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ARYA Atherosclerosis

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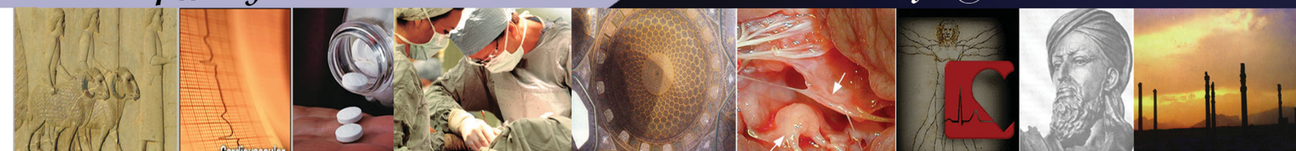

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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

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Pulmonary artery banding using polytetrafluoroethylene; Choice of material

Mohammad Hassan Nezafati[(1)], Pouya Nezafati[(2)], Mehdi Kahrom[(3)]

Editorial

Date of submission: 09 May 2017, ***Date of acceptance:*** 18 July 2017

Pulmonary artery (PA) banding was introduced by Muller and Dammann in 1952 as a palliative operation for patients with congenital heart defects characterized by high pulmonary blood flow and pressures in situations that the definite surgical repair of congenital heart defects should be deferred.[1] This operation was suggested to protect the pulmonary vascular bed from irreversible changes until the main cardiac pathology could be corrected by definitive cardiac surgery. They removed a wedge-shaped segment from the wall of the PA and reduced the lumen size by suturing the edges together, followed by banding the PA with a 1-cm wide band composed of several layers of polyethylene film sutured over cotton umbilical tape.[1] Pulmonary artery banding has recently gained interest and mainly used in infants with complex defects where mortality of early repair is prohibitive or where the Fontan procedure is the only "repair" possible.

Since that time, Muller and Dammann's original technique has been greatly modified and many other banding materials have been utilized including cellophane, silk, cotton umbilical tape, nylon, Teflon, and Dacron.[2] These materials can cause reaction in the PA wall and surrounding tissue, leading to severe fibrosis, stricture, cutting through the vessel wall, incorporation, and calcification.[3] These reactions and complications make debanding procedure more difficult or impossible, necessitate additional procedures for PA reconstructions and increase the risk of the final corrective procedure. None the less, pulmonary artery banding will continue to be an important palliative procedure in some neonates with cardiac disorders, too small to allow definitive correction of their defects.

The difficulty and complications encountered when we attempted to deband some types of materials led us to utilize polytetrafluoroethylene (PTFE) strip and report our experience to demonstrate the effectiveness and outcome produced by PA banding with this material.

The authors usually prefer a left anterolateral thoracotomy through the third or fourth intercostal space. However, if a concomitant closure of patent ductus arteriosus (PDA) and/or repair of coarctation of aorta are required a left lateral thoracotomy is performed. Usually, the third intercostal space is entered; the pericardium is opened only at its superior border over the great arteries, with care taken to leave it intact over the ventricular mass and the ductus or ligamentum arteriosum is dissected and ligated. The tissue plane between ascending aorta and PA is dissected out over a limited area halfway between the sinutubular junction of the pulmonary trunk and origin of the right pulmonary artery (RPA). The site of band placement is carefully selected in the mid portion of the main pulmonary artery (MPA) trunk, and distortion or injury to the pulmonary valve or impingement on the branch pulmonary arteries is avoided. Aggressive dissection in this area is discouraged because it increases the chance of migration of the band over time. Once circumferential access to the pulmonary trunk is achieved, the band is prepared and placed around it. A 3-mm-wide strip is cut and fashioned from a relatively thick (0.4 to 0.6 mm) PTFE sheet. Width of band material should be broad enough to minimize erosion through the PA wall.

The degree of constriction depends on the underlying cardiac lesion and balance of systemic and pulmonary blood flow. Once the band is positioned, the systemic and the PA pressures are continuously monitored. The surgeon then gradually reduces band circumference, evaluating both band gradient and oxygen saturation (SaO_2) as end points. When the band adjusts to its final circumference, its two ends are fixed and sutured together. The band is also anchored with 5-0 Prolene suture to the PA adventitia to prevent band

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migration. The MPA is handled very carefully because it is often dilated, thin-walled, and susceptible to injury.

Pulmonary artery banding takedown is usually performed at the time of the intracardiac repair through a median sternotomy. The PTFE band is simply dissected free from surrounding tissue. The band can almost always be cut and removed without damaging the underlying artery and simple band removal may be all that is necessary. Adequate diameter of pulmonary trunk is usually obtainable without need for any PA reconstruction.

The authors have experience with more than 280 patients with pulmonary hypertension who underwent PA banding with expanded PTFE over 9-year period from June 2007 to October 2016. Our preliminary series included 360 patients in whom other materials had been used during PA banding from 1997 to 2007. Indication to perform PA banding was infants too small to allow definitive correction of their defect with the presence of a clinically and instrumentally significant pulmonary hypertension, not amenable to non-surgical therapy.

Although total corrections of cardiac anomalies are being performed in smaller infants, PA banding is still used as a palliative surgical procedure for some congenital cardiac defects. Nowadays, PA banding is clinically considered not only for classical indications like functionally univentricular cardiac pathologies, but also for more controversial cases like multiple ventricular septal defects (VSD), complete atrioventricular septal defects (AVSD), and transposition of great arteries (TGA).[4,5]

The value of short-term PA banding in certain congenital cardiac anomalies is no longer debatable. Interest is now focused on how to minimize the complications of PA banding and how to perform complete debanding when it is time for corrective procedure of the cardiac anomaly.

There have to date been few studies specifically addressed the choice of band material for PA banding. In an animal study by Stark et al.[6] different materials such as plaited silk, Teflon tape, cotton umbilical tape, and nylon tape were used in swine for pulmonary artery banding. Microscopically documented damage to PA seemed to be related to the degree of constriction but not to the width of the band or to the material from which it was made. In another animal study by Cordell and Suh,[2] cotton umbilical tape, Teflon tape, or 2 different thicknesses of silastic tape reinforced with Dacron were used in piglets. They concluded that silastic tape, reinforced with Dacron tricot, is the most suitable material with least tissue damage employed for pulmonary artery banding.

In our preliminary series of non-PTFE band material, when the band would remain in place longer than 6 months, the area of banding usually became stenotic and required reconstruction in 65% of cases. This repair could be achieved by resection of scarred segment and end-to-end reanastomosis of the proximal and distal of main PA or by vertical incision of the PA followed by pericardial or synthetic oval-shaped patch repair of the arteriotomy.

The authors have specified their technique by using expanded PTFE strip with inert nature in order to obviate the PA banding morbidity and complications. When PTFE was applied for PA banding, the fibrosis and reaction of the tissue to the band was minimal during debanding. When total correction is planned, the PTFE band could be pulled easily through the tunnel of fibrous capsule formed around it. In all patients, the band could be removed easily through formed smoothly surfaced tunnel after cutting the PTFE band and removal of fixation sutures. The pulmonary trunk showed a certain amount of distensibility after debanding without damaging effect on internal surface of the artery.

In patients banded with PTFE, pulmonary artery banding takedown can be performed very comfortably and debanding of PTFE lets the pulmonary artery to expand without any scar formation or fibrosis and none of our patients in this group required PA or valve repair.

In conclusion, with our experience, safety and favorable results of pulmonary artery banding with PTFE strip should result in a more widespread use of this material to obviate the PA banding complications.

Conflict of Interests

Authors have no conflict of interests.

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Gensini scores and well-being states among patients with coronary artery disease: A comparison study

Reza Rostami[(1)], Mahdi Najafi [(2)], Reza Sarami[(3)], Ali Bozorgi[(4)], Majid Soltani[(5)], Payman Salamati[(6)]

Original Article

Abstract

BACKGROUND: World Health Organization (WHO) considered Mental Health Continuum (MHC) as a good instrument for well-being studies. Moreover, gensini score (GS) is an intensity index for coronary artery disease (CAD). The aim of our study was to compare GSs among patients who had coronary artery disease with different well-being states.

METHODS: This was a cross-sectional study conducted in Tehran Heart Center, Iran, in 2013. The study population consisted of 50 non-depressed patients who were candidates for coronary artery bypass graft (CABG). All of the participants were interviewed according to the Iranian version of Mental Health Continuum (IV-MHC) and were allocated to flourishing, maternal mental health (MMH) and languishing states based on the related classification criteria. GS was calculated for each participant. Data were analyzed by SPSS.

RESULTS: Forty one (82%) patients were in flourishing, 9 (18%) in MMH and nobody was in languishing states. The mean (standard deviation) of GS was 90.43 (44.424) and 89.67 (33.378) for flourishing and MMH ones, respectively (P = 0.962). There was no statistically significant correlation between GSs and well-being states (all Ps > 0.050).

CONCLUSION: Considering IV-MHC classification, all of our patients were only allocated to flourishing and MMH states. There was no relationship between intensity of CAD and the states (P > 0.050). We recommend further research with larger sample sizes for better evaluation of the Iranian version of the instrument.

Keywords: Coronary Artery Disease, Depression, Mental Health, Iran

Date of submission: 11 May 2016, ***Date of acceptance:*** 10 July 2017

Introduction

Recently, some psychologists have presented a new model explaining complete mental health as a combination of lack of major depression during the last 12 months and having subjective well-being. In this model, subjective well-being has been introduced as a complete state of positive feeling and positive functioning in life, and categorized into emotional well-being, psychological well-being, and social well-being.[1-3] Moreover, non-depressed individuals have been categorized in the three subjective well-being states including flourishing, languishing, and maternal mental health (MMH). Flourishing is a state of mental health that individuals have no depression and are surrounded with high positive emotions and functions. Languishing is a level of absurdity in individuals who are empty of emotions and positive functioning, however they are not depressed. Languishing persons have neither illness nor positive subjective well-being in terms of mental health.[4-7]

Psychologists have created a questionnaire and named it Mental Health Continuum (MHC) or Keyes' well-being questionnaire for evaluating and categorizing individuals in different groups of well-being states.[8-12] World Health Organization (WHO) has recently taken this instrument into

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consideration and recommended its evaluation and examination in other non-American societies.[13] Hence, Keyes' MHC was favorably received attention by other scientists and researchers from other countries like Canada, Italy, Australia, and Egypt.[14-18] Likewise, the Iranian version of Keyes' mental health continuum (IV-MHC) has been used widely in recent years.[19,20]

Different studies confirmed the strong and consistent association between depression and coronary artery disease (CAD).[21,22] One of the best indices for showing the intensity of CAD is Gensini score (GS). The advantage of this index is that GS provides a quantitative variable for statistical analysis. GS is a scoring system and is mainly calculated based on the involved artery, the extent of atherosclerosis and the existence of collateral.[23] The aim of this research was to compare GSs in different groups of individuals, who had CAD and were hospitalized in Tehran Heart Center, Iran, in 2013, with subjective well-being states.

Materials and Methods

Sixty-one patients who were candidates for coronary artery bypass grafting (CABG) and were hospitalized in Tehran heart center (affiliated with Tehran University of Medical Sciences) enrolled in this cross-sectional study conducted in October 2013. Their functional classes were one or two and they did not have any accompanying active disabling diseases. They were selected randomly and consecutively from patient admission list before the surgery. Patients were interviewed using general health questionnaire-28 (GHQ) items for depression evaluation.[24] In this stage, 8 patients were diagnosed as depressed and were excluded and the rest were evaluated according to MHC. Three patients could not understand the questions of MHC and were excluded. Ultimately, 50 patients were included in our preliminary study.

The general health questionnaire contained 28 questions about 4 sub-scales of physical signs, anxiety and sleeping disturbances, social impairment, and severe depression. The questionnaire was created by Goldberg in 1972 and shows the state of interviewed participants during the past month.[24] Each sub-scale included 7 questions and each question had 4 replies including not at all, almost normal, more than normal, and exceedingly over normal. Numerating was based on the following criteria; the first alternative had zero score, the second had one, the third had two, and the fourth had three scores. The score above 6 was considered in sub-scale of depression as a disease, and these participants were excluded from the study. This questionnaire was standardized to Iranian version by Taghavi.[24]

The Keyes' MHC contained three main scales including emotional well-being, psychological well-being, and social well-being and thirteen subordinated sub-scales.[9] Emotional well-being contained two sub-scales by itself, one sub-scale item of life satisfaction and six sub-scale items of positive feeling. In life satisfaction item, the respondents were asked a question about the level of their satisfaction in life by choosing from 0 to 10 (0 = not satisfied and 10 = very satisfied). In positive feeling sub-scale, respondents were asked to choose from a list of six signs of positive feelings and selecting a number between 1 to 5 as all, most, some, a little, and none of the time respectively, in order to determine how much they had experienced each sign within last 30 days.

The 6 psychological well-being sub-scales were as self-acceptance, autonomy, environmental mastery, purpose in life, personal growth and positive relations with others. The psychological well-being scale contained 18 items for evaluating 6 aspects of psychological well-being which were answered based on a 7-rating scale of Likert ranging from completely disagree to completely agree. The social well-being short-scale form was used for examining social well-being.[1] The form, including 15 items for evaluating 5 aspects of social well-being, was answered based on a 7-rating scale of Likert ranging from completely disagree to completely agree.

Being recognized as an individual in the flourishing state, the person should be entitled in upper tertile in one of the 2 sub-scales of positive emotions and six of the 11 sub-scales of positive functions. Being recognized as an individual in languishing state, the person should be entitled in lower tertile of at least one of the 2 sub-scales of positive emotions and six of the 11 sub-scales of positive functions. Consequently, individuals without languishing and flourishing states had MMH.[9]

Recently, Keyes et al. suggested another method for the classification of individuals among flourishing, MMH, and languishing groups. He has named the previous classification as categorical and the new method as continuous. In the categorical method, the scores of 13 sub-scales were simply added up together and final classification of individuals was determined based on total score. In this way, individuals with well-being score located in one-third of upper level were named flourishing, the

next one-third were known MMH and the last group were called languishing.[25]

Keyes' well-being questionnaire was standardized by Joushanlou et al in our country in 2006.[19] They reported the internal consistency of the subordinated sub-scales between 0.43 to 0.85.

A cardiologist calculated GS of studied patients through evaluating the coronary arteriograms. Considering the specific diagram and table, he first scored three variables of severity (ranged from 1 to 32), segment location multiplying factor (ranged from 0.5 to 5), and collateral adjustment factor (ranged from 1 to 16) and then multiplied them.[26] Both questionnaires (GHQ and MHC) were completed by a trained general practitioner during the interviews. Both categorical and continuous methods were used for calculating subjective well-being states. Scoring the GSs were done by one of the assistant professors of cardiology in Tehran Heart Center, Tehran, Iran. This research was designed and approved based on the ethical rules of Tehran University of Medical Sciences. The research project was explained to the patients and verbal consents were received.

Kolmogorov-Smirnov (KS) test was used to examine the distribution of the numeric variables. Once the KS test values violated the assumption of normality for the variables, we used Mann-Whitney test for the data analysis. Student's independent t-test was used for the remained numeric analysis. We also used Pearson correlation test for exploring the correlation state of some variables. Alpha was considered less than 5 percent. We used SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA).

Results

The mean and standard deviation (SD) of patients age were 58.9 and 8.75, respectively. 43 (86%) of patients were men, 49 (98%) were married and 42 (84%) were employed. The mean ± SD of individuals educational experience was 7.42 ± 5.60 year. The descriptive statistics of subjective well-being scales are mentioned in table 1. In the next step, the patients well-being states were evaluated using two above-mentioned methods. Considering the categorical method, 41 (82%) were allocated to the flourishing group and 9 (18%) to the MMH group. None of the patients was in the languishing group. For the next step, GSs of patients in flourishing and MMH groups were compared (Table 2). The mean ± SD of GS for flourishing individuals and those having MMH was 90.43 ± 44.42 and 89.67 ± 33.38, respectively. The difference between the two groups was not statistically significant (P = 0.962).

Table 1. Descriptive statistics of the subjective well-being scales in the patients

Indicator	Mean ± SD
Life satisfaction	7.34 ± 2.25
Positive feelings	23.26 ± 4.51
Self-acceptance	16.98 ± 3.45
Autonomy	15.28 ± 2.99
Environmental mastery	18.06 ± 2.98
Purpose in life	12.80 ± 2.71
Personal growth	16.76 ± 3.22
Positive relations with others	17.72 ± 2.79
Social acceptance	11.76 ± 3.37
Social contribution	16.32 ± 4.01
Social coherence	12.84 ± 4.56
Social integration	16.28 ± 3.47
Social actualization	9.96 ± 3.19

SD: Standard deviation

Then, the patients well-being scores were calculated by the second method (continuous method). 40 (80%) patients were allocated to the flourishing group and 10 (20%) to the MMH group. None of the patients were in the languishing group. For the next step, the GSs of the flourishing and MMH patients were compared (Table 2). The mean ± SD of GS for the flourishing individuals and those having MMH was 89.06 ± 44.621 and 95.20 ± 33.177, respectively. There was no statistically significant difference between the two groups (P = 0.686).

Table 2. Comparing gensini scores between flourishing and moderately mentally healthy patients based on categorical and continous methods of classification

Method of classification	Groups of well-being	Count	Mean ± SD	P*
Categorical method	Flourishing	41	90.43 ± 44.424	0.962
	MMH	9	89.67 ± 33.378	
Continuous method	Flourishing	40	89.06 ± 44.621	0.686
	MMH	10	95.20 ± 33.177	

* Independent t test

SD: Standard deviation; MMH: Maternal mental health

The mean and SD of patients emotional, psychological, and social well-being scales and total subjective well-being score are mentioned in table 3. Pearson correlation coefficients were analyzed among the above scales with GSs and none of them was significant (P > 0.050). Also, GHQ sub-scales were compared between the two groups of flourishing and MMH and no statistically significant difference was found (P > 0.050) (Table 4).

Table 3. The descriptive statistics of patients well-being scores and correlation measures between well-being and gensini scores

Type of Scale	Mean ± SD	r	P*
Emotional well-being	30.60 ± 5.92	0.009	0.951
Psychological well-being	97.86 ± 8.76	0.017	0.905
Social well-being	67.56 ± 8.74	0.263	0.065
Total well-being	196.02 ± 16.79	0.149	0.302

* Pearson correlation test
SD: Standard deviation

Pearson correlation was recruited to analyze different GHQ scales and its total score with subjective well-being scores and its total score. Although some of the items were statistically significant, none of them had coefficients of correlation more than 0.513 (Table 5).

Discussion

None of the participant in our research was allocated in the languishing group. By comparing GSs between the flourishing and MMH groups, we did not find any statistically significant difference (Table 2). We used both categorical and continuous methods for classifying individuals into well-being states. However, we did not find any difference between the two methods. Furthermore, we analyzed the correlation between the GSs with the score of each scale and the total score of subjective well-being in order to evaluate the existence of any relationship (Table 3); however, no correlation was found.

There is no study evaluating the relationship between the subjective well-being scales and CAD severity. However, Keyes and Grzywacz[27] and Keyes et al.[28] and Keyes and Simoes[29] found that being in the lower level of well-being was correlated with mental disease and increased risk of death, including the risk of cardiac death (by any known causes at any age and any gender). Moreover, Keyes[30] classified 3032 Americans between the age of 25 and 74 into four groups of depressed, flourishing, languishing, and MMH in a survey in 2004 and then examined them in terms of having some illnesses like cardiovascular diseases. The Keyes' study showed that the lowest incidence of cardiovascular disease was related to the flourishing and the highest one was related to the depressed groups. Also, the incidence of cardiovascular disease among depressed people was 1.7 times greater than the others and flourishing individuals had the lowest risk of cardiovascular disease.[30]

We did not recognize any significant difference by comparing the four sub-scale scores of GHQ between the two groups of flourishing and MMH as well (Table 4). Moreover, we analyzed the correlation between the four sub-scale scores of GHQ and its total score with the three sub-scale scores of well-being and its total score (Table 5). However, no cases was detected with coefficients of correlation more than 0.513.

Since we found no correlation among all of our analyses, the probable causes should be precisely reviewed. First, Keyes used composite international diagnostic interview short form scale for discriminating depressed from non-depressed participants in similar studies[9], but we used GHQ which is an instrument commonly used in our country. Moreover, it seems that the Iranian version of the instrument should be reevaluated. Based on the method of the standardization of IV-MHC,[19] the following challenging points are considered. 1- they did not examine their participants based on the existence of depression at the beginning of the study and they classified all participants into the three groups of flourishing, MMH, and languishing.

Table 4. Comparing general health questionnaire sub-scales between flourishing and moderately mentally healthy patients

GHQ Sub-scale	Well-being status group	Count	Mean ± SD	P*
Physical symptoms	Flourishing	41	4.12 ± 2.72	0.190
	MMH	9	6.67 ± 3.43	
Anxiety a sleep disturbances	Flourishing	41	4.41 ± 3.58	0.206
	MMH	9	6.11 ± 3.66	
Social impairment	Flourishing	41	8.29 ± 1.62	0.129
	MMH	9	9.22 ± 1.72	
Severe depression	Flourishing	41	0.81 ± 1.23	0.420
	MMH	9	1.11 ± 1.36	

* Independent t and Mann-Whitney U tests
SD: Standard deviation; GHQ: General health questionnaire; MMH: Maternal mental health

Table 5. The correlation between general health questionnaire sub-scales and well-being scales

GHQ Scales	Well-being Scales			Total
	Emotional well-being	Psychological well-being	Social well-being	
Physical symptoms	-0.354*	-0.278	-0.195	-0.374*
Anxiety and sleep disturbances	-0.474*	-0.445*	-0.171	-0.489*
Social impairment	-0.341*	-0.358*	-0.053	-0.336*
Severe depression	-0.309*	-0.172	0.082	-0.156
Total	-0.513*	-0.458*	-0.133	-0.496*

* Pearson correlation test, P < 0.050
GHQ: General health questionnaire

2- for conducting factorial analysis, the number of samples should be 10 to 20 times more than the number of items. Hence, it seems that Bakhshi et al.[31] and Joshanloo et al.[32] should have analyzed at least 400 participants for analyzing 40 items. 3- in SPSS, it is not suggested to use linear factor analysis with Pearson correlation matrix among items without considering psychometric characteristics (such as equal difficulty index for all the questions). 4- the researchers used Cronbach alpha coefficient for analyzing data, but it seems that using ordinal theta analysis is more appropriate in such cases. 5- the authors considered the distribution of quantitative variables as normal. Whereas, control of normality needs a test. 6- appropriate rotation of principal components method should be a varimax rotation. 7- considering exploratory factor analysis table, the remaining of at least 3 questions for assumed factors were neglected in psychometric criteria. 8- interestingly, there has been some researches in Iran, in which the researchers have used the Iranian version of Keyes' social well-being scale solely.

Keyes introduced his short form of MHC in 2008 as an appropriate replacement for future studies.[33] Redelinghuys studied 451 urban and 599 rural Africans by using general health questionnaire and Keyes' MHC-short form in 2012. The results showed that self-efficiency decreased the stress and caused better subjective well-being.[18]

It is worth mentioning that the Keyes' instrument focus is depression and does not consider other diseases. So, individuals who are suffering from other mental diseases are considered having subjective well-being and can be allocated in any of the three groups of flourishing, MMH, and languishing.

One of the limitations of our study was that he individuals were patients who were hospitalized and were scheduled to be under open cardiac surgery a few days after the interview. Therefore, some of them were under surgery stress. Hence, the results of this research should be interpreted cautiously. Additionally, we just studied 50 individuals and our small sample size might have led to observe insignificant differences.

Conclusion

We did not succeed in assigning any person in a languishing group of the IV-MHC. Moreover, we did not find any relationship between the intensity of CAD and well-being states of individuals. It seems that using IV-MHC should be interpreted more cautiously. By performing further studies with larger sample sizes, we can reach to an appropriate evaluation from Iranian version of this scale.

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Conflict of Interests

Authors have no conflict of interests.

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Design and implementation of a combined observational and interventional study: Trends of prevalence, awareness, treatment and control hypertension and the effect of expanded chronic care model on control, treatment and self-care

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Original Article

Abstract

BACKGROUND: Lack of information about hypertension leads to failure in detection, treatment and reduced estimation of this disease effects. So, a comprehensive study, named trends of prevalence, awareness, treatment and control hypertension among the adults in Isfahan, Iran (2001-2016) and evaluation of the effect of expanded chronic care model (ECCM) on control, treatment and self-care, has been designed. This study explains the aspects of design and methods of its implementation.

METHODS: This study was conducted in four stages in 2014-2016. In the 1st stage, valid questionnaires were made to assess knowledge, attitude and practice, and self-care. In the 2nd stage, the status of prevalence, awareness, treatment and control and hypertension risk factors was assessed. In the 3rd stage, a two-group clinical trial was conducted to evaluate the effectiveness of ECCM on hypertensive patients and their families. In the 4th stage, the results of hypertension prevalence and its risk factors in adults in 2016 were compared with two other studies undertaken in 2001 and 2007.

RESULTS: To develop the questionnaire, face and content validity, internal and external reliability, and construct validity were examined. Prevalence, awareness, treatment and control of hypertension and risk factors among 2107 adult individuals were determined in Isfahan. In a clinical trial, 216 hypertensive patients were randomly assigned into intervention and control groups. Finally, a sample size of 8073 people was used to determine and compare the 15-year-old trend of hypertension and its affecting factors.

CONCLUSION: It is obvious that the final findings of this study will play a key role in health and research policy and provide a suitable model for implementing appropriate interventional measures at the provincial and national levels.

Keywords: Hypertension, Blood Pressure, Risk Factors, Self-Care, Educational Models, Iran

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Introduction

Declaration of the United Nations general assembly has emphasized on the prevention and control of non-communicable diseases (NCD) and its destructive impact on health, socio-economic development and poverty alleviation.[1] Hypertension (HTN) is one of the risk factors of cardiovascular diseases (CVD) and has important health and economic consequences throughout the world. It is predicted that the number of people suffering from HTN reaches approximately 1.56 billion in 2025.[2]

In the last decade, rapid social and economic changes in Eastern Mediterranean and Middle East countries have increased the prevalence of many risk factors for CVD such as HTN. In the Middle East, on average, its prevalence is 21.7%,[3] in some other studies 10 to 17%,[4] and in Iran it is 26.6%.[5]

Accurate description of Epidemiology HTN in the community to identify the causes and deal with them is considered the main strategy for increasing longevity and promoting public health. Moreover, it is the basis for prevention of NCD, and

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identification, prevention and control of its risk factors.[1] In the treatment of HTN, important risk factors such as obesity, diabetes, dyslipidemia, and smoking should be controlled along with controlling blood pressure numerical values. These factors enhance the effect of each other and increase the overall risk of CVD in these patients synergistically, more than the sum of individual risk factors.[6]

Despite the importance of health policies, recent studies have shown that in most parts of the world, governments do not have policies for preventing or managing NCD.[7] Lack of information and data on the prevalence of HTN has led to a failure to diagnose and treat the disease and reduce the estimates of the effects of the disease.[8] Moreover, there are still many problems about how to treat and cure patients and how to deal with their performance in Iran, including the province of Isfahan. In general, the speed of the prevention, control and treatment of HTN is slower as compared to the speed of its spread; therefore, broader and more comprehensive policies need to be implemented.

This article explains the aspects of the design and implementation methods of a doctoral dissertation. This dissertation is a part of a national study entitled "the impact of self-care management and adopted Iranian guidelines for hypertension treatment on improving the control rate of hypertension", with Isfahan cardiovascular research institute research code 91004751.

This work aims to explain the aspects of the design, implementation, and sampling methods of a large study about 15-year-old process of prevalence, awareness, treatment and control of HTN in the adult population of Isfahan and evaluating the impact of a caring model on control, treatment and self-care and knowledge, attitude and practice (KAP) of community about this disease.

Materials and Methods

The implementation process of the present study was conducted in four stages. In the 1st stage, a validated questionnaire was developed about KAP of the people about HTN and complications resulting from its increase, the risk factors of HTN in the society, prevalence, awareness, control and treatment of HTN, self-care, self-efficacy and adherence to medication in HTN patients. In the 2nd stage, a cross-sectional study was carried out to assess the current status of HTN and some risk factors in Isfahan, Iran in 2015-2016. In the 3rd stage, a two-group clinical trial was performed to evaluate the effectiveness of expanded chronic care model (ECCM) on patients undergoing treatment for HTN and their families. In the 4th stage, the factors affecting the trend of HTN in the city of Isfahan, Iran were separately determined in a total population of both healthy adult men/women and HTN patients. To do this, data from cross-sectional study of 2015-2016 were compared with data from the study of Isfahan healthy heart program (IHHP), 2001-2007.[9,10]

Procedure of the 1st stage of the project: designing valid questionnaires: This 13-month stage was aimed to design a valid questionnaire for this study. According to the objectives, hypotheses and research questions, first, a number of the questions from the World Health Organization (WHO) stepwise approach[11] and a number of the questions from IHHP[10] were used to prepare the questionnaire of the project. Moreover, the initially arranged questionnaires were further organized and developed by referring to valuable books and articles, and also after examining the most recent national clinical guidelines for the prevention, assessment and treatment of HTN, scientific resources and other similar questionnaires which had been designed to assess patients HTN self-care and self-efficacy, KAP of the HTN patients and complications resulted from its increase. Then the face validity of the questionnaire was determined by the expert panel. In these meetings, according to the individuals' suggestions, the questions were modified and consequently, the items became simpler, more appropriate, more understandable and restricted.

Then, the content validity was evaluated using two criteria of content validity index (CVI) and content validity ratio (CVR). Polit et al.[12] and Ayre and Scally[13] have explained how to calculate CVI and CVR. To calculate the CVR, 25 specialists and experts were asked to give their opinions about each item in the form of a three-part range (it is necessary, it is important but not necessary, it is not necessary). In addition, to calculate CVI, viewpoints of 17 experts and specialists were used to determine the relevance, simplicity and clarity of the options of the questionnaire by giving a score from 1 to 4.[14] Moreover, the reliability of the questionnaires was calculated using two types of reliability, i.e. internal and external reliability. To do so, the designed questionnaire was given to 12 individuals who were representative of the target population and internal consistency was calculated using Cronbach's alpha and a value of higher than 0.70 was confirmed.

Then, to determine the reliability, the questionnaire was given to the same people, for the second time, after 14 days. Intraclass correlation coefficient (ICC) was calculated and the values more than 0.9 were confirmed.[15,16]

Finally for KAP and self-care and self-efficacy questionnaires, construct validity was determined using exploratory factor analysis. Furthermore, confirmatory factor analysis was performed on KAP questionnaire. Exploratory factor analysis (for each variable, 10 samples) was used to measure construct validity. It was also determined whether questions which have been designed to evaluate an index or particular trait had a common factor loading and these factors were significant. The questionnaire of self-care, self-efficacy and adherence to medication was conducted on 203 patients with HTN and KAP questionnaire was conducted on 220 individuals. According to Lawshe table, the items with CVR ≥ 0.5 and CVI ≥ 0.61 were selected.[13] Confirmatory factor analysis of KAP questionnaire was also conducted on 440 people.

The variables evaluated in the final questionnaire: Generally there were multi-part questionnaires, in which, their first part included demographic characteristics such as age, sex, marital status, education level, occupation or their spouse's occupations, socioeconomic status, number of children, the number of people with HTN in the family, HTN risk factors (diet, tea and coffee consumption, cigarettes and tobacco consumption, alcohol, exercise, stress), current diseases and medication, hospitalization history, questions about HTN during pregnancy and contraception methods, and information about the blood pressure measurement.

The second part included the questions about knowledge (20 questions, with answers of true, false, I do not know), attitude with 18 questions based on 5-point Likert scale (strongly agree to strongly disagree), practice on blood pressure with 17 questions based on 5-point Likert scale (always to never), the complications raised from HTN increase, and HTN risk factors.

Part three contained a special form of physical examination including measurements of height (cm), weight (kg), waist, abdominal, hip and neck circumferences (cm), arm length and circumference (cm), pulse rate (per min) and regularity or irregularity of the pulse, systolic and diastolic blood pressure (mmHg) of right and left arms at three times.

Part four of questionnaire was related to individuals known to have HTN and the questions were about how to control and measure blood pressure, reasons for not visiting a doctor for pressure control, who told them the first time that they have high blood pressure, HTN treatment and medication, family history of diseases, presence of HTN complications, adherence to medications (7 questions with 5-point Likert scale (always to never), self-efficacy with 8 questions based on 5-point Likert scale (I am not sure to quite sure) and self-care with 16 questions based on 5-point Likert scale (strongly agree to Strongly disagree).

Procedure of the 2nd stage of the project: an examination of the current status of HTN prevalence, awareness, control and treatment, and some risk factors in Isfahan, Iran: A new cross-sectional study was conducted to determine HTN prevalence, awareness, control and treatment and some risk factors on the adult population of Isfahan, Iran within 7 months (August 2015-March 2016). Inclusion criteria were the samples with 18 years or older and the residents of Isfahan, Iran. Exclusion criteria were any limitations on measuring blood pressure from the arm such as arm casting, existence of a shunt or fistula in the hands, fasting or any special diet for obesity or for weight loss at the time of sampling for the patients or their families, suffering from Cushing and pheochromocytoma, undergoing treatment with peritoneal dialysis or hemodialysis, suffering from mental illnesses and cancer, and pregnancy.

If the subjects were not willing to continue to participate in the study, the reasons for not-participating were presented in a report.

Sample size and sampling methods of the 2nd stage: In this study, considering the prevalence of HTN, 18.9%,[17] type I error ($\alpha = 0.05$), the margin of error ($d = 0.018$), 1818 people were selected using the following formula. Z value for a confidence level of 0.95 from normal distribution table was 1.96.

$$n = \frac{Z^2 P(1-P)}{d^2}$$

The number of individuals in each age group (18-29), (30-39), (40-49), (50-59), (60-69) and (over 70) was determined based on relative distribution and sex distribution of population by age groups in the community.[18] According to the objectives of this study, multistage random cluster sampling was conducted, families were selected randomly and based on the proportion

of the population covered by the concerned health centers.

The city of Isfahan, Iran has two health centers, i.e. No. 1 (21 centers) and No. 2 (26 centers), and they were considered as clusters of Isfahan. Based on the evidence provided by the health department of the province, in terms of socioeconomic status, the health centers of Isfahan are divided into three categories of good, fair and poor. Moreover, in the proportion of the population covered by health centers and using the lottery method, 18 centers were selected.

In the health centers, a list of files was presented and the samples were selected via systematic random sampling. After finding the addresses and referring to their homes, an eligible person over 18 who has met inclusion criteria was randomly selected from each family. Since all of the families in the city of Isfahan do not have a file at their health centers, sampling continued up to the next ten households from the right hand of this household. These people were given a reference card to health centers in their neighborhoods so that they could refer to the center with their medications and health insurance card to measure blood pressure and fill in the questionnaire. Sampling continued until the determined sample size was obtained. This sample size was according to age groups and sex distribution (equal numbers of women and men) in that center.

In the health center, attendees were initially asked to sign a written consent form. While the person was sitting, the questionnaires were completed by interviewing with full accuracy. Initially, the first and second parts of the questionnaire about demographic information and KAP were filled, and then the individuals were resting for 5 minutes in a quiet environment. The WHO standard conditions were observed when measuring the blood pressure.[19] This means that the people were sitting on backed chairs and did not get their legs crossed. Their soles of the feet were on the floor, the hands were at the heart level and the palms were upward. Systolic and diastolic blood pressure was measured three times (with a standard protocol) from both right and left arms, using a digital calibrated brachial sphygmomanometer. There was a one-minute interval between each measurement and all three times were recorded.

Then a brief physical exam including height and weight measurement, waist, neck and abdominal circumferences were performed, and the measurements were recorded on a special physical examination form. At the end, there was a brief reception to thank them. Moreover, individuals with a previous history of HTN completed the questionnaire of self-care, self-efficacy and adherence to medication.

At the end of the same day, the completed questionnaire was sent to Isfahan HTN Research Center so that the data entry unit imputed the information into the Epi Info software (CDC, The United States). Then the questionnaires were archived in a safe place. The data entered into the computer at various stages were checked for errors using the interim analyses, and then these errors were fixed.

Validity and reliability of the data collection instrument: Ten interviewers with previous experience and with no history of physical or mental disabilities attended the HTN Research Center to receive training for two months. Adequate explanations on how to complete the questionnaires were presented to them by the researcher. In addition, they obtained the expertise required to measure blood pressure, and body dimensions including height, weight, waist circumference, etc. After being approved by the executor, official letters were issued to them from Isfahan Cardiovascular Research Institute, Isfahan, Iran.

The tool used in this research includes a digital brachial sphygmomanometer, Microlife WatchBP Office ABI (Microlife WatchBP AG, Widnau, Switzerland), which was compared with a mercury sphygmomanometer. This device was verified several times in a row on 1-3 individuals. In addition, other tools including meters (plastic meters calibrated using a metal meter), digital scale (calibrated with a five kg weight every day) and valid questionnaires from the 1st stage of the study.

Procedure of the 3rd stage of the project: implementation of a two-group clinical trial with before and after design (intervention and control groups): This stage aimed to investigate the effect of ECCM on control, treatment and self-care of HTN. This stage was conducted on identified individuals suffering from HTN who was under treatment from the 2nd stage, within 10 months. Since one of the main strategies to prevent and control chronic diseases is educating through patient- and family-centered intervention, which is based on ECCM[20,21] and the latest guide clinical, self-care was taught to patients with HTN and one of their family members involved in taking care of the patient in the intervention group. Then, the results were reviewed and analyzed regarding the

control and treatment of the disease, self-care, adherence to medication and KAP of patients.

The sample size in the 3rd stage of the project:

A total of 252 of individuals (138 women and 114 men) had been diagnosed with HTN from the previous study, and 216 of them were randomly selected. Permuted-block stratified randomization (based on age, gender and education) was used to assign the subjects to either intervention (n = 108) or control (n = 108) groups.

The required sample size in each group was estimated at 90 (using the following formula), given a significance level of 0.05, a statistical power of 80% and the normalized effect size of $\Delta = 0.3$ to $\Delta = 0.9$, pertaining to the pre- and post-intervention score difference reported in the reference articles.[22-24] To achieve a higher precision and considering the 20% chance of attrition, the sample size was increased to 108 per group, i.e. the number of samples at this stage in intervention and control groups was 216 people. Figure 1 presents consolidated standards of reporting trials (CONSORT) flow diagram of the participants in the 3rd stage of the project.

$$n = \left(\frac{1+\varphi}{\varphi}\right)\frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2} + \frac{z^2_{1-\alpha/2}}{2(1+\varphi)}$$

$Z_{1-\alpha/2} = 1.96$; $Z_{1-B/2} = 0.84$; $\phi = 1$

The procedure of the 3rd stage of the project:

The content of the instructional booklet was prepared, printed and copied for the patients and their families. The booklet contained training on HTN and the importance of its control, the side effects of uncontrolled HTN, the available non-pharmacological treatments and healthy lifestyle choices, such as proper physical activity, stress management, restrictions on smoking, the importance of a healthy diet, especially the level of salt intake and dietary approaches to stop HTN (DASH).

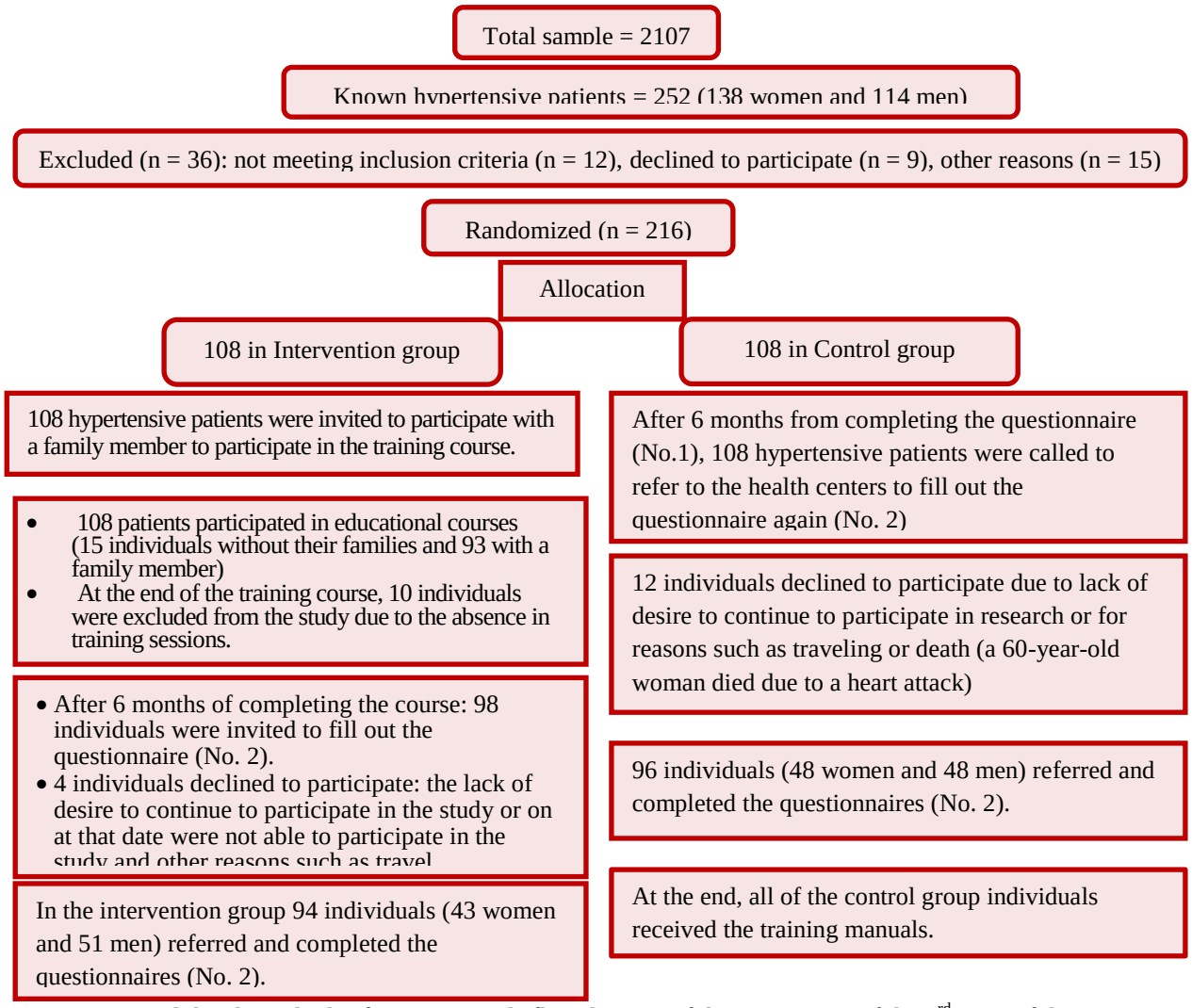

Figure 1. Consolidated standards of reporting trials flow diagram of the participants of the 3rd stage of the project

Then, the team members who were supposed to teach the patients and families were appointed by the head of HTN Research Center and executor of the plan. Six 2-hour training sessions were held for the team to improve the capacity and coordination, to integrate educational content, and to achieve full control on HTN guidelines. The team members included general practitioners (two), PhD by research student with a Master of Nursing (one), and nutritionists (two).

In intervention group patients with HTN were given invitation and reference cards so that they could refer to the health center in their neighborhoods with their family members on specified days. Then, the training program was conducted to change the behavior of them and promote patient and family engagement in their own care. Moreover, it intended to improve their participation in the treatment process. The training program was carried out in health centers for 8 hours (two hours per week) in groups of 10 to 15 individuals. The teaching methods included lectures, booklets, PowerPoint, pictures and discussions followed by questions and answers.

There were followed up calls once a month, lasted for 6 months, to see if they were following self-care behaviors. In addition, the previously learned points were emphasized and questions were answered during these phone calls. In the intervention group, an absence in more than two training sessions was an exclusion criterion from the study. Six months after finishing the educational course, the interviews were used to complete the questionnaires again for the intervention group. Blood pressure and weight measurements were also taken by standard methods. Moreover, before and six months after the intervention, the KAP questionnaires were filled by questioning the families.

In the control group, the treatment programs continued as same as before wherein six months later the questionnaires were filled out again and blood pressure and weight measurements were taken by standard methods. Educational contents in the form of educational manuals were also given to the control group at the end of the study.

Procedure of the 4th stage of the project: assessing the trends of HTN and its risk factors: At this stage, the data from three repeated cross-sectional studies with independent samples in 2001, 2007 and 2016 were used to determine the 15-year-old process of factors affecting prevalence, awareness, treatment and control of HTN in the adult population of Isfahan.

The number of samples in the 4thstage of the project: A total of 8627 individuals participated in these three studies. After the integration of data related to these three studies, management and processing of data were performed. Then, errors and data inconsistencies were eliminated, and the final file was prepared for data analysis. Finally, the data obtained from 8073 individuals were used to determine trends and also to compare the factors affecting the prevalence, awareness, treatment and control of HTN.

In IHHP 2001 and 2007, 3703 and 2660 adult residents of Isfahan, Iran were interviewed respectively. But, only 3427 and 2539 individuals who had completed data about blood pressure, age, and gender were included for data analysis. In 2016 study, 2107 adults were interviewed, and were included for analysis.

The sampling method in IHHP[10,25] was random cluster sampling. In 2001, the health center No. 2 was selected as a cluster. In 2007 and 2016, health centers No.1 and 2 were selected as clusters in Isfahan. The information of these individuals was available on biostatistics department of cardiovascular research institute. These data were utilized to determine the 15-year-old trend of prevalence, awareness, treatment and control of HTN in the adult population of Isfahan, Iran. Sample size, gender and age distribution, methods and places of sampling, inclusion and exclusion criteria, the start and end of each sampling are presented in table 1.

In this study, descriptive and inferential statistical methods were used. In order to achieve the research results, the collected data were coded and were analyzed using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA). Statistical methods including parametric tests such as Student's independent t-test, paired t-test, and non-parametric tests such as Mann-Whitney and Wilcoxon tests were used. Moreover, chi-square test and other statistical methods such as correlation analysis, linear regression, logistic regression, analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used in accordance with the assumptions.

The ethical code of this research project is IR.MUI.REC.2016.3.790. Presence in research environments was done by obtaining and presenting an introduction letter from the cardiovascular research institute of Isfahan, Iran and HTN Research Centre.

Table 1. Distribution of the reviewed sample size and sex in adult group of the 4th Stage

Phases		First phase sample size 2001			Second phase sample size 2007			Third phase sample size 2016		
		Women [n (%)]	Men [n (%)]	Total [n (%)]	Women [n (%)]	Men [n (%)]	Total [n (%)]	Women [n (%)]	Men [n (%)]	Total [n (%)]
Age groups	18-29 year	590 (17.2)	603 (17.6)	1193 (34.8)	444 (17.5)	482 (19.0)	926 (36.5)	349 (16.6)	369 (17.5)	718 (34.1)
	30-39 year	383 (11.2)	430 (12.5)	813 (23.7)	305 (12.0)	302 (11.9)	607 (23.9)	233 (11.1)	253 (12.0)	486 (23.1)
	40-49 year	267 (7.8)	313 (9.1)	580 (16.9)	205 (8.1)	211 (8.3)	416 (16.4)	171 (8.1)	176 (8.4)	347 (16.5)
	50-59 year	192 (5.6)	178 (5.2)	370 (10.8)	141 (5.6)	134 (5.3)	275 (10.8)	135 (6.4)	145 (6.9)	280 (13.3)
	60-69 year	151 (4.4)	152 (4.4)	303 (8.8)	90 (3.5)	90 (3.5)	180 (7.1)	73 (3.5)	82 (3.9)	155 (7.4)
	≥70 year	72 (2.1)	96 (2.8)	168 (4.9)	67 (2.6)	68 (2.7)	135 (5.3)	56 (2.7)	65 (3.1)	121 (5.7)
	Total	1655 (48.3)	1772 (51.7)	3427 (100.0)	1252 (49.3)	1287 (50.7)	2539 (100.0)	1017 (48.3)	1090 (51.7)	2107 (100.0)
Total sample size = 8073			3427			2539			2107	
Sampling method		-Sampling based on age and sex distribution in the Isfahan urban population -Multi-stage include: quota, stratified, clustering, random, proportional to size, systematic simple random			-Sampling based on age and sex distribution in the Isfahan urban population -Multi-stage include: quota, stratified, clustering, random, proportional to size, systematic simple random			-Sampling based on age and sex distribution in the Isfahan urban population -Multi-stage include: quota, stratified, clustering, random, proportional to size, systematic simple random		
Sampling locations		15 health centers			15 health centers			18 health centers		
Inclusion criteria		residents of Isfahan city and aged 19 or above			residents of Isfahan city and aged 19 or above			residents of Isfahan city and aged 18 or above		
Start time and end of sampling		2000-2001			2006-2007			2015-2016		

The aim of this study was explained for each unit of study and authorities of the research environment and informed consent was obtained from individuals to participate in the research. In addition, the data collected in this study remained confidential. At the end, an educational manual was given to all HTN individuals participating in the study.

Results

The results of this study focus on developing the questionnaire. In addition, face and content validity, internal and external reliability, and construct validity of instruments were examined. Likewise, prevalence, awareness, treatment and control of hypertension and risk factors among 2107 individual adults in Isfahan, Iran were determined. In a clinical trial, 216 hypertensive patients were randomly assigned into intervention and control groups. Finally, a sample size of 8073 individuals was used to determine and compare the 15-year-old trend of hypertension and its affecting factors.

Discussion

CVD and their risk factors are considered to be among the most important health problems in many countries including Iran. HTN has certainly been known as a factor causing CVD in the world.[26] Failure to recognize risk factors and lack of access to adequate health services could lead to a situation in which patients are not receiving effective treatments. Therefore, screening and monitoring patients with HTN are the primary objectives of preventing cardiovascular disease and considerable efforts have been made in this area.

In Italy, a descriptive study was conducted on trends in prevalence, awareness, treatment, and control of blood pressure, recorded from 2004 to 2014 during world HTN day. This study included 10051 individuals from the general adult population and was carried out in three periods from 2004 to

2010 (3115 individuals), 2011 to 2012 (3795 individuals) and 2013 to 2014 (3141 individuals). Within the overall sample of the population, prevalence and treatment did not change significantly, although HTN awareness and control increased from 65.8% to 67.4% ($P < 0.001$ for trend). At the same time, blood pressure control in diagnosed and treated hypertensive patients increased from 50.0% to 55.5% and finally increased to 57.6% ($P < 0.001$ for trend).[27] Likewise, the prevalence, knowledge, treatment, and control of HTN has been determined in our study.

A large-scale study in Northern California was conducted to compare rates of HTN control on 652763 subjects from 2001 to 2009 in the health system HTN registry (record) and treatment team members used guidelines which were updated every 2 years. Guidelines were disseminated through emails, pocket cards, videoconferences, and lectures. Follow-up measurements were also performed by the medical team. The subjects were examined 2 to 4 weeks after taking medication. Implementation of this program had a significant increase in HTN control.[28] Similarly, the members of treatment team have trained patients based on the guidelines in our study.

The results of the National Health and Nutrition Examination Surveys (NHANES) in 2011 and 2012, on 13431 individuals from 30 different study locations in the United States showed that 82.8% of adult patients with HTN were aware of their diseases and 51.9% had their blood pressure controlled to less than 140/90 mmHg. The rate of treatment and control of HTN in women has been more than men. Moreover, awareness, treatment and control of HTN among young adults (18-39 years) were lower as compared to older individuals. The healthy people 2020 program aim is to treat 69.5% of all adults with HTN. However, based on the NHANES, 75.7% were currently taking medication to lower their blood pressure and this amount has been above and beyond the expectations. Although the control of HTN has neither met the goal of the healthy people 2020 program (61.2% by 2020) nor the million hearts initiative program (65% by 2017), these results provide evidence for continued efforts to improve HTN control and achieve these goals.[29]

Another study used regression models to evaluate the trends in prevalence, awareness, management and control of HTN from 1999 to 2010 among 28995 men and women adults in the United States. In 2009 to 2010, among 5764 participants in NHANES, the prevalence of HTN was 30.5% for men and 28.5% for women. The HTN awareness rate was 69.7% among men and 80.7% among women. The HTN control rate was 40.3% for men and 56.3% for women. From 1999 to 2010, the prevalence of HTN remained constant. Although HTN awareness, management, and control improved, the overall rates remained low and unsatisfactory (74.0% for awareness, 71.6% for management, 46.5% for control, and 64.4% for control in management). Worst of all, there was no improvement from 2007 to 2010.[30]

According to the past three decades reports, early diagnosis and treatment of HTN and its risk factors, as well as public health policies to reduce behavioral risk factors, have led the gradual decline in the rate of mortality from heart disease and stroke in high-income countries.[31,32] Moreover, due to chronic and debilitating nature of HTN and lack of control and appropriate treatment for it, it seems sensible and essential to apply a model which is proportionate and compatible with the conditions of these patients. Self-care should be emphasized, so it can help patient accept sustained health behaviors. Moreover, it will result in improving and maintaining health and in order to institutionalize it, in each country researches on practical methods should be done in accordance with the local cultures of that region.

Conclusion

This study in an adult population of Isfahan is considered as one of the major studies in Iran and intends to examine the epidemiology of HTN and its influencing factors. In addition, by implementing a caring model and using the latest clinical guide of localization, it evaluates the impact of this model on the control and treatment of HTN using the patient and the family strength in self-care activities. This model has a lot in common with studies of HTN throughout the world. Some characteristic features of this study include regular planning and appropriate organization of administrative procedures, having a strong executive team, preparation and use of questionnaires and valid tools, having a significant sample size, observing the age and sex ratios of the population in urban areas. Obviously, the final findings of this study will play a key role in health and research policy and provide a suitable model for implementing appropriate interventional measures at the provincial and national levels.

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Conflict of Interests

Authors have no conflict of interests.

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Factors associated with the no-reflow phenomenon following percutaneous intervention of saphenous vein coronary bypass grafts

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Original Article

Abstract

BACKGROUND: We investigated clinical and procedural factors associated with the no-reflow phenomenon following percutaneous coronary intervention (PCI) of the saphenous-vein grafts (SVG).

METHODS: A cross-sectional study was done on patients who had undergone PCI of the SVG. Patients' medical documents were reviewed for demographic, clinical, laboratory, and procedural data. Slow/no-reflow was defined based on the thrombolysis in myocardial infarction (TIMI) grade (0 to 2). Univariate and multiple logistic regression analyses were performed to investigate factors associated with slow/no-reflow and $P < 0.050$ was considered as significant.

RESULTS: A total of 205 patients were studied (81% man, mean ± standard deviation of age was 66.8 ± 9.6 years). Slow/no-reflow was found in 38 (18.5%) patients. High diastolic blood pressure ($P = 0.010$), leukocytosis ($P = 0.017$), diffuse lesions ($P = 0.007$), degenerated SVG ($P < 0.001$), proximal lesions ($P < 0.001$), thrombosis ($P = 0.013$), and lower number of used stents during procedure ($P = 0.032$) were associated with slow/no-reflow in unadjusted analyses. Factors independently associated with slow/no-reflow were pre-procedural high diastolic blood pressure with odds ratio (OR) = 3.858 [95% confidence interval (95% CI), 1.157-12.860], degenerated SVG with OR = 5.901 (95% CI: 1.883-18.492), proximal lesions with OR = 5.070 (95% CI: 1.822-14.113), pre-intervention TIMI grade with OR = 0.618 (95% CI: 0.405-0.942), number of used stents for PCI with OR = 0.074 (95% CI: 0.011-0.481) for > 1 stent, and length of stents used for PCI with OR = 0.100 (95% CI: 0.019-0.529) for > 30 mm stents.

CONCLUSION: This study on the clinical and procedural factors associated with the slow/no-reflow phenomenon following PCI of the SVG can be used in risk estimation of this serious complication and tailoring preventive strategies to at-risk patients.

Keywords: Angioplasty, Coronary Artery Bypass, No-Reflow Phenomenon, Percutaneous Coronary Intervention, Saphenous Vein

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Introduction

Coronary artery bypass grafting (CABG) is a common revascularization technique in patients with coronary artery disease.[1] Although CABG has more long-term benefits than percutaneous coronary intervention (PCI) for severe cases,[2] failure of the venous grafts limits the long-term efficacy of CABG.[3] Failure of the saphenous vein graft (SVG) is a common complication following CABG, which is associated with considerable morbidity and mortality.[3] Despite advances in surgical techniques and medical treatments, significant stenosis is seen in up to 60% of the venous grafts at 10 years following CABG.[3] Depending on the time from surgery, various factors contribute to the development of the vein graft failure, from technical factors to the long-term atherosclerotic degeneration and hyperplasia of the graft intima. Patient-related risk factors have been reported as smoking, dyslipidemia and hypertension, and also genetic predisposition.[3]

Revascularization of the diseased SVG with PCI has been associated with better outcomes than repeated CABG and is the currently preferred method.[3] However, PCI of the SVG is not complication free. Distal embolization and slow or no-reflow after PCI of the SVG occurs more frequently than intervention on native coronary

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vessels.[4] The no-reflow phenomenon occurs in up to 15% of the SVG-PCI and is associated with high risk of major adverse cardiac events and mortality.[5] Yet, the pathophysiology of the no-reflow phenomenon is not clear. Some proposed mechanisms are distal embolization with thrombus and macro-debris, vasospasm, and leukocytes plugging.[6]

Current procedural and pharmacological strategies have limited success for the management of no-reflow phenomenon.[7] Accordingly, prevention is of great importance and is probably the only effective measure to approach this potentially serious complication.[8] For this aim, a systematic analysis of various possible clinical and angiographic predictors of no-reflow is required. A limited number of studies have been done in this regard so far. Current evidence has suggested a number of possible predictors such as clinical presentation, presence of thrombus, and degenerated SVG.[9-11] Considering the lack of data in this regard, we investigated the association of a number of clinical and procedural factors with slow/no-reflow (SNR) following PCI of the SVG.

Materials and Methods

This cross-sectional study was conducted on patients who had undergone CABG between Mar 2011 and Feb 2015 in the Chamran and Sina Heart Centers of Isfahan, Iran. Patients for whom angioplasty of the coronary grafted saphenous vein has been done were included into the study. Patients for whom PCI has been done for more than one saphenous vein and those who had major complications during the procedure (e.g. myocardial infarction, cardiogenic shock) were not included into the study. The sample size was calculated as 200 patients using the G*Power software (version 3, University of Düsseldorf, Düsseldorf, Germany) and estimating 10 factors associated with SNR to be evaluated in the logistic regression model. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (grant # 394095) and patients' data were used anonymously.

The following data were gathered by reviewing patients' medical documents retrospectively: age and gender, pre-procedural measured systolic and diastolic blood pressure (SBP and DBP, respectively), past medical history with regards to the coronary risk factors including smoking, hypertension, dyslipidemia, and diabetes mellitus. Laboratory data were reviewed for anemia (hemoglobin of < 13 g/dl in men and < 12 g/dl in women), high creatinine (> 1.3 mg/dl in men and > 1.1 mg/dl in women), leukocytosis (white blood cell > 10000 per mcl), and hyperglycemia (random blood glucose ≥ 200 mg/dl). Estimated glomerular filtration rate (eGFR) (ml/min/1.73m^2) was calculated by the chronic kidney disease epidemiology collaboration (CKD-EPI) formula.[12]

The following data were gathered regarding disease characteristics: length of the lesion (diffuse, tubular, or discrete with length of > 20, 10-20, and < 10 mm, respectively), degeneration score (0: ≤ 25%, 1: 26-50%, 2: 51-75%, 3: >75%), percentage of stenosis (categorized to 75-90%, 90-99%, or 100%), location of the stenosis (proximal, mid part, and/or distal),[13] and presence of thrombosis. Procedural data were reviewed for direct stenting, using a balloon (pre- or post-dilation), a number of the stents used, length of the stents (categorized to > 30, 25-30, 15-25, or < 15 mm),[13] and using distal embolic filters during angioplasty.

The study primary outcome was the occurrence of the SNR. The Slow- and no-reflow were defined as acute impairment of blood flow to thrombolysis in myocardial infarction (TIMI) grade of 2 and 0–1 respectively, despite successful treatment of the vessel obstruction.[14] Angioplasty procedures have been performed by two experienced interventional cardiologists using standard techniques.[13] In case of visible thromboses, longer stents were applied to cover them all.

Data were analyzed using the SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Data are presented as the mean ± standard deviation (SD) for quantitative variables or number (valid percent) for categorical variables. Quantitative data were checked as with normal distribution using the Kolmogorov-Smirnov Test. Student's independent t-test (for quantitative data with normal distribution), Mann-Whitney Test (for quantitative data without normal distribution and for ordinal data) and chi-square or Fisher's exact tests (for categorical data) were applied for comparison of patients with SNR and those with normal reflow. Spearman and Pearson correlation were applied to check the correlations among the variables. A P of less than 0.050 was considered statistically significant in these analyses. Stepwise logistic regression analysis was performed to find possible independent predictors of SNR. Possible predictors were considered as those variables associated with the SNR in univariate analyses with P < 0.100. Odds ratios (OR) and 95% confidence intervals (95% CI) are mentioned wherever needed.

Table 1. Demographic data, medical history, and laboratory data in all patients and comparison between patients with normal reflow and slow/no-reflow after procedure

Variables	All (n = 205)	Normal reflow (n = 167)	Slow/no-reflow (n = 38)	P
Age (year) (mean ± SD)	66.8 ± 9.6	67.0 ± 9.0	66.3 ± 11.8	0.681*
Man	166 (81.0)	136 (81.4)	30 (78.9)	0.819**
Coronary risk factors based on medical history [n (%)]				
Smoking	50 (24.4)	41 (24.6)	9 (23.7)	> 0.999**
Hypertension	122 (59.5)	99 (59.3)	23 (60.5)	> 0.999**
Dyslipidemia	57 (27.8)	46 (27.5)	11 (28.9)	0.843**
Diabetes	54 (26.3)	41 (24.6)	13 (34.2)	0.227**
Pre-procedural blood pressure				
Systolic blood pressure ≥ 140 mmHg [n (%)]	81 (39.5)	66 (39.5)	15 (39.5)	> 0.999**
Diastolic blood pressure ≥ 90 mmHg [n (%)]	30 (14.6)	19 (11.4)	11 (28.9)	0.010**
Laboratory data [n (%)]				
Anemia£	44 (21.5)	38 (22.8)	6 (15.8)	0.391**
High creatinine¥	35 (17.1)	24 (14.4)	11 (28.9)	0.053**
Leukocytosis§	13 (6.3)	7 (4.2)	6 (15.8)	0.017**
Hyperglycemia‡	19 (9.3)	15 (9.0)	4 (10.5)	0.759**
eGFR < 60 ml/min/1.73m^2	66 (32.1)	50 (29.9)	16 (42.1)	0.178**

* Student's independent t-test; ** Fisher's exact test; £ Hemoglobin < 13 g/dl in men and < 12 g/dl in women; ¥ Serum creatinine > 1.3 mg/dl in men and > 1.1 mg/dl in women; § White blood cell count > 10000 per mcl; ‡ Random blood sugar > 200 mg/dl
eGFR: Estimated glomerular filtration rate

Results

A total of 280 patients were evaluated during the study, among which 75 patients were not eligible for the study. Finally, data of 205 patients were included in the analyses showing that 81% are man, and mean ± SD of age was 66.8 ± 9.6 years. Thirty-eight (18.5%) of the patients had SNR after PCI including 23, 9, and 6 patients with post-PCI TIMI grade of 2, 1, and 0, respectively. Demographic data, medical history, and laboratory data with the comparisons between the two groups of patients with SNR and normal reflow are summarized in tables 1 and 2. There was no difference between the two groups regarding age, gender, or frequency of coronary risk factors (P > 0.050). Compared to those with normal reflow, patients with SNR had more frequent pre-procedural high DBP (28.9% vs. 11.4%, P = 0.010), high creatinine (28.9% vs. 14.4%, P = 0.053), and leukocytosis (15.8% vs. 4.2%, P = 0.017) (Table 3). There was also a non-significant difference between the two groups in kidney function (eGFR < 60: 42.1% in SNR vs. 29.9% in normal reflow, P = 0.178).

With regards to the disease and procedural characteristics, patients with SNR had longer lesion length (26.3% vs. 12.7% with diffuse lesions, P = 0.007), higher SVG degeneration scores (71.1% vs. 29.9% with scores of 2 or 3, P < 0.001), more frequent proximal lesions (76.3% vs. 35.9%, P < 0.001) and less frequent mid part and distal lesions (25.9% vs. 66.4%, P < 0.050), more frequent thrombosis (42.1% vs. 21.6%, P = 0.013), and lower number of used stents during procedure (18.4% vs. 24.6% with more than one stent used, P = 0.032) (Table 2). There was a non-significant difference between the two groups in stenosis severity with 100% stenosis being more frequent in patients with SNR (28.9% vs. 9.6%, P = 0.105). Also, stent length tended to be shorter in these patients (P = 0.095)(Table 2). In total, distal embolic filters have been used in 19 (9.3%) patients with no difference between the two groups of patients with SNR and normal reflow (P = 0.759).

Possible predictors of the SNR (with P < 0.100 in univariate analyses) were included into a stepwise logistic regression model. At first, the stenosis severity was negatively associated with SNR which was against the univariate analysis results, probably due to a high correlation with the pre-intervention TIMI grade (Spearman's rho coefficient = -0.620, P < 0.001). Accordingly, stenosis severity was excluded from the model. Possible predictors of SNR are summarized in table 3, and only factors with the significant association are presented. Positive factors independently associated with the SNR were pre-procedural DBP of ≥ 90 mmHg with OR = 3.858 (95% CI: 1.157-12.860), degenerated SVG with OR = 5.901 (95% CI: 1.883-18.492), and having proximal lesions with OR = 5.070 (95%

Table 2. Disease and procedure characteristics in all patients and comparison between patients with normal reflow and slow/no-reflow after procedure

Variables	All (n = 205)	Normal reflow (n = 167)	Slow/no-reflow (n = 38)	P
Length of lesion [n (%)]				0.007*
Diffuse > 20 mm	31 (15.1)	21 (12.7)	10 (26.3)	
Tubular 10-20 mm	34 (16.6)	25 (15.1)	9 (23.7)	
Discrete < 10 mm	139 (67.8)	120 (72.3)	19 (50.0)	
Degeneration score [n (%)]				< 0.001*
3 (>75%)	37 (18.0)	25 (15.0)	12 (31.6)	
2 (50-75%)	40 (19.5)	25 (15.0)	15 (39.5)	
0-1 (< 50%)	128 (62.4)	117 (70.0)	11 (28.9)	
Degree of stenosis [n (%)]				0.105*
100%	27 (13.2)	16 (9.6)	11 (28.9)	
90-99%	123 (60.0)	106 (63.5)	17 (44.7)	
75-90%	55 (26.8)	45 (26.9)	10 (26.3)	
Stenosis location [n (%)]				< 0.001†
Proximal	89 (43.4)	60 (35.9)	29 (76.3)	
Mid part	65 (31.7)	59 (35.3)	6 (15.8)	
Distal	56 (27.3)	52 (31.1)	4 (10.5)	
Thrombosis	52 (25.4)	36 (21.6)	16 (42.1)	0.013†
Direct stenting	74 (36.1)	62 (37.1)	12 (32.4)	0.706†
Using balloon (pre-/post dilation)	133 (64.9)	107 (64.1)	26 (68.4)	0.708†
No. of stents [n (%)]				0.032*
0	16 (7.8)	8 (4.8)	8 (21.1)	
1	141 (68.8)	118 (70.7)	23 (60.5)	
> 1	48 (23.4)	41 (24.6)	7 (18.4)	
Stent length [n (%)]				0.095*
> 30 mm	41 (20.0)	38 (23.0)	3 (9.1)	
25-30 mm	25 (12.2)	21 (12.7)	4 (12.1)	
15-25 mm	79 (38.5)	64 (38.8)	15 (45.5)	
< 15 mm	53 (25.9)	42 (25.5)	11 (33.3)	
Using distal embolic filters [n (%)]	19 (9.3)	15 (9.0)	4 (10.5)	0.759†
Baseline TIMI flow (mean ± SD)	2.33 ± 1.08	2.53 ± 0.94	1.42 ± 1.17	< 0.001*

The following variables were considered as ordinal variables: length of lesion, degeneration score, the degree of stenosis, number of stents, and stent length. The stenosis location and using balloon was considered as nominal variables. P represents the overall comparisons for these variables.

* Mann-Whitney test; † Fisher's exact test

TIMI: Thrombolysis in myocardial infarction

CI: 1.822-14.113). Negative factors associated with SNR were pre-intervention TIMI grade with OR = 0.618 (95% CI: 0.405-0.942) and the number of stents used for PCI with OR = 0.074 (95% CI: 0.011-0.481) for > 1 stent, and the length of stents used for PCI with OR = 0.100 (95% CI: 0.019-0.529) for stents > 30mm of the stents (Table 3). Because the decision on the number of stents used during PCI might have been affected by the presence of SNR, a second model was conducted without this factor, finding positive and negative factors similar to the previous model.

Discussion

The aim of the present study was to investigate possible clinical and procedural factors associated with the SNR phenomenon following PCI of the SVG. The rate of SNR phenomenon after SVG-PCI in our study (18.5%) was similar to other reports (about 14%).[9,10] Success of the PCI for diseased SVG is limited by the no-reflow complication which is associated with about 15% increased risk of mortality and 30% increased risk of post-procedural acute myocardial infarction (AMI).[15] Accordingly, finding predictors of this serious complication would be helpful for promptly tailoring preventive strategies to at-risk patients. In our study, we found possible associations of a number of patients, lesions, and procedural characteristics with the occurrence of SNR after SVG-PCI. Pre-procedural high diastolic blood pressure, proximal location of the lesion, and

Table 3. Stepwise logistic regression analysis of predictors of slow/no-reflow after procedure

Variable	OD (95% CI)	P
Positive predictor		
Pre-procedural diastolic blood pressure ≥ 90 mmHg	3.858 (1.157-12.860)	0.028
Degenerated SVG (score of 2-3 vs. 0-1)	5.901 (1.883-18.492)	0.002
Lesion location (proximal vs. others)	5.070 (1.822-14.113)	0.002
Negative predictor		
Pre-intervention TIMI flow	0.618 (0.405-0.942)	0.025
No. of stents (indicator 0)		
1	0.223 (0.052-0.956)	0.001
> 1	0.074 (0.011-0.481)	0.006
Stent length (indicator < 15 mm)		
15-25 mm	1.122 (0.370-3.402)	0.839
25-30 mm	0.391 (0.087-1.756)	0.221
> 30 mm	0.100 (0.019-0.529)	0.007

Nagelkerke R square = 0.415

SVG: Saphenous-vein coronary bypass grafts; TIMI: Thrombolysis in myocardial infarction; OD: Odds ratio; CI: Confidence interval

degenerated SVG were found as independent positive predictors of SNR after SVG-PCI in our study. Also, pre-intervention TIMI grade and the number and length of the stents used for PCI were found as independent negative predictors.

A limited number of studies have systematically investigated possible predictors of no-reflow after PCI of SVG. Patients' characteristics and clinical presentation may provide valuable data in this regard. Similar to our results, two other studies found no association between patients' age and the risk of no-reflow.[9,10] Only one report by Liu et al. found older age associated with distal embolization after SVG-PCI.[11] However, studies on patients referring with AMI have reported an association between patient's age and risk of no-reflow after PCI.[16,17] Diabetes and hyperglycemia may be associated with the no-reflow phenomenon as a result of impaired microvascular function and/or worse functional recovery.[18] An association between hyperglycemia/diabetes and no-reflow is reported in patients who had AMI following PCI of the coronary vessels.[18,19] However, our study, as well as others,[9-11] found no such association in PCI of the SVG. With regards to the possible association between lipid profile and no-reflow, the results of previous studies on patients presenting with AMI have been controversial.[20,21] Our study, as well as others,[9,10] found no association in this regard for the SVG-PCI. Neither hypertension nor smoking is consistently reported as factors associated with no-reflow after PCI in patients with AMI,[22-24] or after SVG-PCI.[9-11] Although we found no association between history of hypertension and SNR, there was an association between pre-procedural high diastolic blood pressure (≥ 90 mmHg) and occurrence of SNR in our study which was independent of other evaluated factors. High diastolic blood pressure can reflect an uncontrolled chronic hypertension which may increase the risk of no-reflow. On the other hand, hypotension at admission (systolic blood pressure < 100 mmHg) is reported as an independent predictor of no-reflow after PCI in patients with AMI.[17] This can be attributed to decreased blood flow in the lesion site and increased plugging of the leukocytes, another risk factor of the no-reflow phenomenon.[25] With regards to the patients' drug history, previous studies have failed to demonstrate association of no-reflow with specific medications (e.g. glycoprotein IIb/IIIa inhibitors).[9,26]

The only strong and consistent clinical characteristic predicting no-reflow in SVG-PCI is reported as presenting with AMI. Hong et al.[9] found no-reflow about two times more frequent in patients presenting with AMI compared to those referring with unstable/stable angina (24% vs. 13%). In another study, Sdringola et al.[10] found acute coronary syndrome (i.e. AMI and unstable angina) were significantly more frequent in patients with no-reflow than those with normal reflow (78% vs. 45%). Most of the patients in our study have been referred with stable/unstable angina. A number of patients with AMI had cardiogenic shock and were excluded from the study. Accordingly, we had limitations in this regard and were not able to evaluate the role of clinical presentation in development of SNR. Differences among the previous studies can be attributed to differences in defining the no-reflow phenomenon and more importantly to differences in patients' characteristics (e.g. clinical presentation). At this

time, the only clinical factor that can be considered as an independent predictor of no-reflow after SVG-PCI is AMI. Considering the limited number of reports on SVG-PCI, further investigation is necessary regarding patients medical history.

With regards to the laboratory findings, we found associations of leukocytosis and abnormal serum creatinine level with SNR after SVG-PCI. According to some evidence, white blood cell count[27] and neutrophil/lymphocyte ratio[28] can predict the occurrence of no-reflow after PCI and subsequent adverse cardiac events in patients referring with AMI. Our study is the first to report such an association in SVG-PCI. Possible mechanisms in this regard include mechanical plugging of leukocytes,[25] releasing oxygen free radicals leading to local edema,[29] and functional interactions between leukocytes and platelets in the microcirculation[30] which impair the flow upon reperfusion. Therefore, leukocytosis (and more precisely the neutrophil/lymphocyte ratio) can be considered as a predictor as well as a target for intervention in order to prevent no-reflow after SVG-PCI. The association between renal function impairment and incidence of and recovery from no-reflow after PCI in patients presenting with AMI is controversial.[26,31,32] Possible mechanisms include an association between renal function and coronary flow[33] and more severe renal function impairment in patients with the more severe illness. Other attractive laboratory data which is shown predictive for no-reflow after PCI in patients referring with AMI is the c-reactive protein (CRP).[34-36] Increased atherosclerosis associated with inflammation, promotion of microvascular thrombus formation and obstruction, and vasoconstriction via increased cyclo-oxygenase expression is suggested as possible mechanisms.[35,37] There is no data on the value of this laboratory test in predicting no-reflow after SVG-PCI and studies are warranted in this regard.

Characteristics of the lesions and angiographic findings during PCI on SVG may be helpful in estimating the risk of no-reflow and individualizing interventional approaches. We found an important association of having proximal stenosis and no-reflow after SVG-PCI. Proximal lesions in our study were accompanied with degenerated SVG, thrombosis, diffuse lesions, and complete stenosis more frequently than middle or distal lesions (data not shown). Such coexistence with other risk factors may explain, in part, the association between proximal lesions and no-reflow in our study. Also, proximal lesions may be more prone to disruption by interventional procedures resulting in distal embolization, though there is no direct evidence in this regard. In Sdringola et al.[10] study, ostial lesions (within 3 mm of the proximal anastomosis) were less frequent in patients with no-reflow than those with normal reflow after SVG-PCI (13% vs. 35%). Hong et al.[9] also reported that no-reflow was less frequent in patients with lesions at ostium (8% vs. 22%); however, no difference was among proximal, middle, and distal lesions. It must be noted that distal protection devices which can decrease the risk of distal embolization have been used more frequently in the previous studies (about 40%) than ours (9%). Technically, these devices are more feasible for proximal lesions which may explain the differences among the different results of studies regarding the risk of no-reflow in proximal lesions.

Similar to our results, Hong et al. also reported a higher risk of no-reflow after SVG-PCI in longer lesions,[9] but Sdringola et al. found no association.[10] Liu et al. reported larger plaque volume as an important independent predictor of distal coronary embolization (evaluated by a rise in serum creatine kinase) after SVG-PCI.[11] Lesion length is reported to be associated with no-reflow after PCI on coronary vessels of patients with the acute coronary syndrome.[17,38] Longer target lesion is associated with the larger amount of thrombus and plaque burden. Vessels with a larger diameter can contain larger plaques or thrombus but have slower flow velocity which may describe the association between lesion length and risk of no-reflow. Moreover, compared with the native coronary vessel, the larger, less calcified, and thus more friable plaques of the SVG are more prone to disruption by balloon angioplasty resulting in embolization in the smaller distal native arteries. Similar to our results, previous studies have reported a higher frequency of thrombus in no-reflow than normal reflow (35-41% vs. 7-21%).[9,10] In addition to the above-proposed mechanism, it must be noted that risk of thrombus formation from plaque ulceration is higher in a diffusely diseased SVG. This can explain why thrombus was more frequently observed with a degenerated SVG in our study (41.5% vs. 15.6%), which is an important and independent predictor of no-reflow. Similar to our results, Hong et al. found a higher rate of degenerated SVG in patients with no-reflow compared with those with normal reflow after PCI (62% vs. 36%),[9] and the same result was reported by Sdringola et al. (56% vs. 16%).[10] Therefore, in a degenerated SVG, distal embolization by thrombus or macro-debris from a large plaque after

intervention may play a major role in the no-reflow phenomenon. Another important predictor of the no-reflow phenomenon is the baseline TIMI grade.[17,26,31] Indeed, a less patent vessel prior to PCI can indicate a higher thrombus burden and more probable vasospasm. All of the above, the presentation of a case with degenerated SVG, thrombus, and large plaque or long lesion who had a baseline TIMI grade of less than 3 should be considered highly suspicious for the occurrence of no-reflow after SVG-PCI.

Interventional techniques may affect the risk of no-reflow after SVG-PCI. We found an inverse association between the number of stents used during PCI and the risk of SNR. In the study by Zhou et al. on patients with AMI, using more than one stent was associated with lower risk of no-reflow after PCI (16.7% vs. 27.8%).[17] However, it must be noted that the occurrence of no-reflow itself may affect the decision on the number of the stents being used during PCI. Also, stent length was inversely associated with the risk of SNR in our study. Hong et al. found a similar association after PCI in patients with AMI,[38] but not after SVG-PCI.[9] Shorter stents may be associated with higher risk of dissection and longer stents may better be able to cover unseen thrombi at the edges of the lesions. Unless more data are available, a clear conclusion cannot be made in these regards.

Few reports are available on the possible role of direct stenting in reducing the risk of no-reflow. In patients with AMI, Antoniucci et al.[39] found a lower risk of no-reflow with direct stenting compared with conventional stenting (5.5% vs. 12%). But, Sabatier et al. found no difference in this regard in a randomized trial.[40] We found no association between direct stenting and risk of no-reflow in SVG-PCI which was similar to other reports.[9] Although using distal protection devices has decreased the risk of no-reflow after SVG-PCI [41] and are shown to be cost-effective in this regard,[42] we found no association between distal embolic filters and the risk of no-reflow. It must be noted that distal embolic filters have been used in only 10% of our patients probably due to high costs of such devices. Hong et al. also found no association of using distal protection devices with post-intervention TIMI.[9] Differences among the studies may be related to interventional cardiologists' expertise and technical difficulties with these devices.[41]

Our study had a number of limitations to be mentioned. The study had limited sample size to precisely investigate a large number of factors that might predict SNR. Data were gathered retrospectively which might increase the risk of information bias. Also, the diagnosis of no-reflow in our study was only based on the TIMI grading. Intravascular ultrasound imaging and post-procedural electrocardiography and cardiac enzymes can provide more valuable data. Moreover, we could not gather data on the timing of the SVG disease which is important regarding the possible predictors.

Conclusion

We found possible associations of a number of patients, lesions, and procedural characteristics with the occurrence of slow/no-reflow after PCI of SVG. The pre-procedural high diastolic blood pressure (≥ 90 mmHg), proximal lesion location, and degenerated SVG were positive independent predictors, and pre-intervention TIMI grade and the number and length of the stents used for PCI were negative independent predictors of slow/no-reflow after SVG-PCI in our study. Such data can be used in risk estimation of the no-reflow phenomenon and tailoring preventive strategies promptly to at-risk patients.

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Conflict of Interests

Authors have no conflict of interests.

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Allopurinol prophylactic therapy and the prevention of contrast-induced nephropathy in high-risk patients undergoing coronary angiography: A prospective randomized controlled trial

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Original Article

Abstract

BACKGROUND: Contrast-induced nephropathy (CIN) is considered to be a possibly severe complication of radiography and thus, remains to be the main cause of acute kidney injury (AKI) for inpatients. A clinical trial was executed to measure the preventive effect of allopurinol against CIN in high-risk patients undertaking coronary angiography.

METHODS: Through randomized controlled trial, 140 patients with at minimum two risk factors of CIN, undertaking coronary angiography, were randomly allocated to the allopurinol (n = 70) or control group (n = 70). Those in the allopurinol group received allopurinol (300 mg) a day before their coronary angiography and intravenous hydration for 12 hours before and after their procedure, while members of the control group only received intravenous hydration. Serum creatinine (SCr), blood urea nitrogen (BUN) and uric acid were measured before and 48 hours after the procedure. CIN was defined by a 25% increase in SCr or the concentration of > 0.5 mg/dl, 48 hours after coronary angiography.

RESULTS: CIN was observed in 8 (11.4%) patients in the allopurinol group and 11 (15.7%) patients in the control group. There was no significant difference in the incidence of CIN between the two groups at 48 hours after coronary angiography (P = 0.459). In the allopurinol group, the median SCr concentration decreased non-significantly from 1.16 mg/dl to 1.13 mg/dl, 48 hours after coronary angiography (P = 0.189). In the control group, the median SCr concentration increased significantly from 1.11 mg/dl to 1.2 mg/dl, 48 hours after coronary angiography (P < 0.001).

CONCLUSION: Allopurinol presents no considerable effectiveness over the hydration protocol for development of CIN in high-risk patients.

Keywords: Contrast Media, Allopurinol, Coronary Angiography

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Introduction

Contrast-induced nephropathy (CIN) is a well-known common and severe complication of administering iodinated contrast after angiocardiography or radiology procedures.[1,2] CIN, in clinical studies, is defined as the 44.2 μmol/l (0.5 mg/dl) or 25% above baseline elevation of serum creatinine levels within 24 to 48 hours following iodinated contrast administration without an alternative cause.[3-5] The precise pathophysiological mechanisms of CIN are multifaceted and yet remain indistinct. The occurrence of CIN in patients who undergo coronary angiography is increasing, alternating from 2% up to 50% in the general population and high-risk patients, respectively, with situations such as chronic kidney disease (CKD) or certain risk factors.[2,3,6,7] The most serious risk factors of CIN comprise congestive heart failure (CHF), age > 75, diabetes mellitus (which is linked to enhanced risk, even in patients with preserved renal function), hypotension, hypertension, decreased renal perfusion, female gender, high-osmolar contrast, contrast volume, urgent versus planned

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percutaneous coronary intervention (PCI) and most importantly, CKD.[8,9] CIN is the third prominent cause of AKI for inpatients, featuring more than 10 % of all renal failure patients. It is also linked with enhanced risk of CKD progression and dialysis, increased morbidity and mortality and elevated healthcare costs.[3,10] Hence, preventive measures should be put in place for CIN, which yet poses a challenge among physicians. Currently, periprocedural intravenous hydration via iso-osmolar and/or low-osmolar contrast agents in place of high osmolar agents on the one hand, and limiting the dose of contrast media, on the other hand, are established approaches against CIN.[1,11] Several pharmacologic and therapeutic interventions have been practiced to lessen the incidence of CIN. Among them are N-acetyl-L-cysteine (NAC), calcium antagonists, nicorandil, ascorbic acid, diuretics, statins, sodium bicarbonate, fenoldopam, atrial natriuretic peptide, adenosine antagonists and other agents.[3,9,12-14] NAC among the mentioned solutions has gained substantial attention leading to several clinical trials and meta-analyses that attempted to evaluate the efficiency of NAC in preventing CIN. Nevertheless, NAC results have been controversial undermining the actual therapeutics suitable for this purpose.[1,3,15,16]

Allopurinol, as an inhibitor of xanthine oxidase (XO), has been widely used to treat gout and hyperuricemia. Recently, beneficial contributions of allopurinol into CIN prevention have been shown, so that it can protect kidney by inhibiting XO activity and blocking the generation of oxygen radicals and the production of uric acid.[10] Nevertheless, few reports are available about the preventive effect of allopurinol on CIN. Therefore, the aim of this study is to investigate whether allopurinol could reduce the incidence of CIN in high-risk patients undergoing coronary angiography.

Materials and Methods

The proposed protocol of this research was approved by the Ethics Committee of Qom University of Medical Sciences, Iran (Approval No: IRCT2014072318389N2), and a written informed consent was obtained from all patients prior to admission. This study was carried out in accordance with the principles of the Declaration of Helsinki.

This study was a prospective, open-label, randomized controlled trial. All patients (adults > 18 years) scheduled for coronary angiography (from October 2015 to March 2016) were screened against inclusion and exclusion criteria at Shahid Beheshti Hospital, Qom, Iran. Inclusion criteria encompassed at least moderate risk (risk score above 6) of CIN, as laid out by Mehran et al. risk score[7] which includes congestive heart failure, hypertension and diabetes mellitus (noted in their past medical history), age above 75 years and renal insufficiency which is defined as the estimated glomerular filtration rate (eGFR) less than 60 ml/minute/1.73m^2 or baseline serum creatinine more than 1.5 mg/dl. On the other hand, the exclusion criteria included end-stage renal insufficiency (eGFR less than 15 ml/minute), acute renal insufficiency, pregnancy and lactation, pulmonary oedema, cardiogenic shock, multiple myeloma, history of an allergic reaction to contrast agents or allopurinol, contrast media exposure within seven days before the procedure, uremia, renal failure resulting in receiving dialysis and the administration of NAC, metformin, dopamine, theophylline, sodium bicarbonate, mannitol, fenoldopam, diuretics and nephrotoxic medicines within 48 hours before a procedure. Prior to the procedure, a cardiologist on every participating patient conducted a comprehensive history and physical examination.

A total of 140 eligible patients were randomly assigned to either the allopurinol group or the control group, using a balanced block randomization protocol. Patients in the allopurinol group received 300 mg (100 mg, three times a day, oral, n = 70) allopurinol 24 hours before a procedure and intravenous hydration (1 ml/kg/hour) via normal saline, a maximum 100 ml/hour for 12 hours before and after coronary angiography, whereas patients in the control group (n = 70) received intravenous hydration via the same method. Serum creatinine (SCr), blood urea nitrogen (BUN) and uric acid were measured before coronary angiography and at 48 hours.

Several parameters were analyzed in the overall population. The glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault formula, (140–age) × weight (kg) / (SCr × 72), in men patients, and women patients adjusted by × 0.85. Kidney function was classified according to the stages set by the US National Kidney Foundation and defined by the eGFR value as normal kidney function: GFR ≥ 90 ml/minute and no proteinuria, mild kidney damage: GFR of 60–89 ml/minute with evidence of kidney damage, moderate damage: GFR of 30–59 ml/minute, severe damage: GFR of 15–29 ml/minute, and kidney failure (dialysis): GFR < 15 ml/minute/1.73m^2.

All tests were executed at the same laboratory using the same methodology. Coronary angiographies were accomplished through the femoral artery using the low osmolar nonionic contrast agent iohexol (Omnipaque, GE Healthcare, Cork, Ireland). Echocardiographic evaluations were also conducted for all patients before the procedure. Heart function was categorized according to the left ventricular ejection fraction as normal ≥ 55%, mild heart failure = 45%–54%, moderate heart failure = 30%–44%, and severe heart failure < 30%.[17]

The main endpoint of the study was the development of CIN, which is defined by elevated SCr levels at 44.2 μmol/l (0.5 mg/dl) or 25% above the baseline within 48 hours after coronary angiography without an alternative cause.[5] Secondary endpoints were determined to be changes of SCr, BUN, uric acid and eGFR within 48 hours after coronary angiography.

According to Erol et al.,[10] the sample size for the significance level of 0.050, with the power of 80%, has estimated approximately 70 patients in each group. Categorical data were presented as number and percentages, and the continuous data were stated in form of mean ± standard deviation (SD). Comparison of continuous variables was analyzed by a Student's t-test and Paired t-test for normally distributed, and the Mann-Whitney U-test and Wilcoxon rank sum test for non-normally distributed values. The Shapiro-Wilk test was used for testing the normality of distribution. The categorical variables were compared using the chi-square test or Fisher's exact test if the expected frequency was less than 5. The analysis of covariance (ANCOVA) was used to analyze mean differences between two groups after intervention with adjustment for baselines. Post-hoc pairwise comparisons were done with Sidak approach. Statistical significance was defined as $P < 0.050$. All calculations were analyzed with the SPSS for Windows (version 17, SPSS Inc., Chicago, IL, USA).

Results

Patient baseline characteristics are given in table 1. No significant differences were observed between the two groups for the baseline clinical characteristics.

In the allopurinol group, the median SCr concentration decreased non-significantly from 1.16 mg/dl to 1.13 mg/dl within 48 hours after angiography ($P = 0.189$). In the control group, the median SCr concentration increased significantly from 1.11 mg/dl to 1.2 mg/dl within 48 hours after angiography ($P < 0.001$) (Table 2).

Table 1. Baseline clinical and procedural characteristics of the patients

Variables	Allopurinol group (n = 70)	Control group (n = 70)	Total	P*
Men [n (%)]	54 (77.1)	46 (65.7)	100 (71.4)	0.134
Heart failure [n (%)]	62 (88.5)	63 (90.0)	125 (89.3)	0.425
Diabetes [n (%)]	29 (41.4)	27 (38.5)	56 (40.0)	0.730
Hypertension [n (%)]	45 (64.2)	42 (60.0)	87 (62.1)	0.601
Hypercholesterolemia [n (%)]	27 (38.5)	23 (32.8)	50 (35.7)	0.480
Smoking [n (%)]	23 (32.8)	16 (22.8)	39 (27.9)	0.187
Family history of heart disease [n (%)]	3 (4.2)	7 (10.0)	10 (7.1)	0.189
ACE inhibitor consumption[n (%)]	59 (84.2)	56 (80.0)	115 (82.1)	0.508
Statin consumption[n (%)]	55 (78.5)	56 (80.0)	111 (79.3)	0.835
Calcium blocker consumption[n (%)]	6 (8.5)	3 (4.2)	9 (6.4)	0.301
Iohexol [n (%)]	60 (85.7)	64 (91.4)	124 (88.6)	0.421
Age (year) (mean ± SD)	60.3 ± 12.6	62.1 ± 10.4	61.2 ± 11.6	0.356
Body mass index (kg/m^2) (mean ± SD)	26.8 ± 3.6	26.4 ± 3.2	26.6 ± 3.4	0.807
Hematocrit (mean ± SD)	43.6 ± 3.4	43.9 ± 4.7	43.7 ± 4.1	0.690
Mean arterial pressure (mmHg) (mean ± SD)	98.3 ± 12.8	96.3 ± 13.5	97.3 ± 13.2	0.353
Left ventricle function (%) (mean ± SD)	40.6 ± 9.7	41.8 ± 9.2	41.2 ± 9.4	0.425
Duration of suffering from hypertension (year) (mean ± SD)	3.1 ± 3.6	3.3 ± 3.8	3.2 ± 3.7	0.781
Duration of suffering from diabetes (year) (mean ± SD)	3.0 ± 4.5	2.7 ± 4.5	2.8 ± 4.5	0.648
Dose of contrast agent (ml) (mean ± SD)	41.1 ± 15.5	40.1 ± 14.4	41.1 ± 14.9	0.409

* Student's t-test for normally distributed and Mann-Whitney test for non-normally distributed values. The categorical variables were compared using chi-square test

ACE: Angiotensin-converting enzyme; SD: Standard deviation

Table 2. Biochemical and renal function changes before and 48 hours after coronary angiography

Variables	Allopurinol group (n = 70)	Control group (n = 70)	P*
SCr (mg/dl) (mean ± SD)			
Pre-angiography	1.2 ± 0.3	1.1 ± 0.3	0.161
48-hours post-angiography	1.1 ± 0.2	1.2 ± 0.2	0.043
P**	0.189	< 0.001	-
BUN (mg/dl) (mean ± SD)			
Pre-angiography	40.3 ± 17.2	38.8 ± 14.4	0.374
48-hours post-angiography	36.6 ± 15.1	41.6 ± 14.0	0.002
P**	0.023	0.096	-
Uric acid (mg/dl) (mean ± SD)			
Pre-angiography	6.1 ± 1.9	5.8 ± 1.5	0.874
48-hours post-angiography	5.1 ± 1.8	5.9 ± 1.7	0.010
P**	0.096	0.631	-
eGFR (ml/minute/1.73m^2) (mean ± SD)			
Pre-angiography	75.8 ± 28.1	74.2 ± 24.9	0.723
48-hours post-angiography	78.5 ± 25.4	70.5 ± 21.2	0.045
P**	0.129	0.045	-

* Student's t-test for normally distributed and Mann-Whitney test for non-normally distributed values; ** Paired t-test for normally distributed and Wilcoxon rank sum test for non-normally distributed values.
SCr: Serum creatinine; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; SD: Standard deviation

In the allopurinol group, the median eGFR increased non-significantly from 75.8 ml/minute/1.73m^2 to 78.5 ml/minute/1.73m^2 within 48 hours after angiography (P = 0.129). In the control group, the median eGFR decreased significantly from 74.2 ml/minute/1.73m^2 to 70.5 ml/minute/1.73m^2 within 48 hours after angiography (P = 0.045) (Table 2). Overall, changes in SCr, eGFR, BUN, and uric acid within comparison groups before and after the study were compared in tables 2 and 3.

CIN occurred in 11 out of 70 (15.7%) patients in the control group and in 8 out of 70 (11.4%) patients in the allopurinol group. There was no significant difference in the incidence of CIN between the two groups within 48 hours after angiography (P = 0.459) (Figure 1).

Discussion

The hypothesis of this study is that allopurinol has a preventive effect on the development of CIN. However, our results showed that prophylactic oral administration of allopurinol causes no significant reduction in CIN incidence as compared with the control group in high-risk populations for the development of CIN.

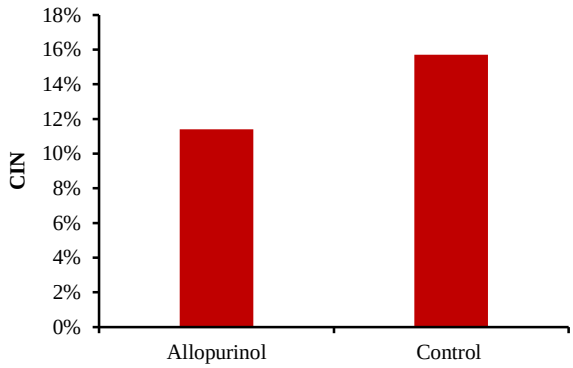

Figure 1. The incidence of contrast-induced nephropathy is not significant between treatment groups (P = 0.459)
CIN: Contrast-induced nephropathy

Table 3. Results of ANCOVA adjusting for age and baseline values of dependent variables

Group (Allopurinol vs. Control)	MMD	SE	95% CI for MMD	P*
SCr (mg/dl)	-0.106	0.026	(-0.157-0.055)	< 0.001
Uric acid (mg/dl)	-0.991	0.157	(-1.302-0.681)	< 0.001
BUN (mg/dl)	-5.786	2.042	(-9.824-1.748)	0.005
eGFR (ml/minute/1.73m^2)	6.785	2.050	(2.710-10.850)	0.001

* ANCOVA after adjusting for age and baseline values of dependent variables
MMD: Marginal mean differences (after intervention between two group); SE: Standard error of the mean; CI: Confidence interval; SCr: Serum creatinine; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate

Our study revealed significant differences in SCr, BUN, uric acid and eGFR within 48 hours after coronary angiography between two groups which may suggest the supportive effects of allopurinol on renal dysfunction. Our findings are inconsistent with the previous studies[10,18] reported that allopurinol along with hydration may prevent CIN in high-risk patients undergoing coronary procedures. In the study conducted by Erol et al., 79 patients with a serum creatinine concentration > 1.1 mg/dl received allopurinol (300 mg, oral) for 24 hours prior to cardiac catheterization and intravenous hydration (1 mg/kg/h normal saline for 12 hours pre- and post-contrast). In this study, the incidence of CIN within 48 h and 96 h after the procedure was significantly lower in allopurinol group compared to the control group.[10] Mean total dose of contrast agents used in the present study was about 40 ml, i.e. lower than those of previous studies.[10,18] These findings suggest that perhaps allopurinol is beneficial when administered at a different dosage or frequency in patients who received high doses of contrast agents. However, few studies have focused on preventive effects of allopurinol on CIN, so that more evidence on the efficacy of allopurinol in patients with high risk of CIN development are required.

It has been accepted that hydration and the use of low-osmolar contrast agents assist in preventing CIN in patients undergoing coronary angiography.[4,19] In this study, we also used these methods in treatment groups. The current contrast medium can be categorized by osmolality into high-osmolar contrast media (HOCM, ~ 1000-2500 mosmol/kg), low-osmolar contrast media (LOCM, ~ 400-800 mosmol/kg) and iso-osmolar (IOCM, 290 mosmol/kg). High osmolar contrast media was replaced by low/iso-osmolar contrast media due to better tolerability, fewer side effects and importantly to ensure a reduced incidence of CIN.[4,8] We also used Iohexol (low-osmolar, non-ionic contrast medium) to reduce complications and CIN incidence.

While the precise pathophysiology mechanism of CIN remains indistinct, possible direct and indirect pathophysiologic effects of contrast exposure that have been suggested include renal vasoconstriction, which initiates decreased oxygenation of the medulla causing ischemia and renal injury, direct tubular toxicity due to creation of oxygen free radicals that lead to acute tubular necrosis, and decreased in glomerular filtration because of alterations in tubule-glumeral regulatory mechanisms.[4,9,20,21] The exact mechanisms of the effect of allopurinol on CIN are unknown. However, it has been suggested that allopurinol protected the kidneys by attenuate through the production of oxygen free radicals caused by the xanthine inhibitory effects and also preserved the glomerular filtration rate through intra-renal regulatory mechanisms.[10]

Our study was constrained by a number of limitations. First, it was a single-centered non-blinded study. Second, in contrary to direct measurement, creatinine clearance was calculated using the Cockcroft-Gault formula. Third, the studied population was limited in size. Nevertheless, a larger multi-centered double-blinded randomized trial comprising other clinical settings would be beneficial in validating the beneficial effects of allopurinol in CIN prevention.

Conclusion

In conclusion, our findings revealed that allopurinol had no considerable effectiveness over hydration protocol in high-risk patients on CIN prevention. Nevertheless, according to the noteworthy variances observed in biochemical markers, we consider that the use of allopurinol could be effective on renal function and yet further controlled clinical trials are required to warrant regarding the comparative efficacy of allopurinol for the prevention of CIN.

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Conflict of Interests

Authors have no conflict of interests.

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Persian Registry Of cardioVascular diseasE (PROVE): Design and methodology

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Original Article

Abstract

BACKGROUND: Our aim was to create and establish a database called "Persian Registry Of cardioVascular diseasE (PROVE)" in order to be used for future research and in addition, as a tool to develop national guidelines for diagnosis, treatment, and prevention of cardiovascular disease (CVD). In this paper, the design and methodology of the PROVE pilot study will be discussed, launched in Isfahan, Iran, in 2015-2016.

METHODS: Through establishing PROVE, patients' data were collected from hospitals and outpatient clinics prospectively or retrospectively and followed up for a maximum of three years based on the type of CVDs. The inclusion criteria were as patients with acute coronary syndrome (ACS), ST elevation myocardial infarction (STEMI), stroke, atrial fibrillation (AF), heart failure (HF), congenital heart disease (CHD), percutaneous coronary intervention (PCI), and chronic ischemic cardiovascular disease (CICD). Specific protocols, questionnaires, and glossaries were developed for each registry. In order to ensure the validation of the protocols, questionnaires, data collection, management, and analysis, a well-established quality control (QC) protocol was developed and implemented. Data confidentiality was considered.

RESULTS: In order to register patients with ACS, STEMI, stroke, HF, PCI, and CICD, the hospital recorded data were used, whereas, in case of AF and CHD registries, the data were collected from hospitals and outpatient clinics. During the pilot phase of the study in Isfahan, from March 2015 to September 2016, 9427 patients were registered as ACS including 809 as STEMI, 1195 patients with HF, 363 with AF, 761 with stroke, 1136 with CHD, 1200 with PCI, and 9 with CICD. Data collection and management were performed under the supervision of the QC group.

CONCLUSION: PROVE was developed and implemented in Isfahan as a pilot study, in order to be implemented at national level in future. It provides a valuable source of valid data that could be used for future research, re-evaluation of current CVD management and more specifically, gap analysis and as a tool for assessment of the type of CVDs, prevention, treatment, and control by health care decision makers.

Keywords: Cardiovascular Disease, Registries, Disease Management, Data Collection

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Introduction

The gradual reduction in birth and death rates, along with the increase in life expectancy has led to an unprecedented growing rate of the older adult population.[1] There are 600 million people aged 60 years and over, across the world and the number

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expected to double by 2025.[2] This is a global burden and Iran is not an exception. According to the Iranian Ministry of Health Statistics on the age pyramid, Iran is currently transitioning from a dominantly young to a dominantly older population.[3]

Aging can affect cardiovascular (CV) function, consequently causes diseases and results in mortality and morbidity.[4] Several studies have reported a higher prevalence of cardiovascular diseases (CVD) and its associated risk factors in Iranian population.[5-11]

Globally, CVD is the leading cause of death, and CV death in Iran, constitutes 38% of all deaths, compared to the global rate of 31%.[12]

Since 2001, The Isfahan Cohort Study (ICS), Iran, conducted on more than 6000 healthy adult subjects, followed up for the occurrence of CV events, reported a high incidence and mortality rate due to CVD, and urged health policy-makers to take action to prevent and control CVD.[13-15]

A disease registry can enhance the quality of care, and encourages health care providers to lean towards a more patient self-care approach, and to adopt better health care services by identifying the gaps and challenges in treatment and care. Having a registry in place will be very helpful to generate research data, in order to raise public awareness and take more effective steps, towards disease prevention and control. It could also help experts developing therapeutic guidelines for more effective and evidence-based disease management options.[16]

Considering the benefits of having a disease registry database, Isfahan Cardiovascular Research Center (ICRC), a the World Health Organization (WHO) collaborating center, primarily had established a CVD registry for acute coronary syndromes (ACS) and stroke in 1999, based on the WHO Multinational Monitoring of trends and determinants in Cardiovascular disease (MONICA) method.[17] Through that earlier registry, data from over 150,000 patients with ACS and 37000 patients with stroke were collected and patients were followed up for mortality or morbidity; details of this registry have been previously reported.[18-25] The aforementioned experience led us to design and develop a more comprehensive and improved registry database for patients with different types of CVD, namely the Persian Registry Of cardioVascular diseasE (PROVE), in 2015. Data collection, protocols, and questionnaires as well as frequency, method, and duration of follow-ups differ, according to the type of CVDs.

To the best of our knowledge, PROVE is the first national comprehensive CVD registry database, established in Iran with the less similar registry in the Eastern Mediterranean region. This paper describes the design and implementation of PROVE in Isfahan, as a feasibility study.

Materials and Methods

PROVE is a registry, in which patients' data from hospitals or outpatient clinics are collected. It was initiated in late 2014 and launched in March 2015. Ethics approval was obtained from the Ethics Committee of Isfahan University of Medical Sciences.

Patients with ACS, stroke, heart failure (HF), atrial fibrillation (AF), percutaneous coronary intervention (PCI), and congenital heart disease (CHD) were recruited and followed up, since 2015 and more recently, chronic ischemic cardiovascular disease (CICD) was incorporated, in 2016. All diagnoses were made based on the International Classification of Diseases (ICD 10).

Since we aimed to use the registered data in PROVE, as a potential tool for developing national diagnosis, treatment, and prevention guidelines for patients with CVD, we identified interested cardiologists as principle investigator (PI) of each type of CVDs, all members of the steering committee of PROVE. Furthermore, a data collection team was formed, consisting of trained nurses and general practitioners, worked under the supervision of cardiologists and a neurologist.

The quality control (QC) committee, consisting of epidemiologist, statisticians, specialized physicians, and information technology staff was developed, concomitantly with the steering committee and the head was selected from the steering committee members. Figure 1 shows the management flowchart of the PROVE program.

Each type of CVD registry had a team who carried out their own search and analysis, in order to develop a methodology for collecting data, monitoring data entry, and following up the patients. Each team developed their relevant questionnaire protocol and a glossary specific to the type of CVD registry. Concomitantly, all staff responsible for the data collection, either through medical records or face to face interviews with patients, received a basic systematic training for the AF, ST elevation myocardial infarction (STEMI), HF, and CICD, joined the European Observational Research Program (EORP).[26]

Data were collected, according to the established protocol and glossary, using the questionnaires. Since the registry of patients with ACS and stroke

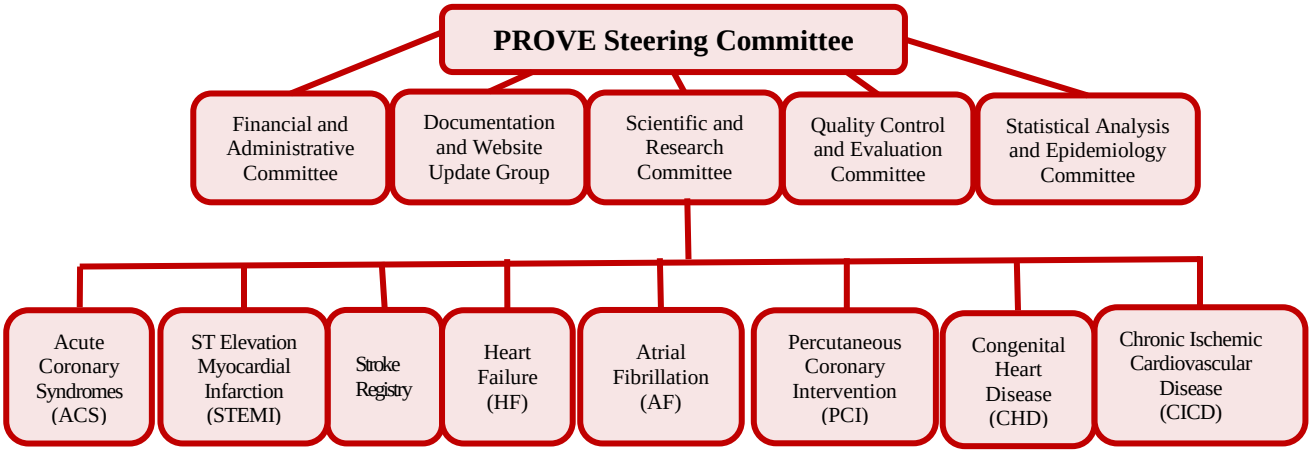

Figure 1. The management flowchart of the Persian Registry Of cardioVascular diseasE (PROVE) program

had begun earlier in 1999, using WHO MONICA protocol and questionnaires,[17] the data collection and registration were incorporated in PROVE; meanwhile, the registration of ACS was continued, using the same protocol, but the stroke registry method was derived from a WHO Stepwise approach[27] and the European Registry.[28]

Two methods were used for data collection: cold pursuit method where the patients' data were collected from the medical records, and hot pursuit method, whereby patients' data were collected by face to face interviews with patients.[29] Eventually, a website was created for PROVE, in order to present a brief introduction to the program.[30]

Data collection methods for different type of CVDs

PROVE/Stroke: Patients with stroke were originally registered, based on the WHO MONICA protocol, and were followed-up for 28 days, since the events occurred. Using the initial questionnaire, data regarding the patients' demographic characteristic, symptoms of the disease, medical history and used prescribed medications, diagnostic tests, treatment course, physical examination, and presence of risk factors were collected. The follow-up form inquired brief data on the patients' medical status and conditions. The MONICA questionnaire does not have any option to investigate and register the type of stroke, however, the newly developed protocol by WHO, named WHO Stepwise does.

By proceeding into the PROVE program, the WHO Stepwise protocol and the European registry were used to develop a new questionnaire to register patients with stroke using cold pursuit method.[27] The stroke registration personnel received three initial trainings of two-hour long and monthly one-hour retraining session.

The new questionnaire included patients' demographic characteristics, personal medical and drug history, risk factors, heart and brain imaging, blood test results, treatments received in the hospital and complications (if any), discharge prescriptions, and patient's status, as well as the definite diagnosis of the type of stroke, according to computed tomography (CT) scan or magnetic resonance imaging (MRI).

The patients were followed up by the phone or in person at the 1st, 3rd, and 12th months, using the Barthel Index and the Modified Rankin Scale (MRS). The reliability and validity of these two questionnaires had previously been investigated, in Iranian population.[18] Moreover, secondary prevention measures, rehabilitation status, and the incidence of new CV events were examined in the follow-up.

PROVE/AF: Data regarding patients with AF were jointly registered with EORP, using population-based protocol. We gathered patients' data from two Isfahan University of Medical Sciences (IUMS)-affiliated hospitals, and the main electrophysiology (EPS) clinics in Isfahan.

Case report forms (CRF) were completed by on-site trained nurses, and then reviewed by an EPS expert, before submitting to EORP database. All nurses received six initial trainings of two-hour long and a retraining session every two months. The registered patients' were followed up on annual basis, up to three years.

PROVE/HF: A questionnaire was developed, based on the Swedish Heart Failure Registry (S-HFR)[31] and the Acute Decompensated Heart Failure Registry (ADHERE).[32] The validity of the questionnaire was investigated and approved by the QC committee. This registry was performed on patients with HF who were hospitalized, due to decompensated or acute HF. The questionnaire collected data on demographic characteristics,

medical history, sign and symptoms at admission, treatment regimen, and diagnostic tests. The HF registry personnel received three initial trainings of two-hour long and a monthly retraining session.

The patients' follow-up protocol was either by phone or, if necessary, a visit by a specialist physician on the 1st, 6th, and 12th months after discharge. The follow-up form inquired the patients' status, used medications, new diagnostic tests, and in case of death, place and the reason of death.

After one year of the implementation of a pilot registry for HF, as planned to join EORP/HF, the initial PROVE/HF protocol switched to EORP/HF protocol, for alignment on a joint effort.

PROVE/PCI: The PCI registry was started in the largest referral hospital of cardiac and cardiosugery in the province. Data collection initiated by interventional cardiology fellows and residents, alongside a research nurse, and under supervision of PIs.

PCI questionnaire included information on demographic characteristics, medical history and records on previous diagnostic and treatment measures, results of coronary artery angiography, details on PCI intervention, acute and sub-acute complications of the PCI (if any), and in-hospital and long-term outcomes. Several training and re-training sessions were held and are still ongoing. Patients who underwent PCI for any reason were recruited in this registry. The follow-up protocol is similar to the PROVE/HF registry.

PROVE/CHD: A population-based protocol was used to register CHD. The questionnaire was developed by cardiac pediatricians and validated by the QC experts. It was used to collect the following data on different types of CHDs: demographic characteristics, medical history, pregnancy history, maternal diseases, family history of CHDs, clinical presentations, diagnostics findings, used medications and recommended follow-up, and disease management plans. Data were collected by five pediatric cardiologists and their fellows, at three university-affiliated referral hospitals and private clinics.

Patients were followed up by phone calls or a visit at the clinic, depending on the type and severity of the disease and interventions or treatments they received, the time of admission, performance and type of cardiac surgery, and the probability of medication side effects or new medical condition occurring during the course of treatment.

PROVE/STEMI: In order to register patients with STEMI, and since our plan was to join the EORP/STEMI registry, their questionnaire and protocol were used, when all the alignments and feasibility studies were completed. The registration of patients with STEMI was begun in three IUMS-affiliated hospitals, and then the number of hospitals was gradually increased. The inclusion criteria comprised of all patients with STEMI diagnosis based on electrocardiography (ECG), new left bundle branch block (LBBB), and those who died upon admission with at least one STEMI diagnosis on ECG. All completed CRFs were carefully reviewed by two cardiologists, before submitting to EORP. Data were collected based on past medical history, significant events in the course of hospitalization [from the onset of chest pain until seeking medical help, referrals, diagnoses, hospitalizations, and dispatches (if any)], examination upon arrival, and the type and time of treatment. Furthermore, angiography and PCI results (if any), laboratory data, left ventricular function, disease course and complications during hospitalization, type and dosage of medications before and during hospitalization, and at the time of discharge, and ultimately the patients' status at the time of discharge, and future rehabilitation plans were studied. The nurses appointed to collect the data, received ten initial trainings of 2-hour long and a monthly one session of retraining.

The long-term follow-up of the patients was performed, over the phone and in person in a one-year period. The follow-up form includes data on vital status, physical activity, history of CV events, history of hospitalization for any cardiac or non-cardiac reasons, and history of surgical or interventional CV procedures performed within one year of the STEMI diagnosis, a complete medication history, left ventricular function, and some biochemical factors. All the patients with STEMI were also registered in the older ongoing ACS registry based on WHO MONICA protocole.[17]

PROVE/CICD: The CICD registry was initiated based on the hot pursuit method, in the same hospital that the PCI registry had been implemented and is ongoing. This registry started as part of EORP[26] and based on their protocol. Cardiologists familiar with EORP/CICD began to register and follow up all registered patients. Eligible patients were all aged above 18 years with stable angina and a history of myocardial infarction (MI) or heart revascularization. Patients' demographic data, medical history, risk factors, diagnostic tests, and treatment measures were registered. The patients' were followed up for a year, in person or by phone.

Table 1. Characteristics of cardiovascular disease registry based on different types of disease

Type of diseases	Questionnaire based on	Follow-ups	Methods	Settings
Stroke	Researcher-made	1, 3, and 12 months	Cold pursuit: Refer to archive patient records	Hospital based
AF	EORP	Once/year for 3 years	Hot pursuit: Interviews with patients	Population based (hospital and clinics)
HF	Researcher-made	1, 6, and 12 months	Cold pursuit: Refer to archive patient records and switch to Hot pursuit later	Hospital based
PCI	Researcher-made	1, 6, and 12 months	Hot pursuit	Hospital based
CHD	Researcher-made	Depending on the patient's disease and conditions	1) Hot pursuit: Interviews with patients 2) Cold pursuit (in one of the centers): Refer to archive patient records	Population based (hospital and clinics)
STEMI	EORP	12 months	Hot pursuit: Interviews with patients	Hospital based
CICD	EORP	12 months	Hot pursuit: Interviews with patients	Hospital based
ACS and stroke	WHO MONICA[8]	28 days	Cold pursuit: Refer to archive patient records	Hospital based

AF: Atrial Fibrillation; HF: Heart Failure; PCI: Percutaneous Coronary Intervention; CHD: Congenital Heart Disease; STEMI: ST Elevation Myocardial Infarction; CICD: Chronic Ischemic Cardiovascular Disease; ACS: Acute Coronary Syndrome; EORP: European Observational Research Program; MONICA: Multinational Monitoring of trends and determinants in Cardiovascular disease

The follow-up after discharge data were the same as the enrollment one.

Table 1 presents the registered diseases and their details in PROVE.

Consent and Confidentiality

All the patients were ensured of the confidentiality of their data and signed an informed consent form, for having their data collected. In order to maintain a full confidentiality of the patients' information, a registration code (additional to a national code) was assigned, to be used for research purposes, instead of the first and last name. The registration code is unique to each patient and formed by a non-identifiable combination of patient information, such as the first and last name, and date of birth, as inspired by Huffman coding.[33,34] With this coding system, the software used to create PROVE has the capability to capture each patient's data and categorize it in a right place even if the patient has been hospitalized for a different type of CVD, on any other occasion. We created a second code to ensure the confidentiality and to have an alternative, in case the first code is lost.

Quality Control

To ensure the quality of PROVE, and as an internal quality control measure, all PIs were responsible to collaborate with QC experts to evaluate their specific disease registry. Quality control measures taken, were as follows: setting a list of minimum required information to enter into the registry, ensuring the forms used to enter the data are user-friendly, providing a complete and easy-to-use protocol with a related glossary to be used in case of ambiguity, reviewing the data entry to ensure the quality, training all personnel responsible for data collection, ensuring the data are collected with the highest quality and least missing info, visual inspection of the forms, and regular interim analysis. The QC experts, with the collaboration of PIs, were responsible to incorporate into the registry protocols or questionnaires, all the recommendations based on interim analysis, evaluation, and monitoring of the results.[35]

To ensure a high quality data collection, in addition to the internal QC, an external audit was conducted by experts, not members of the PROVE team. They studied the protocols, questionnaires, glossaries, and inclusion criteria for each disease, before starting the audits. This would make the data more comparable and less biased, when compared with data from other countries (comparability). Moreover, the QC committee ensured 1) the timeliness of the data by registering the PROVE data in a preset time period, i.e. within two weeks of generating the medical record of a new patient at the target hospital and up to nine months, depending on the type of the disease; 2) the accuracy and validity of the data, by accurately registering the data, with no errors; and 3) lastly the completeness of data, by achieving the ultimate goal and by registering 90% of the admitted patients in hospitals, with any type of diseases .

A second expert also reviewed the diagnostic accuracy. To validate the clinical diagnosis, an

independent cardiologist not affiliated with PROVE team, examined 10% of the records, using the diagnosis checklist in each protocol. The independent cardiologist then would report any error to the PIs. This was performed by examining 10% of the hospital records and comparing the registered and collected data. In case of any errors, the assessment team would report the error to the PIs.

Data were analyzed using SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA,). Descriptive statistics were calculated, based on clinical characteristics of the registered patients. Quantitative variables were expressed as mean ± SD or median and interquartile range (if required). Qualitative variables were summarized as counts (percent). To assess content validity of questionnaires, we used a content validity ratio (CVR) and content validity index (CVI) scores.

Results

The number of patients whose data were entered into PROVE database by September 2016, for each type of disease was as follow:

A total of 1195 patients with HF were recruited, 928 based on clod pursuit method (61.96% men, and 38.4% women) and 267 based on hot pursuit method. There were 9427 registered patients with ACS (54.5% men and 45.5% women) of whom 809 registered with STEMI (79.97% men and 20.03% women). Patients registered with AF were 363 (50.68% men and 49.32% women), with stroke 761 cases (50.72% men and 49.28% women), with CHD 1136 subjects (51.4% men and 48.6% women); those who underwent PCI were 1200 (74% men and 26% women), and there were 9 cases of CICD. CRFs for cases of AF, STEMI, HF, and CICD cases were sent to the EORP site.

After assessing the data by QC committee on HF registry, and challenges faced, the PIs decided to change the HF registry to hot (prospective) pursuit.

Table 2 presents the number of recruits and sites, according to the type of CVDs.

Discussion

We presented here our feasibility study of the national comprehensive CVD registry, the way it was developed and implemented. Additionally, we discussed the patients' recruitment methods, follow-up, data collected, and QC measures.

Researchers often use disease registries to understand where a disease management modality stands, for a given medical condition. These critical databases have always been used to help us understand how to deliver quality care and what outcomes are achieved. Furthermore, findings from registries could help policy makers to better assess the magnitude of health-related issues and assist them in setting priorities for interventions, in order to prevent and control the diseases.

Table 2. Registered patients with cardiovascular disease in Isfahan, Iran, by September 2016

Registered Diseases	Number of registered participant	Time of onset	Number of target centers and hospitals
ACS/WHO/MONICA	9427*	March 2015	All of the Isfahan hospitals
STEMI/EORP	809	September 2015	3 government hospitals affiliated to Isfahan University of Medical Sciences
Stroke/WHO/Stepwise and European registry	761	March 2015	All of the Isfahan hospitals
HF	COLD: 928 HOT:267	March 2015 April 2016	All of the Isfahan hospitals 2 government hospitals affiliated to Isfahan University of Medical Sciences
AF	363	March 2015	2 government hospitals affiliated to Isfahan University of Medical Sciences and 1 referral clinic
CHD	1136	September 2015	3 government hospitals affiliated to Isfahan University of Medical Sciences, 2 referral clinics and 2 referral intensive clinics
PCI	1200	September 2015	1 government hospital affiliated to Isfahan University of Medical Sciences
CICD	9	June 2016	1 government hospital affiliated to Isfahan University of Medical Sciences

ACS: Acute Coronary Syndrome; MONICA: Multinational Monitoring of trends and determinants in Cardiovascular disease; STEMI: ST Elevation Myocardial Infarction; EORP: European Observational Research Program; HF: Heart Failure; AF: Atrial Fibrillation; CHD: Congenital Heart Disease; PCI: Percutaneous Coronary Intervention; CICD: Chronic Ischemic Cardiovascular Disease

* ACS including patients with STEMI

CVD is the leading cause of death globally, and specifically in Iran. A registration system for patients with CVD, especially ACS, stroke, HF, and AF could offer valuable information on the course of these diseases, its diagnosis and treatment, acute phases and chronic conditions, medications, in-hospital and out-of-hospital complications, and clinical outcomes.

In the past half-century, major advances have been made in the field of cardiology with the introduction of angiography and coronary artery interventions. In some cases, the effectiveness and safety of the treatment methods were challenged and alternative treatments were proposed, based on the patients' information through registries.[30]

As noted earlier, some of the disease registrations are performed through hot pursuit, and some through cold pursuit. Each of these methods has pros and cons. For example, hot pursuit requires more on-site personnel and it is therefore more costly, and prone to miss some information on holidays or when the registration personnel are absent from work. Nevertheless, since this method allows the information to be registered simultaneously with the occurrence of the CV event, it gives a more thorough access to relevant information, and the registration outcome is more complete.

With the cold pursuit, however, registration can be performed months or years later than the occurrence of the CV event and with fewer personnel; but the information derived from previous records and documents may be incomplete.[28]

In appreciation of a distinct need for real and accessible data on CVD, the European Society of Cardiology (ESC) stated that registries are required for evaluating the epidemic of CVD, the diagnostic, treatment methods, and promotion of the guidelines. Therefore, The EORP was established in 2009 with the aim of creating a better understanding of medical performance, based on the collected data and in order to invite interested countries to join and cooperate.[26] Therefore, we decided to join EORP and collaborate in the registry of some types of CVDs in PROVE such as AF, STEMI, CICD, and HF.

PROVE CVD types that have joined EORP use hot pursuit only. However, due to the shortage of personnel, it is currently running on a limited number of centers and it will be gradually run in other centers, when the challenges of the registry are clarified and upon completing the feasibility study.

The CHD questionnaire is short and mostly contains clinical questions; therefore, it is completed by the patients in physicians' offices and by the on-site personnel at the hospitals.

As for the registration of stroke and ACS, since the MONICA questionnaires were extensive and the number of personnel cooperating with the project was limited, registration has begun in the form of cold pursuit in many years ahead; however as a pilot study, some IUMS-affiliated hospitals have switched to hot pursuit registration.

In many registries, consisting of several diseases, both hot and cold pursuit methods are often used; eg: Global Registry of Acute Coronary Events (GRACE) that uses both methods (hot and cold) pursuits, based on the conditions. The GRACE registry enrolls patients with ACS, like STEMI, non-STEMI, and ACS without biomarker and their risk predictors, as well as in-hospital and six-month outcomes.[36]

In PROVE, a number of disease registrations are hospital-based, because of the limited number of personnel, or large number of patients, or the lack of specialized clinics, such as CICD, stroke, HF, ACS/MONICA, and STEMI.

A number of diseases' registration is population-based, for example, registries for AF and CHD. The reason could be either because of the protocol they follow; such as the EORP protocol requires a population-based registration, or because they have detected reliable paths, before proceeding with this type of registration, as the case in CHD.

The collection of long-term follow-up data is often an important component of the disease registries. Follow-up data are often critical to the registry's objectives;[37] hence, we followed our patients for longer time periods, after they were discharged from the hospitals.

Different registries in PROVE suggested different times and intervals for the follow-up of patients. Those who use cold pursuit method like stroke and HF have periodical follow-up in a short interval, in order to avoid loss of patients and the associated information. Other registries have follow-up periods in line with their own protocols.

Limitations and strengths: To the best of our knowledge, to date, no comprehensive registry has been established in Iran or in the Eastern Mediterranean region, including as many types of CVD, as in PROVE. We believe that PROVE could help to fill the gap on CVD effective management, prevention, and control, by providing valuable data.

Furthermore, our joint collaboration with EORP will allow a larger pool of data to be compared, and in addition, to obtain scientific knowledge on an international scope. The continuous QC, all throughout the initiation and implementation of PROVE, is a point of strengths for this initiative.

However, this program suffers from some limitations, such as lack of continuous funding source, lack of a proper infrastructure for implementation, less committed clinicians to collaborate, and limited hospitals to participate without expecting financial incentives.

Conclusion

PROVE development and implementation as a feasibility study was successful. While the implementation was initiated in Isfahan, scale-up pilot study at the national level, has been started. This registry can generate a valuable data pool to be used for purposes, such as improving the current CVD management in participating centers and at a national level, filling the gaps in preventative care, establishing effective treatment and disease control guidelines, and eventually local and international research.

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Project registration code in IUMS is 93121.

Conflict of Interests

Authors have no conflict of interests.

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Effect of crocin, a carotenoid from saffron, on plasma cholesteryl ester transfer protein and lipid profile in subjects with metabolic syndrome: A double blind randomized clinical trial

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Original Article

Abstract

BACKGROUND: Metabolic syndrome is defined by insulin resistance and a clustering of other cardiovascular risk factors. Crocin is a carotenoid derived from the stigmas of the saffron flower and had previously been shown to affect lipid profile. However, the mechanism for this function is not well understood. The present trial aimed to investigate the possible effect of crocin on plasma levels of cholesteryl ester transfer protein and lipid profile in individuals with metabolic syndrome.

METHODS: This was a randomized, double-blind, placebo-controlled, clinical trial consisting of an 8-week treatment with crocin, or placebo tablets between April and June 2014, in the Nutrition Clinic of Ghaem Teaching Hospital, Mashhad, Iran. Participants were randomly assigned to take a 30 mg/day crocin (n = 22) in the intervention group or placebo (n = 22) in the control group. Anthropometric, hematological and biochemical parameters were measured and recorded during pre and post-treatment periods.

RESULTS: Whilst plasma cholesteryl ester transfer protein was increased in the group taking the crocin tablet by 27.81% during the trial period (P = 0.013), the difference between the crocin and placebo groups was not significant (P = 0.116). Moreover, the percent changes in cholesterol (P = 0.702), triglyceride (P = 0.080), low-density lipoprotein (LDL) (P = 0.986), high-density lipoprotein (HDL) (P = 0.687) and fasting blood glucose (P = 0.614) did not differ significantly between intervention and control groups.

CONCLUSION: Although crocin supplements increased the serum cholesteryl ester transfer protein in patients with metabolic syndrome, this change was not significant between treatment and placebo groups.

Keywords: Cholesteryl Ester Transfer Protein, Crocin, High-Density Lipoprotein Cholesterol, Low-Density Lipoprotein Cholesterol, Metabolic Syndrome, Saffron

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Introduction

Cholesteryl ester transfer protein (CETP) is present in serum and enables transfer of cholesteryl esters from high-density lipoprotein (HDL) to triglyceride-rich lipoprotein, leading to a lowering of plasma HDL cholesterol (HDL-C) concentrations.[1,2] HDL metabolism and remodeling is related to the metabolism of triglyceride-rich lipoprotein and is determined by CETP and phospholipid transfer protein (PLTP). Plasma concentrations of CETP are associated with fat

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mass and a reduction in fat mass can lead to a decrease in serum CETP level reciprocally.[3]

Saffron (Crocus sativus *L*), is a bulbous perennial plant that contains more than 300 volatile and non-volatile components, including safranal, crocin, picrocrocin and some other carotenoids.[4] Saffron appears to be effective in several human health problems, as demonstrated in clinical trials.[5] The potential pharmacological effects of saffron are due to the presence of crocetin (mono and diglycosyl esters of polyene dicarboxylic acid) and crocin (digentiobiosyl ester of crocetin) carotenoids.[6] Crocin has been shown to have hypolipaemic,[7,8] antitumor,[9,10] antiulcer[11] and antioxidant[12,13] effects. It also has the ability to alter learning behavior[8] and cardio-protective properties.[14,15]

Metabolic syndrome is defined by a clustering of cardiovascular risk factors and is associated with a state of chronic low-grade inflammation. Endothelial dysfunction, insulin resistance, hyperuricemia, high blood pressure, cardiovascular diseases, obesity and type 2 diabetes are associated with metabolic syndrome and may be responsible for some of the poor outcomes associated with this condition.[16-18]

Since abnormal levels of low-density lipoprotein cholesterol (LDL-C), HDL-C, triglyceride (TG) as well as changes in plasma CETP are important features of metabolic syndrome[19] and few studies have investigated the relationships between crocin administration and the above factors, this study was conducted to assess the effect of crocin on changes in serum CETP and lipid profile.

Materials and Methods

A double-blind, placebo-controlled study was conducted using a parallel design over a period of eight weeks between April and June 2014, in the Nutrition Clinic of Ghaem Teaching Hospital, Mashhad, Iran. Forty-four patients with metabolic syndrome (MetS), aged from 18 to 70 years, were recruited for this study. MetS was defined according to 3 of the following criteria proposed by the National Cholesterol Education Program (Adult Treatment Panel III) report (ATPIII): high waist circumference (> 102 in men and > 88 in women), impaired glucose tolerance and insulin resistance (fasting blood glucose or FBG > 100), dyslipidaemia with raised serum triglycerides (TG > 150), and low serum HDL-C (HDL < 40 in men and HDL < 50 in women), and a high blood pressure (> 130/85 mmHg).[20] The sample size was determined based on 27.6% changes in HDL level after crocin administration, according to the results reported by Nikbakht-Jam et al.[21] considering the type one (α) error of 0.050 and power of 0.900, using Stata Statistical Software, Release 11.0 (Stata Corporation, College Station, TX, USA).

Subjects were allocated into one of two groups, an active intervention group (10 men, 12 women) and a control group (8 men, 14 women) (Figure 1).

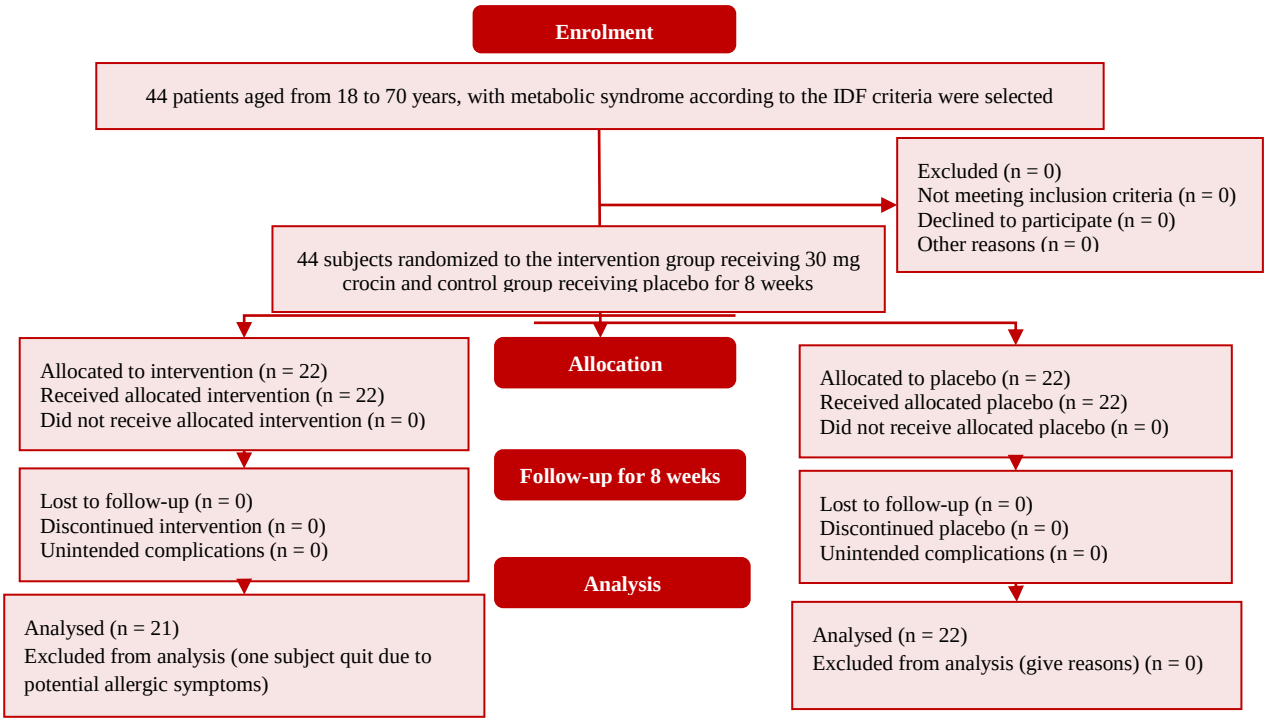

Figure 1. Flowchart of the participants in the randomized clinical trial
IDF: International Diabetes Federation

The allocation was carried out randomly by an experienced researcher using random number tables of patients referred to the clinic. The intervention group received 30 mg crocin tablets twice a day based on the results of the previous studies,[21,22] and the control group received a placebo for 8 weeks by a researcher who was blinded to the group. Subjects who were pregnant, lactating, or had systemic diseases with or without relevant treatments (e.g. immunodeficiency syndrome, rheumatoid arthritis, gout, asthma, insulin treatment in the diabetic patients) were excluded from the study.

The study was a part of a research project, approved by the Ethics Committee of the Mashhad University of Medical Sciences, Iran (No. IRCT2013080514279N1).

After obtaining informed consent, standard anthropometric data including height, weight, waist circumference and hip circumference were measured and initial biochemical tests were performed. Standing height was measured using a wall-mounted stadiometer (the subjects were shoeless and wore light clothing). Maximum hip circumference and minimum waist circumference (between below the chest and above the navel) were measured respectively as hip and waist circumference, using a tape measure to the nearest 0.1 cm. Body weight (kg), body fat (%) and body mass index (BMI) were measured using Tanita BC-418 bioelectrical impedance analysis device (Tanita Corp., Tokyo, Japan).

According to American Heart Association (AHA) guidelines, similar dietary advice was provided to all participants. Compliance with the research protocol was reviewed by a research technician who contacted the subjects every two weeks.

Plant material Crocus sativus *L.* stigma was provided by Novin Saffron Co. (Mashhad, Iran). The method of extraction has been described previously.[23] Crocin tablets were manufactured according to the method described by Nikbakht-Jam et al.[21] and contained 30 ± 0.8 mg per tablet. The placebo tablet matched the crocin tablet in size and shape and contained starch and permitted colouring. An industrial pharmacy specialist supervised quality control tests including hardness, weight variation, disintegration time, drug content and dissolution tests.

Fasting blood samples (20 ml serum) were taken from volunteers before and after the intervention for measurements of fasting blood glucose level, triglyceride, total cholesterol, HDL and LDL. Samples were transferred to the laboratory of Nutritional Science and Technology Group, Mashhad, Iran, for routine tests. The samples were taken prior to starting the trial and at the end of the 8th week. All biochemical measurements were carried out using an AutoAnalyzer BT3000 (BioTechnica, Italy).

Plasma CETP concentration was measured by enzymatic methods using commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cusabio, China) on a ELISA STAT Fax instrument (Awareness Technology, Inc., USA). The assay was performed as follow: after preparation of reagents, samples and standards, 0.1 ml standard or sample was added to each well, incubated at 37 °C for 2 hours and liquid of each well was removed. 0.1 ml Biotin antibody was added and the plates were incubated at 37 °C for 1 hour. After aspiration and washing for 3 times, 0.1 ml horseradish peroxidase-conjugated avidin was added and incubated at 37 °C for 1 hour. 0.09 ml 3,3',5,5'-tetramethylbenzidine (TMB) substrate was added to each well and incubated at 37 °C for 20 minutes. Finally, 0.05 ml of stop solution was added to stop the enzymatic reaction and optic density absorbance at 450 nm in a microplate reader was read.

Data are shown as mean ± standard deviation (SD) and median (interquartile range) respectively, for normally and non-normally distributed variables. The normality distribution of continuous data was assessed by Kolmogorov-Smirnov test. CETP and other factors measured during the study were compared before and after the intervention using paired t-test (for normally distributed data) and Wilcoxon test (for non-normally distributed data). The percent changes between intervention and control groups were compared using Student's independent t-test (for normally distributed data) or Mann-Whitney test (for non-normally distributed variables). Categorical data were compared using chi-square test. P less than 0.050 was considered statistically significant. All data analyses were performed using SPSS software (version 18, SPSS Inc., Chicago, IL, USA).

Results

At baseline, there were no significant differences between the groups regarding age (P = 0.297), body mass index (P = 0.136), waist circumference (P = 0.500), hip circumference (P = 0.433), the prevalence of diabetes mellitus (P = 0.909), hypertension (P = 0.909) and cardiovascular disease (P = 0.527) (Table 1).

Table 1. Baseline characteristics of intervention and placebo groups

Baseline factors		Intervention group (n = 22)	Placebo group (n = 22)	P
Gender	Women	12 ± 54.50	14 ± 63.60	0.540*
	Men	10 ± 45.50	8 ± 36.40	
Age (year)	Women	44.50 (24.75-51.50)	46.00 (32.25- 51.50)	0.297†
	Men	33.10 (29.85-35.42)	34.90 (31.80-37.92)	0.408†
Body fat		38.70 (27.77- 41.60)	39.20 (29.97-43.20)	0.751†
TG (mg/dl)		151.00 (111.50-204.25)	151.00 (117.50-224.50)	0.618†
Fasting serum values				
LDL (mg/dl)		163.50 (120.25-204.25)	122.00 (110.25-165.50)	0.069†
HDL (mg/dl)		37.00 (31.75-46.00)	39.00 (31.00-44.50)	0.896†
FBG (mg/dl)		92.50 (84.50-105.25)	95.50 (89.00-123.75)	0.295‡
CETP (µg/ml)		0.32 (0.26-0.43.00)	0.34 (0.30-0.37)	0.916†
WC (cm)		109.91 ± 8.94	111.91 ± 10.50	0.500‡
HC (cm)		114.73 ± 8.55	116.84 ± 9.14	0.433‡
Cholesterol		232.18 ± 66.52	209.19 ± 38.41	0.175‡
Diabetics§		5 (31.3)	5 (29.4)	0.909*
Hypertensive‖		5 (31.3)	5 (29.4)	0.909*
Cardiovascular disease¶		2 (13.3)	1 (7.1)	0.527*

Categorical data are presented as number (%) and continuous data as mean ± standard deviation (SD) in the case of normal distribution or median (Interquartile range) in the case of non-normal distribution; * Chi-square test; † Mann-Whitney test; ‡ paired t-test; § Diabetes was diagnosed by a medical history and taking diabetic drugs or high blood glucose (FBG ≥ 126); ‖ Hypertension disease was diagnosed by a medical history and taking blood pressure drugs; ¶ Cardiovascular disease was diagnosed by the medical history and use of heart disease medications

WC: Waist circumferences; HC: Hip circumferences; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FBG: Fasting blood sugar; CETP: Cholesteryl ester transfer protein

As illustrated in table 2, the median (interquartile range) of the percent change of serum CETP after intervention among crocin and placebo groups were 12.23 (0-31.49) and zero (-19.42- 27.12), respectively. In the intervention group, the average increase of CETP was 27.81%, while in the placebo group the average increase was just 2.83%. The difference between CETP before and after the intervention was statistically significant (P = 0.013), while no difference was observed during this period of time in the placebo group (P = 0.881). However, these changes in crocin and placebo groups were not statistically different (P = 0.116).

Among patients in the crocin group, the average changes in serum cholesterol, TG, LDL, HDL and FBG after eight weeks of treatment were 0.14% (P = 0.390), 27.48% (P = 0.355), -5.49% (P = 0.058), 31.84% (P = 0.004) and 7.97% (P = 0.495) compared to the baseline values. The corresponding outcomes for placebo group were -3.02% (P = 0.398), -7.27% (P = 0.079), -5.76% (P = 0.281), 36.50% (P < 0.001) and 3.20% (P = 0.681), respectively. We did not observe any significant difference between the intervention and placebo groups regarding the above average changes in cholesterol (P = 0.702), TG (P = 0.080), LDL (P = 0.986), HDL (P = 0.687) and FBG (P = 0.614) (Table 3).

We also investigated the crocin effect on CETP changes based on the TG levels. We did not observe any significant CETP changes between intervention and placebo groups either in hypertriglyceridemic (> 200 mg/dl) (P = 0.530) or in normotriglyceridemic (< 200 mg/dl) (P = 0.230) subjects.

Table 2. Plasma cholesteryl ester transfer protein mass before and after the intervention

Interventionor placebo		Median (IQ range) (µg/dl)	Percent change median (IQ range)	P for change from baseline	Difference between the changes in the two groups
Intervention	Before	0.32 (0.26-0.43)	12.23 (0-31.49)	0.013*	0.116†
	After	0.37 (0.32-0.62)			
Placebo	Before	0.34 (0.30-0.37)	0 (-19.42-27.12)	0.881*	
	After	0.32 (0.26-0.45)			

Data are presented as Median (Interquartile range); * Wilcoxon test; † Mann-Whitney test

IQ: Interquartile

Table 3. Lipid profile and fasting blood glucose before and after intervention between intervention and placebo groups

Variables	Intervention group		P	Placebo group		P	P between two groups
	Before	After		Before	After		
Cholesterol	232.18 ± 66.52	220.09 ± 55.60	0.390*	209.19 ± 38.41	199.95 ± 50.10	0.398*	0.702*
TG	151.00 (111.50-204.25)	160.50 (102.00-227.25)	0.355†	151.00 (117.50-224.50)	144.00 (111.00-206.00)	0.079†	0.080†
LDL	163.50 (120.25-204.25)	121.00 (102.00-170.75)	0.058*	122.00 (110.25-160.50)	115.00 (72.25-161.25)	0.281*	0.986*
HDL	37.00 (31.75-46.00)	50.00 (40.50-56.25)	0.004*	39.00 (31.00-44.50)	51.50 (43.50-62.50)	< 0.001*	0.687*
FBG	92.50 (84.50-105.25)	88.50 (79.25-105.25)	0.495†	95.50 (89.00-123.75)	100.50 (90.50-120.50)	0.681†	0.614†

Data are presented as mean ± standard deviation (SD) in the case of normal distribution or median (Interquartile range) in the case of non-normal distribution; * Paired or Student's independent t-test; † Wilcoxon or Mann-Whitney tests

TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FBG: Fasting blood sugar

Discussion

Metabolic syndrome is a complex of cardiovascular risk factors such as high lipid profiles, low HDL, high FBG, hypertension and abdominal obesity.[20,24] Identification and management of metabolic syndrome is very important for controlling the risk of subsequent disorders.[25] CETP is a protein playing an important role in the modulation of plasma lipids and lipoproteins.[26] Therefore, it can contribute to developing metabolic syndrome and atherosclerotic disease.[19,27]

Elevation of HDL-C via inhibiting CETP appears to be an attractive strategy for reducing the risk of cardiovascular events among high-risk patients. Four CETP inhibitors including torcetrapib,[28] dalcetrapib,[29] anacetrapib[30] and evacetrapib[17] have been assessed in clinical trials, but no benefits have been demonstrated in terms of clinical outcomes.[31] Therefore, there is a growing interest in using traditional medicine as an alternative for the effective prevention of cardiovascular risk factors.

Results of the current study showed that crocin supplements were associated with a significant increase in the serum CETP concentration, although no significant change was observed after receiving placebo. To the best of our knowledge, this study was carried out as the first clinical trial of administrating crocin tablets among patients with metabolic syndrome for evaluating CETP changes. Therefore, it is not possible to make any comparisons with other similar studies. As a known mechanism, crocin can affect the lipid profile through a high selectivity for pancreatic lipase activity.[32] Previous studies have also suggested that a Taq1B polymorphism of CETP gene may be associated with the development of metabolic syndrome.[26]

Although crocin treatment was associated with a reduction in cholesterol, LDL and FBG levels and increase in TG and HDL concentrations in the intervention group, only the changes in HDL was statistically significant. These results are in contrast with those observed in some previous studies. Sheng et al. showed that treatment with crocin (25 to 100 mg/kg per day) significantly reduced TG, total cholesterol, LDL-C and very low-density lipoprotein cholesterol (VLDL-C) in rats as a result of inhibiting pancreatic lipase and malabsorption of fat and cholesterol.[32] Such discordance between the results might be due to different study subjects (human in this trial) and low sample size of this study. Desired clinical results will be achieved when a CETP inhibitor affect both HDL-C and LDL-C concurrently.[31] In the current study, HDL-C increase was significant in both intervention and placebo groups during the study period, possibly due to the effects of dietary change. However, it did not differ between these groups, and therefore does not suggest a beneficial application of crocin for patients with metabolic syndrome.

The observed effect of crocin on lipid profile and FBG were similar to the findings of another previous study.[21] It was suggested in some studies that CETP mass is the rate-limiting factor in changing lipid profile of hypertriglyceridemic patients (> 400 mg/dl),[33] whereas subjects in our trial had lower TG levels, indicating undesired results. However, comparing the effect of crocin on CETP level between patients with different TG levels (upper and lower than 200 mg/dl) did not show any significant differences.

Sandhofer et al. reported that women have higher plasma CETP levels than men because of higher subcutaneous adipose tissue.[34] In the current study, the frequency of both gender, as well as other factors, was the same in the intervention and placebo groups due to the random allocation design of the study. This group matching suggests that the observed findings of the crocin effect are independent of the above potential confounding factors.

One of the limitations of our study was the *ex* vivo quantification of CETP levels which gives a measure of the amount of CETP in serum, while the potential function of crocin by inhibiting CETP activity is in vivo. The low sample size of the participants was another limitation of the study which can lead to the low power of the analysis.

Conclusion

In conclusion, a significant increase in the CETP and HDL levels following treatment with crocin among patients with metabolic syndrome was observed. However, these changes were not significantly different from those observed in the placebo group. Further studies with longer follow-up periods, larger sample size and different doses of crocin are suggested to investigate the exact effect of crocin on CETP and lipid profile among different groups of patients.

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Conflict of Interests

Authors have no conflict of interests.

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Septal hematoma due to stent implementation in the septal course of the left anterior descending artery

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Case Report

Abstract

BACKGROUND: The interventricular septal hematoma (IVSH) is a rare and potentially lethal finding. There are variously reported etiologies including instrumental damages during cardiac interventions. Although there are not enough studies available, conservative management is considered as a preferable approach in stable patients.

CASE REPORT: A 45-year man smoker with the previous history of percutaneous coronary intervention (PCI), admitted with unstable angina in present visit. Coronary angiography showed significant in-stent restenosis (ISR) of the left anterior descending (LAD) artery stent. During our intervention for treatment of the ISR, the wire movement caused a diffuse dissection without any runoff, in the distal portion of the LAD. Therefore two stents were deployed in the dissected segment with a short overlapping segment. Unfortunately, the overlapping segment of these stents was located in the myocardial bridge segment. Therefore the contraction of the interventricular septum (IVS) caused a scissor-like movement of the stents, and they ruptured the LAD into the septum. Therefore, the contrast agent was accumulated in the IVS. Immediately, a graft stent was deployed in the overlapping segment of stents and perforation became sealed. In echocardiography, the IVS diameter increased to 30 mm. Since the patient was hemodynamically and electrically stable, he underwent conservative approach and after two months the septum returned to the normal size.

CONCLUSION: During PCI on the LAD artery, the implantation of stents in the septal course with a short overlapping segment can result in coronary perforation, and therefore IVS hematoma by the scissor effect. Septal hematoma may cause life-threatening arrhythmias or ventricular septal rupture, but if it is asymptomatic or uncomplicated. Conservative management is the best strategy.

Keywords: Percutaneous Coronary Intervention, Myocardial Bridge, Hematoma

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Introduction

The interventricular septal hematoma (IVSH) is a rare finding in cardiology practice. Chest trauma, myocardial infarction,[1,2] and instrumental manipulation during cardiac surgery or percutaneous coronary intervention (PCI) may lead to myocardial and IVSH. While some patients are symptom-free, lethal arrhythmias or ventricular septal rupture (VSR) may occur as the adverse cardiac events.[3] In this report, we will discuss a case of IVSH due to stenting of the left anterior descending artery in its myocardial bridge segment.

Case Report

The patient was a 45-year man smoker with a history of coronary artery disease. He had undergone coronary angiography in another center due to acute coronary syndrome, six months prior to the present admission. The angiography revealed significant diffuse stenosis in the proximal segment of the left anterior descending artery (LAD), at the bifurcation of a well-developed diagonal branch. Furthermore, a muscle bridge was also detected in the mid-portion of LAD. Besides, the proximal portion of the right coronary artery (RCA) had significant diffuse stenosis. The echocardiography at that time revealed hypokinesia of anterior wall and the ejection fraction was about 45%. Percutaneous coronary intervention (PCI) had performed on the proximal portion of the LAD with a 2.75 × 19

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drug-eluting stent (DES). He had been discharged in stable clinical condition.

After 6 months, the patient was admitted with unstable angina in our cardiology ward. Again, the coronary angiography was performed and showed significant in-stent restenosis of the LAD stent, and significant stenosis of the ostium of the well-developed diagonal branch which was behind the stent. The RCA was as before.

We decided to do PCI on RCA and kissing balloon inflation of the LAD-diagonal lesion, using a non-compliant drug-eluting balloon (DEB) in the LAD stent. A 3-33 mm DES was implanted in a proximal portion of the RCA.

For treatment of in-stent restenosis of the LAD artery and the diagonal branch stenosis, we advanced a hydrophilic wire into the LAD and another tapered-tip wire through the struts of the LAD stent into the diagonal branch. Final kissing balloon inflation was performed by using two non-compliant (NC) balloons (3 × 15 mm DEB and 2.5 × 12 mm NC-balloons in the LAD and diagonal arteries). Unexpectedly, a diffused dissection without a distal runoff (type F) appeared in the mid to distal portions of the LAD due to the wire to-and-fro movement. Primarily and according to the available stents, the distal portion of the dissected segment was covered by using a 2.75 × 26 DES (Figure 1).

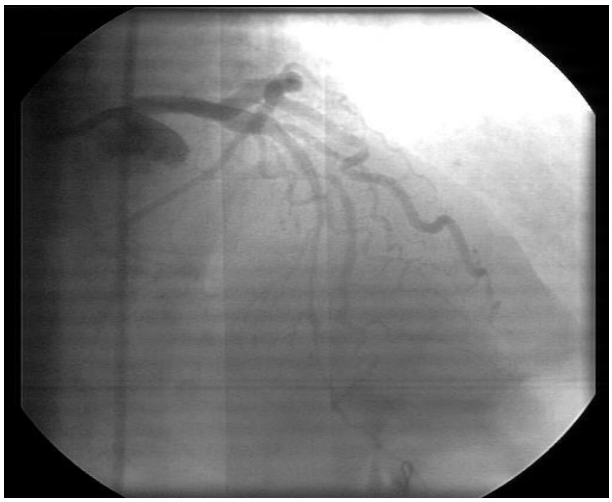

Figure 1. Wire dissection at the distal segment of left anterior descending

Then another stent (2.75 × 16 mm) was implanted in the proximal segment of the dissection with a short overlapping segment of the first stent (about 1-2 mm). These two stents covered the septal course of the LAD (called as the myocardial bridge). The thrombolysis in myocardial infarction (TIMI) flow 3 of LAD was restored. The post-dilatation was performed by using a 3-15 NC balloon. But after some minutes, the diagonal ostium recoiled and the patient suffered from chest pain due to impaired diagonal artery flow. Obligatorily a 2.5 × 8 stent was deployed in the diagonal branch with the T-stenting technique. Before terminating the procedure, we observed contrast opacification around the LAD (Figure 2).

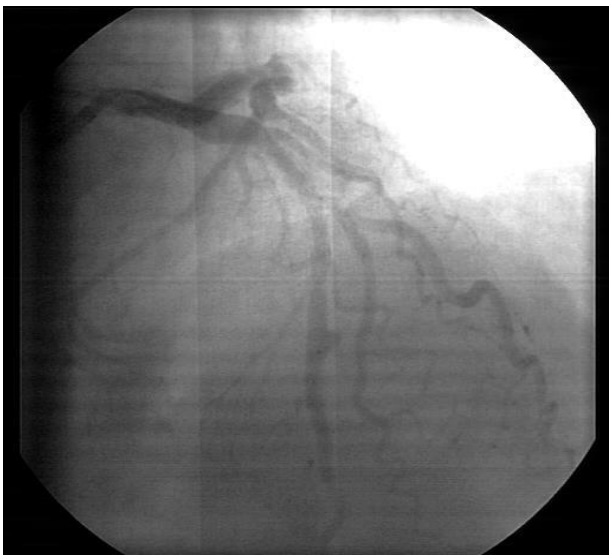

Figure 2. Enlarging opacification around the left anterior descending, impending to rupture

It resembled an enlarging sac which suddenly ruptured (Figure 3).

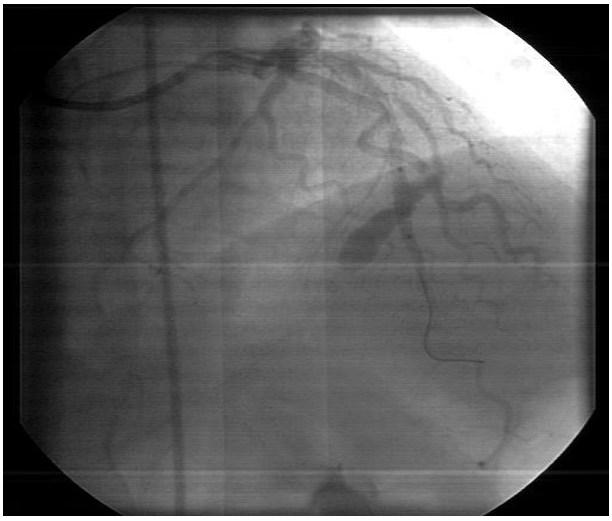

Figure 3. Rupture of left anterior descending to ventricular septum

Therefore, a graft stent was deployed

immediately at the overlapping segment of the stents and it sealed the perforation (Figure 4).

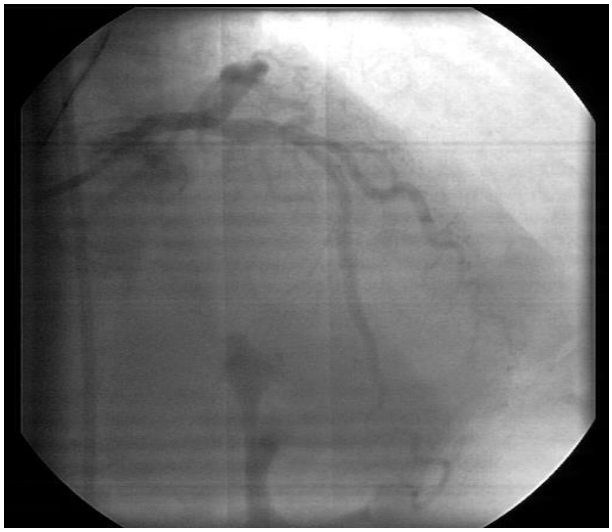

Figure 4. After graft stent deployment

In this stage, the heparin effect was reversed by prothamin sulfate. The echocardiography at the same time showed a voluminous (about 30 mm) ventricular IVSH (Figure 5).

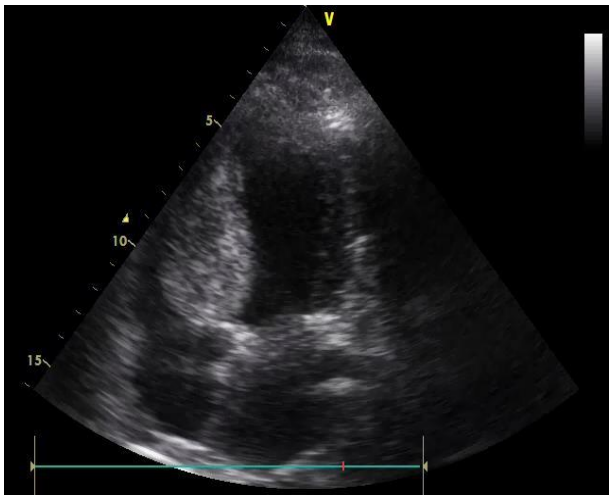

Figure 5. Ventricular septal hematoma

After 10 days and before discharge, another angiography revealed the stent of the diagonal branch was under-expanded. Therefore final kissing balloon inflation of the LAD and diagonal artery stent was done and it made full expansion of both stents.

The patient was closely observed postoperatively and underwent echocardiography every 15 days. During the next two months follow up, the size of the hematoma reduced and septum size returned to normal range. Moreover, the wall motion abnormalities were resolved (Figure 6).

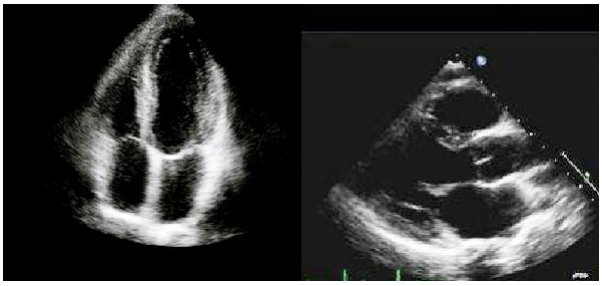

Figure 6. Returning of septal diameter to the normal range

Discussion

It has been reported that different clinical settings such as acute myocardial infarction, coronary artery bypass surgery, ventricular septal defect repair, chest wall trauma and aortic valve disease could cause a myocardial hematoma. Although this complication is rare, it can cause serious conduction or hemodynamic abnormalities including outflow obstruction, high-grade atrioventricular block, ventricular septal rupture, abscess transformation and tamponade. The septal perforating artery injury may lead to ventricular IVSH that can occur during wire or microcatheter negotiation through the branch,[2] or suturing the septal patch at the time of ventricular septal defect (VSD) repair,[4] or even during cardiac resynchronization therapy defibrillator (CRT-D) implantation.[5]

In almost all reports, patients had responded to conservative treatment instead of surgical evacuations, especially when they were hemodynamically and electrically stable. In a case report, the ventricular septal rupture associated with an IVSH resolved after 5 weeks.[2] In another report IVSH with 4 cm diameter resolved in 6 weeks.[5] A case series reported 2 cases of IVSH and coronary ventricular fistula after chronic total occlusion percutaneous coronary intervention (CTO-PCI).[6] One of their patients developed a large IVSH 6 hours after PCI. While the patient general condition was stable and without any arrhythmia, they decided to follow their patient by serial echocardiography and the hematoma was resolved after 3 months of follow up. The other patient who developed sinus tachycardia and intermittent chest pain was managed in a different way. They could successfully resolve perforation from the LAD by deploying covered stent across the collateral vessel.[6] Murthy et al. reported a case of dual coronary perforations into the left ventricle (LV) resulted from balloon dilatation of under-expanded distal stent.[7] The coronary perforation showed extravasation of contrast to LV. They managed their asymptomatic patient's both perforations by

covered stents.[7] Higuchi et al. reported a case of complicated PCI in a 56-year man.[8] During the PCI of chronic total occlusion (CTO) lesion, while they were trying to pass a stiff guide wire to the diagonal branch, extravasation of blood into subepicardial space led to cardiogenic shock. As they could not evacuate all the blood surrounding the LV by percutaneous pericardiocentesis, a median sternotomy was performed to remove the hematoma. Their patient received percutaneous cardiopulmonary support after the surgery and continuous drainage of blood from pericardial space was proceeding. The echocardiography showed hematoma of lateral LV. Because of their patient's hemodynamic condition and multi-organ dysfunction, they could not perform a thoracotomy, resulted in patient's death 3 weeks after surgery.[8] Galiuto et al. reported intramural atrial hematoma because of dissection of coronary artery side branch during PCI in a 79-year woman.[9] They used myocardial contrast echocardiography in order to get a characterization of blood supply status of hematoma. While their patient developed persistent postprandial chest pain and dysphagia, they decided to perform surgical exploration and successfully drained the entire amount of clots and blood.[6]

The septal injury in our case was due to the scissor effect of two stents with the short overlapping segment, in the septal course of LAD artery (myocardial bridge segment). Because there was no symptom or arrhythmia, we observed the patient closely. Furthermore, heparin was discontinued but dual antiplatelet therapy continued. The hematoma spontaneously resolved after 8 weeks.

Finally, it seemed that serial echocardiography should be performed in stable patients until the hematoma is resolved. In case of enlarging hematoma, or any other complications, surgical evacuation of the hematomas should be considered.

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Conflict of Interests

Authors have no conflict of interests.

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