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ARYA Atherosclerosis

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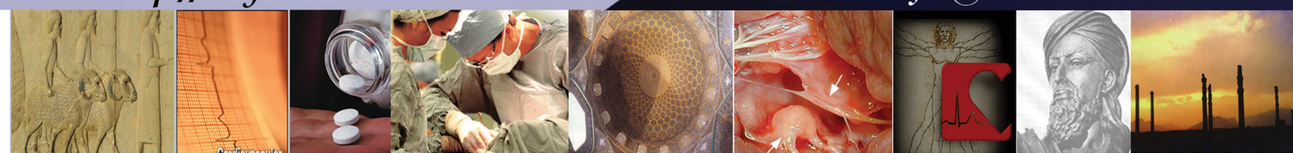

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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

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* All the words of the article containing the references; each table is considered as 300 words.

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Effects of an orientation tour on preoperative anxiety in candidates for coronary artery bypass grafting: A randomized clinical trial

Reyhaneh Niknejad[(1)], Mohsen Mirmohammad-Sadeghi[(2)], Mohammad Akbari[(3)], Ahmad Ghadami[(4)]

Original Article

Abstract

BACKGROUND: Candidates for cardiac surgery usually suffer from preoperative anxiety. Although there are various anxiety reduction techniques, it is unclear which one is the most effective. Therefore, the present study was conducted to explore the effects of an orientation tour on preoperative anxiety in candidates for coronary artery bypass grafting (CABG).

METHODS: In this randomized clinical trial study, 70 patients who were candidate for CABG were recruited from February 2016 to May 2017. They were randomly assigned to two groups of 35. The intervention group members were taken on an orientation tour and the control group received routine care. Data were collected using the State-Trait Anxiety Inventory (STAI).

RESULTS: The statistical tests revealed that there was no significant difference between the intervention group (42.43 ± 13.24) and the control group (45.11 ± 10.19) with respect to the pre-intervention state anxiety level (P = 0.340); however, before surgery, the state anxiety level was significantly lower in the intervention group (34.83 ± 11.15) than in the control group (47.69 ± 11.30) (P < 0.001). Moreover, the independent t-test showed that there was no significant difference between the intervention (43.71 ± 12.04) and control (45.03 ± 8.76) groups with respect to the pre-intervention trait anxiety level (P = 0.600). Nevertheless, before surgery, the trait anxiety level was significantly lower in the intervention group (35.40 ± 10.24) than in the control group (46.91 ± 9.51) (P < 0.001).

CONCLUSION: The preoperative orientation tour had a positive impact on the anxiety level in the candidates for CABG. Hence, the tour can be used as a remarkably effective technique for reducing anxiety.

Keywords: Anxiety, Coronary Artery Bypass Grafting, Orientation

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Introduction

Cardiovascular disease (CVD) is viewed as the most important cause of mortality and disability worldwide.[1,2] In 2013, it accounted for 17.3 million out of 54 million deaths globally; in other words, 31.5% of deaths were due to CVD.[3] According to the American Heart Association (AHA), CVD causes one out of three deaths in the United States (US) and an average of 2150 Americans die of CVD per day, which roughly equates to one death every 40 seconds.[4]

Coronary artery disease (CAD) is common in Iran and the age of developing it has reduced. The disease is one of the leading causes of mortality and disability in this country and the risk of developing it has increased.[5,6] The incidence rates of CVD events are 1168 and 1436 per 100000 person in year in Iranian women and men, respectively.[7] When patients with an ischemic stroke fail to respond to medical treatment, the coronary artery bypass grafting (CABG) is the only effective option for them.[8]

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CABG is common in developed countries. Over 5155000 and 17000 patients have undergone it in the US and Australia, respectively.[9,10] In Iran, 60% of heart operations are CABG. One of the problems that candidates for cardiac surgery face is preoperative anxiety.[11] Among the most common anxiety-provoking factors are awaiting surgery, hospitalization, a disturbing memory of a patient who had died of the same disease, and fears of death and unexpected outcomes.[11,12] Anxiety leads to an increase in levels of catecholamines, adrenocortical hormones, prolactin, cortisol, and prostaglandin. Increased anxiety levels affect the cardiac output, blood pressure, heart and respiratory rates, myocardial oxygen consumption, and plasma concentrations of adrenaline and noradrenaline, thereby carrying a health risk.[2,13] Anxiety could be not only preoperative but also postoperative.[14,15] High anxiety levels in patients undergoing CABG can have serious consequences for them.[16]

Pre-CABG anxiety has negative effects on the physical and mental well-being of patients and influences the outcome of their medical treatment.[11,17] According to a study by Tully et al., pre-CABG anxiety increases the risk of death. Preoperative anxiety is seemingly at the highest level in CABG patients and this is when symptoms of angina worsen.[18] This is consistent with the results of a study by Krannich et al. It showed that 34.0% and 24.7% of CABG patients had experienced preoperative and postoperative anxiety, respectively.[19] In general, it could be argued that most CABG patients suffer from different anxiety levels.[20,21]

Hence, since anxiety affects surgical outcomes and the recovery process and causes postoperative complications, it is essential to examine the anxiety level in patients. In fact, they should be under both physical and psychiatric examination. Furthermore, examining the postoperative anxiety process helps detect patients at risk of postoperative anxiety.[17] Fears, uncertainties, potential complications, and unexpected outcomes are sources of anxiety and stress in patients.[11,22] Uncertainties resulting from lack of knowledge can cause anxiety.[23]

Medical team members can reduce injuries caused by surgery and maintain the health of patients. Surgical technologists can prevent complications and risks such as the increased heart rate, myocardial infarction (MI), and adverse outcomes by knowing the anxiety level and type and applying suitable interventions, thereby helping patients recover quickly.[24] Studies show that educational interventions play an important role in reducing anxiety in candidates. Different methods are used for training researchers and each has its own impact. Hence, experienced operating-room nurses can help reduce this stress and anxiety using modern educational methods. The intra-unit training is a common method for reducing anxiety in patients. They can watch instructional videos and receive peer education. It should be noted that despite these trainings, patients may still experience anxiety.[17,25,26]

According to many studies, in order to desensitize people to stress and reduce their anxiety using mental health strategies, they should rehearse stressful situations.[27] Hence, the current study was carried out to explore the effects of an orientation tour on preoperative anxiety in CABG candidates. In fact, the study attempts to show whether the anxiety level in patients rises or decreases after they visit operating rooms and units and speak with inpatients.

Materials and Methods

This randomized clinical trial study was performed on 70 CABG candidates who had attended in Shahid Chamran Hospital in Isfahan, Iran (a large educational hospital in center of Iran) from December 2016 to May 2017. The inclusion criteria were as follows: being over 40 years old, giving full consent for participating in the study, undergoing CABG for the first time, being ready for surgery, having no acute or chronic physical and mental disorders, having basic literacy skills, being no emergency case, and having no medical education. Exclusion criteria were as follows: indicating a reluctance to participate in the study, wishing to be hospitalized somewhere else, and receiving good or bad news during the study.

The necessary sample size was calculated as a minimum of 23 participants per group at a confidence interval (CI) and test power of 95%.[28] Accounting for potential participant loss, 35 patients per group were subsequently recruited for a total of 70 patients. In this parallel-group trial, the subjects were randomly assigned to two groups, namely control (n = 35) and intervention (n = 35) by the flip of a coin.

Patients were randomly allocated to a group by a person uninvolved in the sampling and data collection process. Group allocations were performed using random sequencing. The participants and care providers were aware of the group allocation, but those who assessed outcomes were blinded. The process of selecting study

samples was repeated until the required sample size was obtained. It took about 6 months continuously and we did not have any problem and stopping.

The data were collected using the State-Trait Anxiety Inventory (STAI) both before the tour and before surgery. The data collection questionnaire had three sections, namely demographic characteristics, state anxiety, and trait anxiety. The validity and reliability of the questionnaire had been confirmed in a study by Dehghan-Nayeri and Adib-Hajbaghery in Iran (α = 0.94).[29] The patients completed the questionnaires about half an hour prior to the intervention at 4:00 p.m. and half an hour before surgery at 6:00 a.m.

There were 20 items for assessing trait anxiety and 20 for state anxiety. Each item was rated on a four-point scale. For state anxiety, the four-point scale was as follows: 1) very low, 2) low, 3) high, and 4) very high. The scale for trait anxiety was as follows: 1) almost never, 2) sometimes, 3) often, and 4) almost always. The minimum score was 20 and the maximum score was 80. The state-anxiety inventory scoring was interpreted as follows: 20-31 as mild anxiety, 32-42 as lower than moderate anxiety, 43-53 as higher than moderate anxiety, 54-64 as relatively severe anxiety, 65-75 as severe anxiety, and 76 or higher as very severe anxiety. The trait-anxiety inventory scoring was interpreted as follows: 20-31 as mild anxiety, 32-42 as lower than moderate anxiety, 43-52 as higher than moderate anxiety, 53-62 as relatively severe anxiety, 63-72 as severe anxiety, and 73 or higher as very severe anxiety.[28]

The control group patients were individually informed by a nurse or a trainer about the routine surgical procedure in the unit the day before surgery. On an orientation tour, the intervention group patients were also informed about the procedure individually the day before surgery from 4 p.m. to 6 p.m. An anesthesia technician, a nurse, and one of the researchers led the tour, which lasted 40 minutes: 10 minutes for visiting an unoccupied operating room during an evening shift, 5 minutes for visiting the intensive care unit (ICU), 10 minutes for vising the surgical unit, getting acquainted with personnel and patients there, and answering questions about CABG, and 15 minutes for speaking with inpatients. None of the participants during the intervention were excluded.

There were two types of variables, namely independent (orientation through the tour) and dependent (anxiety) variables. Demographic variables included age, gender, marital status, and disease duration.

Ethical considerations were taken into account in the present study. Authorities were briefed about the research objectives and granted the researchers a permit. The subjects were not charged for participating in the study. They were assured that their personal and private information would remain confidential. The study results were reported to authorities in the School of Nursing and Midwifery in Isfahan University of Medical Sciences and Shahid Chamran Hospital. This clinical trial was approved by the Research Ethics Committee in the university (code: 396704) and Iranian Registry of Clinical Trials (IRCT) (code: IRCT20180601039934N1).

In order to analyze the data, the independent t-test was used to compare the two groups with respect to the continuous quantitative variables, i.e., age, weight, height, and disease duration. Normality of distribution of the data was tested by Kolmogorov-Smirnov test (K-S test); a P-value greater than 0.05 indicated that the observed distribution of a variable was not statistically different from the normal distribution. The Mann-Whitney U test was applied to compare the two groups with respect to the demographic variables, namely the education level and the economic status. A comparison was made within the groups before and after the intervention using the paired t-test. Data analysis was performed using the SPSS software (version 22, IBM Corporation, Armonk, NY, USA). A P-value below 0.050 was considered statistically significant.

Results

The independent t-test showed that there was no significant difference between the two groups with respect to the mean age, weight, height, and disease duration; accordingly, the two groups were considered homogenous ($P > 0.050$) (Table 1). The Mann-Whitney U test revealed no significant difference between the groups with respect to the education level and the economic status ($P > 0.050$) (Table 2). According to the paired t-test, the mean scores of state anxiety and trait anxiety in the intervention group were significantly lower before surgery (34.83 ± 11.15, 35.40 ± 10.24, respectively) than before the intervention (42.43 ± 13.24, 43.71 ± 12.04, respectively) ($P < 0.001$); however, there was no significant difference between the mean scores of state and trait anxiety before surgery (47.69 ± 11.30, 46.91 ± 9.51) and the mean scores of state and trait anxiety before intervention (45.11 ± 10.19, 45.03 ± 8.76) in the control group ($P > 0.050$) (Table 3).

Table 1. The mean age, weight, height, and disease duration in the two groups

Variable	Intervention group (n = 35)	Control group (n = 35)	Test
	Mean ± SD	Mean ± SD	P*
Age (year)	60.15 ± 11.29	60.71 ± 8.22	0.810
Weight (kg)	71.31 ± 10.25	72.93 ± 13.58	0.620
Height (cm)	163.21 ± 17.91	166.78 ± 10.80	0.370
Disease duration (month)	40.63 ± 9.47	32.13 ± 8.42	0.510

* P-values refer to comparisons of mean age, weight, height, and disease duration between intervention and control groups (independent t-test)
SD: Standard deviation

Discussion

The aim of the present study was to determine the effects of a preoperative orientation tour on the anxiety level in CABG candidates who had attended Shahid Chamran Hospital in Isfahan. The intervention group members were in the age range of 40-81 years and the control group members were in the 48-75 age range. Moreover, 23 patients (65.7%) were men and 12 patients (34.3%) were women. In old age, the risk of CAD is higher, which emphasizes the need for diagnostic tests. Furthermore, aging is one of the major risk factors for atherosclerosis and CAD, which is reported in men over 55 and in women over 45 years of age.[30] In pre-menopausal women, female hormones reduce the risk of CAD significantly.[31,32]

In the intervention group, 91.4% of the patients were married and 91.4% of them were employed. In the control group, 82.9% of the patients were married and 82.9% of them were employed. The majority of patients in the intervention group (71.4%) and in the control group (82.9%) were nongraduate high-schoolers. The reduction of the CVD burden depends on many factors, one of which is the education level. According to Martin et al.[33] and Berkman et al.,[34] there is a significant relationship between the education level of women and cardiovascular risk factors. Gonzalez-Chica et al. reported that patients with poor literacy skills had low self-efficacy, did not follow their diet, and had lower overall quality of life.[35]

The results of the present study revealed that, after the intervention, the patients in the intervention group had significantly lower state and trait anxiety levels than the patients in the other group. In 2014, Kaur et al. investigated the effects of an orientation program on the anxiety level of patients with cancer undergoing radiotherapy for the first time. Their recommendation was that patients should be oriented regarding treatment facilities and what they might expect during the first visit.[36] In 2015, Dehghani et al. examined the impact of a preoperative orientation program on the anxiety level in patients undergoing cardiac surgery and reported that the anxiety level in the intervention group patients had decreased significantly.[37] In the present study, the anxiety level in the patients was assessed before and after the intervention. It decreased but became higher as the surgery hour got closer. The exact preoperative anxiety level was not recorded.

In the present study, the anxiety level in patients was measured before the tour and before surgery in the operating room. It was revealed that the tour had reduced the preoperative anxiety level.

Table 2. The frequency distribution of the economic status and the education level in the two groups

Variable		Intervention group (n = 35)	Control group (n = 35)	Test
		[n (%)]	[n (%)]	P*
Education	Elementary school	9 (25.7)	12 (34.3)	0.250
	Middle school	12 (34.3)	15 (42.9)	
	High school	9 (25.7)	2 (5.7)	
	University	5 (14.3)	6 (17.1)	
Economic status**	Rich	1 (2.9)	3 (8.6)	0.210
	Middle	26 (74.3)	17 (48.6)	
	Poor	8 (22.9)	15 (42.8)	

* P-values refer to comparisons of the economic status and the education level in the two groups (Mann-Whitney U test)
** The economic situation has been reported according to the views of each of the samples in the three categories of rich, middle, and poor

Table 3. The mean scores of pre-intervention and pre-operation state anxiety and trait anxiety in the two groups

Variable	Time point	Intervention group (n = 35)	Control group (n = 35)	Test
		Mean ± SD	Mean ± SD	P
State anxiety	Pre-intervention	42.43 ± 13.24	45.11 ± 10.19	0.340***
	Pre-operation	34.83 ± 11.15	47.69 ± 11.30	< 0.001***
		P ≤ 0.001*	P = 0.070**	
Trait anxiety	Pre-intervention	43.71 ± 12.04	45.03 ± 8.76	0.600£
	Pre-operation	35.40 ± 10.24	46.91 ± 9.51	< 0.001£
		P ≤ 0.001*	P = 0.140**	

* P-values refer to comparison of the mean scores of pre-intervention and pre-operation anxiety in intervention group (paired t-test)
** P-values refer to comparison of the mean scores of pre-intervention and pre-operation anxiety in control group (paired t-test)
*** P-values refer to comparisons of mean scores of state anxiety between intervention and control groups (independent t-test)
£ P-values refer to comparisons of mean scores of trait anxiety between intervention and control groups (independent t-test)
SD: Standard deviation

The reason is that the patients who participated in the tour became familiar with the operating room and special care units, which helped them adapt to the new environment and feel secure. In 2013, Varaei et al. studied the impact of an orientation tour on anxiety and satisfaction levels in candidates for coronary angiography. They reported that the mean score of anxiety was significantly lower in intervention group than in the other group after the tour. During their discharge from the hospital, the mean score was still significantly lower in the intervention group. In addition, there was a significant difference between the two groups with respect to the mean score of satisfaction during their discharge from the hospital.[38] The results of this study are consistent with the results of the present study. Nevertheless, the difference between the two studies is that, although both of them used the same questionnaire for measuring the anxiety level, the mean score of anxiety in candidates for open-heart surgery was higher than that in candidates for cardiac angiography. In fact, the orientation tour could reduce the anxiety level in patients undergoing angiography further, which must have been due to the type of surgery.

It should be mentioned that the intervention group in the present study conversed with inpatients in the surgical unit. This companionship had a very positive and soothing effect on the patients, so that even some of them expressed their satisfaction with the tour and this companionship explicitly. Results of a study by Shamsizadeh et al. are in line with this. They studied effects of peer education on anxiety in CABG candidates and reported that peer education was more effective than direct instruction.[39]

One of the limitations of the present study was that anxiety levels were not compared at different time points, for example, the day after surgery and on the discharge day. Other variables could affect the anxiety level in the patients but the researchers of the current study focused on preoperative anxiety more. It is recommended that future studies consider this comparison.

Conclusion

The results of the current study showed that the preoperative orientation tour had positive effects on anxiety in CABG candidates. Therefore, an orientation tour can be used as a highly effective technique for relieving anxiety and accelerating recovery. It can also help minimize treatment costs associated with a long-term recovery. Definitely, candidates for any other surgery can also benefit from an orientation tour.

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Conflict of Interests

Authors have no conflict of interests.

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Correlation between air pollution and hospitalization due to myocardial infarction

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Original Article

Abstract

BACKGROUND: Air pollution is associated with increased risk of cardiovascular disease (CVD). This study aims to evaluate the correlation between air pollutants and hospitalization due to myocardial infarction (MI) as part of "correlation of air pollution with hospitalization and mortality of CVDs and respiratory diseases (CAPACITY) study".

METHODS: This case-crossover study analyzed the data of 319 patients who were admitted with diagnosis of ST-elevation MI (STEMI) or non-ST-elevation MI (NSTEMI) in three main hospitals of Isfahan, Iran. The data of airborne pollutants including particulate matter < 10 µm (PM_{10}), particulate matter < 2.5 µm ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3) as well as climatic indices (temperature, wind speed, and humidity) at 24 hours, 48 hours, and one week before admission were extracted from CAPACITY study. The conditional logistic regression method was used to evaluate the correlation between air pollutants and MI hospitalization.

RESULTS: 319 patients with mean age of 63.15 ± 28.14 years, including 238 men (74.6%), and 207 patients with STEMI (64.8%) were recruited. The risk of hospitalization significantly increased in patients with STEMI and 10-unit increment in $PM_{2.5}$ at 48 hours before admission [odds ratio (OR) = 3.70, 95% confidence interval (CI): 1.69-7.69]. Although, majority of air pollutants had positive association with hospitalization in patients with NSTEMI, they were not statistically significant.

CONCLUSION: This study showed significant association between elevated $PM_{2.5}$ at 48 hours before admission and hospitalization of patients with STEMI. This finding can warn policymakers to design better care services for patients at risk of acute MI during the times of increased air pollution.

Keywords: Air Pollution, Myocardial Infarction, Hospitalization, Airborne Particulate Matter

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Introduction

Recently, cardiovascular diseases (CVDs) are introduced as the major cause of death and disability around the world.[1] Different individual and environmental risk factors are associated with

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CVDs, while air pollution is currently recognized as the most common environmental risk factor for them.[2] Based on the World Health Organization (WHO) report, seven million premature deaths are attributed to air pollution each year, including 2.4 million deaths due to heart diseases and 1.4 million deaths due to stroke. More than four million deaths are assigned to ambient air pollution.[3]

The relationships between air pollutants and ischemic heart disease (IHD) have been demonstrated in numerous studies.[4,5] Longitudinal studies, particularly in developed countries, have highlighted the long-term effects of pollutants on the incidence of these diseases.[6-8] Time-series and case-crossover studies, on the other hand, have emphasized the short-term impacts of pollutants, especially suspended particles (2.5 μ).[9-11]

A total of 3245 persons/year per 100000 age-standardized disability-adjusted life year (DALY) in Iran is attributed to IHD and it is known as the major cause of mortality in the country.[12] Air pollution is an important risk factors for IHD. Using global models such as WHO's AirQ, multiple researches were conducted to evaluate the actual effect of air pollutant on specific diseases in Iran.[13,14] Other ecological surveys evaluated the effect of air pollution on acute coronary syndrome (ACS) in Iran.[15]

The correlation of air pollution with hospitalization and mortality of CVDs and respiratory diseases study (CAPACITY study) aimed to evaluate the correlation between air pollution and hospital admission or death from heart and lung diseases in Isfahan, Iran.[16] As part of the CAPACITY study, the present study was conducted to evaluate the relation between air pollutants and hospital admission due to ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI).

Materials and Methods

This case-crossover (each case was considered as its own control) study was conducted in the framework of the CAPACITY study. The CAPACITY study was a multicenter well-defined research performed from March 2010 to March 2012. The data of all inhabitants of Isfahan either admitted in 15 hospitals of Isfahan or died with the definite diagnosis of cardiovascular or respiratory disease were collected. The disease was diagnosed based on the International Classification of Diseases-10th revision (ICD-10). The data of air pollutants were obtained from Isfahan Department of Environment (DOE). Time-series and case-crossover design were the two methods conducted for this study. In this study, the data of three main hospitals from 15 medical centers were gathered. More details about CAPACITY study have been presented elsewhere.[16]

This study extracted data related to CAPACITY participants who were hospitalized for myocardial infarction (MI) in three main hospitals of Isfahan (Chamran, Noor, and Al-Zahra Hospitals). The patients' file numbers were used to retrieve their records from hospital archives and collect additional information regarding their hospitalization status. The basic demographic data (age and gender), presence of diabetes mellitus (DM), hypertension (HTN), and current aspirin usage were recorded. The changes in ST segment during the hospital stay, laboratory data namely "troponin, urea, creatinine, and hemoglobin" levels at the admission time, left ventricular ejection fraction (LVEF) in echocardiography, the angiography results (if any), and patient's conditions at discharge were obtained from the files. The administration of fibrinolytic drugs for patients with STEMI was evaluated and recorded. Patients with incomplete records were excluded from the study.

Information about air pollutants namely carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particulate matter smaller than 2.5 μm ($PM_{2.5}$) and smaller than 10 μm (PM_{10}), and ozone (O_3) were obtained from the CAPACITY data and presented as mean daily concentrations. In CAPACITY study, raw data were collected from six fixed pollution-monitoring stations supervised by Isfahan DOE. Hourly concentrations of pollutants were measured and recorded in Excel files by these stations. The mean concentration of each pollutant was calculated every day of the study span for the all regions of Isfahan. In addition, in order to consider the effects of climatic variables, the file containing mean daily temperature, humidity, and wind speed values was extracted. Data about air pollutants and climatic variables were recorded in current study at 24 hours, 48 hours, and 1 week before admission.

Quantitative variables were presented as mean ± standard deviation (SD) and were compared by independent sample t-test. Categorical data were expressed as frequency and percentage and chi-square test and Fisher's exact test were performed whenever was necessary. Patients were categorized in two groups of STEMI and NSTEMI based on clinical diagnosis. Crude conditional logistic regression model was used to evaluate the association between levels of air pollutants in the time points of 24 hours, 48 hours, and one week

Table 1. Patients' basic characteristics and the mean values of air pollutants and climatic variables during the study period

Patients' basic characteristics	Value	Air pollutants and climatic variables	Value (Mean ± SD)
Male gender [n (%)]	238 (74.60)	O_3 (ppb)	26.98 ± 13.17
History of DM [n (%)]	89 (27.80)	NO_2 (ppb)	43.76 ± 23.24
History of HTN [n (%)]	111 (34.70)	PM_{10} (µg/m^3)	126.18 ± 50.83
History of aspirin intake [n (%)]	59 (18.49)	SO_2 (ppb)	42.58 ± 32.91
ECG changes during admission [n (%)]	209 (65.50)	CO (ppb)	3.77 ± 2.00
Fibrinolytic drugs intake [n (%)]	149 (46.70)	$PM_{2.5}$ (µg/m^3)	53.91 ± 21.43
MI with ST-elevation [n (%)]	207 (64.89)	Temperature (°F)	57.70 ± 18.97
Living at clearance time [n (%)]	288 (90.28)	Dew point (%)	28.16 ± 8.66
Age (year) (mean ± SD)	63.15 ± 28.14	Wind speed (mile/h)	4.86 ± 2.13

DM: Diabetes mellitus; HTN: Hypertension; ECG: Electrocardiography; MI: Myocardial infarction; Ppb: Particle per billion; O_3: Ozone; NO_2: Nitrogen dioxide; PM_{10}: Particulate matter < 10 µm; SO_2: Sulfur dioxide; CO: Carbon monoxide; $PM_{2.5}$: Particulate matter < 2.5 µm; SD: Standard deviation

before admission and hospitalization for MI in the two groups. Adjusted models considering the confounding impacts of temperature, dew point, and wind speed were also performed in both groups. The results were expressed in form of odds ratio (OR) and 95% confidence interval (CI). All ORs were presented for each 10-unit increase in air pollutants. Statistical analysis was done with Stata software (version 9, Stata Corporation, College Station, TX, USA). Statistical significance was assessed at the level of 0.050.

Results

A total of 319 patients with MI with mean age of 63.15 ± 28.14 years, including 238 men (74.60%) and 207 (64.8%) with ST-elevation were recruited in this study. Table 1 summarizes the basic characteristics of study participants and mean daily concentrations of pollutants as well as daily temperature, dew point, and wind speed during the study period.

Tables 2 and 3 present the results of conditional logistic regression on the impact of each 10-unit increment in different air pollutants in association with the risk of hospitalization separately in patients with STEMI and NSTEMI, respectively.

As can be seen in both groups, majority of air pollutants showed direct association with risk of hospitalization; however, only the $PM_{2.5}$ levels at 48 hours before admission increased significantly the risk of hospitalization for STEMI both in crude and adjusted models, in which each 10-unit increment in $PM_{2.5}$ levels increased the hospitalization risk about 3.70 times (95% CI: 1.69-7.69 from adjusted model).

Table 2. The relationship between 10-unit increase in air pollutants before admission and the risk of hospitalization in patients with ST-elevation myocardial infarction (STEMI)

Time of exposure to pollutants	Pollutants	Crude model			Adjusted model*		
		OR	95% CI	P	OR	95% CI	P
24 hours before hospitalization	$PM_{2.5}$	1.30	(0.96-1.75)	0.088	1.37	(0.97-1.96)	0.077
	PM_{10}	1.02	(0.97-1.06)	0.475	1.03	(0.97-1.07)	0.301
	SO_2	1.05	(0.89-1.25)	0.519	1.06	(0.90-1.27)	0.456
	CO	3.03	(0.31-33.33)	0.341	2.86	(0.29-33.33)	0.371
	NO_2	1.09	(0.93-1.28)	0.297	1.07	(0.90-1.27)	0.445
	O_3	1.10	(0.81-1.50)	0.533	1.14	(0.83-1.55)	0.423
48 hours before hospitalization	$PM_{2.5}$	3.03	(1.56-6.25)	0.001	3.70	(1.69-7.69)	0.001
	PM_{10}	1.01	(0.97-1.06)	0.511	1.02	(0.97-1.06)	0.483
	SO_2	0.97	(0.85-1.09)	0.609	0.97	(0.85-1.09)	0.609
	CO	1.02	(0.85-1.22)	0.836	1.02	(0.85-1.23)	0.825
	NO_2	1.03	(0.89-1.17)	0.727	1.02	(0.88-1.17)	0.668
	O_3	0.96	(0.76-1.22)	0.718	0.93	(0.72-1.19)	0.531
1 week before hospitalization	$PM_{2.5}$	1.12	(0.82-1.52)	0.493	1.04	(0.73-1.49)	0.813
	PM_{10}	1.01	(0.97-1.05)	0.585	1.02	(0.98-1.06)	0.353
	SO_2	0.96	(0.87-1.07)	0.404	0.95	(0.86-1.05)	0.375
	CO	1.02	(0.92-1.12)	0.816	1.01	(0.90-1.12)	0.917
	NO_2	1.04	(0.93-1.16)	0.458	1.03	(0.92-1.16)	0.642
	O_3	0.86	(0.71-1.04)	0.105	0.89	(0.72-1.05)	0.150

* Adjusted for wind speed, temperature, and dew point; P-values resulted from conditional logistic regression

$PM_{2.5}$: Particulate matter < 2.5 µm; PM_{10}: Particulate matter < 10 µm; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; OR: Odds ratio; CI: Confidence interval

Table 3. The relationship between 10-unit increases in air pollutants before admission and the risk of hospitalization in patients with non-ST-elevation myocardial infarction (NSTEMI)

Time of exposure to pollutants	Pollutants	Crude model			Adjusted model*		
		OR	95% CI	P	OR	95% CI	P
24 hours before hospitalization	$PM_{2.5}$	1.30	(0.46-3.70)	0.620	7.69	(0.17-333.33)	0.290
	PM_{10}	1.02	(0.93-1.13)	0.579	1.03	(0.92-1.14)	0.550
	SO_2	1.10	(0.83-1.46)	0.480	1.12	(0.83-1.50)	0.438
	CO	1.00	(0.06-15.98)	> 0.999	1.50	(0.08-27.30)	0.760
	NO_2	1.11	(0.78-1.58)	0.529	1.20	(0.81-1.77)	0.340
	O_3	0.93	(0.45-1.93)	0.845	0.92	(0.44-1.95)	0.840
48 hours before hospitalization	$PM_{2.5}$	5.00	(0.69-50.00)	0.110	1.43	(0.11-16.66)	0.830
	PM_{10}	1.01	(0.93-1.08)	0.890	1.01	(0.93-1.08)	0.888
	SO_2	1.01	(0.99-1.04)	0.110	1.01	(0.99-1.04)	0.130
	CO	1.03	(0.78-1.37)	0.800	1.02	(0.77-1.36)	0.801
	NO_2	1.31	(0.93-1.83)	0.110	1.34	(0.93-1.92)	0.101
	O_3	0.64	(0.37-1.10)	0.102	0.64	(0.37-1.10)	0.120
1 week before hospitalization	$PM_{2.5}$	5.00	(0.69-50.00)	0.500	1.43	(0.11-16.66)	0.830
	PM_{10}	1.01	(0.93-1.08)	0.890	1.01	(0.93-1.08)	0.887
	SO_2	1.01	(0.99-1.04)	0.110	1.01	(0.99-1.04)	0.130
	CO	1.03	(0.78-1.37)	0.800	1.02	(0.77-1.36)	0.803
	NO_2	1.31	(0.93-1.83)	0.110	1.34	(0.93-1.92)	0.103
	O_3	0.64	(0.37-1.10)	0.103	0.64	(0.37-1.10)	0.120

* Adjusted for wind speed, temperature, and dew point; P-values resulted from conditional logistic regression
$PM_{2.5}$: Particulate matter < 2.5 μm, PM_{10}: Particulate matter < 10 μm; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; OR: Odds ratio; CI: Confidence interval

Discussion

The current study investigated the association of levels of different air pollutants with hospitalization in patients with STEMI and NSTEMI in Isfahan. In this study, $PM_{2.5}$ concentrations at 48 hours before admission were significantly related with hospitalization in patients with STEMI. In spite of direct associations between the majority of other different air pollutants with hospitalization in studied time points, they did not show any significant relation. Some studies had proposed a direct significant association between the level of air pollutants, except for O_3, and MI incidence.[17] Multiple studies have proposed significant relation between some air pollutants and the admission with diagnosis of STEMI or NSTEMI, while others have rejected the presence of such association. A study in Belgium used a crossover model to evaluate 11428 patients with records in the STEMI registration system during 2009-2013. It found the incidence of STEMI to have significant positive correlations with elevated levels of $PM_{2.5}$, PM_{10}, and NO_2 at 24 hours before MI. Elevations in PM_{10} were more strongly related with STEMI in patients over 74 years of age. In the case of NO_2, however, patients below 54 years of age were at greater risk. This study found the strongest relationship between NO_2 and STEMI.[18] Another study on 673 patients with MI detected the strongest significant association between $PM_{2.5}$ and STEMI just one hour before the onset of STEMI. The relationships between STEMI and PM_{10} levels at 3, 12, and 24 hours before MI were not significant. In addition, no relationship was observed between NSTEMI and exposure to $PM_{2.5}$. Moreover, in patients with a history of HTN, the effect of PM was more prominent. The only method that was used in this study for evaluation of $PM_{2.5}$ effect was case-crossover approach.[19]

Another case-crossover study in the United Kingdom (UK) assessed the association between airborne contaminants and STEMI and NSTEMI. It investigated nearly 523000 patients admitted during 2003-2010. The database of Myocardial Ischaemia National Audit Project (MINAP) in England was used. Air pollutants exposure was evaluated immediately and two days before the onset of the acute cardiac event. The results showed no links between pollutants and STEMI. Contrary to the two studies discussed above, there was a significant relationship between maximum hourly NO_2 concentration per day and the incidence of NSTEMI. This correlation persisted after adjustments for O_3 and $PM_{2.5}$.[20]

In another study, the relationship between hospitalization due to STEMI and air pollutants was investigated using a time-series model in Tabriz, Iran. The results showed STEMI to be significantly

related with maximum hourly NO_2 concentration on the day of admission, and mean 24-hour CO concentration on the pre-admission day. The relationship between 24-hour CO and STEMI was stronger than that between STEMI and NO_2. The study reported no relationships between STEMI and PM, SO_2, and O_3 concentrations.[21]

A time-series study in Spain also revealed associations between hospitalization due to STEMI and increased $PM_{2.5}$, PM_{10}, and NO_2 concentrations.[22] A two-year case-crossover study on 106000 patients with STEMI and 12719 patients with NSTEMI in 26 cities of China indicated an association between increased $PM_{2.5}$ concentration before the onset of the MI and higher risk of STEMI. The incidence of STEMI had significant relationships with $PM_{2.5}$ levels zero to five days before the incidence of the condition. There was, however, no link between $PM_{2.5}$ and NSTEMI.[23]

A recent study on 208 Iranian patients used a case-crossover model to explore the relationship between STEMI and airborne contaminants. According to the results, STEMI was significantly associated with PM_{10} and $PM_{2.5}$. In addition, higher age, DM, and multi vessel involvement had stronger relationships with PM concentration.[24] Evidently, most studies have identified PM as the pollutant associated with the occurrence of STEMI. Furthermore, the majority of previous studies, except for a few,[20] have rejected the presence of significant relationships between pollutants and NSTEMI. Additionally, various studies with different models have used different exposure times. Our study also highlighted a relationship between PM concentrations 48 hours before hospital admission and hospitalization due to STEMI.

Several mechanisms, including coagulation, inflammation, vascular dysfunction, and autonomic dysfunction are involved in ACS (e.g., MI). All these mechanisms lead to thrombosis, binding of circulating platelets to each other, and vessel wall damage. An acute plaque rupture occurs in STEMI which is absent in NSTEMI. In the meantime, endogenous thrombolysis has a critical role in the clot autolysis and preventing complete vascular obstruction. Indeed, the balance between thrombosis and thrombolysis results in the occurrence of STEMI and/or NSTEMI.[25,26] Air pollutants, especially $PM_{2.5}$, appear to increase platelet and fibrinogen activities, stimulate plaque formation, and decrease endogenous thrombolysis.[27,28] This can justify the observed relationship between pollutants and STEMI.

An important limitation in our study was lack of data on patient complaints, clinical demonstrations, and paraclinical outcomes in the health information system at the time of admission. However, other studies, particularly in developed countries, did not encounter such a limitation, because all precise information of patients is available in a data registration system that can facilitate the implementation of extensive studies at a lower cost and time. The other limitation of our survey was the quite small number of study population that leads to relatively unreliable conclusion.

Conclusion

This survey outlined a significant correlation between $PM_{2.5}$ and the increased risk of STEMI. Although the majority of air pollutants showed a direct association with increased risk of hospitalization for STEMI and NSTEMI, none of the observed associations, more likely due to low sample size and particularly few patients in studied subgroups, were statistically significant. These findings can encourage policymakers to design policies for pollutant reduction. It also emphasizes the need for providing better care services on days with elevated air pollution levels and the following days for patients with higher risk of acute MI.

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Conflict of Interests

Authors have no conflict of interests.

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The effect of canola oil compared with sesame and sesame-canola oil on cardio-metabolic biomarkers in patients with type 2 diabetes: Design and research protocol of a randomized, triple-blind, three-way, crossover clinical trial

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Original Article

Abstract

BACKGROUND: Both canola and sesame oils consumption have been associated with favorable effects on cardio-metabolic biomarkers. However, to the best of our knowledge, no study has compared their effects on cardiovascular risk factors. The present study aimed to assess the effect of canola, sesame, and sesame-canola oils consumption on cardio-metabolic biomarkers in patients with type 2 diabetes mellitus (T2DM).

METHODS: This study was a randomized, triple-blind, three-way, crossover clinical trial. The study participants included 102 individuals with T2DM. Their spouses were also included in the study. The participants were entered into a 4-week run-in period. After that, their regular dietary oil was replaced with canola, sesame, or sesame-canola oils (a blend of sesame and canola oils) in three 9-week phases, which were separated by two 4-week washout periods (sunflower oil was consumed during the run-in and the washout periods). Dietary, physical activity, blood pressure, and anthropometric measurements were assessed at the beginning, in the middle (week 4-5), and at the end of each treatment phase. Blood samples were taken at the beginning and at the end of each phase. Serum, plasma, buffy coat, and whole blood samples were extracted and kept at -80 ºC for further analysis. Serum fasting blood sugar (FBS), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were selected as the primary outcomes.

RESULTS: 102 participants with T2DM were randomly assigned to one of the 6 rolling methods. Through them, 93 individuals (91.2%) completely participated in all phases.

CONCLUSION: The present study will provide an exceptional opportunity to examine the effect of canola, sesame, and sesame-canola oil on cardio-metabolic markers in adults with and without T2DM. This trial will also provide a good medium for the investigation of gene-dietary oils interaction in the future.

Keywords: Canola Oil, Sesame Oil, Cardiovascular Diseases, Type 2 Diabetes Mellitus, Clinical Trial

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Introduction

The replacement of saturated fatty acids with polyunsaturated fatty acids (PUFAs) in a diet have led to a decrease in the risk of chronic diseases like type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[1,2] Moreover, it has been reported that PUFAs consumption has several beneficial

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consequences for human health.[3-5] In addition, linoleic acid, which is the most abundant omega-6 PUFA, is associated with decreased T2DM risk,[6] and may improve cholesterol and insulin sensitivity status.[7] Furthermore, omega-3 PUFAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) might improve lipid profile,[8,9] and consequently, the risk of CVD.[10,11]

Canola oil (CO) is proposed as a good source of PUFAs, including linoleic acid, mono-unsaturated fatty acids (MUFAs), and alpha-linolenic acid (ALA), an omega-3 fatty acid that can be converted to DHA and EPA in the human body.[12] It has been suggested that CO intake might improve serum total cholesterol (TC),[13] low-density lipoprotein cholesterol (LDL-C),[14,15] apolipoprotein B to apolipoprotein A1 ratio (Apo B/Apo A1),[15] and triglyceride (TG)[14,16] levels. Additionally, some studies found that CO consumption decreased circulating levels of fasting glucose[14-16] and insulin[13,16], while some other studies could not find the same results.[13,17,18] In contrast, sesame oil (SO) contains high amounts of omega-6 PUFAs and MUFAs[19] such as linoleic and oleic acid, respectively.[20] Furthermore, SO contains significant amounts of antioxidant phytochemicals including sesamin, sesamolin, sesaminol,[21,22] and vitamin E.[19] Sesamin might have anti-atherosclerotic properties[23] and might help to control hypertension.[19,24] In patients with insulin resistance, SO consumption resulted in a significant reduction in serum TC and LDL-C level with no significant effect on TG.[25] However, in a study on patients with diabetes, SO improved not only plasma glucose, TC, and LDL-C, but also TG levels.[19]

To the best of our knowledge, a limited number of high-quality trials have examined the effect of CO and SO on cardio-metabolic markers, which have led to inconsistent results. Moreover, no study has compared the effect of SO with that of CO, which are considered as healthy edible oils. CO is one of the largest sources of edible oils consumed worldwide, and SO has been regarded as a healthy oil in Asian countries for a long time.[19] It is also noteworthy that adults with T2DM experience several metabolic abnormalities particularly in terms of insulin sensitivity, blood glucose levels, and lipid profile, which independently lead to a higher risk of serious disease including CVD.[26] Therefore, the present clinical trial was conducted to assess the effect of SO compared with CO and sesame-canola oil (SCO: a blend of these two edible oils) on cardio-metabolic markers, including lipid profile, glycemic indices, blood pressure, and anthropometric measurements in adults with T2DM and their spouses by replacing participants' regular consumed oils with the mentioned oils.

Materials and Methods

Trial design and setting: This study was a randomized, triple-blind, three-way crossover, clinical trial which aimed to assess the effect of replacing regular oil consumption of adults with T2DM with SO, CO, and SCO on cardio-metabolic markers. The patients' spouses were also included in the present study and received all the interventions because we aimed to replace the oils regularly used at home with the abovementioned oils. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) was used as a framework for reporting the present protocol.[27]

The medical records of individuals referred to Diabetes Research Center of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, were reviewed to identify potential participants based on the eligibility criteria. In the initial visit, after explaining the study procedure to the participants and obtaining their informed consents and medical history, the participants' demographic information and medication use were recorded, and a 24-hour food recall and a 24-hour physical activity recall were completed for the participants. Body composition, anthropometric, and blood pressure measurements were also performed on the first visit by a trained nutritionist. Moreover, the daily energy requirement of the participants and their spouses were estimated using formulas suggested by the US Institute of Medicine (IoM).[28] Thereafter, they received a healthy dietary recommendation, which provided 30-32% of the total energy needs from fats, 50-52% from carbohydrates, and 16-18% from proteins. The study subjects were recommended to maintain their physical activity throughout the study period. Additionally, nutrition counseling was provided by a trained nutritionist.

After the first visit, participants and their spouses were entered into a 4-week run-in period in which their regular consumed oils were replaced with sunflower oil. The intervention oils were provided in the same packages, which were labeled with three codes (B, G, and S), and individuals were randomly assigned to consume them. Each intervention period lasted 9 weeks and 4-week intervals (sunflower oil was provided) separated the intervention periods as washout durations. The study flow diagram is presented in figure 1. The oils were provided for the study participants and their family by investigators.

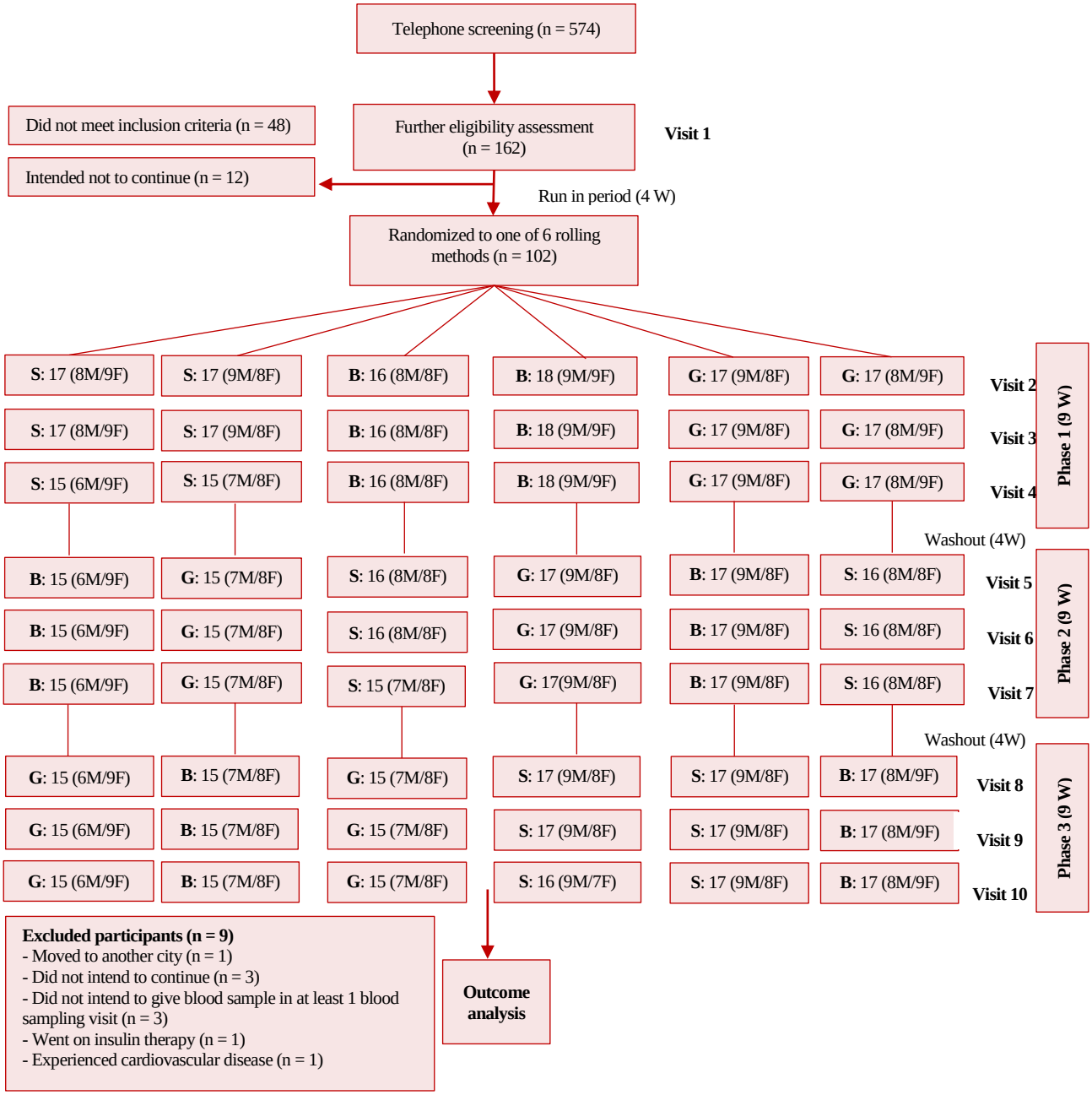

Figure 1. The study flow chart

Participants were randomized to six rolling methods to receive canola oil, sesame oil, and sesame-canola oil with three codes (B, G and S). F: Female, M: Male, W: Weeks

There were three clinical visits at the beginning, in the middle (forth to fifth week), and at the end of each intervention period. The details of all measurements conducted in each visit are provided in table 1. All measurements and blood samplings were also performed for the participants' spouses.

Ethics: The ethical approvals in order to study the effect of dietary oils on cardio-metabolic markers of patients with T2DM and bio-banking of blood fractions for both patients and their spouses were obtained from the ethics committee of Shahid Sadoughi University of Medical Sciences on 29th and 15th May 2016 with reference numbers IR.SSU.REC.1395.25 and IR.SSU.REC.1395.26, respectively. Furthermore, for studying the effect of dietary oils on cardio-metabolic markers in the patients' spouses, who did not have diabetes, another ethics approval was obtained on 29th May 2016 with reference code IR.SSU.REC.1395.247 from the mentioned ethics committee.

Table 1. Details of the study visits[λ]

Measured variable	Phase 1				Phase 2			Phase 3		
	Visit 1	Visit 2**	Visit 3***	Visit 4£	Visit 5**	Visit 6***	Visit 7£	Visit 8**	Visit 9***	Visit 10£
Eligibility criteria assessment	*									
Medical history	*									
Informed consent	*									
Nutrition counseling	*									
Medication use	*	*	*	*	*	*	*	*	*	*
Physical activity	*	*	*	*	*	*	*	*	*	*
24-hour dietary recall	*									
Anthropometric measurements										
Weight	*	*	*	*	*	*	*	*	*	*
Height	*									
Waist circumference	*	*	*	*	*	*	*	*	*	*
Hip circumference	*	*	*	*	*	*	*	*	*	*
Body composition indices										
Body fat mass	*	*	*	*	*	*	*	*	*	*
Lean mass	*	*	*	*	*	*	*	*	*	*
Visceral fat	*	*	*	*	*	*	*	*	*	*
Blood pressure	*	*	*	*	*	*	*	*	*	*
Blood sampling		*		*	*		*	*		*
Biochemical assessments										
FBS		*		*	*		*	*		*
TG		*		*	*		*	*		*
TC		*		*	*		*	*		*
HDL-C		*		*	*		*	*		*
LDL-C		*		*	*		*	*		*
Apo A		*		*	*		*	*		*
Apo B		*		*	*		*	*		*
Lp (a)		*		*	*		*	*		*
Capillary fasting blood glucose			*			*			*	
Compliance										
Three-day food records		*	*	*	*	*	*	*	*	*
Weight measurement of provided oils	*	*	*	*	*	*	*	*	*	*

[λ] All assessments except plasma FFAs profile will be assessed for the participants and their spouses; [**] Visit at the beginning of the intervention phases; [***] Visit in the middle of intervention phases; [£] Visit at the end of intervention phases; FBS: Fasting blood sugar; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Apo A: Apolipoprotein A; Apo B: Apolipoprotein B; LP(a): Lipoprotein a; FFAs: Free fatty acids

The trial was registered in the Iranian Registry of Clinical Trials (IRCT) on 14th of November 2016 (registration ID: IRCT2016091312571N6), and archived at https://en.irct.ir/trial/12622. Informed consents were obtained from all study participants.

Inclusion criteria: Participants who were 18-60 years old, had a minimum of 6 months or a maximum of 10 years history of T2DM, took oral anti-glycemic agents as medication and did not take insulin therapy, had not changed the dose of lipid-lowering medications at least for 3 months prior to starting the study, and provided informed consent to entering the study were included in the present study. Furthermore, the participants should have HbA1c values of less than 8%, and no history of any other diseases like CVD (coronary artery disease, stroke, congestive heart disease) and coronary artery bypass grafting (CABG), kidney or liver diseases [serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels of three times higher than normal values], thyroid disease, and any types of cancer.

Exclusion criteria: Participants who dramatically changed their dietary habits during the study period or went on a special diet, underwent insulin therapy throughout the study period, experienced pregnancy or chronic diseases like CVD or cancer, or intended to discontinue the study for any reason were excluded from the study. We did not consider any inclusion or exclusion criteria for the spouses.

Sample size calculation: The sample size for the present study was calculated based on a formula suggested for crossover studies[29] [$n = [(z\ 1-\alpha/2+z\ 1-\beta)^2 \cdot s^2]/2\Delta^2$] which assumes the type one error of 5% and the type 2 error of 10% (power of 90%), and serum glucose as the key variable.[14] Using this formula, a minimum of 34 participants was calculated as the required sample size. In the present study, we aimed to have enough power to conduct sex specific analyses. The investigators predicted that the attrition rate might be high in the present study; therefore, we targeted to enter 50 men and 50 women with the eligibility criteria.

Randomization: The participants were stratified based on their sex, and then, were randomly assigned to one of the 6 sequences of rolling methods in order to consume the three intervention oils during the study period (SGB, SBG, GSB, GBS, SGB or BSG) (Figure 1). The randomization was implemented using the Statistical Package for Social Sciences software (SPSS) (version 20, IBM Corporation, Armonk, NY, USA) by an independent researcher.

Allocation concealment: The pre-specified rolling methods were written on a paper and were kept in sealed opaque envelopes. At the initial visit, the envelope was opened by the study coordinator when the subject gave informed consent to be entered into the study.

Blinding: This study was designed to be a triple-blind trial. The intervention oils were provided in exactly the same bottles labeled with three codes (B, G, and S) by a responsible person who was not aware of the study objectives. The codes were not released until after the statistical analyses; therefore, neither the study participants (patients with diabetes and their spouses), nor the personnel and the statisticians were aware of the intervention oils until after the statistical analyses.

Chemical analysis of intervention oils: The fatty acids content of the intervention oils and the sunflower oil were assessed using gas chromatography with a flame ionizer detector (GC-FID) (model YL6500 GC, Young ling Instruments, Korea) before their delivery. Mean percentage of the important fatty acids content is provided in table 2. In brief, the fatty acids content of the intervention oils was as follows: 1) CO: 60.95% oleic acid, 8.048% ALA, and 21.87% linoleic acid, 2) SO: 40.95% oleic acid, 0.357% ALA, and 42.62% linoleic acid, and 3) SCO: 52.94% oleic acid, 4.98% ALA, and 30.17% linoleic acid (Table 2).

Primary and secondary outcomes: The present clinical trial was designed to examine the effects of CO, SO, and SCO on fasting blood sugar (FBS) and serum lipid profile concentrations of TG, TC, high-density lipoprotein cholesterol (HDL-C), and LDL-C as the primary outcomes. The secondary outcomes were Apo A, Apo B, lipoprotein(a) [Lp (a)] concentration, blood pressure, and variation in anthropometric and body composition indices.

Anthropometrics measurements: Height was measured using a wall-fixed measuring tape to the nearest 0.1 cm. Moreover, waist and hip circumferences were measured to the nearest 1 cm using a non-stretchable measuring tape. Body weight was measured with light clothes and without shoes to the nearest 100 gr using a digital calibrated scale (mode BF51, Omron, Japan). Body mass index (BMI) is computed by dividing weight (kg) by height squared (m^2), and the waist to hip ratio (WHR) by dividing waist circumference by hip circumference. Visceral fat, lean mass, and body fat percentage were also assessed using a body composition analyzer (model BF51, Omron, Japan). All anthropometric assessments were performed 3 times in each visit and their mean value was recorded as the final value (Table 1).

Table 2. The fatty acid composition of treatment oils*

Fatty acids	Canola oil	Sesame oil	Sesame-canola oil	Sunflower oil
Saturated fatty aids				
Palmitic acid (16:0)	5.369	9.576	7.046	6.870
Stearic acid (18:0)	2.221	5.776	3.940	5.540
Arachidic acid (20:0)	0.295	0.379	0.330	0.360
Behenic acid (22:0)	0.265	-	0.156	0.540
Lignoceric acid (24:0)	-	-	-	0.190
Monounsaturated fatty acids				
Palmitoleic acid (16:1)	0.271	0.198	0.239	0.188
Oleic acid (18:1)	60.950	40.950	52.940	28.460
Erucic acid (22:1)	0.389	-	0.190	
Polyunsaturated fatty acids				
Linoleic acid (18:2)	21.870	42.620	30.170	57.450
Alpha-linolenic acid (18:3)	8.048	0.357	4.980	0.140

* All values are presented as the percentages of total fatty acids.

Blood pressure measurement: Systolic and diastolic blood pressure (SBP and DBP) were measured 3 times in each visit after 5 minutes rest when participants were in the sitting mode, for the right arm with at least 1-minute interval, using a sphygmomanometer (Riester, Germany, model: Diplomat-presameter). The mean of SBP and DBP values was recorded for each visit (Table 1).

Blood sampling: After an overnight fast (10-12 hours), venous blood samples were taken from participants and their spouses between 7-9:30 a.m. in the morning. The blood samples were aliquoted to 3 serums, 3 plasmas, 2 buffy coat, and 2 whole blood samples in DNase- and RNase-free microtubes and stored at -80 ºC until analysis.

Laboratory assessment: FBS, TG, TC, HDL-C, LDL-C, Apo A, Apo B, and Lp (a) were determined from serum samples using an auto-analyzer (model AT^{++}, Alpha-classic, Iran) and Pars Azmoon standard kits (Pars Azmoon Inc., Iran) (Table 1).

Dietary intake measurement: In this trial, 3-day weighted food record (2 weekdays and 1 day of the weekend) was used to measure dietary nutrients intake, including energy, carbohydrate, protein, total fat, saturated fat, MUFAs, and PUFAs intake at the beginning, in the middle, and at the end of the intervention. Therefore, the food records were collected 9 times during the study (Table 1). Participants were instructed by a nutritionist to fill out the food records in the initial visit and were provided with written instructions. The food records were completed by all of the participants. They were asked to record the type and amount of all foods, beverages, supplements, and medications consumed. A digital kitchen scale (model SF-400, Electronic kitchen scale, China) was provided for each participant or the person who was responsible for cooking at home and they were asked to complete the 3-day cooking forms for each visit. The weight of every cooked food and its ingredients were also recorded. The daily food intakes will be computed and converted to grams/day using household measures.[30] Daily energy and nutrients intakes will be calculated using a version of the Nutritionist IV software (version 3.5.2, Axxya Systems, Redmond, Washington, DC, USA) modified for Iranian foods.

Physical activity assessment: Physical activity was assessed using 3-day physical activity records (2 weekdays and 1 day of the weekend). The records were collected 9 times during the study (at the beginning, in the middle, and at the end of each phase). The physical activity data will be converted into metabolic equivalent-min/day (Table 1) using the updated version of the compendium of physical activities.[31] The participants were asked to keep their physical activity level constant during the study.

Compliance: The intervention oils were provided for the participants and their family. Thus, to evaluate compliance, several methods were implemented; 1) the given and returned intervention oil bottles were weighed and will be divided by the number of members usually living in the participants' house, and 2) the 3-day food records will be used to assess the amount of oil consumed by the participants (Table 1).

Medication use: To track the medications used by the participants, they were asked to record the medications and their dose in the food records and the medication use was evaluated at each clinical assessment visit; therefore, the possible changes in medications will be accessible to the study participants (Table 1).

Data management: All data will be kept in the office of the principal investigator (ASA) and will be available only to the investigators for research purposes. The collected data will be entered into a data file and will be kept secure by the principal investigators. The data will also include patients' medical history information. The access to the data will be limited to statistical analyses and interpretation. The collected data will not be used for any other purposes. The biological samples will be kept in a freezer until the analyses and only the principal investigator will have access to the samples. The biological samples will be used only for research purposes.

Confidentiality of the data: All collected data for the present investigation will remain confidential, and the investigators will follow the ethical standards of Shahid Sadoughi University of Medical Sciences. However, the clinical research members of the research team will be aware of the identity of the participants, but not of the intervention oils provided for the study participants during the study.

Each participant will receive a unique identification code so that all information, such as data gathered using questionnaires, measurements, and biological samples, will remain confidential. Full names and other identifying information will not be provided, unless required by law and/or by the research ethics board. The participants will not be identified in any published data or in any result from this study. Moreover, medical records that contain the identity of the participants will be regarded as confidential.

Participant feedback: The report of the primary outcomes will be provided for the study participants in sealed envelopes and in a private meeting with the investigators, as soon as the analyses become completed.

Adverse events and concomitant medications: No adverse reactions were reported during the study period and we did not expect any adverse events because the intervention components were food and they were readily available for people in food stores. The case report form was designed to record any adverse events and to inform sponsors and the institutional ethics board of Shahid Sadoughi University of Medical Sciences. All medications used at the beginning of the trial or during the study period were recorded.

The auditing of the present study was performed by two independent investigators who were not a study team member or sponsor during the recruitment and follow-up periods.

Study status: The study is still ongoing. The recruitment of participants started in April 2016 and the intervention period ended in May 2017. The biochemical assessments of the blood samples are currently being carried out. Furthermore, the investigators are now entering the data and preparing them for statistical analysis in the near future. The project has not led to any publication yet.

Statistical analysis: The statistical analysis will be conducted using IBM SPSS statistical software. The normality of the distribution of the quantitative data will be determined using Kolmogorov-Smirnov test, and the skewed variables will be normalized by transformation before comparison. Baseline and post-intervention measurements will be compared using repeated measures analysis of variance (ANOVA) to determine treatment effects. The effects of treatment oils will be compared using linear mixed method procedure with rolling method between subject factors. The potential confounders like age, sex, baseline BMI, the amount of intervention oils consumed per subject, metabolic equivalent-min/day of physical activity, and the amount of calorie intake will be adjusted as covariates. Sex specific analyses will be conducted. Sensitivity analysis will be performed by excluding those who experienced medication change throughout the study. $P < 0.050$ will be considered as statistically significant for all analyses. The results related to the intervention oils will be compared using the Bonferroni adjustment for multiple comparisons.

Results

Enrollment and dropouts: Among 574 individuals with diabetes, 162 participants underwent the clinical assessments and 114 individuals met the inclusion criteria. In addition, 12 eligible participants did not intend to enter the project through the run-in period. Eventually, 102 participants were randomized to one of the 6 rolling methods (Figure 1).

In phase 1, 2, and 3, respectively, 5, 2, and 2 participants did not participate in the visits; therefore, 93 (91.2%) participants completed all of the study phases and the overall dropout rate was 8.8%. These participants did not continue the study because of the following reasons: did not intend to continue the participation (n = 3), did not intend to give blood sample in at least one visit with blood sampling (n = 3), moved to another city (n = 1), went on insulin therapy (n = 1), and experienced CVD during the study (n = 1).

Discussion

Canola oil (CO) is a good source of oleic acid, ALA, and phytochemicals.[12] Canola has risen from the sixth largest oil crop to the second in the last 40 years and CO is the third largest source of edible plant oil in the world.[32] Several studies have reported the significant improvements in blood lipids,[33-36] FBS,[15,16] blood pressure,[37] and insulin sensitivity[16,17] as a result of consuming a CO-based diet. In a crossover clinical trial with a 3-week intervention period on 20 participants, a CO-enriched diet significantly decreased FBS and lipid profile.[15] Additionally, a 12-week parallel intervention on 70 patients with T2DM indicated a significant reduction in FBS, weight, lipid profile, and blood pressure after CO intake.[14] Furthermore, SO is recognized as a source of high amounts of lignans (sesamin, sesamolin, and sesaminol) and vitamin E, and due to its acting as an antioxidant.[19,21,22] In addition, for over 4000 years, sesame has been grown worldwide particularly in tropical and semi-tropical climates, sandy soils, and under droughty conditions.[38] The health benefits of SO have attracted the attention of many researchers from Asian countries because of its high consumption rate in this area.[24,39] In a parallel trial performed by Sankar et al. on 356 patients with hypertension, SO elevated HDL-C and reduced lipid peroxidation in 6 weeks.[24] This study also reported the beneficial effects of SO on lipid profile, and enzymatic and non-enzymatic antioxidants.[24] A meta-analysis also found that SO consumption significantly reduced TG.[40] SO may improve both SBP and DBP,[19,24] and decrease the

lipogenic enzyme activities.[41] Additionally, the anti-atherosclerotic properties of SO were shown in an animal study.[23] Although both CO and SO are considered as healthy dietary vegetable oils, the effects of these two vegetable oils have not yet been compared. The present study was performed to compare the effect of replacing regular oil consumed by participants with T2DM and their spouses with SO, CO, and SCO on cardio-metabolic markers.

Strengths and limitations: This study was a three-way crossover study in which participants acted as their own controls. Compared to parallel-arm designs, crossover studies are proposed to have more precision and statistical power,[42] and minimize the confounding variables.[43] A recent systematic review reported that few crossover clinical trials have assessed the effect of SO on lipid profile in humans.[40] Furthermore, the mentioned systematic review reported that the intervention duration in the majority of crossover studies regarding the effect of SO on cardio-metabolic markers was less than 6 weeks, which is true for studies assessing the effects of CO as well.[15,18,19,34,37,38,44-55]

Additionally, with 93 study completers and enough biological samples, the present study enables researchers to examine the sex stratified effect of the intervention oils and different markers with high statistical power. Furthermore, this sample size will make studying gene-diet interactions possible in the future. Some strategies such as monthly visits, providing personalized results, and phone follow-ups motivated individuals to continue the study; thus, this trial was completed with a low attrition rate (8.8%). In the present study, we tried to improve the quality using standard methods for randomization, allocation concealment, and blinding which minimize the potential selection bias, confounding factors, and ascertainment bias.[56,57]

Furthermore, the present study, with a 9-week duration for each intervention phase, has a long period of intervention among crossover studies that have assessed the effect of CO[15,33,36,37,45,47-54,58,59] and SO[19,43] on different cardio-metabolic markers. The current study examined SCO, the blend of sesame and canola oil, as a new oil product and we are not aware of any similar studies. Additionally, in this trial, we aimed to replace the common oil intake of participants to assess the effects of the mentioned oils on their routine life.

Medications used by participants were recorded on each visiting day, and the investigators will be able to check the sensitivity of the results by removing those whose medications were changed. All the procedures reported in the present study were also performed for the participants' spouses, and thus, it is possible to investigate the effect of the intervention oils in adults without diabetes.

It should be noted that the exact amount of oil consumed by each person will not be clear; however, we tried to resolve this problem by asking the study participants and their spouses to report the mount of oil consumed as tablespoon in their food records, and the weight of oil provided before and after consumption in each phase was assessed.

Future investigations: The investigators are planning to compare the effect of the intervention oils on markers of glucose control including fasting serum insulin, homeostatic model assessment of insulin resistance (HOMA_IR) and quantitative insulin sensitivity check index (QUICKI), blood markers of kidney function (blood urea nitrogen and serum creatinine), liver enzymes [SGOT, SGPT, alkaline phosphatase (Alp), and gamma-glutamyl transferase (GGT)], markers of oxidative stress, and inflammatory markers in participants with T2DM and their spouses in the near future. The samples will also allow the investigators to examine the possible interactions between gene polymorphisms and intervention oils on cardio-metabolic markers. The principal investigators welcome possible collaborations with interested scientists and novel hypotheses that could be checked using the available samples and data obtained in the current study.

Conclusion

In summary, the current three-way, triple-blind, clinical trial will investigate the effect of replacing regular oil consumed by participants with T2DM and their spouses with SO, CO, and SCO (the blend of sesame and canola oil; a new oil production) on cardio-metabolic markers, anthropometric indices, and blood pressure. This study, with its large sample size and bio-banking of different fractions of blood, will provide the opportunity to explore the effect of dietary oils on different aspects of human health.

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Trial registration: The trial was registered at the Iranian Registry of Clinical trials (http:/www.irct.ir) with the registration code IRCT2016091312571N6 in November 2016.

Conflict of Interests

The study was jointly funded by Shahid Sadoughi University of Medical sciences and Datis Corporation. Datis Corporation did not take any part in the conception, design, and execution of the study protocol, and the reporting of the study results. The corporation did not have any other relationship with the investigators. The authors declare that they have no other potential personal or financial conflicts of interest. The principal investigator (ASA) declares that he has full access to the data and samples provided by this project.

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Immunohistochemical analysis of adiponectin in atherosclerotic lesions of human aorta

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Original Article

Abstract

BACKGROUND: Metabolic syndrome, a cluster of interrelated disorders including abdominal obesity, insulin resistance, dyslipidemia, and hypertension (HTN) plays an important role in development of atherosclerotic lesions in arterial wall. Dysregulation of adipose tissue hormones (adipokines) production is a possible link between abdominal obesity and other manifestations of metabolic syndrome. Adiponectin is a well-known adipokine which affects metabolism and inflammatory response. However, data on its role in atherogenesis are still controversial. The aim of this study is to investigate whether adiponectin is present in atherosclerotic lesions of human aorta.

METHODS: Thirty-five autopsy segments from abdominal, thoracic aortas, and aortic arch of four men (mean age: 57 years) were fixed and stained for lipids [Oil Red O (ORO)], cells [hematoxylin-eosin (H&E)], and adiponectin [indirect immunoperoxidase assay (IPA) method]. Samples of both stable and unstable plaques were selected for analysis. Human adipose tissue, THP-1 monocytes/macrophages, and human endothelial hybrid cell line (EA.hy926) were chosen for detection of adiponectin messenger ribonucleic acid (mRNA) using reverse transcription polymerase chain reaction (RT-PCR).

RESULTS: Adiponectin accumulations were found inside endothelial cells covering both stable and unstable atherosclerotic plaques. Focal depositions of adiponectin were also found in fibrous caps of stable lesions and atheromatous core of both stable and unstable plaques and also in adventitia. RT-PCR revealed mRNA expression of adiponectin gene in adipose tissue, but not in mononuclears and endothelial cells.

CONCLUSION: Adiponectin is present in aortic plaques of humans, but is not synthesized in endothelial cells and mononuclears, at least in culture conditions. Detection of adiponectin in atherosclerotic lesions can serve as indirect evidence of possible participation of this adipokine in atherogenesis.

Keywords: Adiponectin, Atherosclerosis, Aorta, Endothelium

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Introduction

Atherosclerosis is a complex chronic disease of arterial wall, which leads to development of major cardiovascular events including myocardial infarction (MI) and stroke. In spite of intensive research in this field, mechanisms of initiation and progression of atherosclerosis are still not completely understood. In particular, the molecular triggers of focal infiltration of apolipoprotein B-containing lipoproteins in atherosclerosis-prone areas of large arteries still need to be determined. Subsequent events in arterial wall depend on interaction between lipoproteins, extracellular matrix, and intimal cells: endothelial cells, mononuclears, and migrated smooth muscle cells (SMCs).

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Specifics of this interplay will lead either to formation of stable plaque with thick fibrous cap or development of unstable plaque, containing small number of SMCs, substantial necrotic core, and thin fibrous cap confining the active inflammatory process.[1]

One of the important risk factors of atherosclerosis is metabolic syndrome, a cluster of interrelated disorders, including abdominal obesity, insulin resistance, dyslipidemia, and hypertension (HTN).[2,3] These disorders are accompanied by dysregulation of production of adipose tissue-derived hormones and cytokines, named "adipokines", mostly due to expansion of abdominal adipose mass.[4] Adiponectin is a unique adipokine, which production in obesity, opposed to most other adipokines, is decreasing. Adiponectin has insulin sensitizing and lipid metabolism modulating effects, mostly implying its action on liver and muscles, and has some local effects on vascular wall as well.[4,5] Particularly, adiponectin modulates inflammatory response in endothelial cells and macrophages,[6-8] decreases mononuclears adhesion, enhances nitric oxide (NO) production by endotheliocytes,[9,10] inhibits foam cell formation,[8,11] and migration and proliferation of vascular SMC.[12,13] These effects are mediated by adiponectin receptors (AdipoRs), mostly by AdipoR1.[9,10] Recently, expression of T-cadherin in vascular wall was shown, a receptor that specifically binds to high-molecular-weight (HMW) adiponectin and mediates its cardio- and atheroprotective effects in mice.[14-16]

Nevertheless, the data regarding adiponectin influence on development of atherosclerosis are controversial. Adiponectin retarded atherosclerosis development or had no effects on this disease in mice,[17,18] and clinical studies found both negative and positive correlations of plasma adiponectin levels with frequency of atherosclerosis and its outcomes.[19,20] Hypothetically, such controversies could be explained by differences in vascular wall adiponectin accumulation, where this adipokine could act on atherogenesis directly. Previously, adiponectin was found in mouse but not in human aorta.[15,21] The aim of this study was to estimate the adiponectin presence and localization in aortic atherosclerotic lesions of human subjects.

Materials and Methods

For determination of adiponectin protein in aortic lesions, autopsy segments of aortic arch as well as thoracic and abdominal regions of aortas (in total n = 35) have been retrieved from four men (mean age of 57 ± 6 years, range: 50-62 years) who died of acute MI or sudden cardiac death. The exclusion criterion was the history of chronic autoimmune and inflammatory diseases. The study was approved by Ethical Committee of the Institute of Experimental Medicine, Saint Petersburg, Russia.

Samples of aorta were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH: 7.2-7.4). Paraffin and cryostat 3-5 μm slices were prepared for histological and immunohistochemical analysis. For evaluation of plaque stability, preparations were stained for lipids and cells, using Oil Red O (ORO) and hematoxylin-eosin (H&E), respectively. Unstable lesions were characterized by thin, disorganized, or damaged fibrous caps infiltrated with lipids and mononuclears (Figure 1).[22]

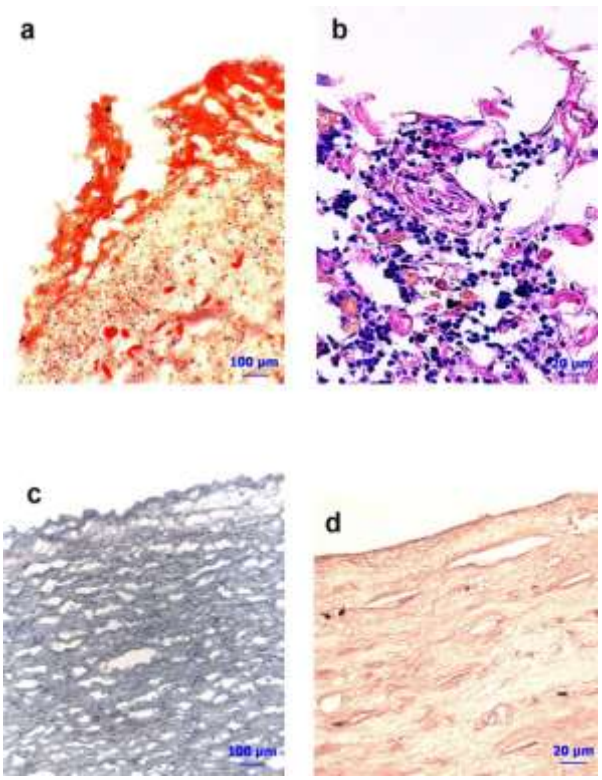

Figure 1. Morphological characteristics of stable and unstable atherosclerotic lesions of human aorta
(a) Huge depositions of lipids in surface layer of destructed fibrous cap of unstable lesion; (b) Mononuclear infiltration in damaged area of unstable lesion's cap; (c) Absence of lipids in the fibrous cap of stable plaque; (d) Absence of mononuclear infiltration in the fibrous cap of stable plaque; a and c: Oil Red O (ORO) staining; b and d: hematoxylin-eosin (H&E) staining

Detection of adiponectin in aortic slices was performed using indirect immunoperoxidase assay (IPA). Endogenous peroxidase was quenched by

treatment with peroxidase blocking reagent (cell and tissue staining kit, R&D Systems). The primary antibodies for adiponectin were taken from human adiponectin enzyme-linked immunosorbent assay (ELISA) kit (conjugate solution, BioVendor); goat anti-Rabbit IgG secondary antibody horseradish peroxidase (HRP)-conjugates were obtained from Abcam (ab97051, 50 μg/ml). The product has been developed after adding 3.3'-diaminobenzidine (brown staining). The nuclei were stained by methyl green (Dako). Negative control without primary antibodies was also assessed (Figure 2c). Microscopy was performed using Leica DM2500, and microphotographs were obtained by Leica DFC420 photocamera and Leica Application Suite software (version 3.4.0).

Quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay: For evaluation of possible adiponectin synthesis in vascular wall, we performed adiponectin qRT-PCR analysis in cell cultures of human macrophages and endothelial cells. For doing this, THP-1, a human monocytic cell line, and EA.hy926, an immortalized endothelial hybrid cell line, were applied in the study. THP-1 and EA.hy926 cells were cultivated, respectively, in RPMI-1640 and Dulbecco's Modified Eagle Medium (DMEM) media, supplemented with 10% fetal bovine serum and antibiotics as described earlier.[23,24] THP-1 mononuclears were differentiated into macrophages by treatment of these cells with phorbol 12-myristate 13-acetate (PMA) (50 ng/ml, 24 h).[23] Total ribonucleic acid (RNA) was isolated from the cells, using TRI reagent (Ambion) according to manufacturer's protocol. 500 ng of RNA was reverse-transcribed and SYBR Green PCR was performed as in Mogilenko et al.[23] Primers were designed using Primer3 software (http://primer3.sourceforge.net/): adiponectin transcript 1, forward 5'-TCTGATTCCATACCAGAGGAGAC-3' and reverse 5'- GCCCTGATGTCAGGAGTTTC-3', adiponectin transcript 2, forward 5'-GATTCCATACCAGAGGGGCT-3' and reverse 5'-ATGACCGGGCAGAGCTAATA-3', CD31, forward 5'- GGCTTGGAGTCCTGCTGA-3' and reverse 5'- AAGCACTGCAGGGTCAGG-3'. CD31 or platelet/endothelial cell adhesion molecule-1 (PECAM-1) was used as a marker of endothelial and mononuclear cells.[25] The specificity of PCR was determined evaluating melting curves and agarose gel electrophoresis of amplicons. The expression of genes of interest was normalized by geometric mean of relative content of three references: β-actin, cyclophilin A (CyPA), and ribosomal protein lateral stalk subunit P0 (RPLP0).[26]

As a positive control for adiponectin gene expression, fragments (3-5 g) of femoral adipose tissue were obtained from one man after liposuction and put into TRI reagent for subsequent RNA extraction and qRT-PCR. Informed consent was obtained from this patient.

Results

Adiponectin detection in atheromas of human aorta: Immunohistochemical analysis of atherosclerotic lesions revealed localizations of adiponectin in different layers of aorta. Local intracellular depositions of adiponectin were visualized in endothelial layer covering both stable and unstable atherosclerotic plaques (Figures 2a and 2b). In addition, adiponectin was found in superficial and deep areas of fibrous caps (Figures 3a and 3b), probably due to migration of this adipokine into depth of vascular wall.

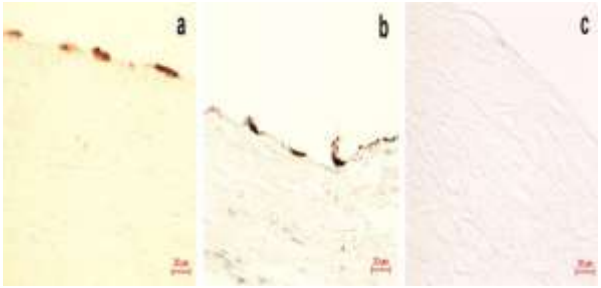

Figure 2. Adiponectin in endothelium of stable and unstable atherosclerotic plaques of human aorta
Focal adiponectin depositions in cytoplasm of endothelial cells covering the stable (a) and unstable (b) atherosclerotic plaques; disorganized fibrous cap and damaged endothelium in unstable plaque are seen in (b); (c) Negative reaction for adiponectin in a preparation of stable plaque, elaborated without primary antibodies [immunoperoxidase assay (IPA)]

Adiponectin has also been identified in atheromatous core of stable atherosclerotic plaques, mainly around lipid deposits (Figure 3d) and in adventitia underneath the stable plaque (Figure 3c). Adiponectin was also detected in deep areas of unstable lesions (Figure 3e).

***Adiponectin gene expression in THP-1 and EA.hy926 cell lines*:** qRT-PCR analysis revealed adiponectin mRNA in adipose tissue but not in EA.hy926 endothelial cells and human THP-1 monocytes/macrophages, while endothelial and mononuclear marker CD31 was expressed in all cell types studied (Figure 4).

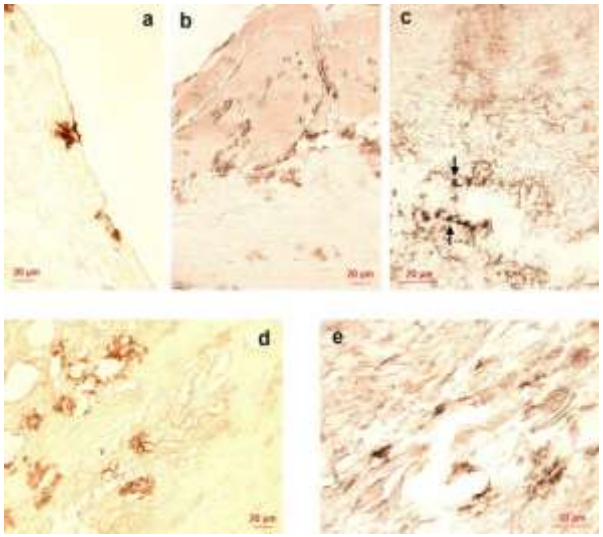

Figure 3. Adiponectin depositions in different parts of atherosclerotic plaque of human aorta

(a) Focal depositions of adiponectin in a surface layer of stable atherosclerotic plaque; (b) Adiponectin in deep areas of thick fibrous cap of stable plaque; (c) The sites of adiponectin depositions (arrows) in adventitia under the stable plaque; (d) Adiponectin depositions at the atheromatous core of stable plaque; (e) Intracellular adiponectin depositions in intima of ruptured plaque [immunoperoxidase assay (IPA)]

Discussion

Clinical,[19,20] animal,[17] and cell culture studies[6-8,10-13] strongly support involvement of adiponectin in atherogenesis. It remains unclear whether adiponectin acts locally in vascular wall.

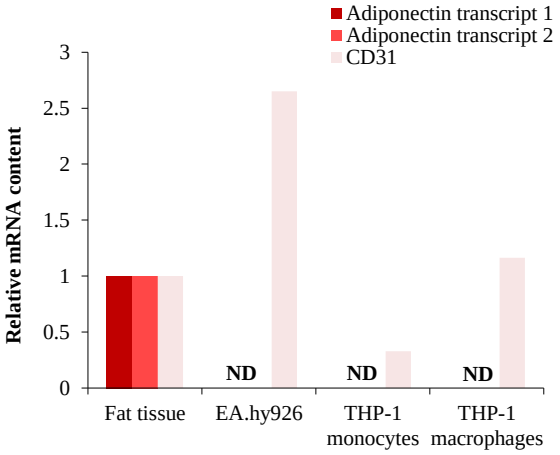

Figure 4. Relative adiponectin and CD31 gene expression in human fat tissue, endothelial hybridoma cell (EA.hy926), and THP-1 mononuclears

Gene expression levels were assessed by quantitative reverse transcription polymerase chain reaction (qRT-PCR) and normalized for the relative content of β-actin, cyclophilin A (CyPA), and ribosomal protein lateral stalk subunit P0 *(RPLP0);* ND: Not detected

We found that adiponectin was present in human aortic atherosclerotic plaques. Adiponectin was found in all layers of aorta affected by both stable and unstable lesions: endothelium, fibrotic cap, atheromatous core, and adventitia. Earlier, Kostopoulos et al.[15] did not find adiponectin protein in human aortic and coronary plaques. Only slight signal was detected in adventitia, probably due to low sensitivity of assay performed. In another research, adiponectin was found in subendothelium of injured but not intact aorta in a patient with aortic aneurysm.[27] Recent study has shown that adiponectin is present in human carotid arteries and plaques, and its content is increased in unstable lesions.[28] Similar to our observations, the authors also found adiponectin in endothelium, fibrous cap, and lipid core, presumably in areas with foam cells. Adiponectin was also detected in both atherosclerotic and normal mouse aortas, mostly on luminal surface and in intracellular vesicles of endothelial cells, and also on the surface of monocytes and SMCs in atherosclerotic lesions.[21] We examined only atherosclerosis-affected aortas, and future studies will reveal if adiponectin accumulation also occurs in normal aortic vessels of humans.

Interestingly, in contrast to above-mentioned observations,[21,27,28] we found focal adiponectin accumulation in vessels. Mechanism of its uneven deposition, particularly in endothelium and fibrous cap, needs further investigation. It could be related to focal processes of atherogenesis such as disturbed permeability of endothelium, its dysfunction, inflammatory reactions, etc. These events could lead to local synthesis, uptake from plasma, or retention of adiponectin in aorta. Adiponectin mRNA was not detected in both normal and atherosclerotic carotid arteries,[28] while it was found in murine aortas in one of the two studies.[29,30] We also have not found adiponectin mRNA in cultured human monocytes/macrophages and endothelial cells, and these data are in line with the absence of this adipokine synthesis in intimal layer of human artery, as was shown earlier.[28]

Uptake, transport, and retention of adiponectin in vessels could be mediated by AdipoRs. Indeed, AdipoRs, AdipoR1 and AdipoR2, are expressed in endothelium, SMCs, macrophages, and foam cells of human carotid artery, i.e., in the same cell types, where adiponectin was detected.[28] T-cadherin, another binding partner for adiponectin, is also expressed in endothelium and SMC of vascular wall.[15,16] Future investigations will reveal whether T-cadherin and AdipoR1/R2 are expressed and colocalized with

adiponectin deposition in human aorta.

We detected adiponectin in both stable and unstable plaques. We did not include in this investigation samples of nonlesioned aorta, so it is not known whether adiponectin specifically accumulates in atherosclerotic regions or also in unaltered areas of aorta. Nevertheless, the presence of adiponectin in aortic plaques suggests possible involvement of this adipokine in atherogenesis. The other limitation is that the data were obtained only from men with one specific age range (50-62 years). Since plasma concentration of adiponectin is gender- and age-dependent, it is not known if women and younger people have the same patterns of adiponectin accumulation as aged men. Finally, we still do not exactly know the source of adiponectin in aortic plaques. RT-PCR analysis of aortic intima/plaques will partially resolve this problem.

Conclusion

We found for the first time the presence of adiponectin in human aortic plaques. Focal depositions of adiponectin were found in endothelium, fibrous cap, atheromatous core of both stable and unstable plaques, and also in adventitia. Adiponectin RNA was not detected in THP-1 monocytes/macrophages and EA.hy926 endothelial cells, but there is possibility of local synthesis of adiponectin in aortic plaques or normal aorta. Detection of adiponectin in atherosclerotic lesions can serve as an indirect confirmation of local involvement of this adipokine in atherogenesis.

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Conflict of Interests

Authors have no conflict of interests.

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Comparing efficacy of receiving different dosages of eptifibatide in bleeding after percutaneous coronary intervention in patients with myocardial infarction

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Original Article

Abstract

BACKGROUND: Acute coronary syndrome (ACS) is a common condition that needs appropriate treatment like percutaneous coronary intervention (PCI). Glycoprotein IIb/IIIa inhibitors (GPI) like eptifibatide prevent procedural ischemic complications after PCI. Eptifibatide has increased the risk of bleeding complications, although it is effective in reducing mortality and morbidity. Eptifibatide is routinely used in bolus and infusion forms and the aim of this study is to evaluate the efficacy of bolus-only dose and bolus + infusion strategy for administrating eptifibatide in bleeding complications and consequences after PCI.

METHODS: This randomized clinical trial was conducted on subjects who experienced PCI after incidence of myocardial infarction (MI). Patients were randomly divided into two groups who received bolus-only dose (n = 51) or bolus + infusion form of eptifibatide (n = 50). Then, PCI blood pressure, mean time duration of hemostasis after arterial sheath removal, laboratory data, need for blood transfusion, and presence of bleeding complications were evaluated. After 6 months, patients were followed for needs for additional coronary interventions.

RESULTS: The mean age of participants was 61.68 ± 1.50 years. The prevalence of men was 70.29%. There was no significant difference in mean of systolic blood pressure (SBP) and diastolic blood pressure (DBP) during hospitalization ($P > 0.050$). The mean time duration of hemostasis was 8.13 ± 0.45 minutes in the bolus-only group and 16.46 ± 0.71 minutes in the bolus + infusion group ($P < 0.001$). There was no significant difference in the hemoglobin (Hb) level, platelet count, white blood cell (WBC), blood urea nitrogen (BUN), and creatinine level ($P > 0.050$).

CONCLUSION: The results of this study suggested that bolus-only dose of eptifibatide before PCI could be able to decrease significantly bleeding complication and other clinical and cardiovascular outcomes.

Keywords: Eptifibatide, Percutaneous Coronary Intervention, Bleeding, Dosage, Infusion, Myocardial Infarction

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Introduction

About 17 million people worldwide die due to cardiovascular diseases (CVDs) including acute coronary syndrome (ACS).[1] ACS is a common condition caused by plaque rupture and thrombosis which needs proper treatment interventions.[2]

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The main aim of treatment is establishing reperfusion which is done by fibrinolytic therapy or percutaneous coronary intervention (PCI).[3]

Glycoprotein IIb/IIIa inhibitors (GPI) are potent antagonists for platelet aggregation that can prevent procedural ischemic complications after PCI.[4] GPI have anti platelet, anti-thrombotic, and anti-inflammatory features and studies reported that treating patients with ACS with GPI before PCI can improve this intervention efficacy and facilitate it.[5,6]

Eptifibatide (Integrilin®, Millennium, Schering-Plough Corporation) is a GPI that inhibits adhesion of fibrinogen and von willebrand factor (VWF) to GP IIb/IIIa receptors and usually is prescribed in combination with aspirin or heparin in patients with angina who are candidate for coronary interventions.[7] In patients with myocardial infarction (MI) who were treated with PCI, using high dose of eptifibatide reduced 35% of mortality and morbidities.[8] Recent studies reported that routine treatment with eptifibatide had significant clinical benefits and reduced death rate, MI, and need for urgent revascularization.[9]

Although administrating eptifibatide in patients who are candidate for PCI is beneficial, this type of medication increases risk of bleeding, which leads to discontinuing treatment with this medication.[8] Extended eptifibatide infusion after successful PCI has a number of complications. Long-term exposure to this medication can increase the risk of bleeding after arterial sheath removal. In addition, extended infusion of medications increases hospital stay of patients who underwent PCI and rises practical issues related to post-PCI inter-hospital transport.[10] In a cohort study on patients with MI who experienced PCI using one bolus dose of eptifibatide in comparison to routine treatment, no significant differences in clinical outcomes and complications were observed, but one bolus dose of eptifibatide was more cost-effective.[11] According to the wide use of GPI medications like eptifibatide in patients who are candidate for PCI and the high prevalence of bleeding complications of these medications, evaluating suitable treatment time duration of them is necessary. This study aimed to compare the effect of receiving bolus-only dose and bolus + infusion form of eptifibatide on bleeding complications and consequences after PCI on patients with MI in Isfahan, the third populated province in Iran.

Materials and Methods

Study design and population: This nonrandomized clinical trial was done from February 2015 to September 2016 in the Chamran Hospital which is a referral university hospital in Isfahan. The study design was approved by regional bioethics research committee of Isfahan University of Medical Science (IRCT code: IRCT2017071935183N1).

In total, 108 patients who suffered from MI and were candidate for angioplasty interventions entered in the study and after obtaining written content and considering exclusion criteria, 101 subjects were analyzed. The inclusion criteria were: 1) age more than 18 years, 2) increased troponin enzyme level, 3) electrocardiogram (ECG) changes, 4) being candidate for angioplasty, 5) having no contraindication for administrating eptifibatide, and 6) patient's willingness to participate in this study. Exclusion criteria included: 1) history of stroke, 2) treating with anti-coagulants, 3) treating with medications that had interaction with eptifibatide, 4) being candidate for angiography without PCI, 5) being candidate for thrombectomy, 6) sensitivity to eptifibatide, 7) having uncontrolled high blood pressure, 8) dialysis patients, and 9) patient's unwillingness to participate in this study. In addition, the patient's creatinine clearance < 50 mg/min was another exclusion criterion. About 1 mcg/kg/min of eptifibatide was infused and if patients had creatinine > 4 mg/dl, they were excluded from study. All patients were monitored in hospital after PCI.

Procedure and variables assessment: Sample size was determined based on the previous studies. Patients were selected by using availability sampling methods and then divided into two groups using random sampling allocation system. Patients in both groups received 180 mcg/kg eptifibatide in bolus form from peripheral vessel in 8 minutes during their PCI. After PCI, patients in the first group received routine treatment including 75 mg Clopidogrel in every 12 hours. Patients in the second group received routine treatment in addition to 10-hour infusion of 2 mcg/kg/min eptifibatide with maximum dose of 15 mcg/hour.

After that intervention data were extracted from each patient's records, they were entered in the questionnaire as follows: demographic data (age and gender), physical examination outcomes [mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) during hospitalization and the lowest SBP and DBP, the mean time duration of hemostasis after sheath removal], laboratory data during hospitalization and discharge [hemoglobin (Hb), platelet, white blood cell (WBC), blood urea nitrogen (BUN), creatinine], need for receiving blood

products, and presence of bleeding and hematomas during hospitalization. After discharge of patients, they were followed for 6 months and after 6 months, authors contacted patients with telephone call and asked them if they had experienced any cardiovascular intervention during these 6 months.

Statistical analysis: Data were entered into SPSS software (version 19, SPSS Inc., Chicago, IL, USA) and then analyzed. For reporting quantitative and qualitative variables, we used mean ± standard deviation (SD) and number and percentage, respectively. Kolmogorov–Smirnov test (K-S test) was used for checking normality assumption. For analyzing quantitative variables, t-test was used and for comparing qualitative variables chi-square test (or Fisher's exact test) was used. P-value less than 0.050 was consider as statistically significant.

Results

In this study, 120 patients were assessed for eligibility and 12 of them were excluded because of not meeting inclusion criteria (n = 5) or declining to participate in this study (n = 7), and 108 patients were randomly divided into two groups, each group containing 54 patients. Figure 1 shows that how 101 patients (51 in the first group and 50 in the second group) were analyzed. In this study, the mean age of participants was 61.68 ± 1.50 years. Among participants, 20.80% (n = 21), 27.72% (n = 28), and 51.48% (n = 52) had ST-elevation MI (STEMI), Non-STEMI, and stable ischemic heart diseases (SIHds), respectively. There were not any significant differences between two groups in distribution of these types of CVDs (P = 0.710).

In the first 96 hours after PCI, patients did not show any deaths, MI, or stroke in both groups. The need for receiving blood products in the first week after PCI was occurred in 5.8% (n = 3) of patients in the first group and no patients in the second group needed this blood transfusion (P = 0.310).

The mean time duration of hemostasis after sheath removal was 8.13 ± 0.45 minutes and 16.46 ± 0.71 minutes in the first and second groups, respectively (P < 0.001). The mean SBP and DBP and also the lowest SBP and DBP during hospitalization were not statistically different between two groups (P = 0.320 and P = 0.630 for SBP, P = 0.510 and P = 0.400 for DBP).

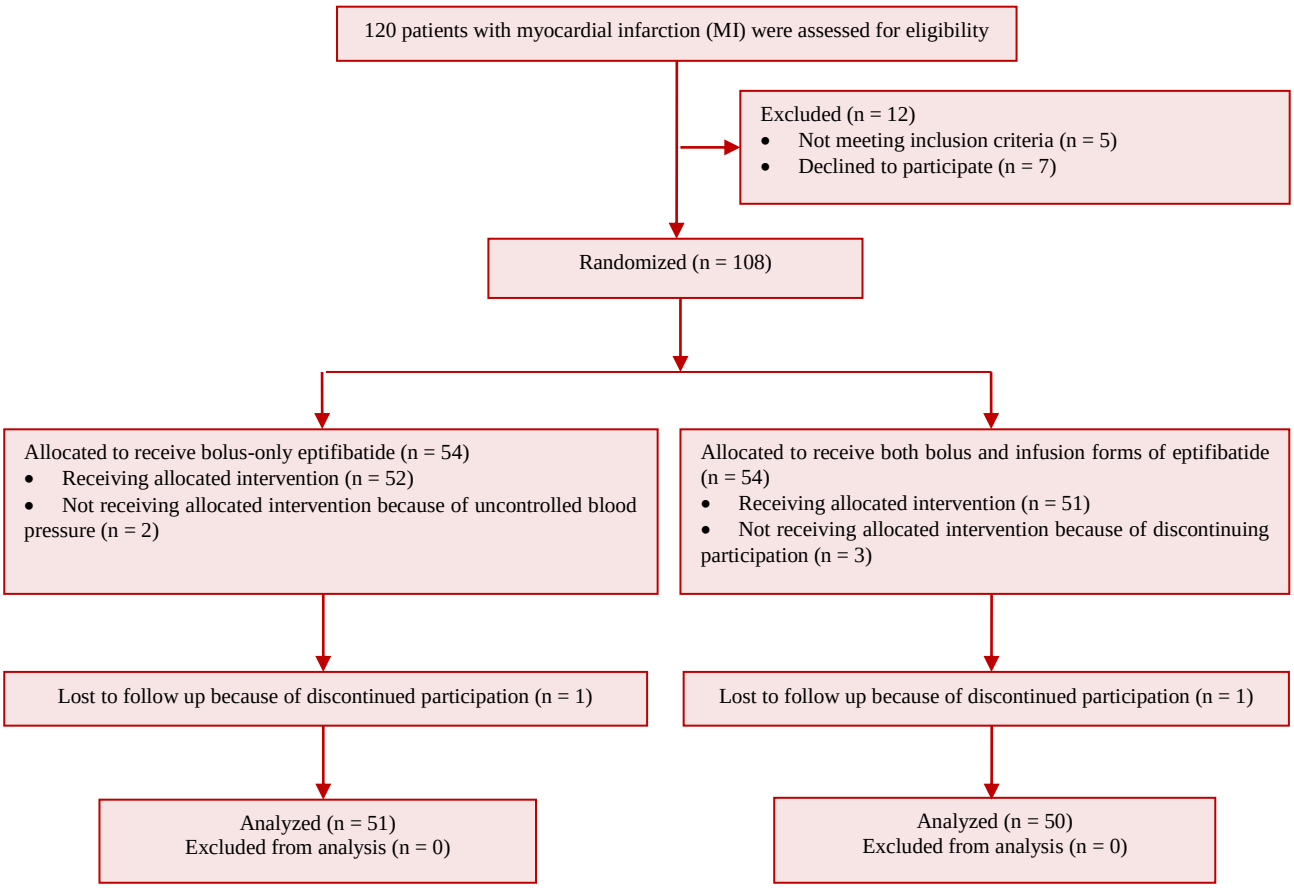

Figure 1. Participation in this study

Table 1. Clinical and laboratory measurements

Variables		Bolus-only eptifibatide (n = 51) Mean ± SD	Bolus plus infusion eptifibatide (n = 50) Mean ± SD	P*
Mean SBP during hospitalization		136.70 ± 3.90	131.67 ± 8.24	0.320
The lowest SBP		107.45 ± 2.34	107.08 ± 4.71	0.630
Mean DBP during hospitalization		84.77 ± 2.44	82.27 ± 4.63	0.510
The lowest DBP		69.52 ± 1.72	66.81 ± 2.54	0.400
Mean time duration of hemostasis (minute)		8.13 ± 0.45	16.46 ± 0.71	< 0.001
Hb	During hospitalization	13.71 ± 0.23	14.60 ± 0.32	0.470
	At discharge	13.33 ± 0.37	13.60 ± 0.78	0.660
Platelet count	During hospitalization	218.89 ± 4.72	218.17 ± 18.78	0.840
	At discharge	243.38 ± 23.96	195.00 ± 39.61	0.730
WBC	During hospitalization	8608.13 ± 559.27	10900.00 ± 1177.18	0.150
	At discharge	8924.28 ± 948.48	10951.25 ± 3844.81	0.390
BUN	During hospitalization	27.53 ± 3.30	31.83 ± 3.72	0.130
	At discharge	35.89 ± 3.92	34.20 ± 3.37	0.790
Creatinine	During hospitalization	1.10 ± 0.04	1.10 ± 0.11	0.220
	At discharge	1.07 ± 0.05	1.28 ± 0.16	0.200

* Independent t-test

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Hemoglobin; WBC: White blood cell; BUN: Blood urea nitrogen; SD: Standard deviation

The mean level of Hb, WBC, platelet, BUN and creatinine were not different between two groups during hospitalizations and in discharge time (P > 0.050). Comparing these variables in each group between the time of hospitalization and discharge did not show any significant differences (P > 0.050) (Table 1).

Evaluating bleedings and hematoma showed that there was just 1 patient (1.96%) in the first group who had severe bleeding with hemodynamic impairment and patients in the second group did not show any bleedings (P = 0.580). About 13.72% (n = 7) in the first group and 50% (n = 25) in the second group showed hematoma in the site of angiography that most of these hematomas were < 5 cm. There was a significant difference between two groups in the presence of hematoma in the site of angiography (P = 0.030). Retroperitoneal hematoma was just occurred in 1.98% (n = 2) of participants that both of them were in the first group (P = 0.430) (Table 2).

Patients follow-up 6 months after PCI showed that about 25.5% (n = 13) of patients in the first group and 38.0% (n = 19) in the second group did not need any additional cardiovascular intervention. Among those who needed additional coronary intervention in 6 months duration after PCI, patients in the second group needed angiography and PCI and those in the first group needed angiography, PCI, stent, and even coronary artery bypass graft (CABG). Comparing these interventions between two groups did not show any statistical significant differences (P = 0.060) (Table 3).

Table 2. The prevalence of bleeding and hematomas among patients who received bolus-only from or bolus+ infusion form of eptifibatide

Variables		Bolus-only eptifibatide (n = 51) [n (%)]	Bolus plus infusion eptifibatide (n = 50) [n (%)]	P*
Bleeding	No bleeding	50 (98.03)	50 (100)	0.580
	Mild	0 (0)	0 (0)	
	Moderate	0 (0)	0 (0)	
	Severe	1 (1.97)	0 (0)	
Hematoma size (cm)	Less than 5	4 (7.84)	15 (30.00)	0.030*
	5-10	1 (1.96)	14 (7.00)	
	More than 10	2 (3.92)	3 (6.00)	
Retroperitoneal hemorrhage	Yes	2 (3.92)	0 (0)	0.430

* Fisher's exact test

Table 3. The needs for more intervention in both groups (receiving bolus-only from or bolus + infusion form of eptifibatide) after six months

Variables	Bolus-only eptifibatide (n = 51) [n (%)]	Bolus plus infusion eptifibatide (n = 50) [n (%)]	P*
No more intervention	13 (25.50)	19 (38.00)	0.060
Angiography	5 (11.11)	4 (8.00)	
Angiography + PCI	25 (55.56)	26 (52.00)	
CABG + PCI	1 (2.22)	0 (0)	
CABG + angiography	2 (4.44)	0 (0)	
Angiography + PCI + stent	5 (10.10)	0 (0)	
PCI + stent	0 (0)	1 (2.00)	

* Fisher's exact test

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft

Discussion

This study evaluated 101 patients with MI who were candidate for angiography and PCI for the effects of administrating eptifibatide in bolus and infusion forms. This study showed that although there was no difference in short-term and long-term outcomes between these two methods of administrating the medication, the prevalence of bleeding was significantly higher in those who received eptifibatide in infusion form.

Abrupt coronary artery closure after percutaneous coronary revascularization is one of the main causes of mortality and morbidity accompanied with this procedure.[12] Despite the routine use of aspirin and heparin, ischemic complications were seen in 8%-10% of cases.[13] Platelet adhesion, activation, and aggression are the key processes leading to thrombosis. The end stage of thrombosis formation is binding of fibrinogen to platelet integrin GP IIb/IIIa. GPI are medications that inhibit the end stage of this process and reduce ischemic complications after coronary interventions.[14]

This study showed that bleeding events were more probable in patients who had longer exposure to eptifibatide, although there were similar clinical outcomes between two groups. One study that evaluated eptifibatide in patients with NSTEMI showed that there were not any differences between eptifibatide and placebo in incidence of bleeding complications after PCI. In this study, the prevalence of bleedings was 2.7% and the most common type of bleeding was gastrointestinal (GI).[15] In another study on patients with unstable angina, two doses of eptifibatide were compared with placebo and there was no difference between patients in bleeding events and just minor bleeding was more prevalent in those who received any dose of eptifibatide. In addition, platelet count and need for blood transfusion was similar in all participants.[16,17] Most of the studies evaluated eptifibatide in comparison to placebo or other anti-platelet medications; also there are other studies that evaluated various doses of this medication in comparison to each other and there are limited studies comparing different methods of administrating this medication. This study compared the bolus and infusion forms of this medication, although most of the studies administrated this medication in infusion form with different doses. Fung et al. evaluated 624 patients with stable angina, ACS, and STEMI. In this study, patients were divided into two groups and received abbreviated infusion of eptifibatide (less than 2 hours) and standard infusion of eptifibatide (18 hours). In this study, bleeding events were statistically lower in those who received this medication in abbreviated form and the incidence of MI, stent thrombosis, and death 30 days after intervention was not different between groups. This study showed that prescribing eptifibatide in less than 2 hours infusion was successful, uncomplicated, and safe; and shortening infusion duration reduced bleeding events without eliminating the role of GPI.[10] Findings of this study are similar to other limited studies which evaluated the bolus-only strategy of administrating eptifibatide. Kini et al. compared the bolus-only and bolus + infusion forms of prescribing eptifibatide in patients who underwent PCI and showed significant reduction in bleeding complications and equivalent clinical outcomes with bolus-only eptifibatide method when compared with bolus + infusion strategy. It also showed that bolus-only eptifibatide could improve incidence of ambulatory PCI and reduce length of hospital stay and also it was more cost-effective in comparison to bolus + infusion strategy.[18] There is one study that is slightly different from our findings. Bertrand et al.

evaluated the bolus-only and blouse + infusion forms of Abciximab as an GPI on patients who were candidate for transradial coronary stenting and showed that the incidence of bleeding, MI, death, urgent revascularization, and repeated hospitalization was more in those who received just the bolus form of Abciximab.[11] Maybe this study has different outcomes because of using another GPI, and most of the studies which evaluated eptifibatide had similar findings to our study.

GPI can cause thrombocytopenia which increases the risk of serious bleedings. In a study evaluating 9 patients who received eptifibatide and showed thrombocytopenia, there was evidence from platelet destruction that was caused by drug dependent immunoglobulin G (IgG) antibodies. This study suggested that we could evaluate the risk of thrombocytopenia and bleeding in patients who received eptifibatide by screening patients for these antibodies.[19]

The present study suffers from a number of limitations that must be taken into account in the interpretation and generalization of these results. The sample size of this study was too small for generalizing these findings to general population and evaluating the exact differences between eptifibatide bolus only and bolus + infusion strategies and it is better to plan another study with larger sample size. Another limitation is evaluating limited variables as an outcome of this study. Further studies should consider other variables associated with these types of treatment strategies including hospital stay, and patient's satisfaction and quality of life.

Conclusion

This study showed that bolus-only eptifibatide before PCI caused significant reduction in bleeding complications and equivalent clinical and cardiovascular outcomes in comparison to bolus + infusion strategy of prescribing eptifibatide.

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None.

Conflict of Interests

Authors have no conflict of interests.

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Stressors in open-heart surgery patients: A qualitative study

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Case Series

Abstract

BACKGROUND: Open-heart surgery is a stressful experience for the patients and their families. From the moment that patients are told they must undergo surgery until discharge, they experience different degrees of worry and nervousness. This study was conducted with the aim of identifying stress factors in heart surgery patients.

METHODS: This study was performed using a qualitative method on 21 participants (14 patients and 7 caregivers). The research environment was open-heart surgery wards of two educational hospitals in Ahwaz (south of Iran) in 2017. The participants were selected through purposive sampling. The data were collected through semi-structured interviews, and then, analyzed using the qualitative approach of content analysis proposed by Graneheim and Lundmnan (2004).

RESULTS: The 5 themes of "physical stressors", "self-care stressors", "psychological stressors", "religious stressors", and "hospital stressors" were obtained. These themes were the result of the patients' experiences and dimensions of patients' perceptions regarding stressors in open-heart surgery.

CONCLUSION: Stress in patients undergoing open-heart surgery is a contextual and relative concept and a subjective experience, which is experienced as a sense of worry. Identifying and clarifying stressors in open-heart surgery patients for nurses is vital, like a key for improving care quality. Nursing managers in clinical practice can also benefit from these findings regarding heart surgery in improving the care quality and professional performance of nurses.

Keywords: Cardiac Surgical Procedures, Stress Psychological, Stressor Related Disorders, Qualitative Research

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Introduction

Coronary artery bypass graft (CABG) and/or valve repair/replacement are the most common surgical interventions for cardiovascular diseases (CVDs).[1] In Iran, 35-50 thousand heart surgery operations are performed annually.[2] Although open heart surgery is a successful interventional technique in cardiovascular care and treatment, it is a stressful and life-threatening experience accompanied by fear and anxiety for many patients and their families.[3] During this hard period, patients face various physical, psychological, and social stressors and experience a great deal of worry.[4,5] In this regard, studies have shown that confronting numerous stressors from the time of diagnosis until discharge, and lack of fulfillment of physical, psychological, and educational needs cause a sense of shock, disbelief, anger, fear of death, and threat in patients and their families.[3,6] Therefore, understanding updating stressors experienced by open heart surgery patients throughout the whole procedure of diagnosis, treatment, and discharge is essential.[6]

The main issue that aggravates vulnerability in patients is receiving undesirable and unsuitable care, which is not in line with their needs.[7] Doering et al.[8] found that patients undergoing open heart surgery request to be acknowledged as a human by their physicians and nurses during the recovery period; they manage pain, sleep, and other physical problems accurately, and give them care information at the time of discharge.

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The medical team should also know that these patients need different types of information.[8]

Controlling and managing stress and stressors experienced by sick patients should be undertaken by all care providers in the medical team. Attention to this issue will assist in the identification of stressors patients experience during critical care. It will also provide care providers, especially nurses, with a greater insight into the perception of patients about stressors. It can be said that by providing care and more effective and satisfactory interventions, nurses provide the ground for stress mitigation. Managing stressors in heart surgery patients may shorten their hospitalization duration and have a better effect on their improvement and recovery process.[9]

According to studies, the content of cares and interventions may often be based on nurses' perceptions about stressors, not on patients' perceptions. Thus, nurses prioritize patients' problems according to their own perceptions, and perform planned cares accordingly.[10] Using their self-designed instrument to measure stressors in two groups, CABG patients and nurses, Carr and Powers concluded that the nurses' opinions are different from that of patients.[11] In addition, nurses had considered some items as strong stressors for the patients, while the patients themselves had given lower scores to those items.[11]

Regarding the determination of perceived stressors in heart surgery patients and nurses, Yarcheski and Knapp-Spooner concluded that opinions differed and patients had given a higher score to "being far from house and workplace", while nurses had considered "death resulting from disease or surgery" as highly stressful.[12] Overall, nurses had given higher scores to stressful items.[12]

In other words, if nurses' perceptions about the patients' stress are in contrast to the real perceived stress by the patient, they will offer less effective intervention to eliminate or mitigate stressors in patients. Nurses should be able to evaluate stressors in patients accurately to provide the necessary care and focus on their interventions more effectively.[13] Moreover, in different cultures, there is a different perception about stress and stressors. Furthermore, in these various cultures, people act differently in responding to the perceived stresses and apply different solutions to cope with them.[14]

Open-heart surgery nurses take care of patients in different situations in special clinical environments; thus, irrespective of the special conditions of any disease, to understand the real experiences and emotions of patients in clinical practice and promote nursing quality, the concept of stressors should be clarified using individual experiences, i.e., the group of patients undergoing heart surgery. Therefore, conducting qualitative research seems to be essential in the context of Iran. This study was performed with the aim of discovering stressors in open-heart surgery patients.

This study aimed to identify and describe stress factors in heart surgery patients.

Materials and Methods

A qualitative design, based on the content analysis approach, was used for data collection and analysis of the perspectives of Iranian open-heart surgery patients regarding stress factors. Qualitative research aims to explore complex phenomena experienced by clinicians, healthcare providers, policymakers, and consumers in the healthcare system.[15]

The study participants consisted of 21 individuals (14 patients and 7 care provider) who were selected using purposeful sampling. The research environment was the open-heart surgery wards of two educational hospitals in Ahwaz, Iran, from May 2016 to March 2017. The inclusion criteria were hospitalization after undergoing heart surgical operation for the first time, a minimum age of 18 years, consciousness, the ability to talk, and willingness to restate experiences to the researcher. Among the care providers, all individuals in the medical team including informal caregivers, nurses, and physicians were interviewed.

To achieve a comprehensive description of the experiences of participants in the pre-operative and post-operative process or different caregivers, a maximum variation in sampling in terms of age, gender, level of education, type of open-heart surgery, and socioeconomic status was used.[16]

Semi-structured interviews were conducted by the first author (SS). The data were collected using in-depth interviews from May 2016 to March 2017. Following a literature review and input from members of the research team, a semi-structured interview guide was developed. The interview guide was tested in a pilot study with 3 participants. All interviews with the patients were performed at their bedside. Other participants were interviewed in the office of the open-heart surgery wards. Before the interview, explanations were given about the objective of the study, information confidentiality, and recording the interviews.

The main questions used in the interview were: "Please restate your experience about open-heart

surgery" or "What were your concerns when they said you should be operated?". Furthermore, the open question used in interviews with the care providers was "According to your experience, what are the concerns of heart surgery patients from hospitalization to discharge?" This was followed by asking follow-up questions based on the responses and information given by the participant to better clarify the studied concept.

The interviews lasted 20-90 minutes and were audio recorded using a digital recorder, transcribed verbatim, checked for accuracy, corrected, and coded. The transcribed interviews were analyzed using the content analysis approach. Content analysis is used commonly in nursing. Through content analysis, it is possible to distill words into fewer content-related categories.[17] During the data analysis, the interviews were read several times to gain a sense of the whole. The text was divided into meaning units, which were condensed. The condensed meaning units were abstracted and labeled with codes. The codes were sorted into subcategories and categories based on comparisons regarding their similarities and differences. Finally, themes, as the expression of the latent content of the text, emerged.[18] Themes and subthemes that described the open-heart surgery patients' perspectives on providing stress factors were identified.

For establishing trustworthiness, researchers propounded four criteria including credibility, dependability, confirmability, and transferability.[19] To enhance data credibility, prolonged engagement with the research subject and data, and member check (giving back some of the interviews after coding to the participants to investigate the extent of consensus over codes among researchers and participants for comparison) were conducted. For dependability, the researcher recorded and reported the stages and procedure of the research carefully, so that others could also follow up on the research. In addition, confirmability was measured through external check controls, who were familiar with qualitative research. This means that parts of the interview text along with the relevant codes and classes emerged were investigated and confirmed by two observers familiar with qualitative research. For transferability, maximum variation sampling technique, i.e., selection of participants in terms of gender, age, marital status, education, hospitalization duration, type of heart surgery, and occupation, was used.

The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Iran, approved the study's research proposal (IR.AJUMS.REC.2016.386). The official permits were issued by the university and hospital before data collection. Participation in the study was based on the principle of autonomy, and it was performed on the ground of informed consent and willingness to participate in the interview. In addition, the participants were informed that their identity would be kept confidential when the research findings are reported.

Results

Overall, 21 interviews were performed, 14 with heart surgery patients (8 women and 6 men) and 7 with caregivers (3 informal caregivers, 3 nurses, and 1 heart surgeon). The mean age of the patients was 48.64 ± 15.42 years, and they were mostly women (57.1%), married (86.7%), and had undergone CABG surgery (71.4%). Educational level of the caregivers consisted of 1 person with diploma, 2 with primary education, 3 with a bachelor's degree, and 1 with a PhD (Table 1).

As a result of data analysis, 17 subclasses and the 5 themes of "physical stressors", "self-care stressors", "psychological stressors", "religious stressors", and "hospital stressors" were obtained, which were a result of experience and understanding the dimensions of open-heart surgery patients about stressors (Table 2).

Physical stressors: Open-heart surgery is a stressful experience threatening all dimensions of life of many patients and their families. Examples of the characteristics of this theme are stress resulting from physical inconvenience towards medical equipment as well as therapeutic and care procedures, incidence of physical complications or limitations, and restrained eating and drinking. The experience of the participants indicated that passing periods in intubation state during the hospitalization, connection of tubes and drains, and their special limitations and incidence of surgical complications including bleeding off the drains, nausea, vomiting, insomnia and anorexia, thirst, and fear of injections and blood tests were accompanied with fear and worry for all patients.

"A thing was in my mouth, which was very annoying. It was choking me. I felt like I was gradually dying. When they withdrew it, it was as if they took a heavy body out of my chest and I was relieved. The two tubes on my two sides did not let me move. I had to sleep straight and turn my eyes left and right to look. I was really bothered (Male patient)".

"The main problem of patients is related to tracheal tube. They feel that there is a tube in their mouth and most of them say they are being choked [Intensive care unit (ICU) nurse]".

Table 1. The characteristics of participants

No	Relationship	Gender	Age	Marital status	Educational level	Occupation	Type of surgery	length of hospitalization
1	Patient	Female	54	Married	Illiterate	Housewife	CABG	5
2	Patient	Female	66	Married	Higher education	pensionary	CABG	10
3	Patient	Female	56	Married	diploma	housewife	CABG	10
4	Patient	Male	38	Married	Middle school	unemployed	ASD	5
5	Patient	Male	70	Married	Elementary	pensionary	CABG	10
6	Patient	Male	50	Married	Higher education	employee	CABG	6
7	Patient	Female	44	Married	Higher education	employee	CABG	8
8	Patient	Female	65	Married	Middle school	Housewife	CABG	9
9	Patient	Female	18	Single	High school	Student	V.R	10
10	Patient	Male	54	Married	Middle school	Unemployed	CABG	5
11	Patient	Male	37	Married	Middle school	Worker	V.R	5
12	Patient	Male	63	Married	Diploma	Pensioner	CABG	5
13	Patient	Female	28	Single	Diploma	Housewife	Aortic dissection	8
14	Patient	Female	38	Married	Diploma	Housewife	CABG	8
15	Informal caregiver	Female	40	Married	Diploma	Housewife		
16	Informal caregiver	Female	47	Married	Elementary	Housewife		
17	Informal caregiver	Female	45	Married	Elementary	Housewife		
18	Formal caregiver	Female	40	Married	Higher education	Nurse		
19	Formal caregiver	Female	35	Married	Higher education	Nurse		
20	Formal caregiver	Female	30	Single	Higher education	Nurse		
21	Formal caregiver	Male	48	Married	Higher education	Surgeon		

CABG: Coronary artery bypass graft; ASD: Atrial septal defect; VR: Valve repair

"They did not give us water. We did not eat. When I was revived, I pointed with my hand and said water, but they only dropped some warm water on my tongue. I felt intensely nauseous and dizzy (Female patient)".

Self-care stressors: This theme represents a set of stressors that overshadow the health of the patient both potentially and in practice. It disrupts self-care in open-heart surgery patients, and originates in apprehension about personal hygiene, inability to care for oneself, and lack of awareness of the situation and its complications.

"You are not clean. You have not taken a bath. The fact that your body and your clothes are dirty is another cause for stress. Before my surgery, I went to the bathroom and washed my hair. It was difficult for me to accept having dirty hair. It has been several days since I have taken a bath and my clothes have not been changed. This piece of clothing contains thousands of microbes. If it touches my stitches and bandage, I may be infected (Female patient)".

Table 2. The table of the main classes and subclasses

Main classes (themes)	Subscales (subclasses)
Physical stressors	Physical complications
	Physical inconvenience due to medical equipment
	Physical limitations
	Limitations in eating and drinking
	Physical inconvenience due to procedures
Self-care stressors	Self-care defect
	Concern over personal hygiene
	Lack of complete awareness of the situation and its complications
Psychological stressors	Death anxiety
	Waiting anxiety
	Anxiety due to altered body image
	Stress due to impairment in fulfilling roles
	Ambiguity in health
Religious stressors	Limitations in performing religious practice
	Concern over Hijab and suitable coverage
Hospital stressors	Concern over financial costs
	Defective welfare facilities
	Stresses of the medical team

Lack of awareness of the situation is the result of lack of clear response to the patients' questions, lack of explanation of the necessity of performing care and therapeutic measures, lack of explanation of surgical results, lack of education about self-care, etc. All of these causes suggest negligence on the part of nurses in educating the patient, which is the cause of complaints by and confusion in patients and stress among them.

"I have these concerns as to what I should do after the surgery that will be good for me (Female patient)".

"They mostly ask me: "When should I come to the clinic?"; "When can I take a bath?"; "What should we eat?"; "Will you prescribe medication for me or not?"; Should I come to see you after?"; "Can I walk or not?"; "Can I have guest or not?", "Should I use a mask or not?"; "Should I wear socks or not?" (Heart surgeon)".

Psychological stressors: This theme represents a set of the stressors that overshadow the emotional stability of the patient both potentially and in practice, and disrupts psychological balance of open-heart surgery patients. It is interwoven with concepts such as death anxiety, expectation anxiety, bodily image threat, impaired role-playing, and ambiguity in health. Surgical operation was a cause of terror and fear for most patients.

"Before the surgery, I had no hope of surviving even one day or one hour after the surgery (Male patient)".

The patients inability to play their roles and fulfill previous responsibilities in the family or society induced severe fear and concern among them.

"I think what I should do now, compared to the past when I did many things in the house. I wonder if I would be able to hang the curtain again. I did all the household chores and moved all the furniture on my own. I do not think I will be able to do any of that any more (Female patient)".

With the incidence of disease and patients' dire need for surgery, most patients were worried about the costs. Not being able to return to their previous job and finding a job in line with their physical situation, especially for male patients who have an important role in the financial status of the family, was extremely worrisome.

"I am preoccupied with my children, since I have become defective and cannot work. My children are young, and they will soon grow older and want facilities. They want to study; being empty-handed is no use (Male patient)".

A negative and ambiguous view of one's health after the surgery is a cause of concern and distress in patients.

"A patient who has undergone open-heart surgery is not the previous healthy person. This means that they are disabled in terms of their job, life, entertainment activities, marital life, children, and almost everything else (Male patient)".

Corruption of the bodily image in young patients, especially women who have the anxiety of a scar on their chest, is a cause for concern. In this regard, one of the participants said: *"I am afraid that the surgical wound will remain on my body; if it remains, it is really bad (Female patient)".*

"Most young women complain about the chest scar (Heart surgeon)".

Religious stressors: Religious stressors are a set of factors that practically prevents patients from performing their religious practices appropriately. It is characterized by stress due to religious limitations such as preoccupation with performing religious practices as well as concern over Hijab and suitable coverage.

"If you do not say your prayers for some days, you are dirty and unclean; it is really difficult. (Male patient)".

"Hospital clothes are not good at all. One does not have a good coverage. I cannot have a good Hijab, and this bothers me (Female patient)".

Hospital stressors: The stress resulting from hospitalization in the treatment unit is due to shortage of welfare facilities, anxieties caused by the medical team, and concerns over the cost.

Unfavorable atmosphere of the ward including contamination and common toilets, unpleasant odors, low food quality, lack of warm water for bathing, and dirtiness of the ward have caused the patients worry and fear of infection of the surgical wound.

"Yesterday, I told the ward's officer that this ward is not hygienic at all. You say that nobody should come here and touch us, and not to pass over the red line, but all contamination exists in the ward. The ground is covered with soil. The toilets are dirty. We have to use these toilets, but there is only one for both men and women, and it is dirty and terrible. Its terrible odor has overwhelmed the whole ward. We have undergone open-heart surgery; any moment the slightest infection may be transmitted to us. This really annoys me (Female patient)".

Stresses related to the medical team are another characteristic of this theme, which originates in neglecting patients' spiritual and physical needs, lack of easy access to nurses, and undesirable behavior of the medical team. The expectation of all patients is care and attention to their care needs by the nurse.

Provision of care procedures hastily by the nurse without previous justification, due to forgetfulness, delay, and lack of quick and timely presence were very stressful and worrisome for the patients.

"I am not satisfied with the ward. You have to ask them to come and dress the wound, to do this and that. You have to ask for a set of clean clothes. I am not satisfied with this ward. During eating, the nurse is in a hurry to take my

blood pressure. All this upsets me (Female patient)".

Furthermore, all patients consider presence and easy availability of the nurse as a source of reliability, sense of security, and protection. If he or she is not present and does not monitor the patients constantly, the patients have a sense of fear and danger.

"There are four of us, who have undergone open-heart surgery, in this room. They should check us every one hour or half an hour, but unfortunately, no one comes. I want to be assured that a person is looking after me at all times. Two nights ago, when I got sick, I looked around for 20 minutes hoping that someone may come (Male patient)".

With the incidence of disease and the patients' dire need for surgery, most patients were concerned about provision of costs. Inability to pay the cost of surgery and hospital and not having financial supports (insurance services, work support, etc.) intensified this situation.

"We have problems in paying the cost of surgery; 800,000 Tomans should be paid in advance, but we were only able to pay around 400,000 Tomans. My father is a farmer; we do not have anything. After discharge, we should also pay 2 million Tomans. We do not have insurance coverage. Last night, I told my brother that I feel pity for my father who has to pay this cost. I wish I was fine and did not have to give this money. It is difficult for my father to pay this cost (Female patient)".

"*My daughter worries about hospital costs. Her father is unemployed; we are not covered by insurance (A patient's mother)".*

Discussion

The findings of this study include concepts, which in relation to each other represent a set of worries and stresses among heart surgery patients in the hospital environment.

Analysis of the participants' experiences indicated that from the time of diagnosis until surgery and discharge, patients experience anxiety, stress, and worries in different ways in different care situations (being hospitalized in the heart surgery ward, and transference to the operation room and ICU). In the present study, hospitalization in the ICU, inability to talk and express emotions due to intubation, limited activity and dependence on others due to closure of hands and connection of tubes and drains, and extreme thirst were experiences that filled patients with worry.

Confirming this finding, Yava et al. also reported that the perceived stressors for patients in the ICU included fear of death, inability to talk, pain, thirst, and sleep problems.[20]

Most of the patients in this study wanted to receive knowledge and education required for the status of their disease and surgery, type and manner of food and drug consumption, therapeutic and care measures, and the method of self-care. If these needs were not fulfilled, they experienced a sense of fear and danger. Considering facilitator and preventive factors in the program for clearing open-heart surgery patients, Lapum et al. stated that patients feel that they are not prepared enough to return home. Therefore, some of them experience psychological problems, complications, and rehospitalization.[1] Blair et al. found that the most common findings obtained from interviews with patients and their caregivers was a need for a guideline and instructions regarding diet, and education about physical activities after cardiac problems and consumed medications.[21] Furthermore, Shafipour et al. reported that the shortage of information causes increased worry among patients.[3] Moreover, in the study by Mooney et al., half of the participants refused to receive information about heart surgery, as with further search for information and increased awareness, their fear intensified.[22]

In the present study, by hearing the name of surgical operation, most patients were shocked and experienced a sense of fear of death. Similar to our results, in some studies, the first reaction of open-heart surgery patients has been shock and fear of death.[6,23] Nevertheless, in other studies, patients experienced less psychological stress in comparison to their caregivers. However, most of them were very much willing to communicate with other patients who had experienced heart disease like them.[21]

In the present study, the waiting time before the surgical operation caused anxiety in the patients. Studies have shown that the functional and psychological status of patients is aggravated when they become candidates for heart surgery.[24] Pre-operation intervention should be performed to manage the stress of waiting for surgery, as the anticipation is the main concern of patients and highly stressful for them.[23]

The patients in the present study were concerned with the probability of being unable to play their previous role and fulfill their responsibilities in the family and society. Not being able to return to their previous job and provide for their family financially was the main concern of all male patients. They were terrified of the uncertainty of their future status. Research has shown that male patients worry about changes in their life situations and working conditions after their surgery.[3,25] Blair

et al. noted financial issues, poor health care insurance, and absence of income when the patient's spouse is also unable to work as major concerns of cardiac patients and their caregivers.[21]

Young female patients are concerned with the scar on their chest and legs. It seems that the concern with altered mental image of the body was very important to these patients as with other concerns. Kantoch et al. reported that a visible surgical wound such as a heart surgery wound may bring about psychological impairment.[26] It can threaten different aspects of life including bodily image, self-concept, emotional stability, social roles, and lifestyle. Changes in the bodily image and its psychological effects cause identity insecurity, diminished self-esteem, increased emotional stresses, and lowered sexual attractiveness.[26]

With the unfulfillment of religious needs, the patients felt guilty and constantly sought forgiveness from God. They were upset about the uncleanness of their clothes and body, not having complete Hijab, and not saying their prayers, which caused diminished peace in these patients. Studies have indicated that in CABG patients, performing religious practices is effective in mitigating complications and shortening the hospitalization duration.[27]

In the present study, most patients were dissatisfied with and worried about nutritional services. Studies on satisfaction of patients with nutritional services suggest that hospital managers should seriously attend to this issue. Development of a suitable plan for the quality of foods and constant programs is essential.[28]

Patients' dissatisfaction with hygiene in the ward toilets and their poignant odors brought about their preoccupation with surgical wound infection. The participants requested adherence to hygiene, removal of unpleasant odors, and provision of a hygienic environment devoid of any contamination from the ward personnel to attain a safe and non-infective environment.

Aslan and Tosun reported that heart surgery patients who had felt a "poignant odor" in the ICU had experienced a greater sense of fear in comparison to those who had not felt such an odor. This finding can explain the fact that "odor" is a powerful component of the environment. Removal of "unpleasant odors" is one of the most important issues that should be taken into consideration in designing hospital environments. Use of aromatherapy as a strategy to improve the conditions related to odor has been emphasized.[29]

Patients in this study sought peace and special care by the nurses. They believed that heart surgery is different from other surgeries, and it demands a special care by the personnel and medical team. Timely presence, providing proper education, and treating patients suitably are essential. In the absence of nurses or with irregular monitoring by the nurse, the patients felt insecure. Molazem et al. reported that general surgery patients feel secure in the presence of nurses, and feel a sense of danger in their absence.[30] Indeed, patients consider nurses' visits as especially important and physical presence of nurse brings about relief for them more than mere simple care.

Conclusion

The main emphasis of this paper was the investigation of perceptions of open-heart surgery patients regarding stressors from hospitalization to discharge. Identification of these experiences suggests that stress is a contextual and relative concept, and a subjective experience in open-heart surgery patients, which is felt as a sense of worry. This experience may emerge with one or several physical manifestations, hygiene concerns or psychological stresses, religious stresses, or stresses associated with the hospital environment.

Therefore, based on what the patients have said, the results obtained from this study allow for the understanding of stressful situations. These findings should be taken into consideration in nursing care programs to mitigate the effect of these stressors. Accordingly, identifying and clarifying stressors in heart surgery patients for nurses is crucial, like a key for improving care quality. Nursing managers in clinical practice can also benefit from these findings in the area of heart surgery for the improvement of care quality and professional performance of nurses. Nurse educators need to remain cognizant of these factors as they prepare future nurses to care for heart surgery patients in the Persian culture. It should be noted that this study was carried out in the Persian cultural context; therefore, the transferability of the results needs further exploration in future studies in other cultures.

The limitation of the study was that the participants were over 18 years of age; therefore, the results are not applicable to children and adolescents.

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Conflict of Interests

Authors have no conflict of interests.

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Wolff-Parkinson-White syndrome and de Winter patterns; An implication for paying special attention to electrocardiogram

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Case Report

Abstract

BACKGROUND: Despite recent advances in diagnostic techniques in cardiology, electrocardiography (ECG) has yet remained the first and corner stone of detecting emergency cardiac events including myocardial infarction (MI). There are some ECG findings which are considered as equivalents to MI. De Winter ST-T wave pattern is one of the important ECG findings which is thought to be related to left anterior descending artery occlusion. However, the coexistence of this ECG pattern with other ECG abnormalities are not reported widely. In this report, we discussed a unique case of de Winter ST-T wave pattern in a patient with Wolff-Parkinson-White (WPW) syndrome for the first time.

CASE REPORT: A 43-year-old man was referred because of an intermittent typical chest pain. The patient had no cardiovascular risk factor, and was not on any medication; laboratory tests showed elevated and raising troponin I. The first ECG showed pre-excitation (WPW) as well as de winter pattern. According to patient's symptoms and suggestive ECG for probable left anterior descending (LAD) occlusion, emergent angiography was scheduled. The coronary angiography revealed sever LAD artery occlusion. The patient was symptom free after successful percutaneous coronary intervention, and was discharged on medication. The patient remained asymptomatic in 1-year follow-up period.

CONCLUSION: Presence of de Winter ST-T changes with other ECG abnormalities is a rare issue, and here we addressed the first case of WPW and de Winter. The physicians should be aware that ECG changes in patients with WPW should not be interpreted as de Winter ST-T changes and vice versa.

Keywords: Wolff-Parkinson-White Syndrome, Myocardial Infarction, Electrocardiography, Coronary Vessels

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Introduction

Myocardial infarction (MI) is one the most important cardiac emergencies, and ST-elevation myocardial infarction (STEMI) is a well-known electrocardiographic (ECG) pattern of this cardiac disorder. There are important STEMI equivalents including isolated posterior MI, Wellens syndrome, left bundle branch block (LBBB), and de Winter ST-T wave complex.[1]

De winter pattern is an important electrocardiographic pattern which can lead to large myocardial ischemia if left undiagnosed.[2] Although de Winter ST-T wave pattern is not always related to left anterior descending (LAD) artery occlusion, but it is noteworthy to always pay attention to this ECG finding in symptomatic patients.[3]

This electrocardiographic pattern is defined as 1 to 3 mm up-sloping ST segment depression at J point in precordial leads, followed by a tall and positive symmetrical T wave in addition to normal QRS duration, and 1 to 2 mm ST segment elevation in augmented vector right (aVR) lead. This pattern has been associated with proximal LAD occlusion.

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This condition is usually developed 90 minutes after developing symptoms, and will resolve after angiographic intervention of occluded vessel.[4] Although this ECG pattern is not as common as other STEMI equivalents, and is reported in 2% of patients presented with acute MI, however, it may be misdiagnosed as a non-specific revisable ischemia, and tend to delay reperfusion therapy.[4-6]

De Winter ST-T wave pattern is not commonly seen with other electrocardiographic abnormalities. In the present report, we discussed a case of concomitant de Winter ST-T pattern and Wolff-Parkinson-white (WPW) in a patient referred due to cardiac chest pain.

Case Report

A 43-year-old non-athlete man patient was referred to Cardiac Emergency Unit due to an intermittent typical chest pain from 2 days before. The chest pain severity was grade III according to Canadian Cardiovascular Society Angina Grading Scale. The "at-rest" chest pain was started 40 minutes prior to admission, and continued without any other symptoms as shortness of breath or dyspnea. The patient had no cardiovascular risk factor, and was not on any medication.

Laboratory tests showed elevated and raising troponin I (TPI) levels (TPI of 40.2 ng/l at admission time and 1524 ng/l 3 hours later, normal range: ≤ 19 ng/l). Furthermore, the laboratory results revealed dyslipidemia [triglyceride: 72 mg/dl, cholesterol: 222 mg/dl, high-density lipoprotein (HDL) cholesterol: 47 mg/dl and low-density lipoprotein (LDL) cholesterol: 151 mg/dl]. The first ECG showed pre-excitation WPW as well as de Winter pattern (Figure 1).

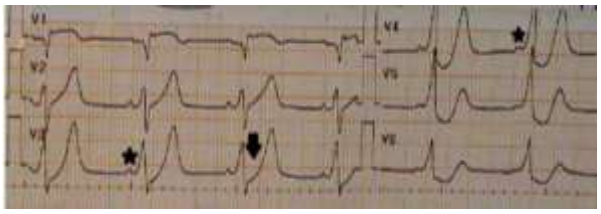

Figure 1. Pre-percutaneous coronary intervention electrocardiography of the patient. The black star shows the delta wave and shortened PR. The black arrow shows upsloping ST segment elevation and tall T wave.

According to patient's symptoms and suggestive ECG for probable LAD occlusion, emergent angiography was scheduled. The coronary angiography revealed sever LAD occlusion (Figure 2). Diagonal, left circumflex and left main arteries were normal, left and right coronary artery had significant lesion at mid part. The patient was symptom free after successful ballooning.

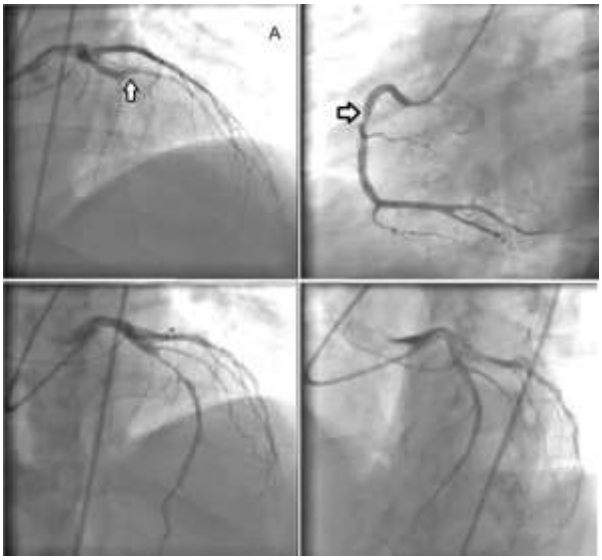

Figure 2. The angiography shows: A. Left anterior descending artery (cut off at mid-part just after first diagonal pointed with arrow); B. Right coronary artery (significant lesion at mid-part pointed with arrow); C. Significant tubular lesion after winning and predilation; D. Successful stenting.

The ballooning was performed by use of guiding catheter Judkins left 6-3.5, and workhouse Guidwire Runthrough Hypercoated was used to pass the lesion. Then semicopliant balloon used for dottering and pre-dilatation of the lesion. After this step, the Resulut Onyx stent 3*32 mm was deployed, and post-dilatation by non-compliant balloon (Apollo 3*20 mm) was done. The post-percutaneous angiography ECG indicated the absence of de Winter pattern (Figure 3). The patient was discharged healthy and aspirin, clopidogrel, atorvastatin, carvedilol, spironolactone, and captopril were prescribed. The patient remained asymptomatic in 1-year follow-up period.

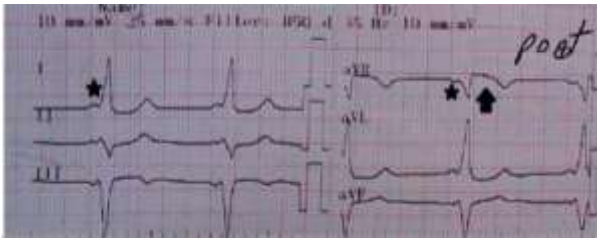

Figure 3. Post-percutaneous coronary intervention of the patient. The black star shows the delta wave and shortened PR. The black arrow shows ST segment elevation in aVR lead.

Discussion

When it comes to acute coronary events, obtaining a standard ECG is the first and tire action in every medical center. Since 1970, scientists have tried to relate different ECG changes to various medical conditions.[7] De Winter ST-T wave complex is a good example, which can predict the coronary involvement in a symptomatic patient. In 2008, de Winter et al. proposed a new ECG pattern in their patients who had proximal LAD occlusion without ST segment elevation.[4] Since then, the de winter ST-T wave changes became popular, and were used as a diagnostic clue for LAD occlusion. In order to better understanding of WPW and de Winter patterns, it will be noteworthy to briefly summarize the differences. During the WPW pattern, negative T waves will be seen while the de Winter will show upright T waves as well as ST segment depression.[8] The delta wave may be a good differentiating clue for diagnosis. The antegrade conduction which will further lead to preexcitation of ventricles and data wave formation. It has been reported that patients with preexictation are more likely to develop arrhythmias including atrial fibrillation, heart failure, and even sudden cardiac death.[9] The next difference is within the QRS segment. The QRS may become broad in WPW while the QRS complex in de Winter is usually normal. In the presence of ST and T wave changes, these changes may be opposite of the positive delta wave. However in de Winter, negative changes of ST segment will be seen with positive and symmetrical T wave.

As mentioned before, de Winter pattern can be seen in different clinical settings including LAD occlusion. A recent meta-analysis reported a weak evidence of the accuracy of this ECG pattern as it can be seen in other clinical settings including hyperkalemic STEMI.[10] Moreover, it has been reported that patients with de Winter ST-T wave pattern can show Wellens syndrome. Wellens syndrome, inverted or biphasic T wave changes in leads V_2 and V_3, is indicative of chronic LAD stenosis.[11] Concomitant de Winter ST-T wave complex with other ECG abnormalities have not commonly been reported. De Winter ST-T wave complex may also indicate occlusion in different parts of LAD. The occlusion may be seen in proximal LAD or even after the first septal perforator.[6,12,13] The pattern has been associated with ventricular fibrillation cardiac arrest after catheterization or defibrillation; although it has not been previously reported with WPW pattern.[5,14] The WPW is a rare disease which has been reported to be seen in 0.5% of patients with sudden cardiac death.[15] A portion of patients with WPW may develop sudden cardiac death, and many may die at rest. It has also been reported that ablation of accessory pathway may not reduce the risk of sudden cardiac death to zero percent.[15] The WPW pattern may simulate or even mask MI. The Q and ST-T waves are masked by delta wave and ST-T changes in WPW.[16] In our patient, despite WPW pattern, we decided to relay on presence of de Winter pattern, which is considered as an equivalent for MI, and decided to perform angiography with the idea of possible LAD occlusion. The physicians should always keep in mind that ECG changes in patients with WPW should not be interpreted as de Winter ST-T changes and vice versa. Although treatment of WPW in such cases is controversial,[17] however, our patient did not agree to undergo any electrophysiological study, and decided to have routine follow-ups.

In the present report, we discussed the first case of de Winter ST-T wave pattern with WPW syndrome. This case demonstrated the importance of performing angiographic studies in patients with de Winter ST-T pattern in order to roll out LAD occlusion. Presence of other ECG abnormalities including WPW should not delay the diagnosis of coronary artery occlusion, and on the other hand, searching for other ECG abnormalities and planning appropriate management in these patients seems to be necessary.

Acknowledgments

None.

Conflict of Interests

Authors have no conflict of interests.

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