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The Role of Medications in Enhancing Patients' Overall Well-being and Quality of Life in Coronary Slow Flow syndrome: A Randomized Controlled Trial

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Abstract

Background: Coronary slow flow syndrome or phenomenon (CSFP) is a coronary artery disease that may cause cardiac ischemia, symptoms, and related complications. This study, conducted as a randomized controlled trial, assessed and compared the effects of a treatment plan comprising aspirin, statin, nitrate, and Nicorandil on the quality of life of patients with CSFP.

Methods: Out of 963 patients who underwent coronary angiography at Booalisina University Hospital in Qazvin, 52 individuals diagnosed with primary CSFP were enrolled in the study. They were randomly divided into two groups, with one receiving a three-drug treatment with 80 mg of aspirin, 20 mg of atorvastatin daily, and 2.6 mg of nitroglycerin every 12 hours (26 patients) and in the second group plus nicorandil 10 mg every 12 hours (26 patients). After two months, the patient's QOL was evaluated and compared using McNew's quality of life questionnaire. The SPSS version 16 software was used for data analysis.

Results: In both groups, after two months, the QOL scores in physical, emotional, social, and overall (P<0.001) were significantly improved compared to the baseline (before the treatment). The comparison between the two groups revealed no statistically significant differences in emotional, social, or overall quality of life scores, but the physical dimension of the quality of life in the group who received nicorandil showed more improvement than the other group (P=0.032).

Conclusion: A combination therapy of aspirin, atorvastatin, and nitrates has been demonstrated to significantly improve the quality of life in patients with Coronary Slow Flow Phenomenon (CSFP). However, the addition of nicorandil to this regimen does not provide significant further improvement, according to present findings.

Keywords: Slow coronary blood flow syndrome, Quality of life, Statin, Nitrate, Aspirin, Nicorandil

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Introduction

Slow coronary blood flow phenomenon (CSFP) is one of the disorders related to coronary arteries, which is accepted as an independent clinical title and is known as syndrome Y, primary and slow coronary flow (PCSF), and slow flow in coronary arteries (SCAF). This phenomenon in its primary type without cause should be differentiated from the secondary types of disorders that are seen during angiography, or coronary angioplasty, or in other coronary artery diseases such as coronary ectasia, coronary spasm, valvular heart diseases, and connective tissue disorders

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↑What is "already known" in this topic:
CSFP does not have an effective and uniform treatment. It produces typic-atypic chest pain and reduces the QOL. Medicines such as Nebivolol, Atorvastatin, Mibefradil, Nitroglycerin and Nicorandil have been reported to be effective in reducing the symptoms of patients.

→What this article adds:
The drug regimen including aspirin, atorvastatin, and nitroglycerin reduces symptoms and improves the QOL, and adding nicorandil to this, despite improving the QOL score in terms of physical activity, does not play a role in improving the of QOL in social and emotional dimensions and in overall.

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(1). CSFP was first proposed by Tambe et al. (1978) as a phenomenon in coronary angiography. This phenomenon is described as a delay in contrast agent passage in the absence of epicardial coronary artery stenosis. Gibson presented a quantitative measure, Corrected TIMI Frame Count, to more describe this phenomenon (2). This criterion is measured and determined by the number of frames required for the contrast material to reach a specific point and provide guidance defined at the end of each coronary vessel.

CSFP can be present in one or all coronary arteries. The prevalence of this phenomenon has been reported in various studies, from a rare finding to a relatively common one, and this difference can be due to the type of definition and evaluation method of the phenomenon (2, 3). Typical and atypical chest pain, chest discomfort, dyspnea on exertion and other chest pain equivalents, disturbance in daily life, and frequent hospitalization of the patient are examples of symptoms and complications of CSFP. Studies showed that CSFP patients are prone to atherosclerosis and coronary artery stenosis (4). Studies examining the impact of CSFP on left and right ventricular function have yielded varying results, but the findings showed that CSFP alone does not have a great effect on cardiac function (5–8). Overall, the evidence showed that CSFP is not absolutely benign, and recommending primary and secondary prevention in these patients seems to be necessary.

Various causes have been described as the basis for the creation of CSFP. For example, the branching angle of the left main coronary artery from the aorta and some anatomical forms that can be the source of disturbance in coronary artery blood flow and destruction of its endothelium can be mentioned (9, 10). The results of histological studies on these patients showed hypertrophy of cardiac muscle fibers, thickening of elastic muscle fibers of small vessels with swelling, disintegration of endothelial cells, and narrowing of vessel lumen. An increase in coronary capillary resistance at rest has also been seen in these patients. Mangeri et al., (1996), in a study, suggested microvascular dysfunction as one of the causes of this disease (11). A meta-analysis of 550 CSFP patients revealed that a higher plasma level of homocysteine was strongly associated with CSFP (12). High plasma levels of homocysteine can cause endothelial dysfunction, generate free radicals, induce oxidative stress, and, finally, endothelial cell damage and dysfunction of microcirculation and CSFP.

In some studies, the diagnosis of CSFP and its relationship with microvascular dysfunction have been questioned. In a study by Utkarsh Dutta et al., in 2023, it was shown that the presence of CSFP is not diagnostic for coronary microvascular dysfunction (lack of response to adenosine) and functional impairment of Endothelial cells (no response to acetylcholine), and it may be necessary to review the guidelines that consider the use of corrected thrombolysis in myocardial infarction frame count (CTFC) greater than 27 is used to diagnose microvascular dysfunction (13).

Currently, there is no standard and accepted treatment for this disease, and standard treatments for stable angina pectoris are often used to control CSFP and reduce patients' symptoms (14). In recent research on the mechanism of creation and treatment of CSFP, the effectiveness of Nebivolol in improving coronary blood flow in angiography and reducing chest pain has been reported. Albayrak and colleagues, in a study, have reported the effect of Nebivolol in improving CSFP symptoms in 90% of patients (15). Hongmen Niu et al. in 2018 reported the effect of atorvastatin in improving angina pectoris and reducing pain, which could be due to the anti-inflammatory effects of Statin (16). Beltrame et al. investigated the effect of Mibefradil, a targeted inhibitor of T-type calcium channels, on CSFP patients. Their study findings indicated that using this drug reduces the frequency and duration of angina in 56% and 78% of CSFP patients, respectively (17). Another drug that was evaluated to reduce the symptoms of CSFP patients is nicorandil. Danesh Sani, in a clinical trial, showed that the use of Nicorandil 70% and Nitroglycerin 30% is effective in reducing chest pain in CSFP patients (18).

CSFP, like other coronary artery diseases, affects the mental and social health and quality of life of the patients by causing numerous symptoms and complications and causing an inability to perform usual life activities (1, 4, 19, 20). It seems necessary to find new treatment methods to enhance these patients' overall well-being and quality of life (21, 22). Nicorandil has dual properties: it acts as a nitrate and an ATP-sensitive potassium channel opener. It functions by dilating and relaxing blood vessels, enhancing circulation, and increasing oxygen delivery to the heart. This helps reduce the frequency and severity of angina attacks. This study was developed with the aim of and implemented in order to explore the effect of a conventional drug regimen of aspirin, statin, nitroglycerin, and nicorandil in reducing symptoms and improving the QOL in CSFP patients.

Methods

Study Design

This study is an open-label, randomized clinical trial with two parallel groups, designed to assess the efficacy of three widely used medications (aspirin, statin, nitrate) and to compare the effect of adding nicorandil to conventional treatment on the quality of life of patients with slow coronary flow.

Inclusion criteria

A patient who was a candidate for coronary angiography based on clinical symptoms, electrocardiographic changes, echocardiography, myocardial perfusion scan or exercise test, and other causes such as arrhythmia or conduction disorders was included in the study.

Exclusion criteria

Any patient with a history of heart failure (CHF), significant coronary artery stenosis, coronary intervention and stenting (PCI and stenting), Coronary artery bypass grafting (CABG), heart attack (MI), and chronic lung disease (COPD).valvular heart disease, connective tissue diseases, atrio-ventricular conduction disorder, patient with anemia (Hemoglobin levels below 11.6 g/dL in women and under

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13 g/dL in men), chronic renal failure (A glomerular filtration rate below 60 mL/min/1.73 m² persisting for at least three months), moderato to sever electrolyte disturbance (serum potassium and sodium level < 3 and < 130 mEq/L, total serum calcium and magnesium concentration < 8.8 and < 1.5 mg/dL respectively), CSFP patients caused by secondary causes, who had the possibility of slow flow in the coronary arteries including coronary artery ectasia, aneurysm, spasm, accidental air embolism during the procedure and congenital anomalies of coronary arteries were excluded from the study by clinical, laboratory, and imaging examinations.

Statistical population and study samples

The statistical population was all those who were referred to the specialized referral center for cardiovascular diseases of BooAliSina Hospital, Qazvin, from 01/05/2023 to 06/30/2023, and were candidates for coronary angiography. Out of a total of 963 angiograms for 67 patients, the phenomenon of slow flow of coronary arteries (Primary Slow Flow Phenomenon) was confirmed. Finally, after a full explanation of the study and completion of the written informed consent form, 52 patients were recruited based on the inclusion/exclusion criteria with convenient sampling and were randomly allocated to each treatment group.

Sample size

The estimated number of participants in each group was calculated to be 21 people, based on a previous study by Beltrame JF et al. (17) and Sani HD et al. (18) With a 5% probability of Type I error and a 20% probability of Type II error, considering a possible 20% loss of participants during follow-up, the sample size for each group was increased to 26 people.

Randomization and masking

Qualified patients were assigned to one of two groups through the random block sampling method, maintaining a 1:1 ratio. Random software allocation version 2 with a fixed size of 4 was used to generate randomized blocks. The main researcher and the patients were unaware of the assigned treatment group, and the drugs prescribed to each patient were prepared by the project partners from the hospital pharmacy and provided to them.

Disease diagnosis method

CSFP was diagnosed using coronary angiography and based on the quantitative evaluation method (Corrected TIMI Frame Count) "CTFC" (Gibson et al., 1996). The criterion of having CSFP was considered based on values greater than two standard deviations from the average CFTC of normal subjects (2). All angiography images were evaluated and reported by two cardiologists with sufficient skill and knowledge and in cases of disagreement, which were, of course, few, the diagnosis of the patient was discussed and finally reviewed in a group with the presence of four cardiologists.

Quality of life measurement method

The McNew questionnaire was utilized to assess the quality of life in the recruited patients. The questionnaire was designed by Ribera et al. in 2006 (23, 24). The McNew 27-inquiry questionnaire measures the quality of life of cardiac patients in three areas: Emotional well-being (14 items), physical health (14 items), and social interactions (13 items). The score of each area is determined based on the average of the scores in the same area, and unanswered questions were not included in the average scores. The maximum score in each area was 7 (highest level of Well-being and overall life satisfaction), and the minimum score was 1 (lowest level of Well-being and life satisfaction). The Persian version of the MacNew questionnaire has been examined in multiple studies, demonstrating comparability to the English version. It exhibits strong internal consistency and reliable reproducibility, making it a suitable quality-of-life assessment tool for population-based research and clinical applications in Iran. Studies have validated the questionnaire's content validity and reliability, and the value of Cronbach's alpha correlation coefficient of the emotional and physical domain is 0.92, the social domain is 0.94, and the overall is reported as 0.95 (25).

Therapeutic intervention

In the first arm, patients were given a three-drug oral regimen (conventional therapy group) including 80 mg aspirin, 20 mg atorvastatin once daily, and 2.6 mg nitroglycerin twice daily (3-drug regimen), and in the second arm, in addition to the above three-drug treatment, nicorandil 10 mg twice daily was prescribed for 2 months. Demographic information, patient history, results of tests and coronary angiography, cooperation and adherence to regular medication, compliance with the prescribed dose, occurrence of any drug side effects, and quality of life outcomes were evaluated both prior to and following the intervention.

Measurable outcome

The main result measured in this research was the improvement of the patient's quality of life measure derived from the quality-of-life index, and the secondary outcome was the symptom relief based on the patient's report.

Statistical methods

Quantitative data results were presented as mean (±SD) and qualitative data as percentage. The Shapiro-Wilk test was used to check the normality of the data. The chi-square test and Fisher's exact test were used to analyze qualitative data. A paired t-test was used to compare the mean within groups, and an independent t-test was used between groups. Analysis of covariance was used to investigate the effect of treatment regarding well-being and control of confounding factors. Age and the number of involved vessels were incorporated into the model as covariates. A significance threshold of less than 0.05 was adopted. Data analysis was performed using SPSS version 16 software.

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Results

Out of a total of 67 CSFP patients, 15 (22.4%), due to various reasons, including non-acceptance and non-cooperation in regular drug use and lack of communication and follow-up, were not eligible to participate in the study and were excluded from the study. 52 Patients were randomly allocated to either of the two treatment groups and finally, 47 patients completed the study according to the protocol (Figure 1).

The average age among the patients in the group receiving conventional treatment was 53.1±11.3 with a range of variation (25-74) and in the conventional treatment + nicorandil group was 53.8±12.2 with a range of variation (22-77), The statistical analysis indicated no notable difference between the average age of the two groups. The frequency distribution of other demographic characteristics is shown in Table 1. The statistical test revealed no significant association with gender distribution, education level, main complaint, and drug abuse between the two study groups. The frequency distribution of the underlying diseases, the clinical characteristics, and the symptoms of the patients are reported in Tables 2 and 3. The statistical test did not show a notable association between the treatment group and these characteristics. The number and frequency distribution of the involved vessels in the patients are reported in Table 4. The analysis did not indicate any significant relationship between the involved vessels and the treatment group.

As shown in Table 5, the average quality of life scores for physical activity, emotional, social, and overall scores in the three-drug group were 3.61± 1.12, 3.35± 0.83, 3.7± 0.7, and 3.54± 0.48 respectively. In the four-drug group, these scores were 3.75± 0.85, 3.29± 0.75, 3.58± 0.65, and 3.55± 0.58, respectively. Statistical tests demonstrated no notable variation in the overall score and the quality-of-life dimensions between the two groups prior to treatment (P>0.57). The average quality of life score in each of the two groups receiving treatment was significantly improved in the physical (P=0.014), emotional (P<0.001), social (P=0.004), and overall scores compared to before the intervention (P<0.001).

The comparison of the quality-of-life score between the two groups showed that the average score of the physical activity dimension of the quality of life in the nicorandil treatment group exceeded the level of the common treatment category, but no statistically notable distinction was identified between the emotional, social dimension and even overall quality of life assessments across both groups (P=0.032).

Within the group receiving combined therapy with nicorandil, none of the drug's side effects, such as headache, nausea, vomiting, fatigue, weakness, dizziness, de-

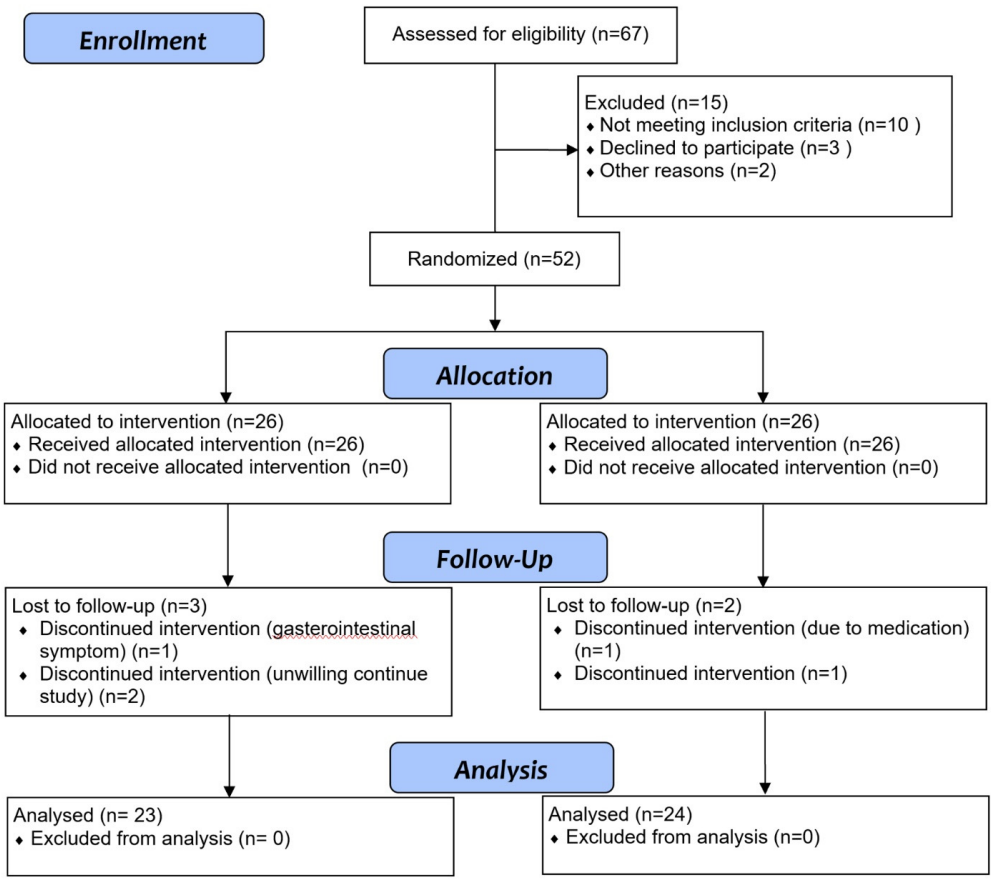

Figure 1. Consort flow diagram of patient enrollment treatment and follow up

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Table 1. Demographic characteristics of subjects for each arm

Variable	Total	3-Drug regimen (n=23)	4-Drug regimen (n=24)	*P*-value
Gender				
Male	25 (53.2%)	11 (47.8%)	14 (58.3%)	0.226
Female	22 (46.8%)	12 (52.2%)	10 (41.7%)	
Education				
Illiterate	7 (14.9%)	4 (17.4%)	3 (12.5%)	0.100
Diploma	26 (55.3%)	13 (56.5%)	13 (54.2%)	
Collegiate	14 (29.8%)	6 (26.1%)	8 (33.3%)	
Chief complaint				
TCP	14 (29.8%)	7 (30.4%)	7 (29.2%)	0.643
ATCP	21 (44.7%)	11 (47.8%)	10 (41.6%)	
DOE	12 (25.5%)	5 (21.7%)	7 (29.2%)	
Addiction				
Nothing	33 (70.2%)	16 (69.6%)	17 (70.8%)	0.226
Cigarette	8 (17.0%)	3 (13.0%)	5 (20.8%)	
Opium	5 (10.6%)	3 (13.0%)	2 (8.4%)	
Alcohol	1 (2.1%)	1 (4.3%)	0(0.0%)	

TCP: Typical chest pain; ATCP: Atypical chest pain; DOE: Dyspnea on exertion

Table 2. Clinical characteristics of subjects for each arm

Comorbidity	3-Drug regimen (n=23)	4-Drug regimen (n=24)	*P*-value
HTN (%)	10 (43.5%)	11 (45.8%)	0.871
DM (%)	8 (34.8%)	7 (29.2%)	0.679
Dyslipidemia (%)	9 (39.1 %)	12 (50.0 %)	0.454
Chest pain	11 (47.8%)	12 (50.0%)	0.882
Familial history for CAD (positive)	2 (8.7%)	5 (20.8%)	0.243
Hs-CRP (above 2 mg/L)	10 (43.5%)	14 (58.3%)	0.308
LVEF (%) at time of admission	47.5±5.2%	48.2±5.7%	0.673
EKG changes (%)	16 (69.6%)	17 (70.8%)	0.924
ST depression	7 (30.4%)	9 (37.5%)	0.609
T wave inversion	5 (21.7%)	4 (16.7%)	0.659
ST depression and T wave inversion	1 (4.4%)	2 (8.3%)	0.576
LBBB and RBBB	3 (13.0%)	2 (8.3%)	0.601
LVEF (%) in follow up period	46.4±4.8%	46.6±4.7%	0.881

Table 3. Symptoms in patients with CSFP for each arm

Comorbidities	3-Drug regimen (n=23)	4-Drug regimen (n=24)	*P*-value
Unstable angina (%)	6 (26.1%)	6 (%25.0)	0.932
Typical chest pain (%)	3 (13.0%)	5 (20.8%)	0.478
Atypical chest pain (%)	3 (13.0%)	2 (8.3%)	0.600
Dyspnea on exertion (%)	2 (8.7%)	3 (12.5%)	0.672

Table 4. Frequency distribution of the number of vessels involved

Variable	Number	Coronary artery anomaly	3-Drug regimen (n=23)	4-Drug regimen (n=24)	*P*-value
Number of vessels involved	1	LAD	4 (17.4%)	5 (20.8%)	0.764
		LCX	2 (8.7%)	3 (12.5%)	0.675
		RCA	2 (8.7%)	4 (16.7%)	0.412
	2	LAD + RCA	2 (8.7%)	1 (4.2%)	0.529
		LAD + LCX	3 (13.0%)	1 (4.2%)	0.276
		LCX + RCA	2 (8.7%)	0 (0.00%)	0.139
	3	LAD+LCX+ RCA	8 (34.8%)	10 (41.7%)	0.624

crease in blood pressure, muscle pain, or increased heart rate, were reported.

Discussion

Although there is no standard and specific medicine for CSFP, several different interventions have been tested, and encouraging results have been generated. Alvarez and colleagues (2018) in a study showed that intracoronary injection of nifedipine eliminates the angiographic findings of CSFP patients, and the use of this calcium blocker is effective in reducing and improving the patient's symptoms (26). Beltrame et al.'s study showed that the administration of Mibefradil causes a relative improvement in angiographic and clinical parameters of CSFP patients (27). Kurtoglu and colleagues showed in their study that dipyridamole, which has a vasodilatory effect on small coronary arteries, can be used for CSFP patients (28). El-Bayrak and colleagues, by investigating the effect of Nebivolol, Revealed that utilizing beta-blockers diminishes chest pain in CSFP patients by improving the endothelial function of blood vessels (15). Cakmak and colleagues showed that the daily administration of 40 mg of simvastatin after 6 months improved myocardial perfusion disor-

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Table 5. Mean scores of qualities of life and its dimensions before and after the intervention

Variable	Before	After	*P*-value (Within group)
Physical Activity			
3-drug regimen	3.61 ± 1.12	4.35 ± 1.11	< 0.001
3-drug regimen+ Nicorandil	3.75 ± 0.85	5.17 ± 1.09	< 0.001
P-value (Between group)	0.627	0.014	
Emotional			
3-drug regimen	3.35 ± 0.83	4.39 ± 1.03	< 0.001
3-drug regimen+ Nicorandil	3.29 ± 0.75	4.67 ± 0.96	< 0.001
P-value (Between group)	0.809	0.349	
Social			
3-drug regimen	3.70 ± 0.70	4.30 ± 0.93	0.004
3-drug regimen+ Nicorandil	3.58 ± 0.65	4.38 ± 0.88	< 0.001
P-value (Between group)	0.573	0.789	
Global score			
3-drug regimen	3.54 ± 0.48	4.35 ± 0.62	< 0.001
3-drug regimen+ Nicorandil	3.55 ± 0.58	4.74 ± 0.80	< 0.001
P-value (Between group)	0.954	0.072	

der (29). Although the outcomes measured in the present study are different from the KAC-Mak study, The results of this research demonstrated that the statins prescription in the treatment regimen improves the overall life satisfaction of patients.

Within a comparative study, Ozdogru and colleagues showed that intracoronary injection of two drugs, nitroglycerin and diltiazem, improves coronary blood flow speed in CSFP patients, and diltiazem is preferable to nitroglycerin (30). The findings of this research further demonstrated that nitrate reduced CSFP complications, which is consistent with the results of our study in terms of reducing complications and improving quality of life.

Chen and colleagues also reported an improvement in chest pain with using nicorandil. The difference between Chen's study and the present study was among the parameters for patient inclusion and exclusion in the study. In Chen's study, patients with heart failure were included, but heart failure was one of the exclusion criteria in our study (31). In a study, Martsevich and colleagues (2017) investigated the role of nicorandil in promoting wellness in patients with stable angina using the Seattle questionnaire. Their study showed that the use of nicorandil improves all aspects of Patients' overall well-being (32). The findings from the Sani et al. study also confirmed the effect of nicorandil on reducing chest pain in CSFP patients (18). In the present study, the quality of life was examined in three physical, emotional, and social dimensions. This study provided evidence that both such a three-drug regimen and the four-drug regimen (three drugs + nicorandil) significantly optimize patient well-being in CSFP across three key areas. Also, the use of nicorandil along with the three-drug regime significantly improves the quality of life in the physical dimension (chest pain, shortness of breath, fatigue, endurance of exercise, and daily physical activities). It is suggested to conduct a study with a longer follow-up period on patients and to study the implications of other drugs in individuals diagnosed with delayed coronary blood flow. The duration for which the patient has been suffering from the symptoms should also be taken into consideration.

A deeper exploration of why nicorandil selectively improves the physical dimension of QOL and does not affect emotional or social domains, as well as a longer-duration, multicenter study design and double-blind study, would provide a better context for the findings.

Conclusion

A three-drug regimen including aspirin, atorvastatin, and nitrates successfully enhances the well-being of CSFP patients, but the addition of nicorandil, although somewhat effective in improving the physical dimension of their quality of life, does not clearly improve all its dimensions.

Authors' Contributions

Design and study team: Hamid Reza Javadi, Behrouz Bokani, Majid Haji Karimi, Amir Javadi, Zohreh Yazdi. Conceptualization: Hamid Reza Javadi, Behrouz Bokani, Majid Haji Karimi. Formal analysis: Amir Javadi, Zohra Yazdi. Writing, review & editing: Hamid Reza Javadi, Behrouz Bokani, Amir Javadi, Majid Haji Karimi, Zohra Yazdi.

Ethical Considerations

The study's research plan received approval from the medical ethics committee of Qazvin University of Medical Sciences (IR.QUMS.REC.1396.235) and registered in the clinical trial system (IRCT20221228056964N1).

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Conflict of Interests

The authors declare that they have no competing interests.

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