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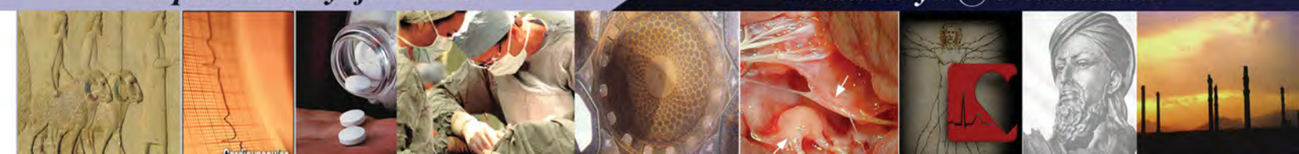

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3. Gaston M. The psychological care of patients following a myocardial infarction [Online]. 2003; Available from: URL: http://www.nursingtimes.net/the-psychologicalcare-of-patients-following-a-myocardialinfarction/199464.article/

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Multicenter historical cohort study of the relationship between shift work and blood pressure

Mohammad Gholami-Fesharaki[(1)], Anoshirvan Kazemnejad[(2)], Farid Zayeri[(3)], Mohsen Rowzati[(4)], Javad Sanati[(5)], Hamed Akbari[(6)]

Original Article

Abstract

BACKGROUND: Regarding the relationship between blood pressure (BP) and shift work (SW), previous studies have reported contradictory results. In the present study, we used Bayesian multilevel modeling to evaluate the association of SW and BP after controlling some confounding factors.

METHODS: Data of this multicenter historical study were extracted from annual observations of the male workers of Isfahan's Mobarakeh Steel Company (IMSC) and Polyacryl Iran Corporation (PIC) in Isfahan, Iran, between 2003 and 2011. In this research, we assessed the effect of SW on systolic BP (SBP) and diastolic BP (DPB) with controlling body mass index, age, work experience, marriage, and education status.

RESULTS: A total of 8613 (IMSC, n = 5314 and PIC, n = 3299) workers participated in this study with a mean [standard deviation (SD)] age of 41.60 (8.30) and mean (SD) work experience of 16.17 (7.89) years. In this study, after controlling confounding factors, we found no significant relationship between SW and SBP and DBP.

CONCLUSION: In general, the results of this multicenter cohort study did not support a relationship between SW and BP. We suggest prospective studies with controlling more confounding factors in this area.

Keywords: Blood Pressure, Multilevel Analyses, Bayesian Method, Iran

Date of submission: 11 Dec 2013, ***Date of acceptance:*** 23 Aug 2014

Introduction

Shift work (SW) is an employment pattern designed to make use of, or provide service across, all 24 h of the clock each day of the week.[1]

"Disruption of circadian rhythms (leading to sleep/wake disturbances, desynchronization of internal processes, and increased susceptibility to disease); disturbed socio-temporal patterns (resulting from atypical work hours leading to family problems, reduced social support, and stress); and unfavorable changes in health behaviors (increased smoking, poor diet, and irregular meals). Moreover, there is evidence that biomarkers, such as cholesterol and other lipids, plasminogen, blood pressure (BP) and cardiac activity show changes related to SW , and may act as mediators of disease processes."[2]

Nowadays many workers work on SW; for example, more than 3.5 million people are shift workers in England.[3] Numerous studies have shown the association of SW with cardiovascular disease,[4] hypertension,[5] atherosclerosis, Type II diabetes, metabolic syndrome,[6] weight gain,[7] etc. but the relationship of SW on BP. Positive,[8-12] negative[13,14] and no association[15,16] between SW and BP were seen in previous studies. Therefore, considering the inconsistency of the available research in this area, we conducted this multicenter cohort study for the first time in Iran to evaluate the relationship between SW and BP.

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Materials and Methods

Inclusion criteria were official employment between 2003 and 2011 with at least 2 years of work experience; exclusion criteria were retirement, death or dismissal. The Medical Ethics Committee of the School of Medical Sciences, Tarbiat Modares University, Tehran, Iran, approved the study (code number: 5271065, Date: 2011/11/05).

In this study, BP of both arms was measured in the sitting position after 5 min rest using a calibrated mercury sphygmomanometer considering BHS-IV guidelines.[17] Furthermore, weight and height were measured by a doctor using calibrated equipment by the mean time interval 1.5 years.

The routine rotating and weekly rotating shifts were scheduled with a clockwise rotation plan (2 morning shifts, 2 evening shifts, 2 night shifts and 2 days off for routine rotating and 3 morning shifts, 3 evening shifts, and 1 day off every 2 weeks, Fridays always off for weekly rotating shifts).

The morning, evening, and night shifts began at 7 AM, 3 PM, and 11 PM, respectively. Day workers worked from 7 AM to 3 PM on weekdays and had Thursdays and Fridays off.

Data were analyzed with SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA) and OpenBUGS (version 3.2.2, OpenBUGS Foundation, Helsinki, Finland) Continuous variables are presented as the mean ± standard deviation, whereas categorical data are presented as frequency and percentages. A Kolmogrov–Smrinov test is used to find out if the recorded data are normally distributed. Chi-square test, NOVA, Kruskal–Wallis test and Bayesian multilevel modeling with skew t-distribution is used to find out any relationship between SW and BP adjusted for age, work experience, marital status and education. Prior distributions and statistical methodology were discussed in works Gholami et al.[18] in this paper, $P < 0.05$ were considered statistically significant.

Results

This study was performed on 8613 male workers of IMSC (n = 5314) and PIC (n = 3299). The average repetition and time interval of each subject were approximately 6.7 and 2 respectively. Table 1 shows a summary of different characteristics of the workers by shift schedule.

According to this table 1, age and work experience were significantly higher in weekly rotating shifts in comparison with routine rotating shifts and day workers. The percentage of workers with academic education was significantly higher in day workers as compared to routine rotating and weekly rotating shift workers.

Table 2 shows the mean changes of systolic BP (SBP), diastolic BP (DPB) and body mass index (BMI) of the employees. According to table 2, no significant difference in mean change was noted according to shift schedule.

Table 3 shows a summary of beta, their standard errors and statistical significance using Bayesian multilevel modeling for the relationship between SW and BP after controlling age, work experience, BMI, marital status and education level.

Table 1. Comparison of the baseline characteristics of the workers at their first health examination, continues variable described as mean and standard deviation (SD) and categorical variable described as frequency and percent

Continues variable	Shift schedule								P
	Routine rotating shift workers (n = 4050)		Weekly rotating shift workers (n = 597)		Day workers (n = 3966)		Total		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
SBP (mm Hg)	118.47	9.82	118.83	10.07	118.22	9.22	118.38	9.57	0.245
DBP (mm Hg)	76.78	6.75	76.62	6.55	76.66	6.41	76.72	6.58	0.665
BMI (kg/m^2)	26.12	3.49	25.79	3.35	26.15	3.57	26.11	3.52	0.064
Age (year)	41.62	8.38	43.31	7.27	41.33	8.33	41.60	8.30	< 0.001
Work experience (year)	16.33	7.68	18.22	6.79	15.70	8.20	16.17	7.89	< 0.001
Follow-up time (year)	5.18	2.95	5.66	2.97	4.94	2.69	5.10	2.84	< 0.001
Categorical variable									
Marital status (married) [n (%)]	3565	89.20	537	91.80	3415.00	88.40	7517.00	89.00	0.051
Education (upper diploma) [n (%)]	632.00	15.60	113	19.00	964.00	24.40	1709.00	19.90	< 0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; SD: Standard deviation; Categorical data were analyzed using the chi-square test; Continuous data were analyzed using ANOVA

Table 2. Comparison of the mean changes of blood pressure and body mass index (BMI) in three shift schedules

Variables	Shift schedule								P
	Routine rotating shift workers		Weekly rotating shift workers		Day workers		Total		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Mean SBP change (mm Hg)	0.01	0.1	0.02	0.1	0.02	0.1	0.02	0.1	0.051
Mean DBP change (mm Hg)	-0.03	0.11	-0.03	0.11	-0.02	0.12	-0.03	0.11	0.617
Mean BMI change, (kg/m^2)	-0.03	0.06	-0.03	0.06	-0.03	0.06	-0.03	0.06	0.238

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; SD: Standard deviation; Categorical data analyzed using chi-square test; Continuous data analyzed using Kruskal-Wallis Test

Table 3. Bayesian multilevel regression results for assessing the effect of shift work on blood pressure (BP) with controlling confounding factor

Response	Predictors	Estimate	SD	95% CI		P
				Lower	Upper	
SBP	Shift schedule					0.755
	Weekly rotating shift/day worker	0.10	0.16	-0.22	0.41	0.543
	Routine rotating shift/day worker	0.19	0.32	-0.43	0.82	0.549
	Age (year)	0.19	0.03	0.14	0.24	< 0.001
	Work experience (year)	0.01	0.03	-0.04	0.07	0.652
	BMI (kg/m^2)	0.65	0.02	0.60	0.70	< 0.001
	Marital status (married/single)	0.29	0.32	-0.34	0.93	0.367
	Education (upper diploma/lower diploma)	-0.45	0.19	-0.82	-0.08	0.016
DBP	Shift schedule					0.254
	Weekly rotating shift/day worker	0.19	0.12	-0.04	0.42	0.111
	Routine rotating shift/day worker	0.03	0.22	-0.40	0.45	0.904
	Age (year)	0.12	0.02	0.09	0.15	< 0.001
	Work experience (year)	0.10	0.02	0.07	0.14	< 0.001
	BMI (kg/m^2)	0.58	0.02	0.55	0.62	< 0.001
	Marital status (married/single)	3.04	0.24	2.56	3.51	< 0.001
	Education (upper diploma/lower diploma)	-1.05	0.14	-1.32	-0.77	< 0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; SD: Standard deviation; CI: Confidence interval

As table 3 shows, no significant difference was noted in the SBP, and DPB according to shift schedule. For significant beta, like BMI, it means that each 1 unit increase in BMI elevated SBP and DPB by 0.65 and 0.58 mmHg, respectively.

Discussion

This multicenter cohort study was designed and conducted to evaluate the effect of SW on BP in all the workers of IMSC and PIC. Regarding the Bayesian modeling approach, our results did not support a relationship between shift-work and SBP (P = 0.755) and DPB (P = 0.245). This finding was consistent with the reports of Yadegarfar et al.,[19] Murata et al.,[20] Virkkunen et al.,[21] Merijanti et al.,[22] Puttonen et al.,[23] Hublin et al.,[12] Gholami-Fesharaki et al.[24] and Sfreddo et al.[25] but inconsistent with some other reports.[8-11,26-29] This lack of association can be attributed to the fact that healthier individuals are usually recruited as shift workers while weaker ones are hired as day workers.[30] Moreover, most of the day workers have administrative jobs and are, therefore, less active, leading to gaining weight (a risk factor of BP elevation). Gholami Fesharaki et al.[31] found a significant increase in BMI (around 0.78 kg/m^2) among day workers compared with weekly rotating shift workers.

On the other hand, since the effect of SW on the worker also depends on the type of work, personal characteristics, workplace environment and shift schedule,[32] the lack of association can also be attributed to other reasons such as better income, and more off-duty days of shift workers when compared with day workers. Although we could not measure workers' income individually in this study because of the confidentiality of financial information, according to the overall data from Division Human Resource

Management, the salary of a shift worker is 10-40% more when compared with the day workers. Hofelmann et al.[33] identified a negative association between SBP and the contextual income.

The strong points of this study were its multicenter pattern, utilizing a complicated and powerful statistical modeling approach for analyzing the data, appropriate sample size, homogeneity of the study population, and calculation of BMI and measurement of BP in the clinic by a physician. Some weak points of the study were non-evaluation of the family history of BP, and inability to evaluate the experience at previous jobs, sleep, income, stress, and job satisfaction as possible confounding factors.

In general, the results of our multicenter cohort study did not support a relationship between SW and BP. To assess the association between SW and BP, we suggest more accurate prospective studies with controlling confounding factors such as family history, occupational history, and psychological factors such as job satisfaction and occupational stress.

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Conflict of Interests

Authors have no conflict of interests.

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Dabigatran versus Enoxaparin in the prevention of venous thromboembolism after total knee arthroplasty: A randomized clinical trial

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Original Article

Abstract

BACKGROUND: Venous thromboembolism (VTE) and deep vein thrombophlebitis (DVT) is a serious problem with high mortality and morbidity rates. This study was conducted to compare efficacy and safety results of the two types of VTE preventing in patients underwent total knee arthroplasty (TKA).

METHODS: Having considered exclusion criteria, 90 patients of 136 ones were registered in the study. Our patients of TKA were split randomly in two groups. Totally, 45 patients received enoxaparin, 40 mg 12 h before surgery and treated by 40 mg daily up to 15 days. The second group (45 patients) were treated by dabigatran 150 mg 4 h after surgery and 225 mg daily up to 15 days. Efficacy was evaluated by Doppler sonography after 15 days for the presence of DVT and safety was determined by 3 months follow-up for all-cause mortality and any major or minor bleedings.

RESULTS: Two groups were similar in baseline characteristics. The efficacy outcome events occurred in 2.2% (2 of 90) of the patients (1 symptomatic VTE in dabigatran and 1 in the enoxaparin group) without significant statistical difference between groups (P = 0.64). In terms of safety, 3 patients (6.6%) in dabigatran and 2 patients (4.4%) in enoxaparin group had major bleeding (P = 0.66) and 8 patients (17.7%) in dabigatran and 7 patients (15.7%) in enoxaparin group had non-major bleeding event (P = 0.81). There were no death, pulmonary emboli, and cardiac events during follow-up.

CONCLUSION: Three months follow-up did not show statistical difference in efficacy and safety between dabigatran and enoxaparin. Future studies with mentioning to later outcomes for checking safety are warranted.

Keywords: Dabigatran, Prevention, Venous Thromboembolism, Enoxaparin, Total Knee Replacement

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Introduction

Venous thromboembolism (VTE) is serious disease with high rate of mortality and morbidities[1] which lead the scientist to recommend some guideline for prevention.[2] However, recently, new agent oral drugs have been introduced which make the long-term VTE prophylaxis more comfortable.[3] One of these drugs is dabigatran, which is a thrombin inhibitor and can be initiated post operatively.[4] This is an important advantage because on a practical level, the exact time for operation is uncertain and affected by preparation time, delays from previous surgical cases. Hence, in contrast to dabigatran, which administered post operatively, using enoxaparin preoperatively may be difficult to ensure that the dose given provides adequate coverage during the operation.[5] Therefore, nowadays using of oral preventive drugs is increasing.

VTE as a pulmonary embolism (PE) is a serious problem with high mortality and morbidity rates.[6,7]

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Major orthopedic surgeries like total knee arthroplasty (TKA) with inducing endothelial damage, reducing venous return and subsequent blood stasis, are responsible for 50% of thromboembolic events in the absence of venous thromboembolic prophylaxis. High incidence of VTE, is leading to recommend evidence-based guidelines in preventing VTE after major orthopedic surgeries.[8-10]

In many European countries, low-molecular-weight heparin (LMWH) is used as standard therapy for prophylaxis of VTE and initiates preoperatively. However, the limitations include parenteral administration, an indirect mode of action, inability to inhibit clot-bound thrombin and association with complications such as heparin-induced thrombocytopenia are discussed for this prophylactic method. Therefore, the introduction of new oral agents like dabigatran etetexilate may alleviate guideline adherence in terms of oral medication instead of injection routs and without the need for routine coagulation monitoring.

Dabigatran etexilate is a thrombin inhibitor which its plasma concentration is not substantially altered by age, gender or body weight, and fixed dose of dabigatran etexilate can be used in most patients.[11,12] With the necessarily of prolong prophylaxis in patients underwent major orthopedic surgeries; using oral agent with no need to monitoring is seemed rational compared with parenteral agents. However, the safety and efficacy of dabigatran compared with traditional drugs like LMWH is also important. Hence, this study conducted to compare efficacy and safety results of the two types of VTE preventing in patients underwent TKA.

Materials and Methods

This prospective randomized trial was conducted from November 2011 to June 2012 in the Department of Orthopedic Surgery at Shariati Hospital (Medical school of Islamic Azad University, Najafabad branch) in Isfahan, Iran. Patients with expected primary TKA, more than 18-year-old participated in the study. Exclusion criteria were any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the normal range within the past month; severe renal insufficiency (creatinine clearance < 30 ml/min); using non-steroidal anti-inflammatory drugs (NSAID) within a week before surgery; active malignant disease. The study was approved by the Ethics Committee of Azad Islami University of Najafabad Branch, and each patient gave informed consent prior to the study, which was performed in accordance with the ethical standards of the 1964 declaration of Helsinki as revised in 2000 with IRCT number 2013082513828N2.

Allocation: After registering demographic data, laboratory exams containing cell blood counts were performed by cell counter Sysmex KX 21 and prothrombin time (PT), partial thromboplastin time (PTT), blood urea nitrogen, creatinine, ALT and aspartate amino-transferase were performed by Hitachi 902. Of the 136 patients initially enrolled in the study, 46 were not included in the final analysis. Of the 46 patients who did not meet the inclusion criteria, 12 patients had history of stroke or myocardial infarction, 20 patients used NSAID within a week prior to TKA, and eight patients had uncontrolled hypertension within prior 3 months. Six patients were unable to get the anesthesiologist's permission for the operation. Remaining 90 patients were randomized based on a table of random numbers generated by random allocation software in regard to simple random allocation[12] by the principal investigator into two groups (LMWH and dabigatran) and underwent TKA in order to technique previously described.[13] In first group (n = 45) enoxaparin (40 mg) 12 h before surgery were used and continued daily to 15 days and in second group (n = 45) dabigatran etexilate - manufactured by boehringer ingelheim 150 mg were started 4 h after surgery and continued with 225 mg daily to 15 days. All patients were followed for 3 months. The treatment period was defined as the time from the first dose to 3 days after the last oral or subcutaneous dose, whichever came later.

Symptomatic and asymptomatic deep vein thrombophlebitis (DVT) and/or symptomatic PE and all-cause mortality, during treatment, were our primary efficacy outcomes. Bilateral Doppler sonography was performed by GE S6 machine at 15 days after first dose treatment for prevention of DVT. PE was diagnosed by ventilation/perfusion scintigraphy, spiral computed tomography. Radiologist who was blinded to trial also applied diagnostic tests for DVT events.

Occurrence of bleeding event during treatment was our primary safety outcome. We considered major bleeding events[10] as: Clinically overt bleeding

associated with ≥ 20 g/l fall in hemoglobin; clinically overt bleeding leading to a transfusion of ≥ 2 units of packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding and bleeding warranting treatment cessation or leading to reoperation.

Non-major, clinically relevant on treatment including spontaneous hematoma ≥ 25 cm^3, wound hematoma ≥ 100 cm^3, epistaxis > 5 min, spontaneous hematuria or a prolonged one after intervention, spontaneous rectal bleeding, gingival bleeding > 5 min were our secondary safety outcomes.

Laboratory tests were performed on the last day of dosing, at 4-6 weeks and 3 months after surgery. All cases of hepatic enzyme abnormalities and suspected cardiovascular events during the study were discontinued the drug and referred to related specialist.

Considering a = 0.05, study power = 80%, d = 0.15 points as the minimal expected difference between the two groups with P1 and P2 = 0.07 (the probably incidence of thromboembolism in TKA), a sample size of 45 patients was considered for each group. SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA) was used to analyze the data using the independent T-test and the fisher exact test for comparing means and percent for quantitative and qualitative data', respectively, between the two groups. P < 0.05 were considered as statistically significant.

Results

A total of 136 patients was considered for the study, but 46 patients were excluded due to past medical history or medications that interfere that our study and finally 90 patients with written consent was enrolled. 38 male (42%) and 52 female (58%). The mean age of our patients was 70 ± 9. The flow of participants is shown in the CONSORT diagram in figure 1. The mean time interval between TKA and performing of Dabigatran was 4 h and the median oral treatment duration was 7 days. The pre-operative, baseline characteristics of the two groups are shown in table 1.

The efficacy outcome including symptomatic VTE and/or symptomatic PE and all-cause mortality occurred in 2.2% (2 of 90) of patients. The incidence of the primary outcome is shown in table 2. According to fisher test, there is no significant difference between enoxaparin group versus dabigatran group.

The safety outcome was shown in table 3. Five patients developed major bleeding during treatment. There is no statistical difference between Dabigatran and Enoxaparin in safety primary and secondary outcomes (P = 0.66, P = 0.81).

Significant liver enzyme elevation (ALT levels more than 3 times of upper limited of normal) was reported in 2.2 and 4.4% of dibigatran and enoxaparin groups. Hence, the two groups were similar in terms of liver function abnormality (P = 0.56). In all cases, the abnormalities returned to the baseline measurement with additional follow-up. Acute coronary events were not occurred in any patients during follow-up.

Table 1. Baseline characteristics of patients

Characteristics	Dabigatran (n = 45)	Enoxaparin (n = 45)	P
Age*	72.1±9.3	68.3 ± 10.1	0.72**
Weight*	77.3 ± 7.6	80.6 ± 10.1	0.85**
Sex (Female) (%)*	28 (62.2)	30 (66.6)	0.97***

* Data are presented as number, mean, standard deviation and percent; ** Independent t test; *** Chi-square test

Table 2. Efficacy outcomes during treatment period

Characteristic	Dabigatran (n = 45)	Enoxaparin (n = 45)	P**
Symptomatic DVT (%)*	1 (2.2)	1 (2.2)	0.99
Symptomatic PE*	0	0	0.99
Death*	0	0	0.99

* Data are presented as number and percent; ** Fisher exact test; DVT: Deep vein thrombophlebitis; PE: Pulmonary embolism

Table 3. Safety outcomes during treatment period

Characteristics	Dabigatran (n = 45) (%)	Enoxaparin (n = 45) (%)	P**
Major bleeding*	3 (6.6)	2 (4.4)	0.66
Non-major bleeding*	8 (17.7)	7 (15.5)	0.81
Elevated of liver enzyme*	1(2.2)	2(4.4)	0.56

* Data are presented as number and percent; ** Chi-square test

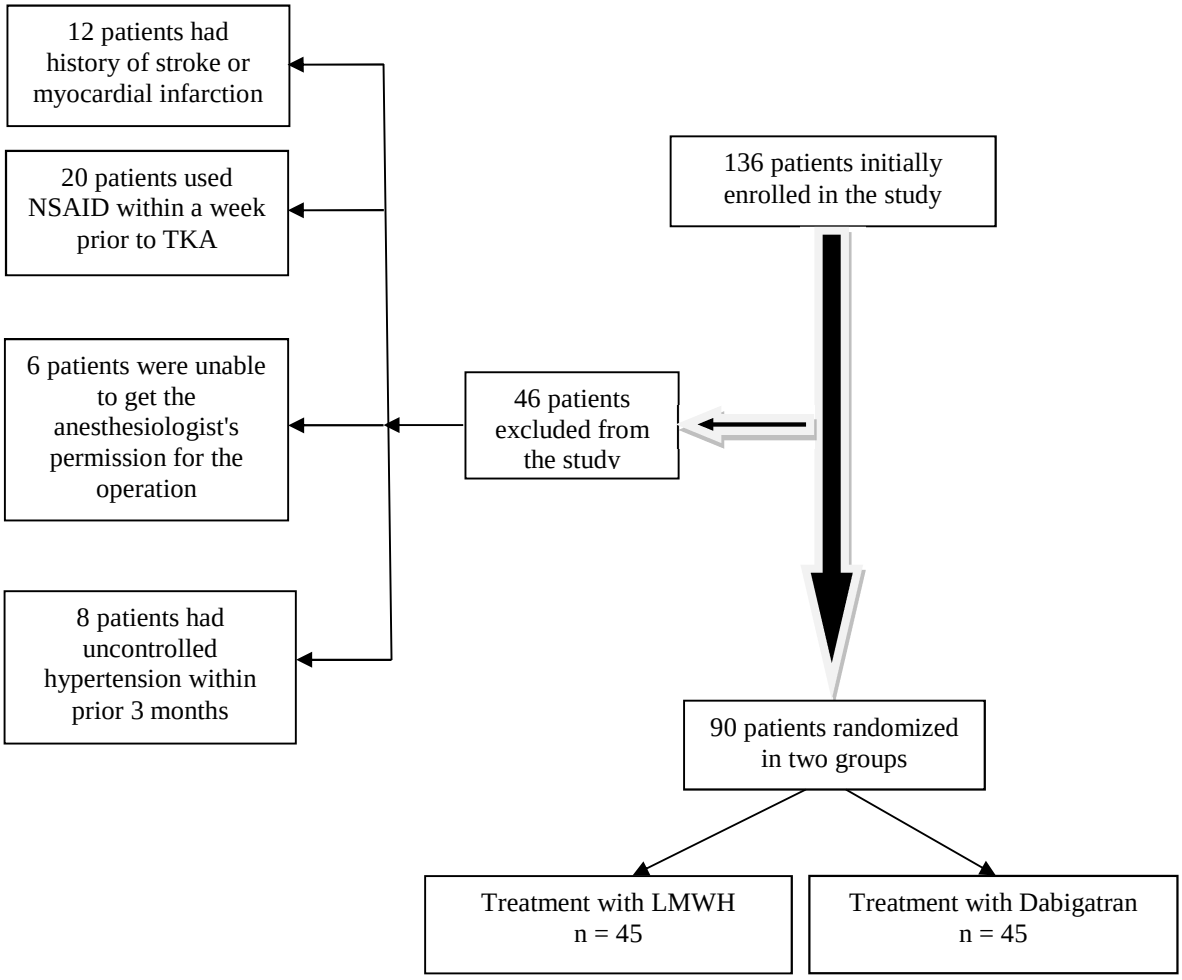

Figure 1. Trail chart of study participants
NSAID: Non-steroidal anti-inflammatory drugs; TKA: Total knee arthroplasty; LMWH: Low-molecular-weight heparin

Discussion

The most important finding of this study was no difference between dabigatran and enoxaparin in the prevention of VTE after TKA. Furthermore, this study showed a good efficacy and safety for dabigatran that was comparable with enoxaparin.

We showed that no significant different between dabigatran and enoxaparin in efficacy and safety outcomes. Our finding supported previous studies.[12,13] Three major trials have been designed in comparison of dabigratan and enoxaparin in safety and efficacy. The RE-NOVATE II trial[12] compared dabigatran etexilate, 220 mg (n = 1157) or 150 mg (n = 1174) once daily with subcutaneous enoxaparin, 40 mg (n = 1162) once daily in patients underwent hip replacement. The RE-MODEL[13] also compared dabigatran etexilate, 220 mg (n = 694) or 150 mg (n = 708) once a day with subcutaneous enoxaparin, 40 mg (n = 699) once daily in patients underwent TKA. In both above studies, dabigatran has comparable results compared with enoxaparin in the primary efficacy outcomes[12,13] which supported our results.

In RE-MODEL trial,[13] 37.7% and 36.4% of primary efficacy outcomes were occurred in enoxaparin and dabigatran (220-mg group) groups. Our findings showed 2.2% of patients in Dabigatran and enoxaparin groups experienced efficacy outcomes events. Although the rates of the primary efficacy outcome were higher in the RE-MODEL trial, but there were no significant differences between groups. Also, this difference may be due to lower sample size in our study.

In terms of safety, both mentioned trials showed same major bleeding rates in dabigatran versus enoxaparin group.[12,13] In RE-NOVATE II, major bleeding was shown in 1.6% of the enoxaparin group, compared with 2.0% of the dabigatran

etexilate 220 mg group.[12] In RE-MODEL, major bleeding events demonstrated in 1.3% of the enoxaparin group, compared with 1.5% of the dabigatran etexilate 220 mg group.[13] Our study showed 4.4% of patients in the enoxaparin group and 6.6% of patients in the dabigatran group had major bleeding event. This is similar between our study and these two trials, which no significant difference has been found between two groups.

In contrast of our findings, RE-MOBILIZE trial[14] which compared 30 mg enoxaparin twice daily with dabigatran etexilate, 220 mg or 150 mg once daily showed numerically fewer major bleeding events in the dabigatran group. It may because of higher dose of enoxaparin compared with our study.

Our study showed no statistical difference in term of between liver enzyme elevations, bleeding outcomes and incidence of acute coronary events between dabigatran and enoxaparin. Furthermore, these findings are supported with above three trials findings.

Our study has strengths including double blinding randomization design and enough follow-up without losing any patient. A limitation of our work is low sample size.

Conclusion

Three months follow-up did not show statistical difference in efficacy and safety between dabigatran and enoxaparin. Also with high prevalence of DVT after major surgery in Iran, Future longer studies with longer follow-up recommended to check the exact effect of dabigatran in preventing DVT.

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Conflict of Interests

Authors have no conflict of interests.

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The effects of different doses of atorvastatin on serum lipid profile, glycemic control, and liver enzymes in patients with ischemic cerebrovascular accident

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Original Article

Abstract

BACKGROUND: Despite established effects of atorvastatin on level of serum lipid profile in patients with different underlying clinical conditions, the effects of this drug on other serum biomarkers remain uncertain. We examined the effects of atorvastatin therapy on lipid profile, glycemic control, and liver enzymes in patients with ischemic cerebrovascular accident without any history or clinical evidences of diabetes, heart failure, renal failure, or hepatic disease.

METHODS: In a randomized double-blinded controlled trial, 140 hospitalized patients with an ischemic cerebrovascular accident were included and randomly assigned to receive either atorvastatin 40 mg (n = 70) or atorvastatin 20 mg daily (n = 70) for 3 months. The levels of biomarkers were measured at the time of administrating drugs as well as at the time of completing the treatment.

RESULTS: A significant reduction was revealed in serum triglyceride, total cholesterol, low-density lipoprotein, non-high-density lipoprotein (HDL) cholesterol, and also aspartate aminotransferase levels as well as a significant increase in serum HDL level following administration of atorvastatin in both case and control groups who received the atorvastatin 40 mg/day and 20 mg/day, respectively (all $P < 0.050$). Although a significant increase in fasting blood sugar and hemoglobin A1c was observed in the case group received atorvastatin 40 mg/day (both $P < 0.001$), but this elevation was not occurred in another group treated with lower dose of the drug (both $P > 0.050$).

CONCLUSION: Daily administration of 20 mg and 40 mg doses of atorvastatin for 3 months provides improvement in serum lipid profiles; however, because of interfering effect of high-dose atorvastatin on glycemic control status, the use of the former dose may be preferred. This is very important in these patients because the positive effects of high-dose atorvastatin in stroke patients are not confirmed.

Keywords: 3-Hydroxy-3-Methylglutaryl-CoA Reductase Inhibitors, Statins, Atorvastatin, Hyperlipidemia

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Introduction

Lipid-lowering treatment using different types of statins effectively reduce the risk for death or cardiovascular events in those with or without evidenced coronary artery disease (CAD).[1,2] Different doses of these medications are now considered for achieving a target low-density lipoprotein (LDL) cholesterol level of < 100 mg/dl and an option of extending to < 70 mg/dl for patients with established CAD or those with chronic diabetes mellitus.[3-5] In this regard, CAD is less likely if the serum LDL cholesterol level is

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below 60 mg/dl than when it is above 80 mg/dl.[6,7] The main mechanism of statins is to reduce LDL levels has been now well-identified that statins can inhibit 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase function as the first committed enzyme of the HMG-CoA reductase pathway, mediating production of cholesterol.[8]

Among different types of statins, atorvastatin is now considered one of the most effective statins, not only for its effects on LDL level as well as the ability to meet recommended treatment guidelines for this parameter, but also for its impact on other lipid profiles such as the level of triglyceride (TG) and also the capacity to modify lipoprotein composition in a non-atherogenic manner.[6,9] In some recent large trials comparing the effects of atorvastatin with other statins, it provided significantly higher lowering effects in comparison with pravastatin as such a 30 days use of the drugs led to reduce the level of LDL cholesterol by 51% and 22%; respectively.[10] Even, the beneficial lowering effects of atorvastatin on inflammatory biomarkers as a main factor for predisposing coronary atherosclerosis were considerably higher than other types of statins.[11,12]

The preventive effects of atorvastatin on cardiovascular events in some CAD risk subgroups including diabetic patients, or those with renal failure have been widely investigated. In this context, the use of atorvastatin in diabetic patients has resulted in reducing all-cause mortality by 52%, coronary mortality by 62%, coronary morbidity by 59%, and stroke by 68%.[13] Furthermore, in patients with both type 2 diabetes mellitus and chronic renal failure, atorvastatin significantly reduced the risk of fatal and nonfatal cardiac events and death from any cause if pretreatment LDL cholesterol is > 145 mg/dl.[14]

Despite established effects of atorvastatin on serum level of LDL cholesterol or other lipid particles, the effects of this drug on other biomarkers still remain uncertain. Hence, the researchers examined the effects of atorvastatin therapy on lipid profile, glycemic control, and liver enzymes in patients with ischemic cerebrovascular accident without any history or clinical evidences of diabetes, heart failure, renal failure, or hepatic disease.

Materials and Methods

In a randomized double-blinded controlled trial (registered in Iran registry of clinical trials with registration number of IRCT201108177358N1), 140 hospitalized patients with ischemic cerebrovascular accident were enrolled. The patients were consecutively selected from all subjects who referred to our center within a 1 year period from July 2012 to July 2013. Patients with any history or clinical evidences of diabetes, heart failure, renal failure, or hepatic disease were not included into the study. Those who were receiving lipid-lowering therapy at the time of admission were not also considered eligible (Figure 1). The study protocol was approved by the Shahid Beheshti University of Medical Sciences review boards, and written informed consent was obtained from all patients. The baseline characteristics including demographics, medical history, and medications were collected by reviewing the hospital recorded files.

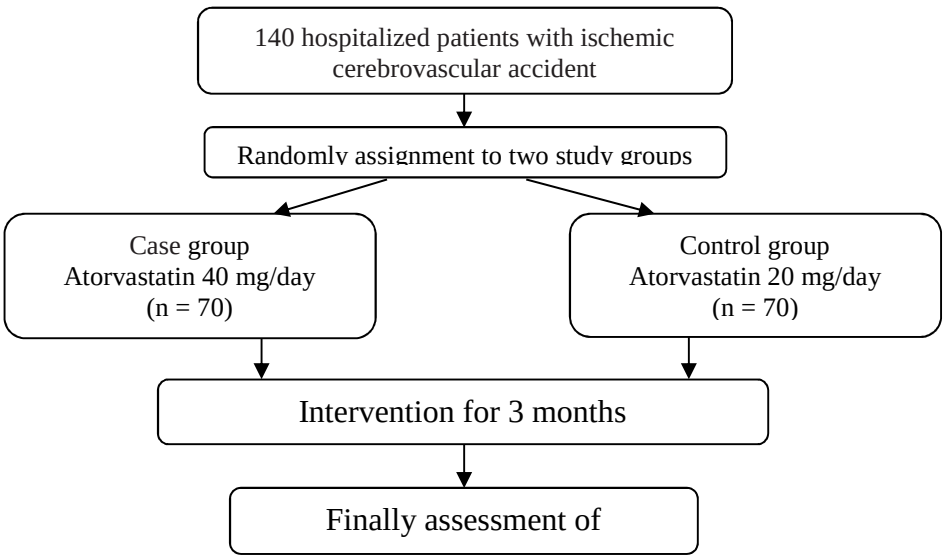

Figure 1. Consort chart for the study

Eligible patients were randomly assigned in a 1:1 ratio to either receive 40 mg of atorvastatin (n = 70) or 20 mg of atorvastatin daily (n = 70) in a double-blind, double-dummy fashion for 3 months. At the time of administrating drugs as well as at the time of completing treatment, blood samples were obtained to measure lipids [TG, total cholesterol, LDL, HDL (high-density lipoprotein), and non-HDL cholesterol], fasting blood sugar, hemoglobin A1c, serum creatinine, and liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. The levels of blood glucose and lipid profile in the sera were determined spectrophotometrically by enzymatic method. Hemoglobin A1c was measured using an ion-exchange high-performance liquid chromatography method using the Diamat Analyzer System. Serum creatinine was also measured using an enzymatic method. Liver enzymes were measured using standard automated kinetic enzymatic assays. The endpoint of the study was to compare changes in these biomarkers following study medications.

Results were presented as mean ± standard deviation or median (1st, 3rd quartiles) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was assessed using both Kolmogorov-Smirnov tests and histograms. Continuous variables were compared using t-test or non-parametric Mann-Whitney U test whenever the data did not appear to have a normal distribution. Categorical variables were, on the other hand, compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of < 5 were observed. For assessing changes in study parameters after drug intervention compared with before that, the paired t test or Kruskal-Wallis test was used. For the statistical analysis, the statistical software SPSS for windows (version 20.0, SPSS Inc., Chicago, IL, USA) was used. P values of 0.05 or less were considered as statistically significant.

Results

As shown in table 1, the two groups receiving different doses of atorvastatin were similar in terms of baseline characteristics including demographics, anthropometric parameters, previous history of hypertension and hyperlipidemia, current smoking, and also baseline laboratory parameters of white blood cell count, hemoglobin level, serum creatinine, and platelet count (all P > 0.050).

Table 2 presents a level of serum biomarkers after interventions compared with before that in both case and control groups. A significant reduction was revealed in serum TG, total cholesterol, LDL, non-HDL cholesterol, and also AST levels as well as a significant increase in serum HDL level following administration of 40 mg/day atorvastatin (all P < 0.001). Also, the control group who received 20 mg/day atorvastatin showed significant reduction in serum TG (P = 0.012), total cholesterol (P < 0.001), LDL (P < 0.001), non-HDL cholesterol (P < 0.001), and also AST levels (P = 0.022) as well as a significant increase in serum HDL (P = 0.005). Although a significant increase in fasting blood sugar and hemoglobin A1c was observed in the case group which received atorvastatin 40 mg/day (both P < 0.001), but this elevation was not occurred in another group received lower dose of the drug (both P > 0.050).

Table 1. Baseline characteristics of the study population

Characteristics	Case group (At. 40 mg) (n = 70)	Control group (At. 20 mg) (n = 70)	P
Male gender	32 (48.3)	31 (44.3)	0.635
Cigarette smoking	17 (25.8)	18 (25.7)	0.989
Marital state	66 (94.3)	65 (92.9)	0.735
Hyperlipidemia	7 (10.6)	6 (8.6)	0.688
Hypertension	24 (36.4)	22 (31.4)	0.532
Family history of CAD	4 (6.1)	5 (7.1)	0.812
Serum creatinine (mg/dl)	0.90 (0.88-1.12)	0.98 (0.90-1.1)	0.770
WBC count × 1000 (/mm^3)	7.8 (6.5-8.1)	7.7 (6.8-7.9)	0.664
Body mass index (kg/m^2)	26.65 ± 3.55	27.67 ± 3.29	0.081
Height (cm)	167.56 ± 7.82	165.21 ± 8.85	0.098
Weight (kg)	76.24 ± 15.97	77.97 ± 12.24	0.473
Serum hemoglobin (mg/dl)	13.85 ± 1.87	14.42 ± 2.25	0.105
Platelet count (/mm^3)	257.60 ± 75.56	249.26 ± 82.25	0.533
Age (year)	57.70 ± 10.08	58.84 ± 9.90	0.501

At: Atorvastatin; CAD: Coronary artery disease, WBC: White blood cell, Data are presented as number (%), mean ± MD, or median (1st, 3rd quartiles)

Table 2. Serum biomarkers following use of atorvastatin between case and control groups before and after interventions

Serum biomarkers	Case group (At. 40 mg) (n = 70)			P	Control group (At. 20 mg) (n = 70)			P	P (between-group)
	Before	After	Difference		Before	After	Difference		
FBS	85.67 ± 13.59	99.86 ± 16.22	92.77 ± 15.52	< 0.001	84.63 ± 26.26	85.21 ± 14.19	84.92 ± 20.18	0.656	< 0.001
HbA1C	5.54 ± 0.55	5.89 ± 0.56	5.72 ± 0.52	< 0.001	5.49 ± 0.66	5.52 ± 0.59	5.51 ± 0.61	0.442	< 0.001
TG	186.17 ± 85.92	156.42 ± 66.98	171.30 ± 77.42	< 0.001	187.46 ± 82.25	158.77 ± 80.25	173.12 ± 81.18	0.012	0.222
CHOL	196.38 ± 37.58	159.88 ± 32.52	178.13 ± 34.42	< 0.001	197.75 ± 34.45	161.21 ± 30.56	179.48 ± 32.14	< 0.001	0.565
LDL	120.89 ± 34.02	90.07 ± 26.50	105.48 ± 30.20	< 0.001	119.25 ± 30.25	94.45 ± 28.08	108.50 ± 29.55	< 0.001	0.112
HDL	35.68 ± 8.80	39.73 ± 9.15	37.71 ± 37.07	< 0.001	34.59 ± 7.79	38.41 ± 10.12	36.50 ± 8.89	0.005	0.065
Non-HDL	160.70 ± 38.77	120.18 ± 31.71	140.44 ± 32.35	< 0.001	158.74 ± 38.89	136.30 ± 34.28	147.52 ± 36.66	< 0.001	0.129
AST	35.67 ± 7.23	27.03 ± 7.92	31.35 ± 7.76	< 0.001	34.46 ± 25.59	27.28 ± 7.75	30.87 ± 29.19	0.022	0.556
ALT	28.14 ± 14.68	25.86 ± 9.33	27.00 ± 10.12	0.224	28.85 ± 12.12	27.54 ± 15.48	28.20 ± 13.03	0.778	0.886

At: Atorvastatin; FBS: Fasting blood sugar; HbA1C: Hemoglobin A1C; TG: Triglyceride; CHOL: Cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein
AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Data are presented as mean ± SD

Discussion

Recent evidences have supported vigorous lipid and glucose interventions in primary and secondary prevention of acute cerebrovascular disease so these evidences support intensive lipid intervention with high-dose statins to produce clinical event reduction in these patients,[15] However, the optimal doses of statins required for clinical relevance of cerebrovascular disease remain obscure. In fact, it is now questioned if doses of statins even higher than standard lipid-lowering doses will result in additional benefit.

The primary main point of the study was to demonstrate the beneficial effect of administrating atorvastatin with the two dosages of 40 mg/day and 20 mg/day for 3 months on different serum lipid profiles. Although it was previously believed that the most prominent effects attributable to statin therapy are its only potent LDL-C lowering properties, but, nowadays, it has been well established that statins, especially atorvastatin can significantly reduce non-HDL-C, and TG. In some recent studies, atorvastatin could reduce TG levels in the range of 10-20%.[16] Even, it has been acknowledged that the higher the baseline TG level, the greater the TG-lowering effect that the baseline TG levels exceeding 250 mg/dl was associated with reductions in the range of 22-45%, whereas more modest reductions have been observed with lower baseline levels.[17] Although these lipid-lowering effects have been shown following administration of different types of statins, but atorvastatin produces greater plasma LDL and TG reductions than other statins that may be due to its long-lasting action, presumably a reflection of longer residence time of atorvastatin and its active metabolites in the liver. The TG reduction with atorvastatin seems to stem from limiting very low-density lipoprotein (VLDL) secretion from the liver and increase in clearance of TG-rich lipoprotein via induced LDL receptors from plasma.[18]

In this particular study, the effects of atorvastatin on lipid profile was similar considering different dosages of the drug and thus administrated lower dose of the drug might be more preferable due to its probable side-effects. Moreover, because of its effects on elevating blood sugar and hemoglobin A1c by the higher considered dose, the use of atorvastatin with 20 mg/day is more emphasized to prevent adverse effects. Similar studies had revealed that the dosage range of atorvastatin is10 to 80 mg once daily provides significant reductions from baseline in TG and LDL levels as well as an increase in HDL cholesterol levels with a well toleration.[19] Even, it has been shown that high-dose atorvastatin therapy does not have a significant additional effect on the reduction of TG compared with a standard dose of 10 mg in both diabetics and non-diabetics patients.[16-20]

Observed elevating effects of high-dose atorvastatin on fasting blood sugar and on hemoglobin A1C can be considered as a major side-effect which could be prevented by using a lower dose of 20 mg/day. Previous studies have presented different controversial findings in triggering/inhibiting effects of atorvastatin on blood sugar and insulin resistance. In previous animal study atorvastatin the inhibited increase in plasma glucose level and in clinical studies, patients with type II diabetes mellitus exhibited significant decrease in HbA1c level after treatment with atorvastatin.[21] In another clinical study, atorvastatin significantly inhibited increase in the 30-min glucose level, decreased plasma insulin levels before 30 and 60 min after glucose loading, and decreased the insulin resistance index, compared with corresponding values in control groups, indicating that atorvastatin seemed to improve glucose metabolism by reduction in insulin resistance.[22] The U.S. Food and Drug Administration announced that the prescribing information for cholesterol reducing drugs in the statin class will include warnings about risk of increased blood sugar levels, HbA1c, and diagnoses of diabetes. Furthermore, some large clinical trials have confirmed our results in elevation of blood sugar following administration of statins. In an Intervention Trial evaluating Rosuvastatin (JUPITER study),[23] the risk of diabetes was 27% higher in patients who received rosuvastatin than placebo treated patients. In that study, 3% of patients that received rosuvastatin compared to 2.4% of patients who received placebo developed diabetes. In pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 (PROVE-IT TIMI 22) study, high-dose atorvastatin was associated with increased blood glucose.[24] Therefore, analysis of other published studies along with this study shows that statins increase HbA1c and/or fasting blood glucose, and the risk of being diagnosed with diabetes regarding of the dose of statin used. In fact, the side effect can be appeared only if higher doses of atorvastatin are being administered; thus, it is more advisable to administer 20 mg of atorvastatin daily. This is very important in these patients because the positive effects of high-dose

atorvastatin in stroke patients are not confirmed.

The present study led to reductions in serum level of AST. Some other studies could also show this effect. In a study by Karpisek et al., after the 3 months therapy, a significant reduction in AST value was observed with no difference in ALT value.[25] Also, Jurukovska-Nospal et al. showed that the elevation in ALT and AST levels greater than twice the upper limit of normal were rarely seen after 12 months of atorvastatin therapy.[26] Farsang et al. also showed that the incidence of AST/ALT < 3 times of the upper limit of the normal range in all patients was only 0.8 % without any rhabdomyolysis.[27] Nonetheless, the hepatic complication of atorvastatin with the two 20 mg/day and 40 mg/day for 3 months is very rare and thus it is ignorable.

The advantages of this study can be discussed from two points. First and foremost, the subjects admitted to study were without previous underlying comorbidities such as renal failure, hepatic dysfunction, diabetes mellitus, or congestive heart failure. Second, the effects of different dosages of atorvastatin were purely examined in patients with cerebrovascular accident. However, small sample size of the study along with a partially short following-up is two potential limitations that should be considered in future studies.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Rheumatoid factor, anti-nuclear antibody in ischemic heart disease: Acute versus chronic patients

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Original Article

Abstract

BACKGROUND: Immunopathological and inflammatory processes play important roles in the initiation and development of ischemic heart disease. Hence, this study aimed to evaluate the relationship between serum levels rheumatoid factor (RF) and anti-nuclear antibodies (ANA) and severity of coronary stenotic lesions.

METHODS: Totally 140 patients with acute coronary syndrome (ACS) (n = 70) and chronic stable angina (CSA) (n = 70) that undergoing coronary angiography were enrolled in this study. ANA by the enzyme-linked immunosorbent assay (ELISA) and serum level of RF was measured by latex method. The severity of coronary stenotic lesions calculated by Gensini score. To analyze the correlations of ANA and RF to Gensini score Pearson correlation test was used. To adjust the effect of age and other confounder factors such hypertension, diabetes, hyperlipidemia and smoking multiple linear regression was used.

RESULTS: The mean serum levels of RF and ANA in CSA group were significantly higher than ACS group after adjusting for the confounder factors (P < 0.050 for ANA). Serum levels of ANA significantly correlated with severity of coronary stenotic lesions calculated by Gensini score (r = 0.40 and P < 0.050). After adjusting confounders, multiple linear regression analysis showed ANA remained independently associated with Gensini scores in ACS group (B = 0.505, P < 0.001).

CONCLUSION: Higher serum levels of ANA may be considered as independent risk factors for ACS.

Keywords: Rheumatoid Factor, Anti-Nuclear Antibodies, Acute Coronary Syndrome, Chronic Stable Angina, Gensini Score

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Introduction

Atherosclerotic cardiovascular disease (CVD) is the major cause of mortality worldwide.[1] Well-known CVD risk factors such as dyslipidemia, high blood pressure, diabetes, smoking, obesity, as well as genetic abnormalities, are related to only about half of the cases of coronary heart disease.[2] A large amount of evidence supports the pivotal role of inflammation and immune responses in all phases of atherosclerosis, from initiation of the fatty streak to final breakout of acute coronary syndromes (ACS).[3] Markers of inflammation, such as C-reactive protein, are predictive of future cardiovascular events in healthy individuals and may be useful in identifying patients with coronary artery disease who are at risk for recurrent CVD events.[3,4] Several studies have documented an increased risk of atherosclerosis and myocardial infarction in patients with rheumatoid arthritis.[5,6] In addition, rheumatoid arthritis is associated with a reduced life expectancy, primarily because of excessive deaths from CVD.[7]

Many recent published data showed that anti-nuclear antibodies (ANA) may contribute to the pathogenesis of atherosclerosis and ANA

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positivity is associated with the presence of coronary atherosclerosis.[8] Although the association between serum levels of some inflammatory marker and ischemic heart disease (IHD) revealed, but the relationship ANA and rheumatoid factor (RF) with severity of coronary stenotic lesions have not evaluated yet.

In the present study, we aimed to find the association between RF and ANA levels with the severity of coronary stenotic lesions.

Materials and Methods

This cross-sectional study was carried out on, 140 consecutive subjects with IHD referred to the Chamran Hospital, Isfahan, Iran, between July 2013 and October 2013. Inclusion criteria are male subjects, which undergoing coronary angiography. Patients were classified into two groups according having ACS (n = 70) and chronic stable angina (CSA) (n = 70). ACS group included ST-elevation myocardial infarction, non ST-elevation myocardial infarction (NSTEMI) and unstable angina. Chronic stable angina typically manifests as a deep, poorly localized chest or arm discomfort (rarely described as pain), reproducibly precipitated by physical exertion or emotional stress, and relieved within 5-10 min by rest or sublingual nitroglycerin.[9] In contrast, unstable angina is defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of three features: (1) occurring at rest (or minimal exertion) and usually lasting > 20 min (if not interrupted by the administration of a nitrate or an analgesic); (2) being severe and usually described as frank pain; or (3) occurring with a crescendo pattern (i.e., pain that awakens the patient from sleep or that is more severe, prolonged, or frequent than previously. Approximately, two-thirds of patients with unstable angina have evidence of myocardial necrosis on the basis of elevated cardiac serum markers, such as cardiac-specific troponin T or I and creatine kinase isoenzyme MB, and thus have a diagnosis of NSTEMI. The clinical diagnosis of myocardial infarction requires an integrated assessment of the history with some combination of indirect evidence of myocardial necrosis using biochemical, electrocardiographic, and imaging modalities.[9]

Exclusion criteria were valvular heart disease, any type of surgery, and trauma during the prior month, cardiomyopathy, liver disease, renal failure, arthritis, malignant diseases, and other inflammatory diseases and oral anticoagulant therapy. Age, smoking habits, history of hypertension and diabetes, dyslipidemia, family history of IHD s and current medications were carefully ascertained. Body mass index was calculated as weight/height^2 (kg/m^2). In patients with acute myocardial infarction, the serum concentration of autoantibodies was measured during 3-5 days after admission. In patients with a history of unstable angina and CSA the measurements were done at admission time. Peripheral blood (4 ml) was collected from two groups, and the serum was separated and stored at −20 °C.

Current smoking habits were self-reported. The body mass index, seated systolic blood pressure (SBP)/diastolic blood pressure (DBP) in the upper arm, and the plasma glucose, serum lipids levels were measured after an overnight fast. The glucose and lipids (total cholesterol, high-density lipoprotein cholesterol and triglycerides) were measured enzymatically. Participants who were not taking lipid-lowering medications were classified as having dyslipidemia if their low-density lipoprotein (LDL) cholesterol concentration exceeded of 160 mg/dl. All participants treated with lipid-lowering drugs were classified as having dyslipidemia. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and currently took antihypertensive medications. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dl and currently taking anti-diabetic treatment.[9,10]

Serum RF levels were measured by latex method. The serum levels of RF were quantitated using standard samples with known concentrations of the factor expressed as IU/ml, provided by the manufacturer. The normal range of RF has been reported to be < 20 IU/ml. The serum levels of ANA were also measured using a commercial the enzyme-linked immunosorbent assay (ELISA) kits. The serum levels of ANA were quantitated using standard samples with known concentrations of antibodies provided by the manufacturers. The serum levels of ANA was expressed as a unit with a normal range of < 1.2 U based on kits indicator.

Gensini score was calculated for each patient according to coronary angiography results. The score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. Reduction in the lumen diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25, 50, 75, 90, 99 percent, and complete occlusion, were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the

functional significance of the myocardial area supplied by that segment: the left main coronary artery × 5; the proximal segment of left anterior descending (LAD) coronary artery × 2.5; the proximal segment of the circumflex artery × 2.5; the mid-segment of the LAD × 1.5; the right coronary artery, the distal segment of the LAD, the postero-lateral artery, and the obtuse marginal artery ×1; and others × 0.5 (112).

Results were presented as mean ± standard deviation for quantitative variables (median and Interquartile range were reported for abnormal variables) were summarized by absolute frequencies and percentages for categorical variables. Logarithm transformed was used for abnormal variables. Continuous variables were compared using t independents sample t-test for normal variables and Mann-Whitney test for abnormal variables. Categorical variables were, on the other hand, compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of < 5 were observed. To analyze the correlations of ANA and RF to Gensini score, we used Pearson correlation test. Regression test was used to determined relationship between ANA, RF and severity of coronary stenosis. Multiple linear regression used to control the effect of age and other confounder factors such hypertension, diabetes, hyperlipidemia, and smoking.

$P < 0.050$ was considered as statistically significant. For the statistical analysis, statistical software SPSS for Windows (version 20.0, SPSS Inc., Chicago, IL, USA) was used.

Results

The mean of age was 56.37 ± 10.75 and 60.0 ± 10.53 in CSA and ACS group, respectively. Table 1 shows baseline characteristics in study population. Pharmacological treatment by Aspirin and statins are more prevalent among CSA group ($P < 0.001$). Then the Gensini scoring system was introduced to evaluate the severity and extent of coronary stenotic lesions. The mean serum levels of RF, ANA and Gensini score in study groups are demonstrated in table 2. The median and isolated thoracic aortitis serum levels of RF in CSA group 3.0 (1.0-5.0) IU/ml were significantly higher than ACS group 3 (1.0-8.0) IU/ml, $P = 0.589$). Pearson correlation test for RF, ANA and Gensini score showed ANA is positively correlated with Gensini score ($r = 0.247$ and $P = 0.004$), but no significant correlation has seen between RF and Gensini score ($r = -0.001$ and $P = 0.994$) (data not shown). After adjusting for confounders such as age, hypertension, diabetes, hyperlipidemia and smoking multiple linear stepwise regression analysis showed ANA remained independently associated with Gensini scores in ACS group ($B = 0.471$, $P < 0.001$) so could be consider as a predictor for coronary artery disease severity (Table 3).

Using multivariate regression analysis for all collected variables, we demonstrated that Gensini scores were significantly associated with ANA (Figure 1).

Table 1. Baseline characteristics in study population

Variable	ACS	CSA	P
Age (mean ± SD)	56.37 ± 10.75	60.0 ± 10.53	0.046
Body mass index (mean ± SD)	25.16 ± 3.92	25.60 ± 3.80	0.494
Hypertension [n (%)]	26 (37.7)	28 (40.0)	0.779
Hyperlipidemia [n (%)]	14 (20.0)	28 (40.0)	0.010
Diabetes mellitus [n (%)]	23 (32.9)	23 (32.9)	> 0.999
Smoking [n (%)]	33 (47.1)	30 (42.9)	0.610
FH [n (%)]	32 (45.7)	27 (38.6)	0.392
Statin use [n (%)]	12 (17.1)	34 (48.6)	< 0.001
Aspirin use [n (%)]	35 (50.0)	55 (78.6)	< 0.001

Chi-square, t test; SD: Standard deviation; ACS: Acute coronary syndrome
CSA: Chronic stable angina; FH: Familial hypercholesterolemia

Table 2. Rheumatoid factor (RF) and Gensini score in study population

Variable	ACS	CSA	P
RF (IU/ml)*	3.00 (1.0-5.0)	3.0 (1.0-8.0)	0.589
ANA (IU/ml)*	0.28 (0.2-0.4)	0.4 (0.3-0.6)	0.001
Gensini	25.70 (13.0-42.5)	26.0 (15.7-58.0)	0.209

* Median (interquartile range); Mann-Whitney test; ACS: Acute coronary syndrome; CSA: Chronic stable angina
RF: Rheumatoid factor; ANA: Anti-nuclear antibodies

Table 3. Relationship between rheumatoid factor (RF) and anti-nuclear antibodies (ANA) with Gensini score (log transformed) in study population

Study groups	Crude				Adjusted model			
	RF		ANA		RF		ANA	
	Standard beta	P	Standard beta	P	Standard beta	P	Standard beta	P
ACS	−0.073	0.55	0.400	0.001	−0.102	0.880	0.505	< 0.001
CSA	−0.020	0.87	0.037	0.767	−0.034	0.797	0.013	0.922

Adjusted model: For controlling the effect of age and other confounder factors such hypertension, diabetes, hyperlipidemia and smoking we used multiple linear regression; RF: Rheumatoid factor; ANA: Anti-nuclear antibodies; ACS: Acute coronary syndrome; CSA: Chronic stable angina

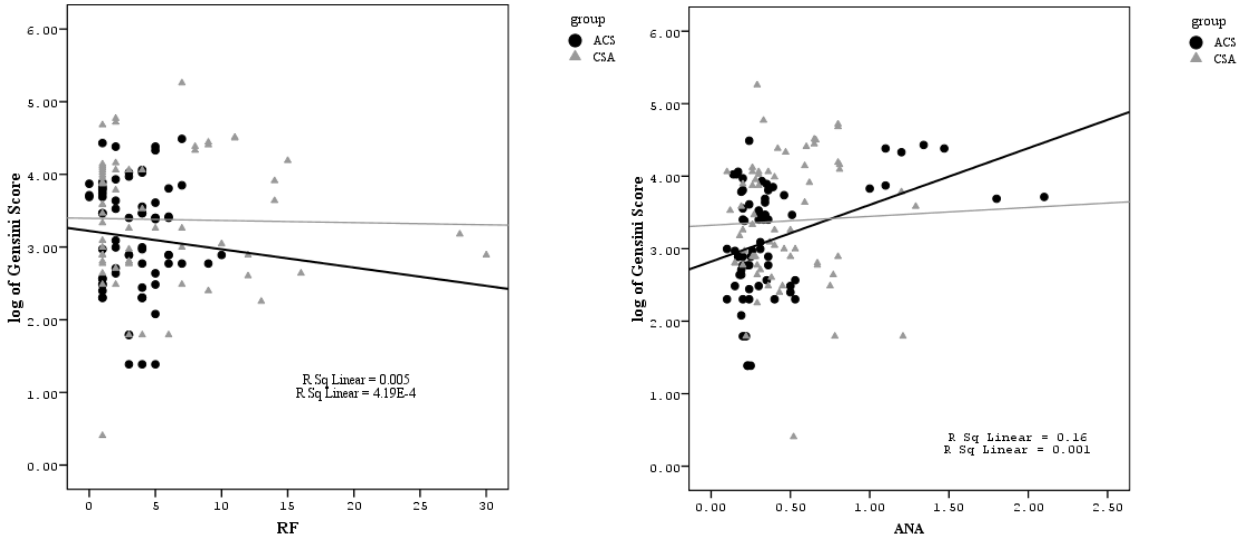

Figure 1. Linear regression analysis to demonstrate relationship between anti-nuclear antibodies and (log transformed) Gensini scores
ACS: Acute coronary syndrome; CSA: Chronic stable angina; ANA: Anti-nuclear antibodies

Discussion

Our results appear to show ANA could be considered as a strong predictor for coronary artery disease. Our results showed an association between RF in male patients with a history of CSA. Moreover, we found that as this study was conducted in a relatively small population, and the correlation was not very strong. However, if the results are confirmed in large studies,[7,8,11,12] the present findings may provide new insights into the physiological roles of RF and ANA in atherosclerosis.

Previous study which carried out by Chang et al. showed RF is present in up to 15% of elderly subjects and may arise through polyclonal B cell activation due to infectious organisms or by antigen-driven proliferation of B cells associated with autoimmune diseases, including rheumatoid arthritis.[13] He demonstrated as RF is strongly associated with rheumatoid arthritis so it is associated with increased cardiovascular morbidity and mortality, the increased risk in their study population is unlikely to be due to active rheumatoid arthritis or its treatment.[14] Other studies have reported that higher level of RF is an independent risk factor for CAD in men from the general population.[15] Our result is the same as that reported by Edwards et al.[16] They investigated whether the presence of RF was associated with an increased risk of coronary artery disease among a population of elderly men and women in the Hertfordshire Cohort Study. They found that RF was associated with an increased likelihood of coronary artery disease in men (odds ratio = 3.1, 95% confidence interval 1.7-5.4, P < 0.001), but not in women. RF appears to cause direct tissue damage in RA as a component of immune complexes via activating the complement system.[17] It may cause damage to the endothelium in a similar manner in IHD. The presence of immunoglobulins and complement components has been demonstrated in atherosclerotic plaques providing evidence for immune complex reactions.[18] Indeed autoantibody productions are conditions strongly associated with RA. A few autoantibodies including anti-oxidized (ox LDL), RF, anti-cyclic citrullinated peptides, ANA, anticardiolipin antibodies are considered autoimmune factors associated with atherosclerosis in autoimmune disease, as well as in the general populations.[19] In the conventional view, the

antigen-antibody reaction is prone to enhance inflammation and results in exacerbation of atherosclerosis.

According to previous studies the RF and ANA are likely to play an important role in atherogenesis, but our result showed that these factors cannot be used as precipitating factor of ACS. However, these factors are not acute inflammatory factors and present in chronic inflammatory disease. Indeed the initiation of the atherosclerotic process can occur early in life,[20] and these auto-antibodies may play role in the initiation of the atherosclerotic process. In the some study association between ANA and IHD was unclear.[21]

Limitation

The present study is limited by its cross-sectional nature and small size population, so we could not evaluate outcome measures. This study strength using Gensini score to evaluate the extent and severity of coronary stenotic lesions.

Conclusion

RF and ANA is likely to play an important role in atherogenesis, but our result showed that Higher serum levels of ANA in patients with IHD may be considered as independent risk factors for ACS.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Evaluating factors associated with uncontrolled hypertension: Isfahan cohort study, Iran

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Original Article

Abstract

BACKGROUND: Hypertension (HTN) considers as one of the most common risk factors, which potentially raises the risk of cardiovascular disease. Regarding high prevalence of HTN among Iranian population this study designed to examine a range of socio-demographic and clinical variables to determine the association with failure to achieve blood pressure control in a cohort of hypertensive subjects.

METHODS: This retrospective cohort study is a part of Isfahan cohort study which carried out on adults aged 35 years old or more. Subjects with confirmed HTN entered in this sub-study. For all subjects questionnaire included socio-demographic characteristics, clinical data and lifestyle behavior completed by trained nurses. Uncontrolled HTN was defined as systolic and diastolic blood pressure more than 140/90 in the presence or absent of pharmacological treatment.

RESULTS: The prevalence of uncontrolled men was significantly higher than controlled in both 2001 and 2007 (P < 0.001). A significant association was found between sex and control of blood pressure: compared with women, being men [odds ratio (OR) = 2.31; 95 % confidence interval (CI) = 1.64-3.24] was significantly associated with uncontrolled HTN in 2001 and (OR = 2.38; 95% CI = 1.78-3.18). Among lifestyle behaviors, tendency for more consumption of salty foods increased the risk of uncontrolled HTN in 2001 by 1.73 times [OR = 1.73, 95% CI = 1.20-2.50, (P = 0.003)]. Patients who were naive to mono-therapy without considering the type of antihypertensive drug were found to be associated with uncontrolled blood pressure (OR = 0.14; 95 % CI =0.1-0.2).

CONCLUSION: Uncontrolled HTN was sex, marital status, diabetes, tendency to salty foods and medication adherence. Assessment of them presence of these risk factors is warranted to recommend an aggressive HTN management with the goal of reducing excessive risk of cardiovascular events caused by uncontrolled HTN.

Keywords: Prevalence, Hypertension, Uncontrolled, Risk Factors

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Introduction

Hypertension (HTN) considers as one of the most common risk factors, which potentially raises the risk of cardiovascular disease (CVD)[1] and consider as a major public health problem in most developed and in developing countries.[2] HTN affects around

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one billion individuals around the world, and the relationship between blood pressure and the risk of cardiovascular events is continuous, consistent, and independent of other risk factors.[3] The national surveillance step-wise study which was done by the Iranian Ministry of Health demonstrated a prevalence of 25% for HTN among adults aged 25-64 years.[4] Moreover, according to available data, the rate of controlled HTN is widely varied among different countries ranged from 2.2% in Eastern Europe, < 5% in China to more than 38.0% in Western Europe, North America and 18.0% in Iran.[5] It follows from all the above mentioned that a growing number of hypertensive patients are faced with undiagnosed HTN and or uncontrolled HTN.[6] More importantly, a large part of the patients (17.6% female and 18.0% of male) faced to uncontrolled HTN in Iran.[7]

Several reports described key variables of uncontrolled HTN, which these barriers varied in different population. 6 poor medication, sedentary lifestyle and unhealthy eating, as well as high salt consumption, have defined as main fences in control of HTN around the world.[8,9]

Many studies have examined risk factors for HTN, and several comprehensive management guidelines have been published.[7,10-12] However, the risk factors for uncontrolled HTN are less well established.[7,11,12] Previous studies claimed that individuals diagnosed with HTN whether they have untreated, undertreated or treatment-resistant HTN, have consistent characteristics that could provide insight to improve blood pressure control.[12-14]

As intensive efforts need to control blood pressure and hence we have to evaluate determinants to achieving higher HTN control rates. The aim of this study was to examine a range of socio-demographic and clinical variables to determine the association with failure to achieve blood pressure control in a cohort of hypertensive subjects.

Materials and Methods

The Isfahan cohort study (ICS), Iran, is a population-based, ongoing longitudinal study of adults aged 35 years old or more, living in urban and rural areas of three counties in central Iran namely Isfahan, Najafabad and Arak.[15] Baseline data collection for the ICS began in 2001. Participants were selected by multistage random sampling and were recruited to reflect the age, sex and urban/rural distribution of the community.[16,17] The Ethics Committee of the Isfahan Cardiovascular Research Center approved the study. The study sample included 6504 subjects 35 ≥ years of age (average 51.0 ± 11.7 years) that had complete demographic data, diagnoses, vital signs, pharmacy utilization, and personal information. In this sub-study, totally 1986 patients with a diagnosis of HTN were identified in the ICS database. The study cohort was 186 cases with controlled HTN and 1732 with uncontrolled HTN in 2001 (Figure 1). All participants provided their informed consent to participate in the clinical examination and follow-up study.

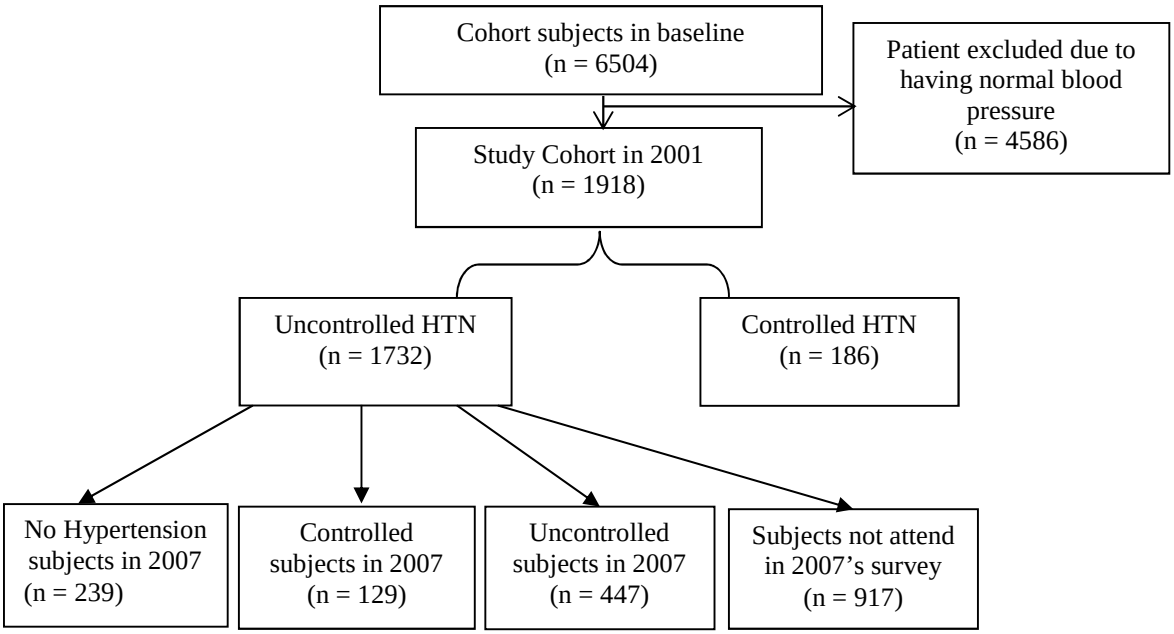

Figure 1: Flowchart of study participants
HTN: Hypertension

This sub-study sought to identify patient risk factors for uncontrolled blood pressure among Iranian patients with HTN. This study evaluated patients with a diagnosis of HTN over a 3-year period between 2001 and 2007.

In addition, each subject had at least 3 HTN diagnostic coding events and at least 3-recorded BP readings. The minimum 3 blood pressure readings occurred within the 3-year study period and were obtained at separate office visits. A subject's blood pressure was measured once, however, if elevated, a repeat BP was taken 5 min later. The lowest blood pressure reading was recorded. HTN was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg17, HTN for diabetic and renal failure patients defined as defined, as a blood pressure ≥ 130/80 mmHg is an extremely common co-morbid condition in diabetes. Subjects who had an HTN diagnosis for < 6 months, patients with no medical record, and patients who were pregnant were excluded from the study.

Uncontrolled HTN was defined as SBP and DBP more than 140/90 in the presence or absent of pharmacological treatment.

After obtaining informed written consent, medical interview and physical examination were conducted. Measurements of blood pressure, anthropometric parameters, as well as fasting blood tests, were carried out following standard protocols and using calibrated instruments as has been described previously.[18] Waist circumference (WC) was taken as the smallest circumference at or below the costal margin. HTN was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg in men and women or treatment of previously diagnosed HTN. Subjects who smoked daily were considered as current smoker. In 2007 (the 7th year of follow-up), participants were invited for repeated laboratory measurements, physical examination and interview using the same protocol as a baseline survey. Laboratory measurement methods were similar in 2001 and 2007 but the auto analyzer was different (Eppendorf, Hamburg, Germany in 2001 and Hitachi 902, Japan in 2007). Both instruments have been validated with an external standard laboratory center.

Pharmacological treatment: using angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, α-blocker, β-blocker, vasodilators, dihydropyridine calcium channel blocker, Non-dihydropyridine calcium channel blocker, aldosterone antagonist, potassium-sparing diuretic, thiazide were consider in this study as mono-therapy or combination therapy.

Data are presented as number (percentage), means and standard deviation, chi-square and t-test were used to compare characteristics between two groups. Multiple logistic regression was used in an explanatory framework for evaluating the relationship between potential determinants of controlling HTN on all the derived demographic, administrative, and pharmacy records. The statistical software SPSS for windows (version 20.0, SPSS Inc., Chicago, IL, USA) was used. $P < 0.050$ was considered to be significant.

Results

A comparison of patient baseline characteristics for controlled and controlled HTN is presented in table 1. The prevalence of uncontrolled men was significantly higher than controlled in both 2001 and 2007 ($P < 0.001$). No significant changes observed between educational level in both 2001 and 2007 between subjects with and without controlled HTN ($P = 0.265$, $P = 0.696$). Regarding comorbid disease diabetes was significantly higher among uncontrolled subjects in 2001 and 2007 ($P < 0.001$). Tendency to using salty food was significantly higher between controlled HTN and uncontrolled patients in 2001 ($P < 0.001$), but in 2007 smoking habit was higher among uncontrolled subjects ($P = 0.020$). Mono-therapy by anti-hypertensive drugs was more prevalent among subjects with controlled HTN ($P = 0.001$), similarly combination therapy by two antihypertensive drugs was more prevalent among patients with controlled HTN ($P = 0.001$).

Table 2 shows demographic and clinical aspects of uncontrolled hypertensive subjects after 7 years of follow-up. After 6 years of follow-up, from 1732 subjects who were uncontrolled HTN in 2001, 129, 447 and 239 patients were controlled, uncontrolled and no signs of HTN respectively. Otherwise, 917 subjects were lost of follow-up. Among above-mentioned subjects mean of age was significantly higher among uncontrolled HTN ($P < 0.001$), whereas, no significant changes has seen regarding education and marital status (0.071, 0.291). Among co-morbid disease, obesity was more prevalent among controlled HTN subjects but diabetes and dyslipidemia was more prevalent among uncontrolled subjects. Lifestyle behavior except tendency to salty food has not any significant difference among groups. No drug usage is more prevalent among uncontrolled subjects (41.2%), ($P < 0.001$).

Table 1. Demographic characteristics of study participants based on control of hypertension (HTN) and year of follow-up

	2001			2007		
	Controlled	Uncontrolled	P	Controlled	Uncontrolled	P
Age	60.67 ± 11.14	57.39 ± 11.65	< 0.001	60.8 ± 10.63	60.8 ± 10.45	0.761
Sex (male)	49 (26.34)	783 (45.20)	< 0.001	82 (30.59)	488 (51.20)	< 0.001
Residency (rural)	36 (19.40)	515 (29.70)	0.003	57 (21.30)	277 (29.10)	0.011
Education						
Illiterate	107 (57.52)	888 (51.27)		110 (41.04)	416 (43.65)	
Primary school	50 (26.88)	541 (31.23)	0.265	93 (34.70)	325 (34.10)	0.696
More than primary school	29 (15.59)	303 (17.49)		65 (24.25)	212 (22.24)	
Insurance	235 (87.70)	827 (87.00)	0.754	-	-	
Marital status						
Married	135 (72.58)	1491(86.08)		222 (83.14)	817 (86.00)	
Single	0 (0)	8 (0.50)	< 0.001	0 (0)	3 (0.30)	0.125
Divorced	1 (0.50)	7 (0.40)		1 (0.40)	0 (0)	
Widowed	50 (29.60)	226 (13.00)		44 (16.50)	130 (13.70)	
Comorbid disease						
Obesity*	46 (24.73)	518 (29.90)	0.140	92 (34.32)	309 (32.42)	0.557
Diabetes	8 (4.30)	375 (21.65)	< 0.001	48 (17.90)	335 (35.20)	< 0.001
Dyslipidemia	22 (91.35)	1548 (91.00)	0.851	209 (78.00)	775 (81.30)	0.222
Lifestyle Behavior						
Smoking habits	27 (14.50)	307 (17.80)	0.388	21 (7.90)	133 (14.40)	0.020
Tendency to salty foods	116 (62.30)	1146 (66.20)	< 0.001	87 (32.60)	303 (31.00)	0.113
Physical inactivity	149 (80.10)	1416(81.75)	0.581	213 (79.47)	743 (77.96)	0.595
Pharmacological treatment						
Mono-therapy	132 (70.90)	458 (26.40)		172 (64.20)	311 (32.60)	
Combination therapy by Two drug	10 (5.40)	66 (3.80)		37 (13.80)	70 (7.30)	
Combination therapy by three	4 (2.10)	9 (0.51)	< 0.001	15 (5.60)	14 (1.50)	0.006
No drug usage	40 (21.50)	1199 (69.20)		44 (16.40)	558 (58.50)	
Knowledge	186 (100.00)	1623 (93.70)		268 (100)	919 (97.20)	
Practice	127 (68.27)	453 (61.88)	0.106	101 (37.70)	166 (31.80)	0.098

* Obesity defined as (body mass index > 30)

Table 2. Demographic and clinical aspects of uncontrolled hypertensive subjects after 7 years of follow-up

Subjects in 2007	Subjects with Uncontrolled Hypertension in 2001 (n = 1732*)			
	Controlled (n = 129)	Uncontrolled (n = 447)	No hypertension (n= 239)	P
Age	62.66 ± 10.62	67.81 ± 10.04	58.86 ± 11.57	< 0.001
Sex (male)	38 (29.50)	209 (46.80)	119 (49.80)	< 0.001
Education				
Illiterate	56 (43.40)	213 (47.70)	88 (36.80)	0.071
Primary school	44 (34.10)	146 (32.70)	86 (36.00)	
More than primary school	29 (22.50)	88 (19.70)	65 (27.20)	
Marital Status				
Married	111 (86.7)	377 (84.7)	209 (88.2)	
Single	0 (0.0)	0 (0.0)	1 (0.4)	0.291
Divorced	1 (0.8)	0 (0.0)	0 (0.0)	
Widowed	16 (12.5)	68 (15.3)	27 (11.4)	
Co morbid disease				
Obesity	52 (40.3)	151 (33.8)	65 (27.2)	0.032
Diabetes	32 (24.8)	190 (42.5)	52 (21.8)	< 0.001
Dyslipidemia	103 (79.8)	365 (81.7)	174 (72.8)	0.025
Lifestyle Behavior				
Smoking Habits	6 (4.7)	23 (5.2)	21 (8.9)	0.127
Tendency to salty Foods	64 (50.0)	243 (54.5)	159 (67.4)	0.001
Physical inactivity	100 (77.5)	345 (77.2)	188 (78.7)	0.905
Drugs				
One drug	76 (58.9)	202 (45.2)	0 (0.0)	
Two drugs	24 (18.6)	50 (11.2)	0 (0.0)	< 0.001
Three drugs	9 (7.0)	11 (2.5)	1 (0.4)	
No drugs	15(15.5)	184(1.2)	238 (9.6)	

* 917 subjects did not attend the 2007 survey.

Table 3. Assessment factors affecting on the uncontrolled hypertension (HTN)

	2001		2007	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.97 (0.96-0.98)	< 0.001	1.00 (0.99-1.01)	0.987
Sex (male)	2.31 (1.64-3.24)	< 0.001	2.38 (1.78-3.18)	< 0.001
Education				
Illiterate	1		1	
Primary school	1.30 (0.92-1.85)	0.140	0.92 (0.68-1.26)	0.620
More than primary school	1.26 (0.82-1.94)	0.294	0.86 (0.61-1.22)	0.405
Marital status				
Married	1		1	
Single	-	-	-	-
Divorced	0.63 (0.77-5.19)	0.671	-	-
Widowed	0.41 (0.29-0.58)	< 0.001	0.80 (0.55-1.16)	0.248
Comorbid disease*				
Obesity	1.29 (0.92-1.84)	0.142	0.92 (0.69-1.22)	0.558
Diabetes	6.15 (3.00-12.60)	< 0.001	2.48 (1.77-3.48)	< 0.001
Dyslipidemia	0.95 (0.55-1.63)	0.857	1.22 (0.88-1.71)	0.223
CVD	1.25 (0.81-1.93)	0.313	0.68 (0.48-0.97)	0.031
Lifestyle behavior				
Smoking habits	1.27 (0.83-1.95)	0.270	1.88 (1.03-3.42)	0.040
Tendency to salty foods	1.73 (1.20-2.50)	0.003	1.29 (0.98-1.69)	0.069
Physical inactivity	0.89 (0.61-1.31)	0.582	1.09 (0.74-1.52)	0.596
Pharmacological treatment				
No drugs	1	-	1	-
Mono-therapy	0.12 (0.09-0.18)	< 0.001	0.14 (0.10-0.20)	< 0.001
Combination therapy by two drug	0.27 (0.11-0.65)	0.002	0.15 (0.90-0.20)	0.085
Combination therapy by three drug	0.08 (0.02-0.27)	< 0.001	0.7 (0.30-0.20)	0.095

Control hypertension (HTN) consider as reference group; Control of Co-morbid disease consider as not having these conditions; OR: Odds ratio; CI: Confidence interval; CVD: Cardiovascular disease

Odds ratios (ORs) > 1 were associated with uncontrolled HTN, and ORs < 1 were associated with controlled HTN (Table 3). A significant association was found between sex and control of blood pressure; compared with women, being men (OR = 2.31; 95% CI = 1.64-3.24) was significantly associated with uncontrolled HTN in 2001 and (OR = 2.38; 95% CI = 1.78-3.18). Education was not associated with blood pressure control in both 2001 and 2007 [OR = 1.26; 95% CI = 1.26 (0.82-1.94) and OR = 0.86, 95% CI (0.61-1.22) respectively]. However, partner status has associated with uncontrolled blood pressure (OR, 0.41; 95% CI [0.29-0.58]) Diabetes considered as a powerful predictor for controlled HTN in both 2001 and 2007 [2001: OR = 6.15; 95% CI (3.00-12.60), 2007: OR = 2.48; 95% CI (1.77-3.48), respectively]. Among lifestyle behaviors, tendency for more consumption of salty foods increased the risk of uncontrolled HTN in 2001 by 1.73 times [OR = 1.73, 95% CI (1.20-2.50), (P = 0.003)] but this item was not associated with control of blood pressure in 2007 (P = 0.069). Patients who were naive to mono-therapy without considering the type of antihypertensive drug were found to be associated with uncontrolled blood pressure [OR = 0.14; 95% CI (0.1-0.2)].

Discussion

This retrospective cohort study recognized major patient features associated with uncontrolled HTN were sex, marital status, diabetes, tendency to salty foods and medication adherence. To the best of our knowledge, this is the first report, which focused on uncontrolled HTN in a sample of cohort Iranian population. Similarly, Egan et al. demonstrated this sex-dependent uncontrolled HTN.[12] Marital status also showed a significant relationship with HTN control, partnered hypertensive patients were at higher risk of uncontrolled HTN. Studies conducted in Europe also evaluated partner status, and its association with HTN. Similarly, in a Dutch population, patients without a partner were found to have had a higher risk for uncontrolled HTN.[19] Similarly, de Gaudemaris et al.[20] and Lessa et al.[21] studied on French population observed that single men might have had an association with the prevalence of HTN; however, this finding was not statistically significant.

Our results showed education could not play a crucial role to having controlled HTN. Similar to our obtained results, a recent study in Brazil has shown that education was not a good predictor for adherence to treatment of HTN.[22] Association of cardiovascular risk factors and blood pressure was described previously.[23-25] But how other cardiovascular risk factors could effect on the control of HTN is still on in debt. Our data showed that there is a potentially negative role of diabetes in the control of HTN for hypertensive patients. Similarly, Bog-Hansen et al. showed uncontrolled blood pressure is in both sexes related to type 2 diabetes.[26] The VIIDA registry, which was also carried out in Spain, identified DM and left ventricular hypertrophy as the main factors associated with lack of BP control.[27]

In this study, although central obesity in subjects with uncontrolled HTN was significantly higher than other group but overall obesity was not significantly associated with control of blood pressure. Previously, Cordero et al. discussed the effect of metabolic alterations associated with obesity might be associated with the intra-abdominal visceral fatty mass.[28] In effect, it was shown that the type of visceral adipose tissue was associated with intolerance to glucose and high lipid levels, even after adjustment for BMI and age. The link between smoking and CVD has been evidently recognized. Our results show that smoking is also associated with uncontrolled HTN. Smoking induces endothelial dysfunction, vasoconstriction, insulin resistance, and dyslipidemia, certain forms of which could explain our results.[29] Instead, smokers are more sedentary and have unhealthy diets, and these are factors, which can directly raise blood pressure. Subjects with unhealthful lifestyles such as propensity to salty foods and diets are also associated with poorer with blood pressure control.[30]

We also found that age and CVD were associated with blood pressure control, which could reflect CVD subjects have better practice about their disease. It seems that these patients are more aware of control of HTN. The number of antihypertensive drugs used showed a much weaker association with control of blood pressure. We did not find any significant difference between type of one drug and control of HTN (data not showed) but these results showed without considering the type of antihypertensive drugs, treatment by one or two drug could not useful to control of HTN, so combination therapy may be useful based on clinical aspects of penitents. Treatment guidelines note that the combination of an angiotensin receptor blocker and a calcium channel blocker, similar to the combination of an angiotensin-converting enzyme inhibitor or an ARB plus a diuretic, provides an effective option for patients with HTN.

For greater success, treatment must always be associated with other non-pharmacological interventions. The cost of medication may be a barrier for the control of HTN and must be an important factor in the choice of antihypertensive drugs.

The results of the study that done by Allemann et al. showed combining antihypertensive drugs with complementary mechanisms of action for the treatment of patients with HTN. They indicated that combination therapy lowers blood pressure to a greater degree than mono-therapy.[31]

Study strengths and limitations

These studies strengthen to random and large patient population reflecting the communities from which it was drawn. In addition, a large number of variables were investigated to explore multiple associations with uncontrolled blood pressure. Although some previous studies reported acceptable control of HTN, but their results were limited to small sample size which were under control by regular clinic visiting. However, several limitations exist in our investigation. First, there are inherent limitations associated with the retrospective cohort study design. Second, in our questionarie we asked about attitude and practice of patients regarding control of HTN but there is a lack of data regarding regular visiting patients in clinics or home monitoring.

Conclusion

Uncontrolled HTN was sex, marital status, diabetes, tendency to salty foods and medication adherence. Assessment of them presence of these risk factors is warranted to recommend an aggressive HTN management with the goal of reducing excessive risk of cardiovascular events caused by uncontrolled HTN.

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Conflict of Interests

Authors have no conflict of interests.

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Self-efficacy strategies to improve exercise in patients with heart failure: A systematic review

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Review Article

Abstract

BACKGROUND: Despite exercise is recommended as an adjunct to medication therapy in patients with heart failure (HF), non-adherence to exercise is a major problem. While improving self-efficacy is an effective way to increase physical activity, the evidence concerning the relationship between strategies to enhance self-efficacy and exercise among HF has not been systematically reviewed. The objective of this systematic review is to assess the effect of interventions to change the self-efficacy on exercise in patients with HF.

METHODS: A systematic database search was conducted for articles reporting exercise self-efficacy interventions. Databases such as PubMed, ProQuest, CINAHL, Scopus, and PsycINFO, and the Cochrane Library were searched with restrictions to the years 2000-June 2014. A search of relevant databases identified 10 studies. Published randomized controlled intervention studies focusing strategies to change self-efficacy to exercise adherence in HF were eligible for inclusion. In addition, studies that have applied self-efficacy-based interventions to improve exercise are discussed.

RESULTS: Limited published data exist evaluating the self-efficacy strategies to improve exercise in HF. Dominant strategies to improve patients' self-efficacy were performance accomplishments, vicarious experience, verbal persuasion, emotional arousal.

CONCLUSION: Evidence from some trials supports the view that incorporating the theory of self-efficacy into the design of an exercise intervention is beneficial. Moreover, exercise interventions aimed at integrating the four strategies of exercise self-efficacy can have positive effects on confidence and the ability to initiate exercise and recover HF symptoms. Findings of this study suggest that a positive relationship exists between self-efficacy and initiating and maintaining exercise in HF, especially in the short-term period.

Keywords: Self-Efficacy, Heart Failure, Exercise

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Introduction

Heart failure (HF) affects 2-4% of general population. Prevalence of HF greatly increases at the age of 75; and hence it reaches 10-20% in the ages 70-80. At early ages, due to coronary artery diseases (CAD) in the past decades of life, HF is more prevalent in men than in women. However, in older ages, the incidence is equal for both sexes.[1] HF accounts for the highest hospital admission expenses for patients with a total of more than $ 20 billion.[2-4]

HF is a debilitating disease which affects patients' function and quality of life (QOL).[2,3] HF is often a progressive process. Breathlessness, fatigue, and reduced exercise capacity are common clinical manifestations of HF.[4] The results of symptoms for the patients are disorders in their lives, and this means that people with HF, who experience

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impaired exercise and functional capacity, experience some restrictions in their lives.[5] Subsequently, poor exercise adherence and deconditioning happen to these patients, and this leads to a decline in the necessary confidence for initiating and maintaining a regular exercise.[6-8]

Guidelines from the European Society of Cardiology recommend that all patients with stable chronic HF should exercise regularly.[1] A number of studies have shown the benefits of exercise for patients with HF,[9] including submaximal exercise capacity[10] lower hospital rate and mortality[7] and improved QOL.[11] Exercise can also reduce many of the symptoms of fatigues and breathlessness because of its effect on the musculoskeletal and cardiovascular systems (European HF Training Group, 1998). For each 1 h exercise, a 5% reduction in all causes of death, a reduction in the rate of hospitalization for all causes, and an increase in maximal oxygen consumption and measures of health status have been observed.[12] Strategies to increase physical activity in these patients can improve disease symptoms and outcomes[13] and help to prevent hospitalizations and worsening of symptoms.[14] 80% of patients who suffer from HF believe that exercise is a health behavior.[15] However, only 39% of them really participate in exercising.[16,17] Indeed, it is difficult for patients with HF to follow and compliance with the recommendations and many of them, even those who have been referred to cardiac rehabilitation centers, do not continue the organized activities.[15]

The researchers have focused the effect of interventions influencing the exercise in HF.[18] Several studies have shown that, in addition to demographic factors, psychosocial factors are also related to physical activity.[19] Among that, self-efficacy has been the most dominant variable.[20] Self-efficacy is a key component in social cognitive theory (SCT) 21. It has been defined as "the belief in one's capabilities to organize and execute the courses of action required to produce given attainments."[21] Studies have shown that those with higher self-efficacy significantly spend more energy to keep physically active.[22] Among cardiac patients who participated in cardiac rehabilitation programs, self-efficacy is a predictor of exercising behavior for 3 months.[23] Furthermore, there is documented evidence that changes in self-efficacy can mediate the effects of behavior change interventions on improving in exercise compliance in chronic obstructive pulmonary disease (COPD).[24]

Self-efficacy is considered as an important predictor of behavior because it works as an independent construct of the skills of an individual's activities. It should be noted that the role of self-efficacy in initiating and maintaining health behaviors and compliance to treatment in other chronic diseases such as diabetes type II has been proven.[25] However, other studies on coronary artery patients showed no association between exercise self-efficacy, the compliance rate, and exercise intensity.[26]

Whilst a number of reviews have therefore attempted to provide evidence of what constructs to target in exercise interventions in HF patients, evidence of how to change these constructs is currently unclear. Self-efficacy has a significant influence on exercising in various clinical conditions, the actual impact of strategies to improve self-efficacy for exercise remains ambiguous. Thus, this review was conducted to assess the effect of interventions to change the self-efficacy on exercise of patients with HF.

Materials and Methods

We searched the literature published between January 2000 and June 2014 in the following database: PubMed, ProQuest, CINAHL, Scopus, and PsycINFO, and the Cochrane central register of controlled. We used both controlled vocabulary (e.g., medical subject heading terms) and key words including HF, congestive HF, chronic HF, cardiac failure, left ventricular failure, physical activity, physical training, exercise, training, aerobic training, and self-efficacy and combination of them. We included articles limited to full studies in the English language.

Whilst a number of reviews have therefore attempted to provide evidence of what constructs to target in exercise interventions in HF patients, evidence of how to change these constructs is currently unclear. Self-efficacy has a significant influence on exercising in various clinical conditions, the actual impact of strategies to improve self-efficacy for exercise in HF remain ambiguous. Thus, this review was conducted to assess the effect of interventions to change the self-efficacy on exercise of patients with HF.

This review included the investigations that focused on HF patients who were 18 years old or greater. In systematic step of search, we chose studies, which had a control group in the design, including clinical trial or quasi-experimental. We also included the studies that had an intervention or a strategy to improve the exercise. We included studies of any type of exercise, training or physical activity (i.e., home-based, hospital-based, or cardiac rehabilitation).

We excluded article if: (1) no definition of HF was given including New York Heart Association functional class (NYHA) or physical examination and impaired left ventricular ejection fraction (2) cross-sectional and other observational studies (3) if self-efficacy reflected confidence in recognizing symptoms and didn't indicate self-efficacy for exercise. (4) HF with preserved ejection fraction (5) poor methodological quality [scored 3 on the physiotherapy evidence database (PEDro) scale].[27]

As the self-efficacy has been shown that self-efficacy is an influential predictor of exercise, the outcome was defined as exercise self-efficacy that lead to increase any type of physical activity. The exercise could be a subset of physical activity that is planned, structured, and repetitive bodily movement done to improve or maintain at least one of the strength, flexibility, or endurance.[28] Exercise could be measured by oxygen consumption at peak exercise test peak oxygen uptake (PVO2), 6 min walk distance test, self-reported questionnaire, or physical function subscale on QOL questionnaires. In this study, exercise and physical activity are generally used interchangeability.

In the initial screen, titles and abstracts of the available electronic resources were reviewed for their potential relevance to the topic by first author (Rajati F). In the included articles, no difference was observed between the three terms of HF, chronic HF, and congestive HF; hence these three phrases were used interchangeably. Keywords that were related to self-efficacy for exercise in HF patients were primarily searched in titles, abstracts and keywords. Then, all articles were reviewed by another author (Hasandokht, T). Kappa coefficient of 0.86 indicated a high degree of agreement in the selected literature. Then, in the second screen, we assessed the articles related to the present review and also articles that did not present enough information in title or abstract by the same two authors to determine whether articles met the inclusion criteria. We excluded some of the articles due to lack of inclusion criteria. At this stage, the Kappa coefficient of 0.89 was obtained. We resolved lack of agreement and final decision about included studies through discussion with a third reviewer.

The quality of individual studies was assessed with the PEDro scale.[27] This scale scores article between 0 and 10 depending on whether the 10 items of methodologic rigor are present or absent. Trails were included if a PEDro score was 4 or more. According to the PEDro, quality was assessed by reviewers (Rajati F, Hasandokht T) independently. Any disagreements between the reviewers were resolved by consensus.

Results

Study search and description of studies

The search to find relative papers located 412 possible references (including duplication between databases): 47 from Pubmed, 16 from PsycINFO, 34 from ProQuest, 20 from cochrane library, and 54 from scopus. All papers that seem relevant from the title and abstract were assessed in full text (n = 30). We excluded 18 studies as they either did not meet review criteria (n = 13)[29-40] were poor methodologic quality (PEDro score, < 4) (n = 1)[41] or the authors reported only the protocol study (n = 4)[42-45] (Figure 1).

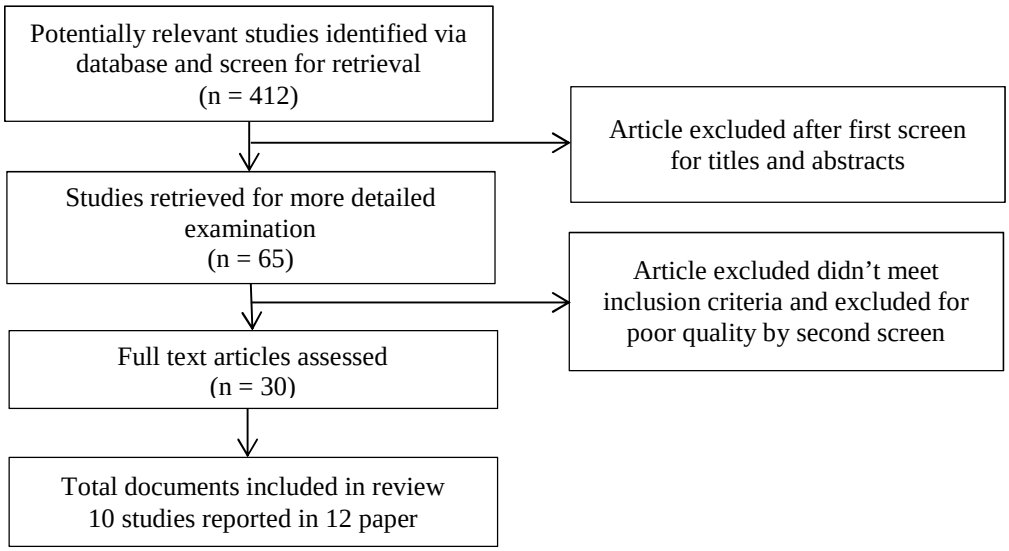

Figure 1. Flow of study selection

This left a total of 8 randomized controlled trials (RCTs) and 2 non-RCT for detailed review. Two studies reported the findings in the four papers.[46-49] Table 1 summarizes the findings of the included articles.

Reviewed studies were conducted in the United States, New Zealand, and Netherlands. The total number of patients enrolled in included studies was 800, and their sample size ranged from 20 to 317. The majority of patients were 65 ± 10 years. Except for one study[46] with II, III, and IV NYHA classification, all the studies included patients with mild (NYHA II) or moderate (NYHA III) HF as measured by the NYHA classification. Three studies were conducted in the cardiac rehabilitation program[48,50,51] Barnason et al.[52] recruited patients a specific group of HF who had undergone coronary artery bypass graft surgery (CABG); Smeulders et al. also included patients with diastolic dysfunction.[53] Most of the studies were performed by Bandura's self-efficacy theory, whilst another study applied the trans theoretical model (TTM) to develop self-efficacy for exercise.[21] All included studies scored over 4 out of 10 on the PEDro scale, with a mean score of 5.6 (range 4- 8) (Table 2).

Evaluation of the amount exercise was various. Intensity of exercise was specified using energy expenditure 51 or exercise capacity. In several investigations, exercise capacity assessed by 6-min WT 6, 46 or PVO2.[54-56] Brodie and Inoue.[46] used a leisure-time questionnaire[57] walk test. Barnason et al.[52] evaluated the differences in exercise level after intervention through cardiovascular risk factor Modification adherence instrument, whilst Collins et al.[51] used the 3-day activity diary. Pozehl et al.[48] used physical function subscale on SF-36 questionnaire. Smeulder et al.[53] measured physical activity level using physical activity scale comprising walking, swimming, bicycling, and other activity domains. Self-efficacy measured using cardiac exercise self-efficacy (CESE) instrument in three included studies.[48,51,55] Brodie and Inoue. used a visual scale of readiness to change physical activity to assess the self-efficacy.[46] Only one of the studies examines the self-efficacy strategies on physical activity but didn't use any self-efficacy instrument.[53] The strategies to increase self-efficacy for exercise were fairly various. Exercise performance, education, self-monitoring, motivational interview, self-management, goal setting, graphic feedback, problem solving used for enhancing self-efficacy. According to data extraction from included studies, we can categorize following strategies used to enhance exercise self-efficacy in patients HF.

Learning by doing

As it is shown in table 2, in the selected studies, the role of exercise performance on changing self-efficacy to increase regular physical activity is clearly evident. Some studies have shown that self-efficacy in patients gradually increases with exercising. Patients who increase intensity, duration, and frequency of exercising step- by step will be better prepared to participate in exercise activities in future.[6,51,56] Therefore, participation in exercise leads to increase self-efficacy for exercise. Self-efficacy in HF is related to the risk factors for cardiovascular disease.[52] In the Barnason et al.'s [52] study, there were significant correlations between all medical outcomes study short form-36 subscale scores and self-efficacy scores at 6 weeks after CABG surgery, except for the mental health subscale in the RC group. The relationship in the intervention group was also significant for the "bodily pain" subscale which represents the special relationship between self-efficacy and physical function of the participants' body. According to the study by Collins et al., which was conducted focusing on cardiac rehabilitation of patients with HF, in the control group after rehabilitation and without any cognitive interventions, self-efficacy of patients did not change for performing physical activities, but in the intervention group the self- efficacy significantly increased.[51] Although there was no significant difference in self-efficacy between two groups, but the improved self-efficacy of rehabilitation of patients after 12 and 36 weeks was still survive.[51]

Recommendation and prescription for home-based exercise through communication intervention lead to increase the self-efficacy in the intervention group compared with the control group in Barnason's et al.[52] study. Collins et al. used the intensity supervised aerobic exercise program for enhancing the self-efficacy in HF patients. In addition to physical function and PVO exercise, self-efficacy of 17% improved in the intervention group.[51] Yeh et al. used the tai chi exercise to increase exercise capacity and functional status in their investigation. The tai chi exercise improved self-efficacy scores after 12 weeks intervention.[55] Furthermore, 12 weeks cardiac rehabilitation program cause to improve self-efficacy of 31%.[48]

Providing successful performance strategies derived from self-efficacy theory used to increase the exercise level in the majority of the included articles. One of the upcoming studies conducted a home-based exercise program in women with HF.[6]

Table 1. Characteristics of Studies Included in a systematic review

Author	Sample size	Design	Purpose	Content of intervention to increase self-efficacy	Duration and type of physical activity/exercise	Outcome measurement	NYHA classification	Findings included self-efficacy and exercise
Barkley and Fahrenwald.[50]	65 Int = 35 (20 male), Con = 40 (24 male)	Quasi-experimental	To determine the effect of an SCI in levels of exercise self-efficacy, levels of barrier self-efficacy, and independent exercise	Attention to minute of exercise, reinforcement/using daily log/persuasion about successful exercise, barrier identify/goal setting, plan setting, overcome barrier/self-monitoring of symptom and exertion level	12 weeks structural exercise with the intensity of 4-5 metabolic equivalents (METs)/3 days/week	- ESE - BARSE scale A self-report of daily independent exercise	Not clear	Patient's self-efficacy for exercise increased from mean (SD) of 85.35 (17.54) to 86.64 (18.90) on ESE scale. BARSE scores increased from mean (SD) 67.69 (21.33) to 78.22 (20.97), and independent exercise increased from mean (SD) 42.59 (77.06) to 116.72 (80.78) min/week. Within group analysis was significant for change in BARSE ($t = 2.347$, $P = 0.03$) and independent exercise ($t = 4.210$, $P < 0.001$)
Brodie and Inoue[46] ,Brodie et al.[47]	60 SC = 20 Int = 18 SC + Int = 22	Randomized three-group controlled intervention Design	Examination of the effect of physical activity "lifestyle" intervention, based on motivational interviewing, on improvement quality of life at 5 months from baseline, compared with routine care	Motivational interviewing/client-centered counseling/problem-solving	Regular physical activity such as walking	- Leisure-time physical activity questionnaire expressed as kcal/kg/day - 3 day physical activity diary - Medical outcomes short form-36 health survey (SF-36) - MLHF questionnaire A visual tool to assess readiness-to-change	II-III-IV	Self-reported physical activity in the short-term increased (>2 kcal/kg/day). Self-efficacy and motivation scores improved after 5 months follow up in comparison with baseline that none of the patients were not in the stages mentioned above in preparation stage improvements in physical functioning ($P < 0.07$) and role physical ($P < 0.02$), on SF-36 were seen
Barnason et al.[52]	35 Int = 18 (14 male), Con = 17 (10 male)	Randomized clinical trial repeated measures	To determine the impact of a home communication intervention for HF Coronary Artery Bypass Graft (CABG) patients, self-efficacy, coronary artery disease risk factor modification and functioning	Symptom self-management/risk factor modification education/self-care for CABG/positive reinforcement	6 weeks home communication intervention (tele health) providing: assessment of patient symptoms, CAD risk factor modification education, Education on CABG recovery, positive reinforcement to increase patients' self-efficacy	- Barnason Efficacy expectation scale - Cardiovascular Risk Factor Modification Adherence - Medical Outcomes Study Short - Form-36	I- II	Patients' self-efficacy increased over time [$F(1,29) = 6.40$, $P < 0.02$] in the intervention group than in the control group

Table 1. Characteristics of Studies Included in a systematic review (continue)

Author	Sample size	Design	Purpose	Content of intervention to increase self-efficacy	Duration and type of physical activity/exercise	Outcome measurement	NYHA classification	Findings included self-efficacy and exercise
Collins et al.[51]	31 Int = 15 (15 male), Con = 16 (16 male)	Randomizd controlled clinical trial	To evaluate the effect of 12 weeks rehabilitation program on quality of life, aerobic fitness, difficulty with symptoms of HF, self-efficacy for exercise, and daily activity levels compare with control group	Increasing gradually exercise	12 weeks Polestriding or/and treadmill walking Cardiac rehabilitation/duration of exercise gradually increased up to 45 to 50 min 3 days/week	- Exercise cardiac self-efficacy - MHLF questionnaire - SF-36-questionnire Physical activity questionnaire	II-III-I	Self-efficacy improved after 12 weeks of training (55.3-12.1 to 63.0-10.9, P = 0.10); 17% improvement in the intervention group compare with the no change in the control group (52.5-16.3 to 52.9-14.7, P = 0.83). self-efficacy improved for patients who continued to exercise at 12 (22%, P = 0.01) and 36 (40%, P = 0.06) weeks. 14% improvement from baseline to 12 weeks on physical functioning score was seen in the intervention group. Difference in the change score on the MLHF was not statistically significant between the 2 groups. Overall activity level was not significantly increased (P = 0.94)
Pozehl et al.[48] Duncan and Pozehl[49]	42 Int = 22 (12 male), Con = 20 (12 male)	Randomized experimental repeated measures	To assess the effects of a 12 weeks multicomponent exercise training intervention (HF Exercise And Training Camp Heart Camp) on self-efficacy	Exercise accomplishment, goal setting, graphic feedback, and problem-solving, role modeling overcome barrier, self-monitoring about heart rate, rating of perceived exercise, and symptom	12 weeks structured aerobic exercise with 40-60% Max HR, 3 days/week in a hospital-based rehabilitation setting, and resistance training 2 days/week at home	- Self-efficacy for exercise MOS SF-36 physical function subscale, KCCQ	II-III	Heart Camp intervention improved patient self-efficacy for exercise over 12 weeks [F(1,2) = 31.25, P = 0.03] compared with a non-significant change [F(1,2) = 2.33, P = 0.27] in control group. The group × time interaction was not significant for the physical function subscale of the SF-36 [F(1,4) = 0.96, P = 0.39] or the physical limitations subscale of the KCCQ [F(1,4)= 0.54, P = 0.50]
Gary[6]	32 Int =16 (0 male), Con= 16 (0 male)	Randomized controlled two-group experimental design	The effect of home-based exercise combined walking and education program on exercise self-efficacy in older women with HF	Increasing gradually exercise	12 weeks Walking with intensity at 40-60% Max HR, 30 min/day, 3 days/week	- Exercise Self-Efficacy, - Outcome expectancy 6-minWT-test - MLHF - A monitor heart rate polar beat watch	II-III	Improving self-efficacy for exercise that resulted in improved functioning on the 6 min Walk Test (203 feet increase in the intervention group via 93 feet decline in the control) increasing physical function on MLHF

Table 1. Characteristics of Studies Included in a systematic review (continue)

Author	Sample size	Design	Purpose	Content of intervention to increase self-efficacy	Duration and type of physical activity/exercise	Outcome measurement	NYHA classification	Findings included self-efficacy and exercise
Maddison et al.[54]	20 (15 male) Int =10 Con = 10	Randomized controlled trial	To examine the effect of a modeling intervention on increase PVO_2 and self-efficacy in people diagnosed with CHF	Role model presentation (DVD)	Exercise test using ramp protocol increasing periods of time (i.e., 2, 4, 6, 8, 10, and 12 min) at three intensities (i.e., easy, moderate, and hard)	- Standardized exercise testing (ramp), - Self-efficacy scale	II-III	The effect of modeling (DVD) intervention on PVO_2 F(1,19) = 4.38, P = 0.05 and self-efficacy F(1,19) = 5.80, P < 0.05 was statistically significant
Yeh et al.[55]	100 Int = 50 (28 male), Con = 50 (36 male)	Single-blind, multisite, parallel-group, randomized controlled trial	To investigate the effect of Tai Chi exercise on improving functional capacity and quality of life in patients with HF	Skill mastery/showing videotape/encouragement	12 weeks Tai Chi with intensity at 50-74% Max HR, 60 min/day, 2 days/week	- Standardized exercise testing (ramp) - 6-min walk test - Metabolic cart - Cardiac Exercise Self-efficacy questionnaire	II-III	QoL improved on MLHF (−19 [−23, −3] in the intervention group versus 1 [−16, 3], P = 0.02 control group). Self-efficacy enhanced on cardiac exercise self-efficacy (0.1 [0.1, 0.6] in the intervention versus −0.3 [−0.5, 0.2], P 0.001) in the control group)
Oka et al.[56]	24 Int = 12 (12 male), Con = 12 (12 male)	Randomized controlled trial	To evaluate the effect of performance of a single treadmill exercise test and participation in a 3-month program of walking and resistance exercise on self-efficacy in HF patients	Exercise performance/skill mastery	12 weeks aerobic walking with intensity at 70% Max HR, 40-60 min/day, 3 days/week	- Exercise test - Borg ratings of perceived exertion scale - Self-efficacy expectations scales	II	Self-efficacy scores for walking improved after 3 months of walking and resistance exercise program (P = 0.04). The relationship between self-efficacy for climbing with physical fitness (r = 0.51, P = 0.01) and walking with physical fitness (r = 0.48, p = 0.02) (measured by PVO_2) was significant
Smeulders et al.[53]	317 Int = 131 (89 male), Con= 186 (141 male)	Randomized, controlled trial	To assess the effects of the CDSMP on health behavior and healthcare utilization in HF	Skills mastery, goal setting, group sessions reinterpretation of symptoms, modelling, and social persuasion	6 weeks exercise which was not clear duration, frequency, or type	- Physical Activities Scale of (a) walking; (b) swimming; (c) cycling; (d) other physical activity	II-III	Physical activity for walking improved at 6 but not 12 months. differences between intervention and control group patients for swimming or bicycling were not significant

SC: Standard care, Int: Intervention group; Con: Control group; PVO_2: Peak oxygen consumption; CABG: Coronary artery bypass graft; Max HR: Maximum heart rate; SCI: Self-efficacy coaching intervention; ESE: Self-efficacy scale; BARSE: Barriers to self-efficacy for exercise; MLHF: Minnesota living with heart failure questionnaire; KCCQ: Kansas City Cardiomyopathy Questionnaire; CDSMP: Chronic disease management program; SD: Standard deviation; NYHA: New York Heart Association; HF: Heart failure

Table 2. Quality of included article using PEDro score (ranging from 0 to 10)

Study	Random allocation	Concealed allocation	Group similar at baseline	Subject blinding	Therapist blinding	Assessor blinding	Less than 15% dropouts	Intention-to-treat analysis	Between-group statistical comparisons	Point measures and variability data	PEDro score
Barkley and Fahrenwald.[50]	Y	N	N	N	N	N	Y	N	Y	Y	4
Barnason et al.[52]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Brodie and Inoue.[46]	Y	Y	Y	N	N	N	N	N	Y	Y	5
Collins et al.[51]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Pozehl et al.[48]	Y	N	Y	Y	N	N	N	Y	Y	Y	6
Gary[6]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Maddison et al.[54]	Y	N	N	N	N	N	Y	Y	Y	Y	5
Yeh et al.[55]	Y	N	Y	Y	N	N	Y	Y	Y	Y	7
Oka et al.[56]	Y	N	N	N	N	N	Y	N	Y	Y	4
Smeulders et al.[53]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	8

Y: Yes, N: No
PEDro: Physiotherapy evidence database

The researcher emphasized the individualized and graded exercise in the intervention group. Program was begun at 40% intensity and 3 days/week. Duration of walking was increased gradually. The goal was to have patients walking at 60% intensity for a minimum of 30 min by the end of 12 weeks. Hypothesis of the study was supported by results that women participated in a walking program would significantly improve their self-efficacy for exercise.[6]

Role modeling

As exercise tolerance assesses by maximal oxygen uptake (vo2), Maddison et al.[54] evaluated the self-efficacy for doing exercise test using role modeling strategy. They provided the observational learning opportunities for patients before performing the exercise. The mean score of self-efficacy for performing exercise tolerance was more in the intervention group than the control group. The model was provided by video film for patients. Maddison et al. conclude self-efficacy served to mediate relations between the role modeling intervention and PVO2.[54]

Role modeling by a physical therapist of cognitive processes was provided to overcome difficulties with exercise. The small-group sessions were held to increase self-efficacy through incorporating social learning, social exchange, and social comparison. Pozehl et al. reported the 31% improvement in self-efficacy for exercise in the intervention group over 12 weeks.[48] Successes of other participants in the cardiac rehabilitation program are a good model to perform the exercise.[50]

Positive feedback

One of the strategies provided how exercise progress for patients was feedback. Dougherty et al.[45] applied self-regulation strategies included education for integrative self-management, self-evaluation, self-monitoring skills and self-reinforcement. They employed self-evaluation and self-reinforcement to control an aspect of behavior over time. Self-efficacy also can increase through verbal persuasion from expert source. One of the studies used motivational interview to promote physical activity.[46] Verbal persuasion trough motivational interview encouraged participants to undertake some form of physical activity, such as walking. In this study, readiness to change ruler, extracted from Procheska and DiClemente's TTM, was used to classify patients in the contemplation (intending to change) phase of behavior change or pre-contemplation (not thinking about becoming more active). The theory-based framework, which proposes that interventions should be tailored to an individual's readiness to change, shaped the project by 46 Using motivational interviewing principles demonstrated improvement in self-efficacy scores. The result of the study also indicated the most patients were either in contemplation or in pre-contemplation changing their activity levels.[46] Brodie and Inoue. evaluated the patients' physical activity by selected aspect of the general QOL (SF-36) questionnaire.[46] Restating the benefit of exercise by cardiologist, coaching by physical therapist, and providing web-based educational material pertain to exercising attended by the intervention in Pozehl et al.[48] Barnason et al. contrasted the effect of usual care with a home communication intervention on exercise. Positive reinforcement was provided to improve patients' self-efficacy related to symptom management and CAD risk factor modification through telephone intervention. Results showed self-efficacy improved over time when patients reinforced in adoption physical activity after CABG.[52] Working staffs with participants to set goal and overcome barriers lead to enhance exercise self-efficacy and self-efficacy to overcome barriers.[50]

Recognition of sign and problem-solving

Symptom assessment education and recognition of symptoms are strategies were used to increase physical activity in several included studies. Brodei et al. used the brain storming in the motivational intervention sessions to find a solution to overcome physical activity barrier.[46] Assessment of HF symptoms (e.g., fatigue or sleep problems) and strategies to manage symptoms through telephone intervention lead to increase patient's self-efficacy in the communication intervention compared with the standard care group in the Barnason et al. investigation.[52] Incorporating several strategies to improve self-efficacy were applied in the Pozehl et al.'s study. These techniques included supervised exercise and performance accomplishment, persuasion, role modeling and vicarious experience, reinterpretation, recognition,[48] and problem-solving relating to symptoms[46,48] such as shortness of breath by, for example, relaxation techniques and breathing exercise.[53] Self-monitoring of symptom severity and self-monitoring of exertion level integrated to the walking program were three components of the 12 week walking intervention in the Gary's educational investigation.[6] Self-monitoring was conducted through measuring the rate of perceived exertion (RPE) borg, a method to determine the level of exercise intensity, and polar beat watch,[58] device to

monitor heart rate.[6,50] The results showed women in the intervention group increased their self-efficacy for adhering to a walking program for a greater duration.[6] Finally, one of the included studies applied several methods such as self-care and managing feelings about HF and education for dealing with symptoms in addition to exercise intervention.[55]

Discussion

The purpose of this study was to investigate recent literature regarding the effect of interventions to improve self-efficacy on HF patients' exercise. 10 studies were identified that examine aspects of self-efficacy and exercise behavior. All studies presented some source of self-efficacy as an intervention such as exercising gradually, providing role model, feedback, self-monitoring, and problem-solving strategies. As the exercise is a necessary component of self-care or self-management in practical management,[59] some studies investigated the effect of self-efficacy on exercise as a part of self-care or self-management behavior.[60] Several studies investigated the relationship between exercise self-efficacy and the exercise in the cardiac rehabilitation program.[48,50] The 14-year review period allowed for investigation of the most-recent studies regarding self-efficacy and exercise behaviors in patients with HF.

The finding of this review suggests that self-efficacy has a positive effect on initiating and maintaining to physical exercise. The significant correlation between exercise self-efficacy scores and any type of exercise defined in the current study reinforce the hypotheses of the predictability role of self-efficacy in exercise performance. Moreover, there is clear evidence demonstrated that self-efficacy plays a marked role in compliance of regular exercise recommendation in CAD.[53] Self-efficacy has been shown to predict physical activity in HF, and enhancing self-efficacy has been demonstrated to have influential short-term effect on adherence to exercise in HF.[6,48,49,61] According to Brodie and Inoue, self-efficacious individuals are expected to develop more success in optimistic behavioral change. In addition, improving in self-efficacy predicts the duration and intensity of physical activity as well as performing the treadmill test.[46] In investigation of cardiac patients, self-efficacy has been considered as a predictor of cardiac recovery management, social, mental and physical, functioning.[52]

Exercise self-efficacy is the degree of confidence in individual capability to initiate and maintain participation in exercise. Provides a framework for achieving skills to manage and change exercise behavior.[50,62] Four strategies influence an individual's level of self-efficacy. The included studies used one or more strategies to improve self-efficacy as a mediator to exercise adherence. They are successful performance/mastery experience, vicarious experience, verbal persuasion and physiological arousal.

Successful performance/mastery experience

This strategy will be useful for HF patients who are not able to undertake higher intensity exercise because of physical limitation, breathlessness, fatigues, and other symptoms. Initiating exercise in a low intensity and then increasing to gradually lead to promote confidence in physical activity. However, researchers suggest successful performance will develop through several self-regulation techniques (i.e., heart RPE, and symptoms), goal-setting, and reward of accomplishment.[48] Some investigations use the RPE, which could assist patients to feel more confident about monitoring exercise intensity level.[49,63,64] Nevertheless, graded mastery experience produces lower effects on self-efficacy than other techniques in non-patients population.[65]

Vicarious experience

Vicarious experience springs from observational learning. Role modeling from a physical therapist makes the exercise easier for patients. Participating in a group exercise may help patients share several strategies to overcome obstacles (i.e., problem-solving and relapse prevention). According to study of Barkley and Fahrenwald[50], the nature of grouping exercise in the cardiac rehabilitation program gives patients the opportunity to practice exercise in a safe environment and to receive feedback from professionals and other skillful exercise participant. Patients who take part in a home-based program, therefore, may be deprived from the feedback and coaching. Role modeling by a physical therapist of cognitive processes provides to overcome difficulties with exercise. The physical therapist and health care provider should be awareness from probability of cardiac rehabilitation participants' fear about exercising outside a clinical setting.[66] There is well documented evidence showed interventions that used vicarious experience produced significantly higher levels of physical activity self-efficacy than studies where this technique was not included in non-patients population.[65]

Verbal persuasion

In accordance with self-efficacy theory, the

messages using verbal persuasion enhances attitude via vicarious experiences. This strategy influences individual to believe in the capabilities to attain a goal.[21] Studies showed interventions that include persuasion and barrier overcoming were related to lower level of self-efficacy those that did not include these strategies.[65] Studies in non-cardiac patients have shown verbal persuasion in e-health intervention is a good strategy for improving self-efficacy. Pozehl et al. administered the web-based educational material related to exercising in HFl.[48] The study of Barkley and Fahrenwald, staff members use verbal persuasion to support patients, reinforce performances, and structure situations that result in success.[50] Providing feedback related to individual progress, and focusing on exercise benefit leads to increase the level of self-efficacy. However, this technique produces a lower level of self-efficacy in adult.[65]

Physiologic and affective states

Symptom assessment education and recognition and reinterpretation of symptoms affect the patients' status to continue exercise48. Professional monitoring of exercise capacity guides patients to a better recognition of changes in physical status, and greater self-management.[43] Education about exercise-based self-monitoring of heart rate, RPE, and symptoms in HF have a positive effect on self-efficacy.[50] Providing reinsurance to individual and guiding to problem solving assist patients to be more self-efficacious in overcoming barriers.[43] However, barrier identification in individual without any chronic disease produces a lower level of physical activity self-efficacy.[65]

The majority of studies showed using any of the techniques above were associated with a higher self-efficacy in the intervention group than the control, except for one study by Barkley and Fahrenwald [50] They concluded no significant between-groups differences. This result may be due to use of the exercise self-efficacy questionnaires that have not been designed specifically for a cardiac population. Whist using the CESE leads to confirm the increasing self-efficacy after intervention in Pozehl et al.[48] and Yeh et al.[55]

Agreement and disagreement with other studies and review

We found three published systematic review about exercise adherence in patients with HF.[18,66,67] Although Krista et al. illustrated social support, goal setting, variety of exercise training, supervised booster exercise to enhance exercise training in HF, they concluded the nature of exercise adherence in these patients is unknown. Based mainly on the results of 20 qualitative researches,[18] conducted that for patients with HF, exercise influenced by patient's perception of their body, which affects self-confidence and motivation to exercise. Our review suggests that considering psychosocial factors to engaging individuals in exercising is very important. Tierney et al. also investigated common strategies used to improve adherence to exercise in HF through nine studies.[18] Authors showed that motivational strategies such as goal setting, positive reinforcement, and problem-solving might be effective in short term. We also concluded that the mention strategies are a part of sources to enhance self-efficacy for exercise and it leads to exercise adherence. However, in nonclinical population, providing persuasion or motivation, and graded mastery produced a lower level of self-efficacy than other strategies.[65]

Limitation of the study

Although the majority of studies included in this review had adequate sample size, some investigation used samples that were not characteristic of the population under investigation.[54] Some included papers didn't use a questionnaire that measured the value of self-efficacy. They reported self-efficacy improved after exercise intervention without any note about using a self-efficacy questionnaire.[53] Common limitations of studies were not blinding assessing outcome. As blinding study HF patients and therapist in RCTs of exercise is very difficult, none of the upcoming studies reported the therapist blinding criteria, with the except of Smeulder et al.'s syudy.[53] However, two studies reported blinding participants.[48,55] Only one of the studies included the patients with NYHA class IV.[46] There was considerable variation between studies in how outcomes were evaluated and this prevented the pooling of findings in a meta-analysis. For example, exercise was determined based on physical subscale on QoL questionnaire, PVO, 6 min WT, or physical activity questionnaire.

Implications and recommendations for future studies

Although education for regular physical activity is available comprehensively as an inevitable part of the HF management, and considering there is an evidence for clinical and psychological benefits, several clinics faces with the fact that cardiac rehabilitation participation and adherence to exercise in these patients are low. Given that the study shows that theory-based intervention can improve exercise self-efficacy in patients with HF,

Besides upon the strategies enhancing motivation such as ongoing feedback to patients, theory-guided behavioral interventions such as SCT, which focusing on self-efficacy could be effective.[54] Improving perceived self-efficacy plays a pivotal role in health status.[68] Patients had a fear of engaging in activities that cause to HF symptoms. Therefore, it would be beneficial to health care professional and physical therapist to know about patients' perceived self-efficacy.[55] Considering the limited number of studies investigating the effect of self-efficacy strategies on exercise in HF, more research is needed in this area. Bandura's SCT provides a good framework that health educators can use to develop interventions that encourage patients with HF to perform exercise. As self-efficacy is the key component of SCT and according to findings of other systematic review in nonclinical population that concluded using only one strategy has a weak impact on self-efficacy,[62] future studies should use incorporated strategies focusing on improving self-efficacy to examine physical activity level in patients with HF. Several studies investigated the role of predictability of self-efficacy in health status and other clinic outcome in patients with HF and COPD[39,68,69] the ability to examine the casualty effect of self-efficacy is limited. This illustrates a need for more studies using clinical trial in this area. In order to minimize variation future study choosing physical activity questionnaire measured the frequency, duration, and intensity components of physical activity is needed.

Conclusion

The evidence shows self-efficacy has a marked effect on performing the exercise in patients with HF. Additionally, this review suggests that all four sources of self-efficacy (i.e., Successful performance, vicarious experience, and verbal persuasion, physiologic and affective states) are important in developing exercise and maintaining exercise behaviors in patients with HF. These strategies in HF could be conducted as performing exercise gradually and graded mastery, applying vicarious experience, providing feedback and persuasion for physical activity, and physiologic and affective interference with HF symptoms and problem-solving regarding barrier of physical activity.[15] However, there is not enough evidence to evaluate which type of strategies is the most beneficial in this process.

Findings of this study suggest that a positive relationship exists between self-efficacy and initiating and maintaining exercise in HF, especially in short-term period. Interventions based on integrating all four sources of self-efficacy might also be helpful to promote exercise adherence in a longer term. The review would benefit from research to identify which components of intervention are related to better exercise outcome in HF.

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Conflict of Interests

Authors have no conflict of interests.

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A case of Marfan's syndrome with multi-level aortic dissections

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Case Report

Abstract

BACKGROUND: Although Marfan's syndrome is a disease with various phenotypes, but the major mechanism of death is cardiovascular complication. Aortic dissection is a major cause of death in Marfan syndrome.

CASE REPORT: A 30-year-old man with severe refractory chest and left flank pain and history of previously surgically repaired Type A aortic dissection was referred to the hospital. His typical manifestations of Marfan's syndrome were identified. Cardiovascular imaging showed an acute spiral dissection in the descending aorta extending to the left renal and femoral arteries with no evidence of thrombosis in its huge false lumen (8 cm). By the diagnosis of acute, expanded, spiral, Type B aortic dissection, he underwent the stent grafting of dissected aorta. He discharged without any complication. On follow-up cardiovascular imaging, thrombosed false lumen in stented aorta from descending aorta to the proximal abdominal aorta was seen.

CONCLUSION: Endovascular treatment of Type B dissection is an effective treatment in Type B dissection, even in patients with Marfan syndrome.

Keywords: Marfan's Syndrome, Aortic Dissection, Endovascular Graft

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Introduction

The leading cause of morbidity and mortality in Marfan's syndrome is cardiovascular complication such as aortic root aneurysm and its subsequent rupture and dissection.[1,2] Here, we report a case with extensive Type B aortic dissection in a known case of Marfan's syndrome with history of surgical treatment of Type A aortic dissection.

Case Report

A 30-year-old male was referred to Emergency Department of Alzahra Teaching Hospital affiliated to Isfahan University of medical Sciences, Iran, with the chief complaint of persistent crescendo-decrescendo chest pain as well as severe refractory pain in the left flank. He has been a known case of Marfan's syndrome since 16 years ago, and it was initially diagnosed by bilateral lens dislocation, chest wall deformity (pectus excavatum), joint elasticity and vascular problems. The patient had previously undergone surgical repair for the diagnosis of Type A aortic dissection. On admission, the patient's hemodynamic status was stable and his vital signs were as follow: blood pressure of right and left arm (140-90 and 150/60 mmHg, respectively), heart rate: 78 bpm, respiratory rate: 30 and temperature: 37 °C. On physical examination, peripheral pulses were palpable. Pulses of left femoral artery, dorsalis pedis and posterior tibialis were weaker than those on the right. His laboratory data were as follow: blood urea nitrogen: 15.4 mg/dl, creatinine: 1.1 mg/dl, blood sugar: 145 mg/dl, white blood cells: 11,300/μ, platelet: 126,000/μ and hemoglobin: 16.6 mg/dl. Electrocardiography (ECG) showed incomplete right bundle branch block. Trans-thoracic echocardiography indicated moderate mitral regurgitation, moderate left atrial enlargement, moderate aortic insufficiency and

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dilated aortic root (4.45 cm) with previous dacron patch placement other ECG measures were within normal limit.

Patient was admitted with a diagnosis of aortic dissection. 64-slice computed tomography angiography (CTA) of thoracic and abdominal aorta was performed after intravenous injection of 100 ml of contrast agent. CTA of thoracic and abdominal aorta demonstrated evidences of flap and dissection originated adjacent the origin of left subclavian artery, extending to the proximal section of left femoral and left renal arteries without the presence of thrombosis in true/false lumens. A huge false lumen (8 cm) was seen. Superior mesenteric artery (SMA) was normally opacified, and celiac artery was originated from SMA as a normal variant. Right renal artery was well opacified and without any evidence of dilation (Figure 1).

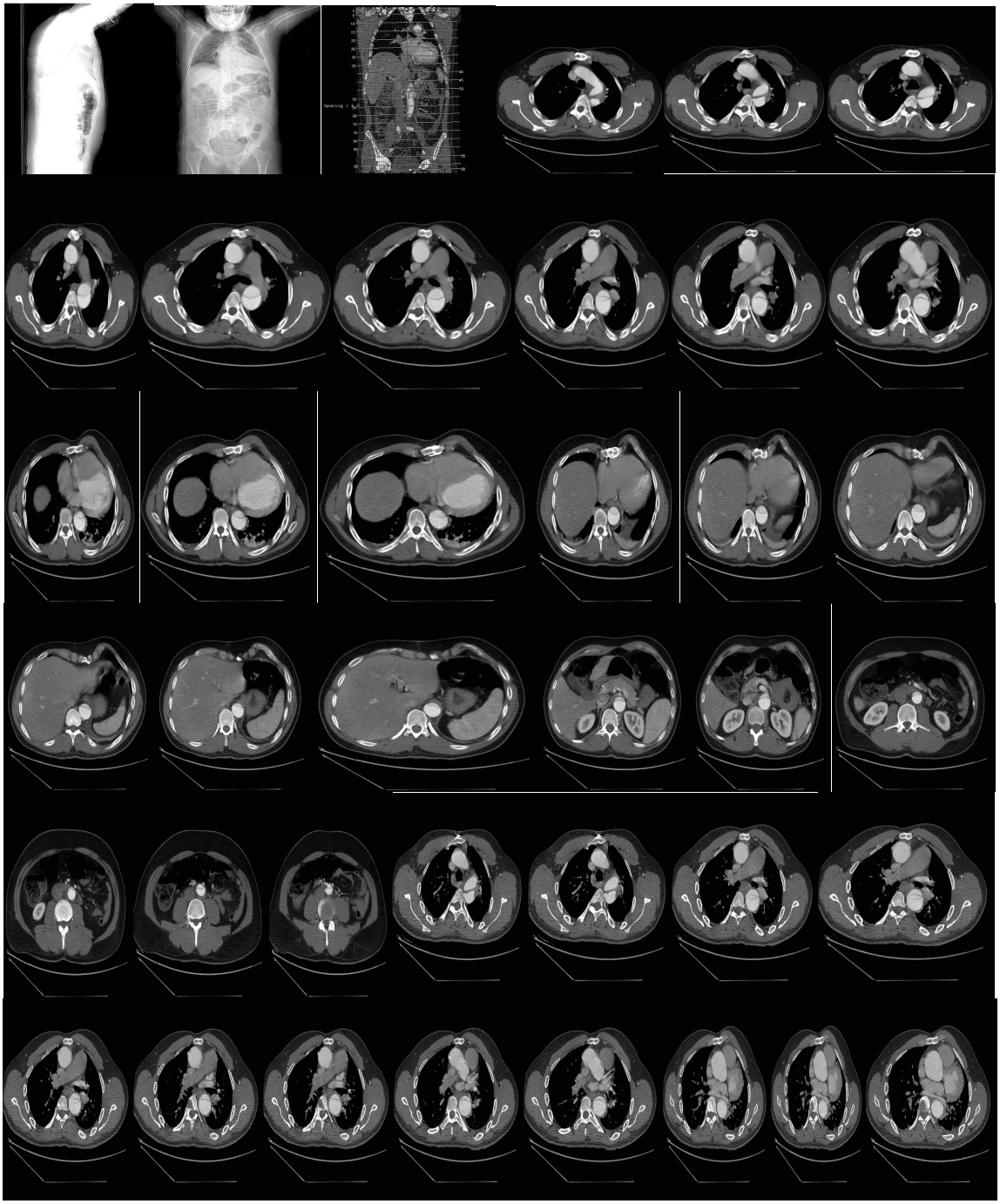

Figure 1. Computed tomography angiography before stent implantation

Aortic angiography showed spiral dissection originating from left subclavian artery and extended to iliac arteries (Video 1). Thus, the diagnosis of acute Type B dissection was confirmed.

He underwent endovascular repair by diagnosis of expanding Type B dissection. Through brachial and femoral access, the wire passed from true lumen and sized with a pig tail catheter was performed. Then, covered stent was previously deployed in ascending aorta. Subsequently, bare metal stent was deployed in descending aorta. Re-angiography of arch, ascending and abdominal arteries showed good results. In final injection, true lumen was seen, and both renal arteries were patented (Video 2). We decided to continue medical treatment for abdominal aorta dissection. After procedure, the force and movement of upper and lower extremities were normal. He was stable during hospitalization. In follow-up CTA, thrombotic false lumen was noted in descending aorta, associated with implanted stent which was placed from descending aortic arch down to the proximal part of abdominal aorta (just before SMA takes off). There was no evidence of aneurismal dilation in the thoracic aorta and major vessels originating from aorta (Figure 2). Left common iliac artery was involved in abdominal aorta dissection with good flow. The patient discharged on beta-blocker, angiotensin II receptor antagonist, aspirin, plavix and atorvastatin. He was serially followed-up after discharge. So far, he is asymptomatic.

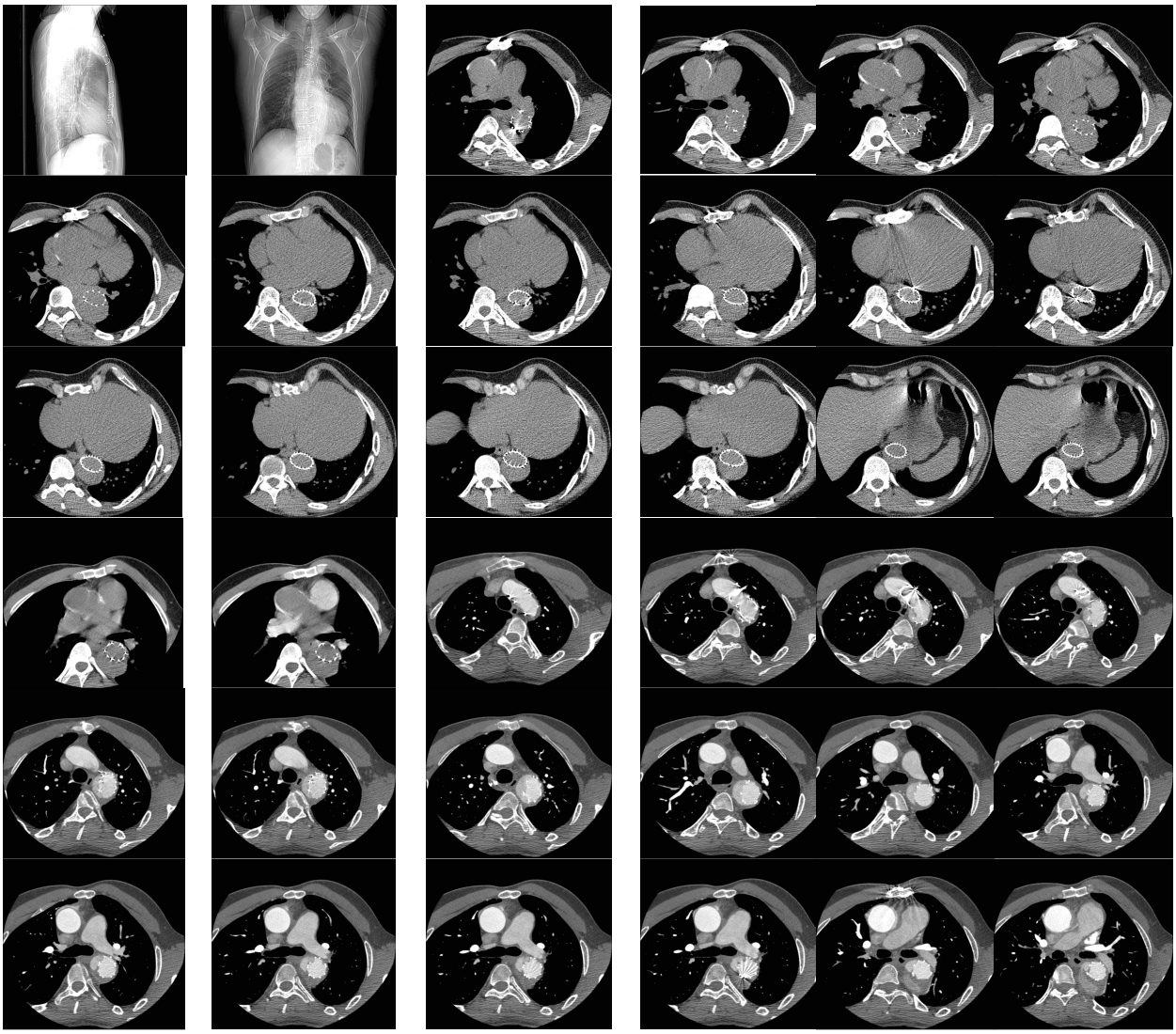

Figure 2. Computed tomography angiography after stent implantation

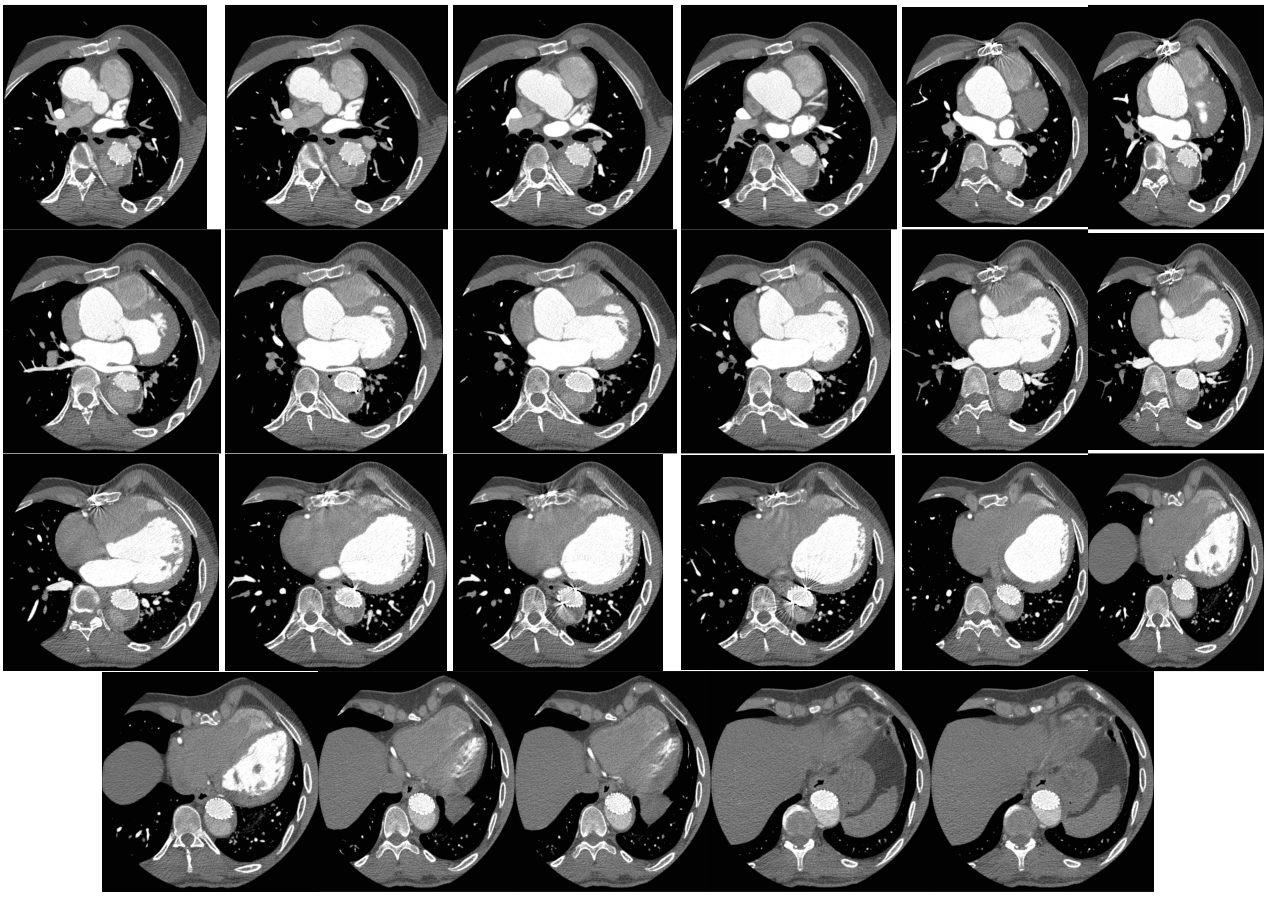

Figure 2. Computed tomography angiography after stent implantation (Continue)

Discussion

Marfan's syndrome, the most frequent inherited connective tissue disorder, is mainly associated with aortopathy such as aortic root dilatation or dissection and aortic valve insufficiency. Type B dissection is more prevalent in such patients' population. These cardiovascular complications limit life expectancy of the patients with Marfan's syndrome. By regular aortic follow-up and prophylactic aortic surgery, these catastrophic events are partly preventable.[3] Endovascular stent grafting in non-Marfan's syndrome patients with type B dissection and descending thoracic aorta is an established therapeutic procedure.[4] However in Marfan's syndrome patients, this procedure carries a significant propensity of endoleaks, surgical conversions and death.[3] Usually, endovascular treatments confront with early and late complications and these endovascular therapies need to be repeated. In this case, we performed a successful endovascular treatment and despite the huge false lumen, no need to repeated procedure happened and the patient was asymptomatic during the observation period. This misshapes mainly occur in Marfan's syndrome patients with chronic dissection.[5] Therefore, endovascular grafting should not be used routinely in such patients. The most of the Marfan's syndrome cases, aortic dissection is associated with aortic dilation. This patient experienced type A aortic dissection which was repaired by surgical treatment and this while he experienced new onset Type B dissection in the aortic location far from the previous site. Indeed, a huge non-thrombotic false lumen was seen in dissected portion that was successfully sealed by stent grafting.

Conclusion

Endovascular treatment of Type B aortic dissection is an elective treatment in type B dissection even in patients with Marfan's syndrome. Close future follow-up is recommended for these patients.

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Conflict of Interests

Authors have no conflict of interests.

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Methadone induced torsades de pointes and ventricular fibrillation: A case review

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Case Report

Abstract

BACKGROUND: Methadone is a synthetic opioid, which has been successfully used in treating heroin addiction and chronic pain syndrome in palliative care for more than 30 years. This drug is a potent blocker of the delayed rectifier potassium ion channel, which may result in corrected QT (QTc) interval prolongation and increased risk of torsades de pointes (TdP) in susceptible individuals.

CASE REPORT: We describe here a case of methadone-induced TdP that deteriorated into ventricular fibrillation, which was resolved after treatment with IV magnesium, potassium, and Lidocaine. Our purpose in this case review was to highlight the risk of cardiac arrhythmias, in particular QTc interval prolongation leading to TdP in a heroin-dependent patient receiving methadone substitution therapy, and then to present a perspective on treatment and prevention strategies of methadone induced prolonged QTc.

CONCLUSION: Methadone-induced TdP is a potentially fatal complication of methadone therapy. As the popularity of methadone use grows, clinicians will encounter more cases of methadone induced TdP, especially in our region, Iran. Hence, a thorough patient history and electrocardiogram monitoring are essential for patients treated with this agent, and alterations in treatment options may be necessary.

Keywords: Torsades de Pointes, Methadone, Ventricular Fibrillation, Prolonged Corrected QT

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Introduction

Methadone is an established and effective pharmacological agent to treat heroin dependent patients and chronic pain syndromes worldwide.[1] Although methadone has proven efficacy in reducing the use of nonprescription opioids and in alleviating pain, it has the potential for serious adverse effects. Methadone delays cardiac repolarization by blocking the rapid component of potassium ion current (Ikr) potassium channels, encoded by hERG or kCNH2 gene and hence it is independently associated with a prolonged corrected QT (QTc) interval and progression to torsades de pointes (TdP).[2,3] QTc prolongation is common in patients with Methadone maintenance therapy, but it does not lead to any significant consequences unless the QTc interval becomes profoundly prolonged (500 ms), exposing patients to developing TdP.[4] TdP is an abnormal cardiac rhythm displaying a regular and wide polymorphic QRS complex tachycardia that twists around the isoelectric baseline.[5] Here is a review on a case presented by TdP and ventricular fibrillation following methadone use.

Case Report

A 65-year-old man presented to the emergency department complaining of feeling unwell, chest pain during exercise, nausea and vomiting for a few days ago. He had recurrent episodes of apnea, palpitation and dizziness since the night before. A review of his past medical history revealed that he was a previous intravenous heroin user who was attending a community methadone substitution

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program. He was prescribed syrup methadone 240 mg daily. He was not known to have cardiac, respiratory, hepatic or neurological disease. Physical examination was remarkable for normal mental status, blood pressure of 140/90 mmHg, pulse of 50 beats/min in sinus rhythm, O_2 saturation: 90%, no cardiac murmurs, and no signs of heart failure. Laboratory studies included potassium of 2 mmol/l and magnesium of 1.4 mmol/l, white blood cell: 12,000/ mm^3, hemoglobin: 15 g/dl, platelet: 222,000/mm^3, blood sugar: 122 mg/dl. We though his hypokalemia was due to prolonged vomiting. His electrocardiogram (ECG) demonstrated sinus bradycardia and a QTc of 550 ms (Figure 1).

The patient was admitted to the cardiology service for ECG monitoring. Shortly thereafter, the patient experienced an episode of TdP and ventricular fibrillation (Figure 2).

Cardiopulmonary resuscitation, defibrillation and Lidocaine administration resulted in a successful return of spontaneous circulation. Lidocaine was an antiarrhythmic agent of choice because it does not prolong QTc anymore in contrast to other antiarrhythmic agents. Potassium and magnesium were administered intravenously to correct hypokalemia and hypomagnesemia. Due to the recurrent episode of TdP temporary pacemaker was inserted, and it was set at rate of 100-120 beats/min to prevent bradycardia. Temporary pace maker (TPM) was removed after 48 h. Methadone was discontinued and substituted with buprenorphine. Over the following 7 days, QTc interval progressively returned to normal limits. Discharge serum potassium and magnesium were 4.5 mmol/l and 2.5 mg/dl respectively. The patient was discharged with buprenorphine and a follow-up at the cardiology clinic, 2 weeks and 1 month later revealed no further cardiac symptoms with a normal ECG. He did not have any electrolyte abnormality at follow-up.

Discussion

Opiate substitution therapy with methadone has been introduced as a pharmacological treatment option for heroin-dependent individuals. The recommended dose for methadone maintenance therapy is about 60-100 mg/day. High dose methadone has been reported to prolong the QTc interval.[6]

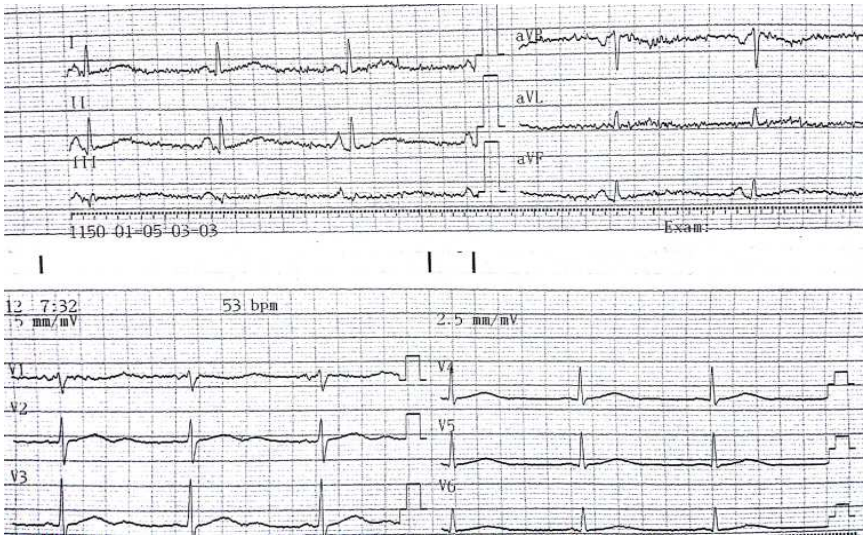

Figure 1. Long corrected QT interval

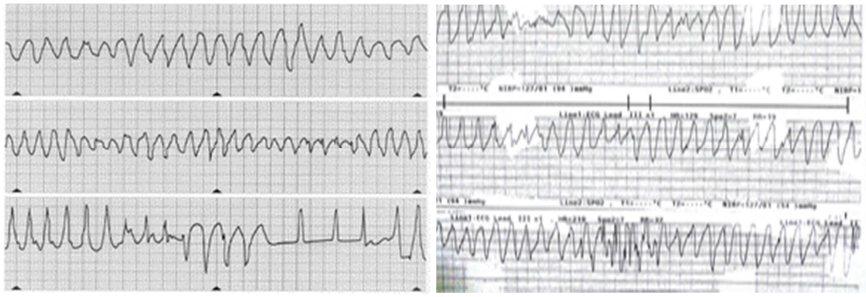

Figure 2. Torsades de pointes

The QT interval is measured from the beginning of the QRS complex to the end of the T wave. The QT interval varies with heart rate and is often corrected for this (QTc). Formula for OT correction that is insensitive to heart rate is: QTc = QT + 1.75 (heart rate-60).[7] A QTc interval of 500 ms or longer can confer an increased risk of TdP. QTc > 500 ms has been reported in 1.3-16% of methadone-treated patients in various cohorts and is rarely associated with methadone doses < 100 mg/day. Although most sudden cardiac arrests on methadone maintenance therapy have been reported at high doses, life-threatening arrhythmias have been described at dosages as low as 29 mg/day.[8,9]

Co-morbid conditions also play an important role in the occurrence of the QTc prolongation or TdP in methadone users. Some of these risk factors are: older Age, cardiac, liver, and renal abnormalities; concomitant use of cocaine and alcohol; ingestion of medications known to prolong the QTc; electrolyte imbalances (hypokalemia and hypomagnesaemia); human immunodeficiency virus infection; and female sex.[10,11] At least one of these risk factors was present in the majority of documented cases of ventricular arrhythmias in methadone maintenance patients.[12]

The pathophysiology of methadone-induced torsades can be explained via two mechanisms. It has been shown that methadone has a negative chronotropic effect due to its chemical similarity to verapamil.[13] It is thought that TdP is mediated through bradycardia since drug-induced arrhythmias generally tend to occur at slow heart rates and are pause - dependent. In addition, experimental studies have demonstrated that methadone inhibits the rapidly activating component of the delayed rectifier Ikr encoded by the hERG or KCNH2 gene, resulting in the cardiac action potential prolongation by delaying repolarization.[14]

Management of methadone-treated patients with prolonged QTc interval without manifest ventricular arrhythmia requires careful consideration of risks and benefits of continuing methadone or altering therapy. In any case, more frequent monitoring, counseling about worrisome symptoms and elimination of contributing factors such as additional QTc-prolonging medications and electrolyte abnormalities are required.

Acute treatment of TdP depends on the patient's hemodynamic status. Defibrillation is indicated when torsades has degenerated into ventricular fibrillation. DC-cardioversion can be used when the patient is haemodynamically compromised but may lead to recurrence of torsades. Lidocaine, mexiletine, or phenytoin can be tried. The correction of any predisposing factor (e.g. hypokalemia) and cessation of any predisposing medication is necessary. Magnesium is the first-line treatment of torsades; 2 g intravenously is followed if required by either a continuous infusion or a further bolus 5-15 min later. Potassium should be administered to achieve high normal levels (4.5-5.0 mmol/l). Temporary ventricular overdrive pacing can also be used in the short term. It prevents bradycardias and pauses and decreases the QTc interval due an increase in heart rate. Alternatively, acceleration of the basic heart rate using isoproterenol may be used. It should be used when the underlying rhythm is slow, the torsades is pause-dependent, and pacing is not able to be implemented. Long-term treatment in acquired long QT syndrome is generally not required.[15] Implants cardioverter-defibrillators (ICDs) have been suggested for patients with symptomatic ventricular arrhythmias who continue to take methadone. ICDs effectively prevent sudden death in these patients, but full risks and benefits of ICD in this patient population are not known.[16]

Although methadone has been reported to induce ventricular arrhythmias, the small risk of TdP should not deter physicians or psychiatrists from offering methadone as a treatment option to heroin-dependent individuals. The treatment of methadone induced TdP centers on prevention and risk stratification. A12-lead ECG should be obtained prior to starting methadone and should be repeated at regular intervals throughout the treatment.[11] Clinicians should carefully review the patient's current medications to look for other drugs that may prolong the QTc. The process should be repeated each time a new medication is added. Patients should be instructed to promptly report any episodes of palpitations or syncope, as well as conditions or therapies that can cause hypokalemia, such as gastroenteritis (diarrhea or vomiting) or the addition of diuretics to the patient's regimen.[17] In patients who experienced methadone induced arrhythmias, methadone should be stopped and an alternative safer medication such as buprenorphine, which is a partial opioid agonist should be considered.[10]

Conclusion

Methadone induced TdP is a potentially fatal complication of methadone therapies. As the

popularity of methadone use grows, clinicians will encounter more cases of methadone induced TdP, especially in our region. Due to the unpredictable nature of QTc prolongation and TdP, clinicians should be alert of how to monitor these medications and to prevent potentially fatal arrhythmias. Periodic ECG monitoring of the QTc interval and discontinuation of offending medications in the setting of prolonged intervals is ideal. Electrolyte disturbances especially hypokalemia, should be promptly corrected. In the case of patients with severe opioid dependency requiring, very high doses of methadone, alternative agents such as buprenorphine, a mixed opioid antagonist/agonist, should be considered.

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Conflict of Interests

Authors have no conflict of interests.

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