PCI TIMI flow compared with PPCI strategy. The mortality rate was too low to evaluate the difference statistically. The limitations of this study were the absence of tenecteplase as the preferred specific thrombolytic agent in our center, time delays in performing PPCI, limitations in exact time recall of the patients, and lack of funds for evaluation of infarct size with advanced imaging modalities. The low number of cases and the limited occurrence of adverse events such as mortality and hemorrhagic complications prevented us to find significant difference between groups. Long-term follow-up of the patients will clarify the outcomes in the future.

Conclusion

In the countries that achievement of well-defined "golden time" in PPCI strategy is difficult, the strategy of thrombolytic administration and rescue or routine PCI remains a good alternative option with very promising results in the trials. The concerns about increased stroke and bleeding risk can be eliminated with careful adjustment of the lytic and antithrombotic doses and meticulous patient selection for the strategy. Performance of reperfusion as soon as possible from symptom

onset is essential and the better outcome is accessible with pre-hospital fibrinolysis. The findings of this study can provide the valid data to provide local guidelines in the management of acute STEMI in regions with long distance to a PCI-capable hospital.

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Conflict of Interests

Authors have no conflict of interests.

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Clinical outcomes of ultrathin strut biodegradable polymer-coated everolimus-eluting stent in patients with coronary artery disease

Suresh V. Patted[1], Ashok S. Thakkar[2]

Original Article

Abstract

BACKGROUND: Evermine 50™ (Meril Life Sciences Pvt. Ltd., India) everolimus-eluting stent system (EES) is a novel ultrathin strut (50 µm) cobalt-chromium coronary drug-eluting stent (DES) platform with biodegradable polymer coating. The Evermine 50 EES-KLES study aimed to evaluate the Evermine 50 EES in terms of 24-month clinical safety and performance in patients with coronary artery disease (CAD).

METHODS: This retrospective study consisted of 171 patients (258 lesions) implanted with Evermine 50 EES for managing CAD. We analyzed the major adverse cardiac events (MACE) incidence, defined as a composite of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization (ID-TLR) at 6-, 12-, and 24-month follow-up.

RESULTS: A total of 171 patients were included with a mean age of 57.85 ± 10.05 years, of which, 139 (81.29%) were men, 69 (40.35%) were hypertensive, and 70 (40.94%) were diabetic. The incidence of MACE was 1 (0.58%), 3 (1.81%), and 4 (2.42%) at 6-, 12-, and 24-month follow-up, respectively. There were three cases (1.82%) of cardiac death and one case (0.61%) of ID-TLR up to 24 months. None of the patients was presented with definite or probable stent thrombosis (ST).

CONCLUSION: This study demonstrated that implantation of ultrathin strut Evermine 50 EES resulted in a low rate of incidence of MACE, indicating a favourable clinical safety and performance profile of Evermine 50 EES in patients with CAD [Clinical Trials Registry-India (CTRI) Number: CTRI/2017/09/009939)].

Keywords: Coronary Artery Disease; Drug-Eluting Stent; Everolimus; Percutaneous Coronary Intervention

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Introduction

The clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) are notably improved after the introduction of second-generation drug-eluting stents (DES). This improvement could be attributed to a reduced risk of restenosis, myocardial infarction (MI), and stent thrombosis (ST) by second-generation DES. As a result, quality of life was better in patients with coronary artery disease (CAD) implanted with second-generation DES as compared to bare-metal stents (BMS) and first-generation DES. However, the persistent presence of durable polymers in the case of first-generation DES provokes chronic inflammatory responses that may lead to delayed endothelization of the stent and positive vessel remodeling, as a consequence of which, the risk of very late ST (VLST) increased. In addition, rate of ST was elevated in thicker stent strut which disrupts the laminar flow and induces flow turbulence, and thereby, activates platelets due to high shear stress.[1,2] With this, the research focus shifted to develop an ultrathin strut biodegradable polymer DES, which provides similar controlled release of a drug but with subsequent degradation of the polymers. Presently, everolimus-eluting stents (EES), of all the available DES, are the most frequently used. The DESSOLVE III and EXCELLENT trials established the non-inferiority of EES to sirolimus-eluting stents (SES) and superiority to paclitaxel-eluting stents in the meta-analysis of SPIRIT trial series.[3-5]

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1- Professor, Department of Cardiology, KLE Academy of Higher Education & Research, Belagavi, Karnataka, India
2- Head, Department of Clinical Research, Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India
Address for correspondence: Ashok S. Thakkar; Head, Department of Clinical Research, Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India; Email: ashok.thakkar@merillife.com

The Evermine 50™ (Meril Life Sciences Pvt. Ltd., India) is an ultrathin strut (50 μm) with biodegradable polymer-based EES system. The Evermine 50 EES-KLES study aimed to evaluate the 24-month clinical safety and performance of the Evermine 50 EES in all-comer patients with CAD.

Materials and Methods

The Evermine 50 EES-KLES was a retrospective, single-arm, all-comers, and single-center study conducted at the KLE Academy of Higher Education and Research (KLE University), Belagavi, India, between April 2016 and December 2016. We included all-comer patients aged > 18 years with CAD. Patients with a history of allergic reaction or hypersensitivity to everolimus, heparin, polymer lactide, cobalt-chromium metal alloy, and glycolide anti-platelet drugs (clopidogrel, prasugrel, etc.), and/or those who refused or were not willing to sign informed consent form were excluded from the study.

The study complied with the Declaration of Helsinki and was approved by the institution's local ethics committee. All included patients provided written informed consent. The trial is registered at Clinical Trials Registry-India (CTRI/2017/09/009939).

The Evermine 50 EES, an ultrathin strut (50 μm) that uses a cobalt-chromium platform, has a unique hybrid design of open and closed cells coated with biocompatible and bioabsorbable polymers, poly-L-lactic acid (PLLA), and poly-lactic-co-glycolic acid (PLGA), which elutes 1.25 μg everolimus per square millimeter of the stent surface area. The available lengths of Evermine 50 EES are 8, 13, 16, 19, 24, 29, 32, 37, 40, 44, and 48 mm, and diameters of the same are 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, and 4.50 mm.

Procedures and post-intervention medications: The PCI procedure was performed according to the current standard guidelines.[6] Before catheterization, all patients were administered with aspirin (75-100 mg) and a loading dose of clopidogrel (300 mg). To maintain intra-procedural activated clotting time of > 250 seconds, intravenous heparin (70-100 units/kg) was administered. Dual antiplatelet therapy of clopidogrel (75 mg/day) or prasugrel (10 mg/day) and aspirin (75-150 mg/day) was administered to all patients after the procedure for 1 year. Beyond one year, following the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, patients were switched to mono antiplatelet therapy.[7]

The clinical outcome, major adverse cardiac events (MACE), was defined as a composite of cardiac death, MI, and ischemia-driven target lesion revascularization (ID-TLR) at 6-, 12-, and 24-month follow-up. MI was defined as the presence of ischemic symptoms, elevation in cardiac enzymes, and/or new electrocardiography changes compatible with MI. ID-TLR was defined as repeated PCI or coronary artery bypass grafting of the target vessel associated with ≥ 50% diameter reduction together with documented ischemia. The definition of the Academic Research Consortium was used to classify ST.[8] Procedural success was defined as technical success with no MACE noted within 24 hours of the index procedure.

Baseline characteristics and follow-up: The baseline characteristics assessed included age, sex, medical history, co-morbidities like diabetes mellitus (DM), hypertension (HTN), chronic obstructive pulmonary disease, history of angina, previous MI, coronary heart disease, and indication for percutaneous transluminal coronary angioplasty (stable angina, unstable angina). The left ventricular function was assessed by two-dimensional (2D) echocardiography. Lesion and procedure characteristics included the target vessel locations, CAD (single/double/triple vessel disease), lesion location, and stent length and diameter. The clinical follow-up was performed at 6, 12, and 24 months.

Based on previously-published studies,[9] the sample size was estimated to be 171 patients, assuming MACE proportion about 4%. The sample size of 171 patients provided the following two sided 95% confidence interval with 0.035 half width (Wilson), 5% alpha and a power of 85%. Categorical variables were represented as frequency and percentages. Continuous variables with normal distribution were represented as mean ± standard deviation (SD). Statistical analyses were performed using the SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Event-free survival rates were constructed using the Kaplan-Meier method.

Results

Baseline demographic characteristics: Between April 2016 and December 2016, 171 patients (139 men, mean age: 57.85 ± 10.05 years) were treated for CAD with Evermine 50 EES. Among these patients, 70 (40.94%) had DM and 69 (40.35%) had HTN. Majority of patients presented with ST-elevation MI (STEMI) (n = 75, 43.86%), followed by unstable angina (n = 42, 24.56%). Baseline demographic

characteristics of the included patients are listed in table 1.

Table 1. Baseline demographic characteristics

Characteristics	Patients (n = 171)
Patient demographics	
Age (year) (mean ± SD)	57.85 ± 10.05
Gender (male) [n (%)]	139 (81.29)
Baseline medical history [n (%)]	
DM	70 (40.94)
HTN	69 (40.35)
COPD	2 (1.17)
Family history of CAD	31 (18.13)
History of angina	15 (8.77)
Previous MI	27 (15.79)
Cardiac status before index procedure [n (%)]	
Stable angina	6 (3.51)
Unstable angina	42 (24.56)
STEMI	75 (43.86)
NSTEMI	20 (11.70)
Asymptomatic	28 (16.37)
LVEF (%) (mean ± SD)	49.19 ± 8.32

DM: Diabetes mellitus; HTN: Hypertension; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; MI: Myocardial infarction; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; LVEF: Left ventricular ejection fraction; SD: Standard deviation

Lesion characteristics: A total of 246 studied stents were implanted during the index procedure. Procedural success was obtained in all patients. More than half of the total patients (n = 100, 58.48%) presented single vessel disease while nearly one-third of patients (n = 55, 32.16%) presented double vessel disease and rest of the patients (n = 16, 9.36%) had triple vessel disease. The lesion characteristics at baseline are summarized in table 2.

Clinical outcomes: Clinical follow-up was completed in 165 (96.49%) patients at the 24-month follow-up. MACE was reported in 4 (2.42%) patients including 1 (0.61%) ID-TLR and 3 (1.82%) cardiac deaths at the 24-month follow-up. None of the patients experienced probable or definite ST. The detailed clinical events are illustrated in table 3.

Table 2. Lesion and procedural characteristics

Characteristics	Patients (n = 171)
Target vessel locations [n (%)]	
LAD	121 (49.19)
RCA	67 (27.24)
LCX	55 (22.36)
Left main	3 (1.22)
Lesion characteristics [n (%)]	
Single vessel disease	100 (58.48)
Double vessel disease	55 (32.16)
Triple vessel disease	16 (9.36)
Post-procedure TIMI III flow	258 (100)
Total number of lesions	258
Total number of study stents implanted	246
Stent per patient	1.43
Occlusion (%) (mean ± SD)	88.39 ± 9.30
Average stent length (mm) (mean ± SD)	23.04 ± 7.01
Average stent diameter (mm) (mean ± SD)	3.14 ± 0.37

LAD: Left anterior descending artery; RCA: Right coronary artery; LCX: Left circumflex artery; TIMI: Thrombolysis in myocardial infarction; SD: Standard deviation

The cumulative MACE-free survival, determined by the Kaplan–Meier method, was 97.66% (Figure 1).

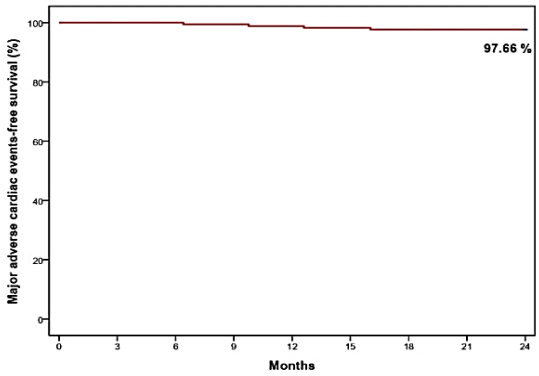

Figure 1. Kaplan-Meier event-free survival rate at 24-month follow-up

Table 3. Cumulative clinical events at 6-, 12-, and 24-month follow-up

Events	6 months (n = 171) [n (%)]	12 months (n = 166) [n (%)]	24 months (n = 165) [n (%)]
All-cause death	4 (2.34)	5 (3.01)	8 (4.85)
Cardiac death	1 (0.58)	2 (1.20)	3 (1.82)
Non-cardiac death	3 (1.75)	3 (1.81)	5 (3.03)
MI	0 (0)	0 (0)	0 (0)
ID-TLR	0 (0)	1 (0.60)	1 (0.61)
ID-TVR	0 (0)	0 (0)	0 (0)
Definite or probable ST	0 (0)	0 (0)	0 (0)
MACE	1 (0.58)	3 (1.81)	4 (2.42)

MI: Myocardial infraction; ID-TLR: Ischemia-driven target lesion revascularization; ID-TVR: Ischemia-driven target vessel revascularization; ST: Stent thrombosis; MACE: Major adverse cardiac events

Discussion

The clinical outcomes of the present study provided confirmation that Evermine 50 EES was safe and effective in all patients with CAD. The possible occurrence of CAD in all-comer patients was due to a high prevalence of DM (40.94%) and HTN (40.35%). Almost one half of patients had double and triple vessel disease. Despite all challenges, procedural success was reported in 100% of cases. Currently, the implantation of DES is the primary treatment choice for coronary artery stenosis.

However, ST has become an important safety issue. Several mechanisms of late ST and VLST have been proposed, including delayed endothelialization, chronic inflammation of arteries, hypersensitivity reactions, and incomplete stent apposition with vessel remodelling. These limitations of BMS and durable polymer DES can be resolved by employing ultrathin strut biodegradable polymer stents.[10-12] Recently, there was an additional confirmation by meta-analysis that newer generation of ultrathin strut DES was related with a 16% reduction in MACE and lower rate of ST as compared to thicker strut DES.[13] Despite the "all-comers" trial design of the present study, the absence of ST and only four patients with MACE at 24-month follow-up showed favourable clinical outcomes of Evermine 50 EES.

The unique design of Evermine 50 EES allows improved arterial healing, reduced blood flow perturbance, faster endothelialisation, and reduced in-stent restenosis.[14,15] In the BIOSCIENCE randomized trial, ultrathin strut biodegradable polymer SES were non-inferior to the reference of thin-strut durable polymer EES in terms of the safety and efficacy of outcomes by the end of 12 months.[16] A previously-reported study demonstrated that the implantations of coronary stents with thinner struts were associated with a reduced risk for angiographic and clinical restenosis when compared to the stent with thick struts.[17] The inflexible stents have resulted in the progression of thicker neointima when compared to flexible stents.[18] Hence, newer ultrathin biodegradable polymer DES was developed to improve the clinical outcomes in a complex type of lesions.

The low incidence of MACE was due to lower severity of disease in approximately 60% of patients at 24-month follow-up (Table 4). ID-TLR and cardiac death were 0.61%, and 1.82%, respectively, and none of the patients experienced any ST at 24-month follow-up. No death was reported due to ST, sudden death, progressive heart failure, and MI.

These 24-month clinical outcomes data demonstrated that apparent clinical benefit was primarily attributable to a reduced risk of MACE rate and ST consequences. However, this conclusion requires further studies with long-term follow-up evidence.

Table 4. Illustrative comparison between the current study population and historic cohorts from previous trials with other drug-eluting stents

Variables	Evermine 50	MiStent[19]	BioMatrix[20]	Nobori[21]	Synergy[22]	Orsiro[22]	Orsiro[23]
Clinical trial	Evermine 50 EES-KLES	DESSOLVE II	COMFORTABLE AMI Trial	NEXT	BIO-RESORT	BIO-RESORT	BIONYX
Number of patients	165	120	575	1617	1172	1169	1245
Strut thickness (µm)	50	64	120	112	74-81	60 or 80	
Polymer type	Biodegradable	Biodegradable	Biodegradable	Biodegradable	Biodegradable	Biodegradable	
Drug	Evermine	Sirolimus	Biolimus	Biolimus	Everolimus	Sirolimus	
Clinical follow-up	24-month	24-month	24-month	24-month	24-month	24-month	
Clinical outcomes [n (%)]							
Cardiac death	3 (1.82)	2 (1.7)	17 (3.0)	37 (2.3)	17 (1.5)	15 (1.3)	20 (1.6)
MI	0 (0.0)	3 (2.5)	7 (1.3)*	59 (3.7)	34 (2.9)	36 (3.1)	39 (3.2)
ID-TLR	1 (0.61)	2 (1.7)#	17 (3.1)	68 (4.4)#	27 (2.4)#	25 (2.2)#	41 (3.4)
ST	0 (0.0)	1 (0.0)	18 (3.2)	27 (1.7)	11 (1.0)	7 (0.6)	13 (1.1)
MACE	4 (2.42)	8 (6.7)	33 (5.8)	--	76 (6.5)	68 (5.8)	107 (8.6)

Clinically driven TLR, *Target-vessel reinfarction

MI: Myocardial infarction; ID-TLR: Ischemia-driven target lesion revascularization; ST: Stent thrombosis; MACE: Major adverse cardiac events

A few limitations of the study need to be acknowledged. First, this was a retrospective, single-center, single-arm study that included a small patient population without a control group for direct comparison. Second, this study provided the safety and efficacy of outcomes of the study stent at short-term follow-up. Third, we did not evaluate the factors associated with MACE in our patients. Hence, further large, prospective, randomized, and multicenter studies are needed to validate the safety and efficacy of Evermine 50 EES.

Conclusion

At the 24-month follow-up, the results depict, the favorable safety and performance of the ultrathin strut biodegradable polymer Evermine 50 EES. However, further evidence in the form of long-term follow-up data or prospective randomized controlled trials is required to compare Evermine 50 EES to the equivalent standard DES.

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Conflict of Interests

Authors have no conflict of interests.

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The effects of nanomicelle of curcumin on the matrix metalloproteinase (MMP-2, 9) activity and expression in patients with coronary artery disease (CAD): A randomized controlled clinical trial

Marzieh Mogharrabi[1], Hamid Reza Rahimi[2], Shima Hasanzadeh[1], Mostafa Dastani[3], Reza Kazemi-Oskuee[4], Saeed Akhlaghi[5], Mohammad Soukhtanloo[6]

Original Article

Abstract

BACKGROUND: Coronary artery disease (CAD) is the most common type of cardiovascular disease. Increasing the expression and activity of matrix metalloproteinases (MMPs) facilitates vascular remodeling and cardiovascular complications. Curcumin (the active ingredient of turmeric) is a potent natural anti-inflammatory agent, with cardiovascular protective effects. The present study was a clinical trial for investigating the effects of curcumin on activity and gene expression of MMP-2 and MMP-9 in patients with CAD.

METHODS: In this study, 70 patients with CAD (with 40%-50% stenosis) were randomly divided into two groups of curcumin (80 mg nanomicelle per day) and placebo. The intervention lasted 3 months. The activity levels of MMP-2 and MMP-9 in serum samples of patients were measured using gelatin zymography assay before and after the intervention. MMP-2 and MMP-9 gene expression in peripheral blood mononuclear cells (PBMCs) was also analyzed using real-time polymerase chain reaction (PCR). Statistical significance was set at $P < 0.0500$.

RESULTS: After 3 months of medication, the expression of MMP-9 produced by PBMCs significantly decreased in the curcumin group (0.811 ± 0.25) in comparison with the placebo group (2.23 ± 0.94) ($P < 0.0001$). Furthermore, the zymographic analysis showed that the administration of curcumin significantly inhibited the activity levels of MMP-2 (12469.7 ± 5308.64 pixels) and MMP-9 (14007.2 ± 5371.67 pixels) in comparison with that in patients receiving placebo (MMP-2: 17613.8 ± 5250.68 pixels; MMP-9: 20010.1 ± 3259.37 pixels) ($P < 0.0500$).

CONCLUSION: Our results show that curcumin can significantly reduce the expression and activity of MMP-2 and MMP-9. Because of the anti-inflammatory effects of curcumin, this compound can be considered as a new strategy for the prevention of cardiovascular events.

Keywords: Curcumin; Matrix Metalloproteinases; Coronary Artery Disease

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Introduction

Coronary artery disease (CAD) is an epidemic disease that will be the single most important disease in terms of mortality, disability, and cost in the world until 2020.[1] Atherosclerosis is currently considered as a chronic and progressive disease in the onset of which the important pathological mechanisms of oxidative stress within the vessel wall and processes are involved.[2]

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1- Associate Professor, Department of Clinical Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2- Assistant Professor, Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
3- Associate Professor, Cardiovascular Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
4- Associate Professor, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
5- Assistant Professor, Psychiatry and Behavioral Sciences Research Center AND Department of Psychiatry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
6- Associate Professor, Pharmacological Research Center of Medicinal Plants AND Department of Clinical Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Address for correspondence: Mohammad Soukhtanloo; Associate Professor, Pharmacological Research Center of Medicinal Plants AND Department of Clinical Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; Email: soukhtanloom@mums.ac.ir

The atherosclerotic lesion is formed due to lipoprotein particles accumulation in the intima of the coronary artery wall and gradually develops into the fibrous plaque, which is rich in extracellular matrix (ECM) proteins. It has now been well established that among many proteases, matrix metalloproteinases (MMPs) are the key enzymes in the transformation of the ECM in physiological and pathological conditions that involve inflammatory processes, such as arthritis, cancer, periodontal diseases, and cardiovascular disease (CVD).[3]

MMPs are a homologous family of calcium-dependent and zinc-containing endopeptidases. Gelatinases (MMP-2, MMP-9) are a subgroup of MMPs which have attracted much attention due to their electrolytic capabilities and elevated levels in cardiovascular lesions.[4] The decomposition of ECM components through the activity of these enzymes reduces the size of the plaque and increases its instability. In addition, gelatinases increase the infiltration of immune-inflammatory cells through direct breaking down of the base membrane and provide the conditions for angiogenesis by stimulating the proliferation of endothelial cells. All of these factors are associated with the growth of plaque and its increased sensitivity to rupture.[5] During the accumulation of platelets, MMP-2 is transferred from the cytosol to the platelets and is released. Therefore, MMP-2 is involved not only in the formation of plaque, but also in its development through its effect on platelet aggregation and the formation of thrombosis. Interestingly, most risk factors ultimately lead to the activation of MMPs. Cigarette smoking, diabetes, high homocysteine, and high lipid uptake cause oxidative stress in intima and media layers of the arteries and ultimately activate MMPs.[6] Given the crucial role of MMPs in atherosclerosis, agents that can suppress MMPs have the potential to be preventive factors in the development of atherosclerosis.

The last decade has witnessed a growing interest in the use of plant-derived products known as phytochemicals. These compounds are used as preventative and therapeutic agents in a wide range of diseases.[7]

One such agent, curcumin or diferuloylmethane (Figure 1), the main component of turmeric, has been shown to be pharmacologically safe and to be involved in the suppression of MMPs in molecular researches. It also suppresses the effects of various inflammatory stimuli. Today, in order to increase the biocompatibility of this compound, new strategies are being used such as the use of adjuvants like Piperine, which prevent the glucuronidation of curcumin, and use of liposomal curcumin, and curcumin nanoparticles and analogs.[8,9] In curcumin nanoparticles, all particles of curcumin have been captured in the hydrophobic section of nanomicelles. These nanomicelles increase the solubility of curcumin in water. After oral administration, soft gel remain intact in the acidic stomach and enter the small intestine. The transfer of curcumin from the water layer at the epithelial cell surface is facilitated by these nanomicelles and the oral absorption of curcumin is increased.[10,11]

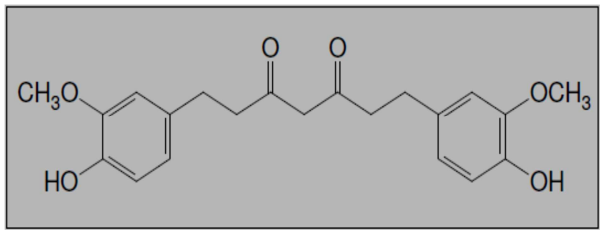

Figure 1. Chemical structure of curcumin

According to recent reports, curcumin is highly pleiotropic, and thus, it can interact with many contributing molecules in the inflammation pathway. Curcumin regulates transcription factors, cytokines, kinases, sticky molecules, regenerative status, and enzymes associated with inflammation.[12] Since irregular inflammatory response plays a major role in the pathogenesis of many CVDs, especially atherosclerosis, the inhibition of inflammatory pathways may be one of the protective mechanisms of curcumin in the cardiovascular system.[13]

Singh and Aggarwal were the first to show that curcumin suppresses the activation of nuclear factor (NF)-β from various inflammatory stimuli.[14] The suppression of this factor suppresses the expression of NF-α-dependent genes that mediate proliferation, invasion, and angiogenesis.[15]

In this study, we tried to find out whether the anti-inflammatory effect of nanomicelle curcumin also involves the inhibition of these MMPs by studying the effect of nanomicelle curcumin on the production of MMP-2 and MMP-9 by peripheral blood mononuclear cells (PBMCs) and their activity in the serum of atherogenic patients with CAD who receive curcumin (medical follow-up indication) as add-on-therapy.

Materials and Methods

The nanomicelle capsules of curcumin (Exir Nano Sina Company, Tehran, Iran), were developed in the Nanotechnology Research Center of Mashhad University of Medical Sciences, Mashhad, Iran

(IRC: 1228225765). Ribonucleic acid (RNA) isolation kit, complementary DNA (cDNA) synthesis kit, and real-time polymerase chain reaction (PCR) kit were purchased from Pars Toos Company, Iran. All other reagents and sterile plastic products were purchased from reliable companies.

The present study was a double-blind randomized clinical trial. All patients and the cardiologist, who followed the patients, were blinded to the treatment until the end of the study.

Subjects who were included in this study were men and women over the age of 18 years who were diagnosed with CAD by the selected cardiologist and consented to participate in this study. Based on angiographic findings, 70 patients with CAD (less than 50% obstruction in their coronary arteries) were selected from the department of cardiology of Ghaem Hospital, Mashhad, Iran. All subjects were randomly assigned to either the nanocurcumin (as nanomicelle 80 mg/day) or placebo-treated group (control condition) using a fixed randomization scheme based on random numbers provided by a computer software. After the screening process, randomization procedures, and diet and lifestyle training were done face-to-face. The subjects were informed that two interventions were being evaluated according to figure 2.

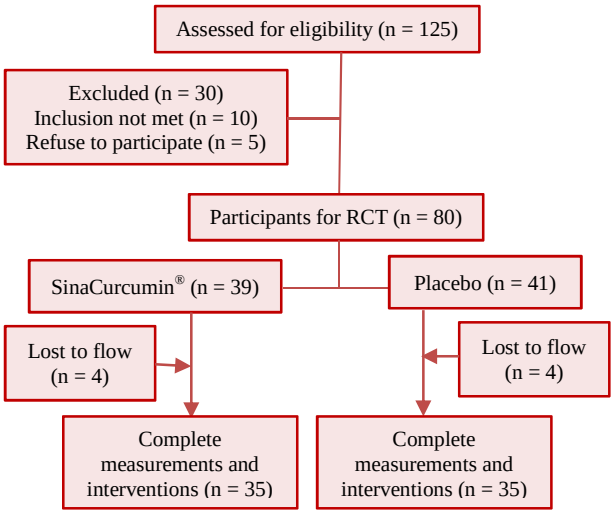

Figure 2. Flow chart of participation and study design
RCT: Randomized controlled trial

The shape and size and all other parameters of the placebo were the same as the other group; the same company provided them for us, without drug as control condition. Sample size was calculated using the frequency data of previous studies,[16-18] with 80% power, 5% level of significance, and a SD of 35.3. We enrolled at least 35 subjects in each treatment group.

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences. A double-blind, randomized, placebo-controlled, add-on clinical trial (the curcumin was added to the recommended medical therapies; Registration code: IRCT2013081114330N1) was conducted in Mashhad University of Medical Sciences.

Procedures and variables assessment

Inclusion and exclusion criteria: Subjects who were included in the present study were diagnosed with CAD by the selected cardiologist, men and women of older than 18 years of age, and they understood the study procedures and agreed to participate in the study. The exclusion and inclusion criteria were similar to those described in the study by Rahimi et al.[19]

Blood samples were obtained an early morning after overnight fasting 3 months after the end of treatment. Blood samples (10 ml) were collected into plain Vacutainer™ tubes, and then, centrifuged (4000 RPM, 4 minutes) for plasma and blood cell separation.

The treatment group received the nanomicelle capsules of curcumin at a dose of 80 mg/day for 3 months. The second group received capsules containing glycerin as a placebo at the same time. At the beginning and end of the treatment period, 10 ml blood samples were collected into plain heparin Vacutainer™ tubes. The samples were evaluated for the activity and expression of MMP-2 and MMP-9. Blood samples were processed using Ficoll to collect the PBMCs; 5 ml of blood sample was added to centrifuge tubes containing 5 ml of Ficoll. After centrifugation for 20 minutes at a rate of 2000 RPM, the plasma layer and PBMC layer could be isolated to evolute the enzyme activity and expression, respectively.

RNA isolation and Real-Time PCR: RNA isolation, cDNA synthesis, and Real-Time PCR were done.

After the total RNA extraction from PBMCs according to the instructions provided on the kit, cDNA synthesis was performed using the cDNA synthesis kit according to the company's instructions. Real-time PCRs were carried out to evaluate the expression of the MMP-2 and MMP-9 genes. Duplicate tests were performed for each gene. The primers used in this experiment are presented in table 1. These primers were designed using the software Primer3 and PubMed database. All results of gene expression were normalized against the β-actin as housekeeping gene. The relative fold change of messenger RNA of MMP2, 9 calculated with 2-ΔΔ CT method. The data used as a relative quantification strategy for quantitative real-time polymerase chain reaction analysis and compared with other groups.

Table 1. Primer sequences used for the quantitative polymerase chain reaction

Primer sequence	Gene name
5'-AACTACGATGACGACAGCAAGT-3'	Forward primer for *MMP-2*
5' -AGGTGTAAATGGGTCCCATCA-3'	Reverse primer for *MMP-2*
5' -CCTGCCAGTTTCCATTCATC-3'	Forward primer for *MMP-9*
5' -GCCATTCACGTCGTCCTTAT-3'	Reverse primer for *MMP-9*
5'-GATCAAGATCATTGCTCCTCCTG-3'	Forward primer for *β-actin*
5'-CAAGAAAGGGTGTAACGCAACT-3'	Reverse primer for *β-actin*

Zymography: Zymography is an electrophoretic technique used for the detection of hydrolytic enzymes. The sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) was copolymerized with a protein substrate such as gelatin, casein, or fibrin. Gelatin zymography was used to detect enzyme degrading gelatin, MMP-2, and MMP-9. The gelatin embedded in polyacrylamide gel digested by active gelatinases (Refolded enzyme) was run through the gel. After Coomassie Blue staining, the areas of the gel digested by the enzyme are visible as clear bands against a darkly stained background.[20]

To detect the activity of the enzymes, serum specimens in each group were mixed with no reducing sample buffer containing 10% w/v SDS, and were electrophoretically resolved through 30% w/v polyacrylamide gels copolymerized with 1% w/v gelatin substrate. The samples were subjected to electrophoresis in substrate gel. After electrophoresis, gels were washed 3 times for 15 minutes each in 2.5% Triton X-100 at room temperature to remove the SDS from the gel, incubated for 18 hours in substrate buffer (50 mM Tris–HCl, 1 mM CaCl2, 0.02% NaN3, 1.5 mM NaCl, and 0.02% Triton X-100, pH 7.5) at 37 °C, stained with Coomassie blue R-250, and destained with ethanol and acetic acid solution. Gelatinase activities were visualized as clear bands in a blue background. To detect bands of MMP-2 and MMP-9, the band's position was compared with the protein marker (Figure 3). Intensity was measured using ImageJ software (LOCI, University of Wisconsin, USA). This software provides the quantization of the bands by counting the number of pixels and plotting the curve, and then, calculating the area under the curve.[20]

All statistical analyses were performed using SPSS software (version 11.5, SPSS Inc., Chicago, IL, USA). Data were expressed as Mean ± SEM [or Median (IQR)]. The normality of data distribution was determined using Kolmogorov–Smirnov test. All quantitative variables were normally distributed. Unpaired t-test was used for comparison of quantitative variables between the two groups. For comparison of these variables before and after the intervention, paired t-test was used. Before the intervention, by adjusting the base value in the two groups, analysis of covariance (ANCOVA) was performed. Moreover, $P < 0.0500$ was considered statistically significant.

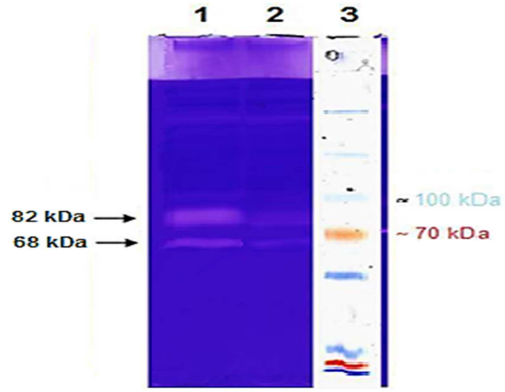

Figure 3. Gelatin zymography on serum samples of patients with coronary artery disease

Equal concentration of serum samples from patients with coronary artery disease were used in gelatin zymography. Lane 1: Bands from the patient's serum before the intervention; Lane 2: bands from the patient's serum after the intervention; Lane 3: a protein marker

Matrix metalloproteinases (MMP-9) and MMP-2 have a molecular weight of 82 and 68 kDa, respectively. The consumption of curcumin for 3 months significantly reduced the activity of the MMP-2 and MMP-9 enzymes.

Results

Demographic data: The collected data on the 70 patients with CAD revealed no significant difference in age and sex between the treatment and control groups ($P > 0.0500$) (Table 2).

Effect of curcumin on matrix metalloproteinase-9 and matrix metalloproteinas-2 activity: Based on the results of zymography, the mean value of MMP-9 levels in the curcumin and placebo groups was 14007.2 ± 5371.67 and 20010.1 ± 3259.37 pixels, respectively. As shown in figure 4, no significant difference was observed in the mean relative activity of MMP-9 between curcumin and placebo groups before the intervention ($P > 0.0500$). However, the mean levels of MMP-9 activity were significantly lower in the curcumin treatment group in comparison to the placebo group after the intervention ($P < 0.0010$).

Table 2. Baseline demographic characteristics of the study population and enzyme activity in the two groups before the intervention

Variable		Groups		P
		Nanocurcumin (n = 35)	Placebo (n = 35)	
Sex	Male	17 (48.5)	14 (40.0)	0.5180
	Female	18 (51.5)	21 (60.0)	
BMI (kg/m^2)	Normal	3 (8.5)	5 (14.3)	> 0.9990
	Overweight	26 (74.2)	25 (71.4)	
	Obesity	6 (17.3)	5 (14.3)	
Smoking habit	Current	4 (11.5)	3 (8.6)	0.9490
	Former	10 (28.5)	9 (25.7)	
	Never	21 (60.0)	23 (65.7)	
Hypertension	Yes	18 (51.5)	21 (60.0)	0.5180
[n (%)]	No	17 (48.5)	14 (40.0)	
Age (year)		56.34 ± 11.17	60.95 ± 10.77	0.1320
MMP-2 Enzyme activity (pixels)		18743.80 ± 5785.70	17826.20 ± 6597.70	0.6220*
MMP-9 Enzyme activity (pixels)		23102.40 ± 5582.70	20353.50 ± 3327.40	0.0700*

BMI: Body mass index; MMP-2: Matrix metalloproteinase-2; MMP-9: Matrix metalloproteinase-9
Data are presented as Mean ± standard deviation (SD) or n (%).
* No significant difference existed in the activity of enzymes (MMP-2 and MMP-9) before the intervention between the placebo and curcumin groups.

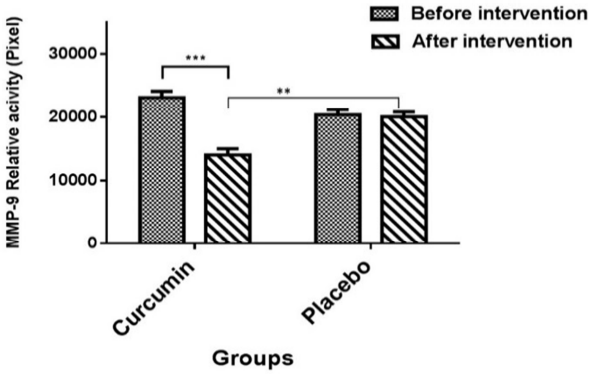

Figure 4. Comparison of the mean matrix metalloproteinase-9 relative activity according to pixels in the two groups (Placebo and curcumin) before and after the intervention

Data are expressed as mean ± standard error of the mean (SEM). Paired t-test showed that matrix metalloproteinase-9 (MMP-9) activity was lower in the curcumin group after the intervention (***P < 0.0010); however, no difference was observed in the placebo group after the intervention compared to before the intervention (P > 0.0500). Enzyme activity after the intervention in the curcumin group was lower than the placebo group (**P < 0.0100).

The results of zymography showed that the mean value of MMP-2 level in the curcumin and placebo groups after the intervention was 12469.7 ± 5308.64 and 17613.8 ± 5250.68 pixels, respectively. As illustrated in figure 5, the mean relative activity of MMP-2 showed a significant decline after the intervention. Furthermore, zymographic findings showed a decrease in the values of MMP-2 gelatinase activity in the group receiving curcumin (P < 0.0010).

The activity of MMP-9 did not differ in the placebo group (P > 0.0500). The activity of this enzyme in the curcumin group was lower than the placebo group after the intervention (P < 0.0500). No significant difference was observed in the activity of enzymes (MMP-2 and MMP-9) between the placebo and nanocurcumin groups before the intervention (Table 2).

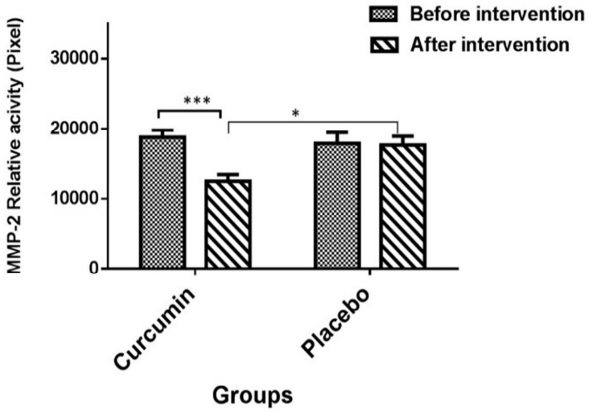

Figure 5. Comparison of the mean matrix metalloproteinase-2 relative activity according to pixels in the two groups (Placebo and curcumin) before and after the intervention

Data are expressed as mean ± SEM. Paired t-test showed that matrix metalloproteinase-9 (MMP-9) activity was lower in the curcumin group after the intervention (***P < 0.0010); however, no difference was seen in the placebo group after the intervention compared to before the intervention (P > 0.0500). The activity of this enzyme was lower in the curcumin group compared to the placebo group after the intervention (*P < 0.0500).

Effects of curcumin on matrix metalloproteinase-9 and matrix metalloproteinase-2 gene expression in human peripheral blood mononuclear cells: In this study, the expression of the MMP-9 gene was compared with the beta-actin gene before and after the intervention. Based on the results of $2^{-\Delta\Delta CT}$, the mean value of MMP-9 level in the curcumin group and the placebo group was 0.811 ± 0.25 and 2.23 ± 0.94, respectively. The analysis showed that the expression of MMP-9 was significantly decreased in the group treated with curcumin ($P < 0.0010$) (Figure 6).

The expression of MMP-2 gene was decreased in response to treatment with curcumin. Based on the results of $2^{-\Delta\Delta CT}$, the mean value of MMP-2 level was higher in subjects in the placebo group (4.497 ± 12.037) compared to subjects treated with curcumin (0.341 ± 0.253). However, this difference was not statistically significant ($P = 0.2894$) (Figure 6).

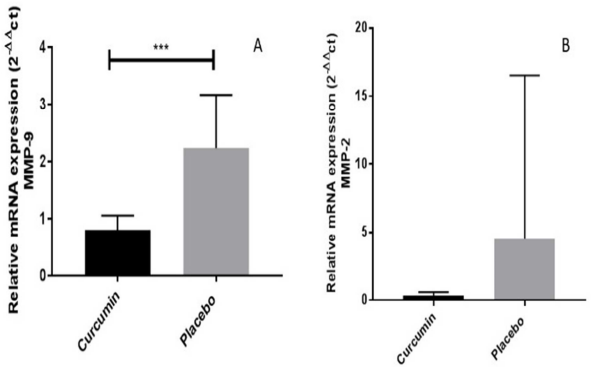

Figure 6. Messenger ribonucleic acid expression of matrix metalloproteinase-2 and matrix metalloproteinase-9 genes in the comparison of the β-actin gene between the placebo and curcumin groups
A: Based on the charts, the mRNA expression of matrix metalloproteinase-9 (MMP-9) showed a significant decrease in the curcumin group compared to the placebo group after 3 months of curcumin administration (***$P < 0.0010$). B: Based on the charts, the mRNA expression of MMP-2 in the curcumin group did not show a significant decrease compared to the placebo group after 3 months of curcumin administration ($P = 0.2800$). Data are representative of at least 2 independent experiments with β-actin used as the internal control.

Discussion

Atherosclerosis is a chronic and progressive disease caused by the development of the focal lesion in the wall of the arteries.[21] Despite a decrease in fat with the use of statins, a significant number of cardiovascular events are observed in patients with atherosclerosis. Further advances in the understanding of the pathophysiology of coronary artery syndrome dismissed. Studies have shown that a large number of cardiovascular events originate from arteries that had no significant obstruction in previous angiograms. Vulnerable lesions are unstable lesions with large lipid nuclei and a thin fibrous cap. Plaque instability is closely related to the spreading of inflammation in the intima, and acute coronary syndromes are caused by plaque rupture. Strengthening the plaque by modifying its structure and its content, instead of changing the luminal diameter, has become a potential new therapeutic goal.[22]

During the process of plaque formation, macrophages penetrate the fibrous cap, and the CD40 ligand on the surface of the T cells binds to their receptor at the surface of macrophages and induces the synthesis of a large number of inflammatory cytokines and proteases, in particular, the MMPs that cause a stable digestion of the matrix. Therefore, these enzymes play a major role in the weakness and rupture of the atherosclerotic plaque.[23]

Various studies have shown that circulating MMPs increase in patients with heart failure and unstable angina. The increased expression of MMPs in plaque atherosclerosis and that their activation causes the plaque to rupture has also been identified. Protecting the vascular wall in the atherosclerotic lesion is one of the ways to stabilize the plaque and prevent its rupture, which is associated with decreased expression and activity of MMPs. These findings suggest that MMP inhibitors can be useful in drug development and are a way to reduce mortality associated with CVD.[24]

The use of natural anti-inflammatory compounds is a safe and attractive solution for modulating inflammatory disorders. Curcumin is an anti-inflammatory food product that has been used for centuries in Asian cultures. Many of the activities of curcumin are associated with the ability of this compound to suppress acute and chronic inflammation.[25] To date, the anti-oxidant and anti-inflammatory properties of curcumin have been well documented, but it has not been completely determined how this inhibitory response regulated by curcumin.[14] Various studies have shown that curcumin targets different molecules, which may include growth factors, growth factor receptors, transcription factors, cytokines, and enzymes. Our findings show that no significant difference existed between the placebo and nanocurcumin groups in terms of the activity of enzymes (MMP-2 and MMP-9) before the intervention (Table 2). Our

results indicate that the consumption of curcumin at the dose of 80 mg/day significantly reduced the expression and activity of MMP-9 compared to the placebo group.

These findings confirm the findings of Saja et al., who reported the inhibition of MMP-9 activity in human PBMCs (in vitro) and in PBMCs in rabbits treated with curcumin (in vivo), and that this inhibition mainly occurs at the level of enzyme transcription.[26] It seems that the decrease in activity of MMP-9 is not due to the activity of the endogenous inhibitor of the enzyme, because studies have shown that curcumin also reduces tissue inhibitor of metalloproteinase-1 (TIMP-1) activity.[26] However, some studies that have investigated the effect of curcumin on the activity of gelatinases in rats' embryonic cardiac cells, suggest that the presence of docking sites for curcumin in the hemopexin domain in gelatinases and prevention of the binding of the substrate to the enzyme are possible mechanisms for reducing activity.[27]

Analysis of anti-angiogenic activity of demethoxycurcumin (curcumin analog) on cultured endothelial cells derived from the human umbilical cord has shown that this compound can reduce the expression of MMP-9 by up to 5 times. Moreover, the evaluation of the gelatinolytic activity of the enzyme through gelatin zymography has shown that demethoxycurcumin, in addition to reducing the expression of the enzyme, also significantly reduces the gelatinolytic activity of the enzyme.[28] Kim et al. also found that the gelatinolytic activity of the MMP-2 enzyme was reduced by the effect of demethoxycurcumin.[28] However, this compound did not have direct inhibitory effects on enzyme activity or any effect on post-translational modifications (PTM). This suggests that the inhibitory effect of this compound may be suppressed due its inhibition of the activation of some of the transcription factors that are commonly involved in the expression of MMPs.[28]

Previous studies have shown that many of the beneficial effects of curcumin are due to its ability to inhibit nuclear factor-kB (NF-kB) activity. Most inflammatory mediators that have been identified, including inflammatory cytokines, chemokines, sticky molecules, enzymes, and kinases, are regulated by NF-kB. Therefore, factors that can reduce the expression of NF-kB and NF-kB regulated gene products have the potential for use as anti-inflammatory agents in inflammatory diseases such as atherosclerosis. Thus, it can be concluded that the inhibition of NF-kB by any compound can reduce the activity of MMPs.[25] By inhibiting the activation of NF-kB, curcumin suppresses the expression of proliferation and cell survival genes, especially MMP-9.[29] MMP-9 promoter is highly protected and contains locations deemed necessary for NF-kB connection. This indicates the participation of NF-kB in MMP-9 regulation.[30]

It has been shown that, in addition to NF-kB, AP-1, another transcription factor, is also affected by curcumin.[31] Both MMP-2 and MMP-9 promoter encoding genes have an AP-1 binding site. However, this position is located in the proximal section of the MMP-9 and in the distal region of the MMP-2 gene.[32] Since the activation of AP-1 and NF-kB transcription factors is required in most cells to maximize MMP-9 expression, it seems that the effect of curcumin on MMP-9 is probably due to a significant reduction in the activity of these factors in endothelial cells.[33]

Our results further indicate that protection provided by curcumin in atherosclerosis can be due to inhibition of the expression and activity of MMP-2 gene. In this study, the expression of MMP-2 also decreased with the biological activity of the enzyme in the group receiving curcumin. The results of this study suggest that curcumin has a potential effect on reducing the expression of MMP-2 mRNA in peripheral blood lymphocytes (PBL) and its activity in the serum. There is much evidence suggesting that among the MMP family members, MMP-2 plays a key role in promoting the migration and proliferation of vascular smooth muscle cells (VSMCs) and instability of atherosclerotic plaque.[34] In addition, the expression of MMP-2 in VSMCs is associated with a wide range of pathological conditions, especially plaque atherosclerosis, and the expression and activity of MMP-2, which significantly increased in vulnerable areas, indicates the pathogenic role of this enzyme in the development of atherosclerosis.[35] Based on the results of this study, the consumption of curcumin can be associated with decreased activity and expression of MMP-2 enzyme. The results of this study are in agreement with that of the study by Zhong et al. that showed that curcumin can significantly reduce MMP-2 activity and expression induced by TNF-α from the NF-kB pathway in cultured rat VSMCs.[36]

One of the limitations of this study was the small number of patients and lack of investigation of gene expression in all groups before the intervention. Although we can refer to previous articles but it is necessary to be done in each study.

Studies have shown that growth factors, cytokines, and hormones can mediate the expression of MMP-2 by activating NF-kB and AP-1 from Ras/MAPK pathways because MMP-2 promoter has binding sites for various transcription factors such as NF-kB, AP-1, and SP-1.[37] The expression of MMP-2 is regulated by extracellular signal-regulated kinase (ERK) activity, which is a component of the MAPK signaling pathway. Moreover, blocking this pathway with ERK inhibitors can suppress the expression of MMP-2. Accordingly, the possible mechanism of curcumin in inhibiting the expression of MMP-2 is the inhibition of the MAPK pathway components, and in particular its ERK component.[38] Contrary to MMP-9, it seems that MMP-2 regulation in endothelial cells (ECs) is more dependent on the ERK path than the P38 MAPK route.[39] Curcumin can suppress AP-1 activity by preventing an increase in phosphorus-ERK and nuclear ERK accumulation.[40]

It has been confirmed that curcumin can reduce endothelial cell damage, which is linked to inhibiting MMPs from the CD40-CD40L pathway.[41] This pathway plays a major role in the inflammatory aspect of atherosclerotic plaque formation, progression, and rupture by suppressing the activity of MMPs.[42]

In addition to T cells, activated endothelial cells, SMCs, and macrophages can also produce CD40 and its ligand. In in-vitro conditions, the binding of CD40 to CD40L in cells present in atherosclerotic lesions triggers atherosclerotic changes such as induction of sticky molecules, the expression of pro-inflammatory cytokines, and MMPs that are present in atherosclerotic plaques.[43]

A study on CD40-CD40L pathway inhibitors has shown that inhibition of this route leads to decreased activity and expression of MMP-2; however, the inhibition of this pathway did not have any effect on MMP-9. The difference in the effect of this inhibitor on MMP-2 and MMP-9 may be due to differences in the cells producing these enzymes. MMP-2 is mainly secreted from macrophages, which are highly capable of producing CD40, whereas MMP-9 is produced in neutrophils.[44] However, in some studies, the simultaneous inhibition of CD40, MMP-9, and TNF-α by curcumin has been reported in mouse coronary artery tissue.[45]

The novelty of this study investigation of the actual results of nanomicelle curcumin on both the expression and enzyme activity of MMP-2 and MMP-9 on PBMC.

Conclusion

In conclusion, our results indicate that curcumin attenuates MMP-2 and MMP-9 expression and activity. Based on the results of this study and previous studies that show the inhibitory effect of curcumin on a range of inflammatory markers, curcumin can be suggested as a new intervention in secondary prevention of cardiovascular events.

Low cost, pharmacological safety, efficacy, and multiple molecular targets have turned curcumin into a promising product for the prevention and treatment of various diseases. However, more studies are required to validate all the benefits of curcumin therapy.

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Conflict of Interests

Authors have no conflict of interests.

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Recurrent cardiac and skin myxomas along with acromegaly: A case report of carney complex

Zivar Shirinpour[(1)], Zahra Farhangiyan[(1)], Nehzat Akiash[(2)], Homeira Rashidi[(3)]

Case Report

Abstract

BACKGROUND: Carney complex (CNC) is an uncommon multisystem endocrine disorder with significant variability of clinical manifestations including mucocutaneous involvement (pigmented lesions, myxomas, blue nevi, etc.), endocrine tumors (adrenal, pituitary, thyroid glands, or testicles), and non-endocrine tumors [cardiac myxomas, psammomatous melanotic schwannomas (PMS), breast myxomas as well as ductal adenomas, and osteochondromyxomas]. To our knowledge, this is the second report of CNC in Iran, presenting with typical manifestations.

Case Report: A 29-year-old man was referred to our clinic to evaluate the likelihood of CNC because of recurrent cardiac myxomas. He sometimes suffered from self-limited episodes of non-exertional palpitation, dyspnea, weakness, and pallor. He had some features of acromegaly (such as increase in acral size and frontal bossing). The laboratory tests revealed a high insulin-like growth factor 1 (IGF1) level, with no growth hormone (GH) suppression after oral glucose tolerance test (OGTT). Pituitary magnetic resonance imaging (MRI) showed a microadenoma (5.79 × 2.80 mm) of the pituitary gland; then, he was diagnosed with CNC, having the following major criteria: recurrent cardiac myxomas, skin myxomas, and acromegaly due to GH pituitary microadenoma, as well as minor criteria: multiple cafe´-au-lait (CAL) spots, several skin tags and moles, and thyroid nodules. In this patient, laboratory tests for Cushing's syndrome were equivocal, whereas pheochromocytoma was proven biochemically but unexpectedly pathology did not confirm it. Rather, the pathology of the right adrenocortical specimen revealed nodular hyperplasia.

CONCLUSION: For patients with recurrent cardiac myxoma, especially with skin myxoma, the diagnosis of CNC should be considered and the search for other associations should be done even in an asymptomatic patient.

Keywords: Carney Complex; Acromegaly; Myxoma

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Introduction

Carney complex (CNC) is an uncommon multisystem endocrine disorder first described in 1985 by Dr. J. Aidan Carney,[1] inherited in an autosomal-dominant manner or occurring sporadically due to a de novo genetic defect,[2] and characterized by spotty skin pigmentation in typical distribution, cutaneous/mucosal or cardiac myxoma, breast myxomatosis, primary pigmented nodular adrenocortical disease (PPNAD) or paradoxically positive Liddle's test, acromegaly secondary to growth hormone (GH) adenoma, large-cell calcifying Sertoli cell tumors (LCCSCT), thyroid carcinoma, psammomatous melanotic schwannomas (PMS), multiple epithelioid blue nevi, breast ductal adenoma, and osteochondromyxoma as major criteria and affected first-degree relative, activating mutations of protein kinase cyclic adenosine monophosphate (cAMP)-activated catalytic subunit alpha and beta (PRKACA and PRKACB), and inactivating mutation of regulatory subunit type I-alpha of protein kinase A (PRKAR1A) gene as supplemental criteria, affecting more than 750 patients distributed in many ethnicities.[3] Inactivating mutations in PRKAR1A gene

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1- Assistant Professor, Diabetes Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
2- Assistant Professor, Atherosclerosis Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
3- Associate Professor, Diabetes Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
Address for correspondence: Zahra Farhangiyan; Assistant Professor, Diabetes Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Email: dr.farhangiyan.z@gmail.com

on chromosome 17q22-24 is present in 70% of the patients.[4] The diagnosis is established in the following situations:[5]

- Exhibiting two or more major criteria
- A pathogenic variant is identified in the PRKAR1A
- Existence of one major and one supplemental criterion

We report a case of CNC presenting with recurrent cardiac and skin myxomas, acromegaly secondary to GH adenoma, and adrenal nodular hyperplasia.

Case Report

A 29-year-old man was referred to our clinic by the cardiologist to evaluate the likelihood of CNC because of recurrent cardiac myxomas. The patient became a candidate for kidney stone surgery by an urologist 2 years ago. In preoperative evaluation according to the previous history of cardiac myxomas, consultation with the cardiologist was requested. Echocardiography revealed a well-defined mobile mass (21 × 19 mm) in left ventricle (LV) and a tag-like mass in opposite part of tumor in anterior LV wall probably beginning of tumor formation; then, the patient was referred to us. He came to our clinic 8 months later (in last year). In history, he sometimes suffered from self-limited episodes of non-exertional palpitation, dyspnea, weakness, and pallor. He denied any headache, fever, weight loss, or sweating.

He had a history of recurrent atrial myxomas in the past 16 years for which he underwent repeated surgeries. At the age of 11, because of dyspnea, anemia, and fever, he was admitted and echocardiography documented a 32 × 32 mm myxoma in left atrium that for which he was operated in the same year, followed by a repeated surgery after 7 years (at 18 years old) for a recurrence (32 × 20 mm left atrial myxoma). He had history of multiple renal calculi. The patient was not on regular follow-up after second surgery till 2 years ago (at 27 years old).

On examination, the patient was obese [body mass index (BMI): 44 kg/m^2]; his cardiac exam showed normal sinus rhythm at 98 beats per minute (bpm), blood pressure of 160/100 mmHg, and no murmur. The lungs were clear. He had multiple spotty pigmentations (lentigines) (Figure 1A) on his face and trunk. Multiple cutaneous myxomas (confirmed histologically) (Figure 1B) and skin tags were seen on his neck, trunk, and abdomen, and there were also several myxomas on the eyebrows, eyelids (Figure 1C), and nipples. He had frontal skull bossing, a big fleshy nose, and large number of moles on his skin. Acanthosis nigricans (AN) was present on his neck. Cafe´-au-lait (CAL) spots (Figure 1D) were seen on both forearms and abdomen. Increased acral size was seen. Family history of such illness was negative.

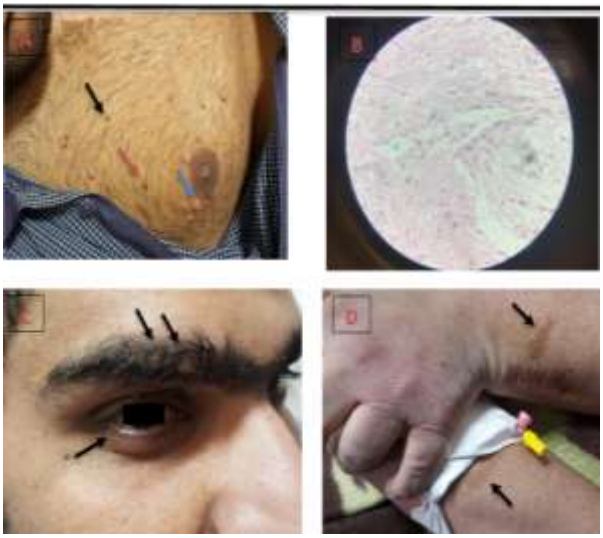

Figure 1. A) Multiple spotty pigmentation, mole, and myxoma (black, red, and blue arrow, respectively); B) Pathology of cutaneous myxoma, a sparsely cellular lesion composed of stellate and spindled fibroblast accompanied by abundant small vessels in myxoid matrix; C) Eye and eyebrow myxomas (arrow marks); D) Café-au-lait (CAL) spots

Because of skin lesions and recurrent cardiac myxomas, CNC was suggested, so further evaluation for other associations was performed. Given the hypertension (HTN) and episodic symptoms suspicious of spell, evaluation for pheochromocytoma was performed. Our investigation revealed 24-hour urinary concentration of vanillylmandelic acid (VMA) of 41 mg/day (reference range: up to 4 mg/day), a metanephrine level of 568 µg/day (reference range: up to 350 µg/day), and normetanephrine level of 895 µg/day (reference range: up to 600 µg/day) (these results were repeated in 2 tests on separate days). Evaluation for acromegaly (performed due to the increased acral size, multiple skin tags, and AN) revealed an elevated insulin-like growth factor 1 (IGF1) of 388 ng/ml (reference range: 109-290 ng/ml). The GH level after oral administration of 75 g glucose (0, 30, 60, 90, 120 minutes) was not suppressed below 1 mg/ml. Thus, pheochromocytoma and acromegaly were confirmed biochemically, and dynamic magnetic resonance imaging (MRI) of sella and abdomen (adrenal glands) (Figures 2A, 2B) showed a microadenoma

(5.79 × 2.80 mm) in the superior part of left posterior of the pituitary gland and a 26 × 13 mm mass with minimal enhancement in peripheral rim in medial to right adrenal gland. The left adrenal gland was normal in size and signal intensity.

Laboratory tests for Cushing's syndrome were borderline: baseline (8 am) morning plasma cortisol level of 9.5 µg/dl (reference range: 5-23 µg/dl), 24-hour urinary free cortisol (UFC) level elevated in one test (274 µg/day, reference range: 50-190 µg/day) and normal in another test (121 µg/day), overnight dexamethasone suppression test (DST) result of 2.6 µg/dl (above 1.8 µg/dl), a low-dose DST result of 6.5 µg/dl, a high-dose DST result of 2.7 µg/dl in plasma and 102 µg/day in UFC, and an adrenocorticotropic hormone (ACTH) level of 15.4 pg/ml (reference range: 7.2-63.0 pg/ml). Prolactin level was slightly high (16.5 ng/ml, reference range: up to 15 ng/ml). Levels of other pituitary hormones were normal. Calcium, phosphorus, and parathyroid hormone were all normal.

The echocardiography showed a well-defined and homogenous mass in LV attaching to papillary muscles and a small mass opposite the papillary muscles suspicious of benign cardiac tumor (20 × 18 mm) (Figure 2C), and he became a candidate for a heart surgery again.

Thyroid gland ultrasound showed multiple cystic nodules with the largest diameter of 3 mm in right lobe. The patient was euthyroid, and breast ultrasound was normal. However, scrotal ultrasound revealed testicular microlithiasis (TM). Brain MRI was performed according to the radiologist recommendation based on the incidental findings noted in pituitary MRI (some T2 hyperintense lesions in frontoparietal subcortical white matter) that revealed multiple ischemic lesions (lacunar infarct, presumably due to emboli from cardiac myxoma) which were seen in right frontoparietal subcortical white matter and bilateral corona radiata, so anticoagulant therapy was started.

Based on clinical and biochemical findings that were in favor of the pheochromocytoma and MRI report on a medial adrenal nodule, finally laparoscopic right adrenalectomy was performed (after preoperative pharmacologic preparation). The adrenal gland was greater than normal macroscopically. Pathology (reported by two pathologists) revealed nodular hyperplasia with one dominant nodule but unexpectedly, the adrenal medulla did not have any lesion (Figures 2D, 2E).

Two weeks after surgery, the patient's symptoms and signs (HTN and tachycardia) were resolved, and 24-hour urinary concentration of VMA (3.9 mg/day, reference range: up to 4 mg/day), metanephrine (47.8 µg/day, reference range: up to 350 µg/day), and normetanephrine (551 µg/day, reference range: up to 600 µg/day) were normalized. This discrepancy between biochemistry and pathology remains questionable.

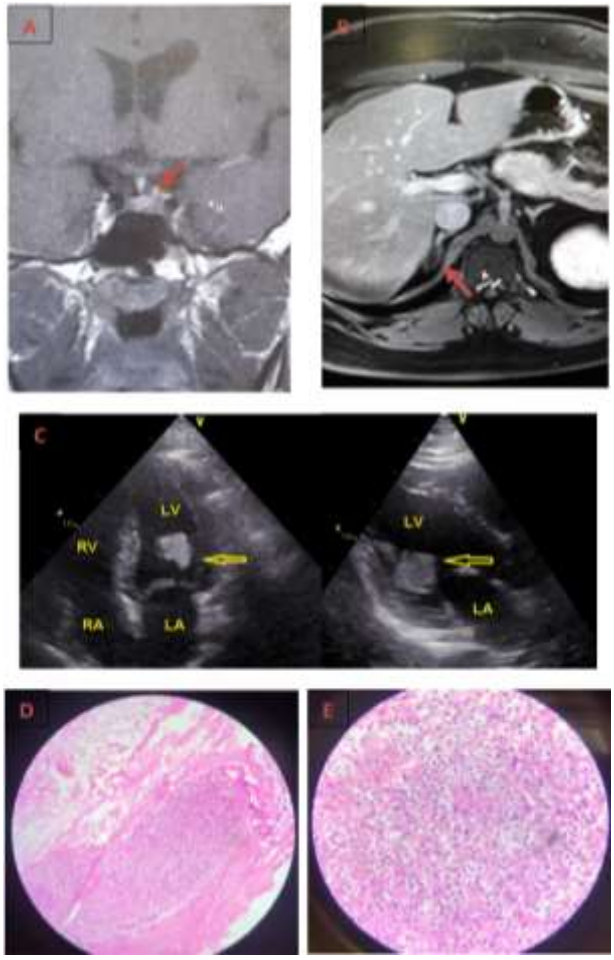

Figure 2. A) Pituitary magnetic resonance imaging (MRI), microadenoma; B) Adrenal MRI, showing nodular thickening of medial limb of right adrenal with subtle rim enhancement; C) Transthoracic echocardiography (TTE), showing a wall-defined and homogenous mass in left ventricle (LV) attaching to papillary muscles; D and E) Right adrenal histopathologic specimens [hematoxylin and eosin (H&E)-stained], adrenocortical hyperplasia with well-circumscribed micronodules

The patient refused transsphenoidal surgery (TSS) for pituitary microadenoma and preferred medical treatment [somatostatin analogues (SSA)] to decide on surgery later. He was referred to the cardiac surgery clinic in order for the cardiac surgeon to decide on cardiac myxoma surgery.

Echocardiography was performed on his first-degree family, of whom none had cardiac myxoma.

Unfortunately, despite frequent emphasis by the medical team, the patient did not have regular follow-ups. He came to our clinic one year after the unilateral adrenalectomy, while he was generally good and did not mention any problem. Blood pressure was 110/70 mmHg and pulse rate was 78 bpm. 24-hour urinary fractionated metanephrines, 24-hour UFC, and overnight DST were normal. IGF1 level was 280 ng/ml (reference range: 109-290 ng/ml) and GH level was suppressed below 1 mg/ml after oral administration of 75 g glucose. He did not accept the risk of cardiac re-surgery.

For all lab tests and adrenalectomy, informed consent was taken from the patient.

Discussion

CNC is a familial autosomal dominant syndrome, involving mesenchymal tumors, spotty skin pigmentation, peripheral nerve, breast and testicular tumors, and GH-secreting pituitary adenoma.[6] We are reporting this case of CNC based on the latest diagnostic criteria mentioned by Correa et al.,[3] with major criteria (cardiac and cutaneous myxomas, GH-producing pituitary adenoma) and minor criteria (several CAL spots, skin tags and moles, and multiple thyroid nodules). To the best of our knowledge, this is the second report of CNC in Iran. In the first case report (published in 2007), Talaei et al. introduced a 27-year-old woman with Cushing's syndrome due to PPNAD and a unilateral adrenocortical adenoma with a pituitary incidentaloma.[7]

Skin lesions in CNC can vary from lentigines and blue nevi to cutaneous myxomas. CAL spots have also been reported. Cutaneous myxomas usually present in the eyelid, external ear canal, nipples, and the genitalia.[3] One of the most common ophthalmologic manifestations is eyelid myxomas.[8] 20%-40% of the patients have cardiac myxomas,[3] around 7% of all cardiac myxomas are associated with CNC.[9] The recurrence rate of myxoma is 20%, and 50% of these cases have more than one myxoma.[10] Most patients have two or more open-heart surgeries because of recurrent myxomas.[11]

The interesting point of our patient is laboratory-proven pheochromocytoma which we did not find any case report indicating the association of CNC with pheochromocytoma in literature. Although the biochemistry was in favor of pheochromocytoma, the pathology did not confirm it. The reason for the positive results of the pheochromocytoma tests was uncertain.

The incidence of acromegaly due to pituitary adenoma is around 10%-12% in these patients.[3,12] Birla et al. reported a 30-year-old man with CNC syndrome characterized by recurrent atrial myxoma and acromegaly due to a novel 22 bp insertion mutation in PRKAR1A.[13] The PRKAR1A gene evaluation is not recommended for all patients, and our patient was not willing to do it due to financial constraints. The most common endocrine tumor in CNC is PPNAD,[3] that affected 25%-60% of the patients with CNC.[11] Cortisol secretion in PPNAD is usually insidious at onset[9] and may be cyclic or periodic.[3] In our patient, although Cushing's syndrome was not confirmed, given the boundary results of tests and pathological appearance of the right adrenal gland, there is a potential for it to occur and precise follow-up is required.

Up to 60% of all patients may have thyroid nodules[11] and 75% of the cases have cystic disease.[3] Hamza et al. reported a case of CNC, a 35-year-old patient diagnosed with Cushing's syndrome (due to primary pigmented nodular adrenal disease) and thyroid carcinoma.[14] In our patient, due to small size of thyroid nodules, fine needle biopsy was not performed, but serial thyroid examination and ultrasound are required.

More than 75% of men with CNC may have LCCSCT.[3] TM was reported in our patient's ultrasound. The relationship between TM and testicular malignancy is controversial.[15] Liu et al. reported a 16-year-old boy with CNC who had multiple microcalcifications of the bilateral testes.[16] According to one study, the incidence of testicular germ cell tumor (GCT) or germ cell neoplasia in situ (GCNIS) was significantly increased in 1347 men with TM compared with those in whom TM was absent.[17]

Close follow-up is suggested for clinical manifestations of the disease (at least yearly), including echocardiography, regular skin evaluation, measurement of UFC and other tests for screening Cushing's syndrome, blood test for GH, IGF1, and prolactin, and imaging such as testicular, thyroid, and breast ultrasound as well as pituitary and brain MRI, if appropriate.

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Conflict of Interests

Authors have no conflict of interests.

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Using technology and electronic devices to provide cardiac rehabilitation services

Mohammad Rafati-Fard[1]

Letter to Editor

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Dear Editor

A brief study on the executive structure of cardiac rehabilitation centers in Iran reveals the limitation of cardiac rehabilitation services provision through smart phones. In spite of the progress of cardiac rehabilitation programs over the last decade, the provision of hospital-based cardiac rehabilitation services in Iran is still a preferred method. This traditional and common model of cardiac rehabilitation faces fundamental challenges such as cost and access constraint, and does not meet the needs of those patients who more need to reduce risk factors, such as older people, women, different ethnic groups and rural populations, low-income people of the society, and most patients who need secondary prevention;[1] as patients who live in neighboring towns and remote areas face several challenges to receive cardiac rehabilitation services and attend such centers. Therefore, providing measures to increase patients' participation in, as well as adherence to treatment and prevent treatment withdrawal, is one of the priorities of cardiac rehabilitation management. Addressing this gap in services delivery is a clear need to develop alternative models to increase access to rehabilitation services via mobile technology; so that, in addition to keeping costs down, the efficiency and effectiveness of services can be improved on a large scale.[2] In this regard, the previous studies support the feasibility and applicability of mobile technology for cardiac rehabilitation in patients with ischemic heart disease.[3] Recent advances in technology and development of mobile applications,[4] and the availability of this technology, have provided significant opportunities to improve health outcomes in at-risk populations. Additionally, by focusing on health behaviors, they have provided opportunities to expand therapeutic and expandable interventions.[5] Therefore, focusing on innovative and electronic services (e.g., using mobile technology and application development) can have the potential to cope with barriers to accessing cardiac rehabilitation, and provide a useful tool to reduce costs and increase participation.[6] However, the innovative services model with an emphasis on mobile technology is an application that can empower patients through digital self-care, and by facilitating services provision for patients living in remote areas, can increase their participation and access to cardiac rehabilitation services. This can be attractive and applicable for a substantial portion of patients. Moreover, the implementation of our proposed plan may affect the adoption of a healthy lifestyle in the long term. Therefore, we suggest that some studies be conducted to investigate the efficacy and applicability of these methods in patients with cardiovascular disease in Iran and in low-income areas.

Conflict of Interests

Authors have no conflict of interests.

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1- Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Address for correspondence: Mohammad Rafati-Fard; Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; Email: rafati2821@gmail.com

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