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Sildenafil's effectiveness in the primary coronary slow flow phenomenon: a pilot randomised controlled clinical trial

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ABSTRACT

Background On the one hand, the primary coronary slow flow phenomenon (CSFP) can cause recurrence of chest pain, prompting medical examinations and further healthcare costs, while on the other hand, it can lead to myocardial infarction, ventricular arrhythmia and sudden cardiac death. Nevertheless, there is not any agreement on the optimal treatment for primary CSFP, so we decided to examine the effectiveness of sildenafil in this context.

Methods This pilot study is a 12-week, triple-blind, randomised, placebo-controlled trial for receiving either 50 mg daily oral sildenafil or placebo. Twenty eligible patients aged 30–70 years from a tertiary hospital in Yazd were randomly allocated in a 1:1 ratio to two groups. The primary outcomes were the alterations in functional capacity (metabolic equivalents, METs), Duke treadmill score (DTS) and angina severity (Canadian Cardiovascular Society (CCS) class). The study protocol registration code is IRCT20220223054103N1.

Results The angina severity in the Sildenafil group improved, with all receivers achieving a state of being asymptomatic during regular physical activity (CCS I). Whereas just 40% of the recipients in the placebo group achieved the same level of improvement (p=0.011). Mean METs at baseline were 9.9 (SD: 3.1) and at week 12 were 13.1 (SD: 3.3) for sildenafil and 9.56 (SD: 2.1) and 9.63 (SD: 2.4) for placebo (difference favouring sildenafil with a median increase of 3.1 (IQR: 1.1 to 4.1, p=0.008)). Median DTS scores at baseline were 3 (IQR: 0 to 9) and at week 12 were 9.5 (IQR: 7.75 to 15) for sildenafil and 7 (IQR: −1.5 to 9.25) and 8 (IQR: 1.5 to 11.25) for placebo (difference favouring sildenafil with a median increase of 5.5 (IQR: 1 to 9.2, p=0.01)).

Conclusions We suggest that a daily low dose of sildenafil could be a valuable therapeutic option for primary CSFP.

Trial registration number IRCT20220223054103N1.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Primary coronary slow flow phenomenon (CSFP) may lead to severe cardiovascular complications and substantial healthcare expenses, but there is currently no optimum therapeutic option available.

WHAT THIS STUDY ADDS

⇒ We discovered that sildenafil might be an effective treatment for primary CSFP.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

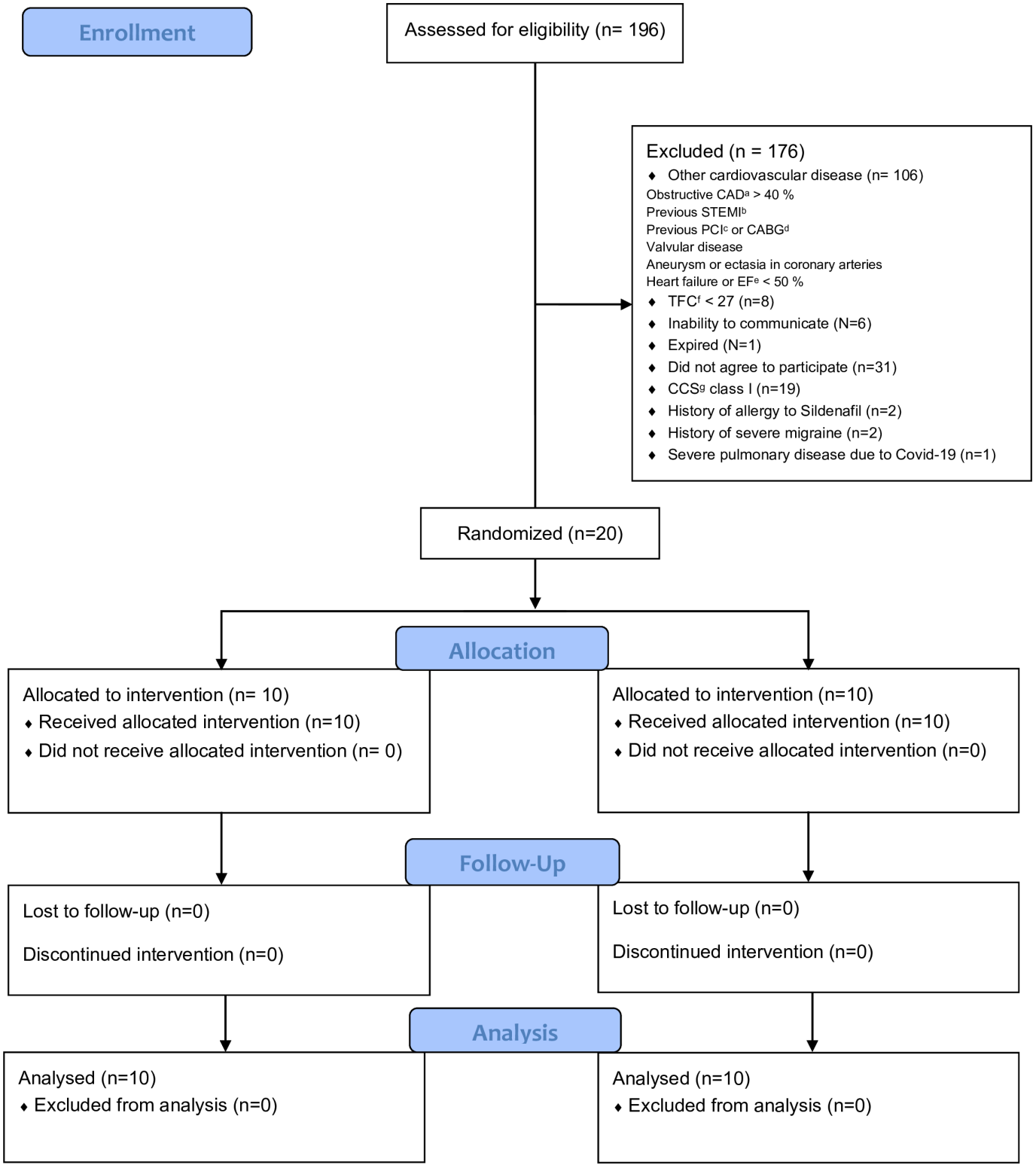
⇒ Sildenafil may have a potential for reducing unnecessary medical referrals and preventing complications in primary CSFP; however, it requires further research.

INTRODUCTION

As the name implies, the coronary slow flow phenomenon (CSFP) consists of delayed distal vessel opacification in the absence of significant epicardial coronary stenosis during an angiographic examination.[1] Studies have reported different incidence rates between 1% and 7%[2]; however, despite its low incidence, it can be associated with recurrent chest pain and referring to medical centres, which can interfere with the quality of life or even lead to myocardial infarction,[3] ventricular arrhythmia[1 4–8] and sudden cardiac death.[2 4] As a result, proper treatment of this problem can lead to an improvement in quality of life, a decrease in unnecessary medical evaluations and healthcare costs, and a decrease in serious cardiovascular issues.

Several types of medication have been used as treatments for this problem, including calcium channel blockers (diltiazem,[9 10] nicardipine[11] and mibefradil[12]), beta-blockers (nebivolol[13 14]), statins[15 16] and vasodilators (nitroglycerin,[10] isosorbide dinitrate[17] and nicorandil[18]). However, there has not been any consensus regarding the optimal choice of treatment.

Knowing the pathophysiology of the problem and the drug's pharmacodynamics is essential for selecting the optimal treatment. The development of primary CSFP is influenced by endothelial dysfunction, which is caused by changes in vascular tone through a decrease in nitric oxide levels.[19] Another



a Coronary Artery Disease
b ST Elevation Myocardial Infarction
c Percutaneous Coronary Intervention
d Coronary Artery Bypass Graft
e Ejection Fraction
f TIMI Frame Count
g Canadian Cardiovascular Society

Figure 1 Enrolment, randomisation, allocation and follow-up.

Table 1 Baseline characteristics of the patients who underwent randomisation

Characteristics	Sildenafil (N=10)	Placebo (N=10)	P value
Age (mean±SD)	49.2±10.8	48.4±8.4	0.68
Body mass index (kg/m^2) (mean±SD)	27.6±5.3	26.7±3.3	0.91
Sex			
Male (N (%))	7 (53.8)	6 (46.2)	>0.99
Female (N (%))	3 (42.9)	4 (57.1)	
Initial manifestation before diagnosing CSFP			
Acute coronary syndrome (N (%))	5 (50.0)	8 (80.0)	0.35
Chronic stable angina (N (%))	5 (50.0)	2 (20.0)	
Canadian cardiovascular society angina class			
II (N (%))	4 (40.0)	6 (60)	0.84
III (N (%))	4 (40.0)	2 (20.0)	
IV (N (%))	2 (20.0)	2 (20.0)	
Risk factors			
Hypertension (N (%))	3 (30)	0	0.21
Diabetes (N (%))	2 (20)	0	0.47
Hypercholesterolaemia (N (%))	3 (30)	3 (30)	>0.99
Smoking (N (%))	2 (20)	4 (40)	0.62
Family history of coronary artery disease (N (%))	4 (40)	7 (70)	0.37
Drug history			
Nitroglycerine (N (%))	4 (40)	2 (20)	0.62
Aspirin (N (%))	9 (90)	8 (80)	>0.99
Statin (N (%))	9 (90)	6 (60)	0.30
ACEI or ARB (N (%))	3 (30)	0 (0)	0.21
Calcium channel blockers (N (%))	1 (10)	2 (20)	>0.99
Beta-blockers (N (%))	7 (70)	4 (40)	0.37
Blood pressure (mm Hg)			
Systolic (mean±SD)	123±14.8	127.6±12.4	0.68
Diastolic (mean±SD)	74.9±12.1	76.9±8.3	0.48
ECG			
Sinus rhythm (N (%))	10 (100)	10 (100)	>0.99
Rate (beats per minutes) (mean±SD)	92.9±16.4	82.0±18.5	0.01
ST depression (N (%))	4 (40)	3 (30)	>0.99
Abnormal T wave (N (%))	3 (30)	6 (60)	0.37
PR interval (mean±SD) (ms)	136±20.6	142±19.8	0.58
QTc interval (mean±SD) (ms)	410.8±30.7	426.2±42.5	0.53
Exercise tolerance test			
Positive test (N (%))	3 (30)	3 (30)	>0.99
Duke score (median (IQR))	3.0 (0.0–9.0)	7 (-1.5–9.25)	0.97
METs (mean±SD)	9.92±3.1	9.5±2.1	>0.99
1 min heart rate recovery (mean±SD)	16±8.4	25±8.3	0.03
Maximum heart rate (mean±SD)	149.8±17.8	140.7±12.1	0.35
Echocardiography			
Left ventricular ejection fraction (mean±SD)	53.5±3.37	54±3.1	0.74
Angiography			
Corrected TIMI frame count of LAD (mean±SD)	56.2±20.7	42.7±7.93	0.25
TIMI frame count of LCX (Mean±SD)	54±14.9	46.6±10.8	0.31
TIMI frame count of RCX (Mean±SD)	54±12	49±19.4	0.34

ARB, angiotensin receptor blocker; CSFP, coronary slow flow phenomenon; LAD, left anterior descending; LCX, left circumflex; METs, metabolic equivalents; RCX, right circumflex; TIMI, Thrombolysis in Myocardial Infarction.

theory regarding primary CSFP suggests that it is associated with heightened inflammatory markers and oxidative stress, which might result in compromised blood flow and the manifestation of angina symptoms in the absence of any stenosis.[20] Sildenafil inhibits the activity of phosphodiesterase 5 (PDE-5) in smooth muscle cells, resulting in reduced breakdown of cyclic guanosine monophosphate (c-GMP). This, in turn, leads to an increase in nitric oxide's smooth muscle relaxation.[21] In addition, it can exhibit antioxidant and anti-inflammatory activities.[22]

Based on the above-mentioned pathophysiology of primary CSFP and the pharmacodynamics of sildenafil, we hypothesised that sildenafil may improve primary CSFP. To test this, we designed a triple-blind randomised controlled clinical trial with parallel groups at a single centre to investigate the impact of sildenafil on clinical symptoms and exercise tolerance test (ETT) parameters like functional capacity (metabolic equivalents, METs) and Duke treadmill score (DTS) in individuals with primary CSFP.

METHODS

This study employed a triple-blind randomised controlled clinical trial with a parallel-group design at a single centre to investigate the impact of sildenafil on clinical symptoms and ETT parameters in individuals with primary CSFP. Twenty patients were randomly assigned in a 1:1 ratio to receive either a daily dose of sildenafil at 50 mg or a placebo. The dosage was selected in consultation with a clinical pharmacologist, considering the available dosage forms in Iran and aiming for a low to medium dose with the least possible adverse effects for this pilot experiment.[23] The study protocol was registered and approved

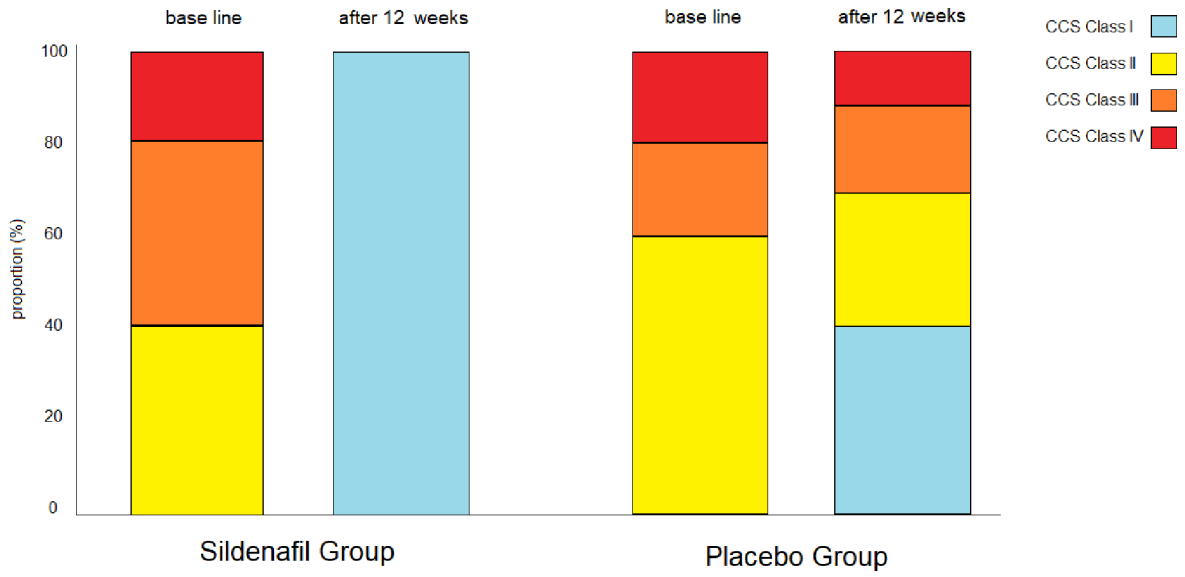


Figure 2 Comparison of CCS class in sildenafil group with placebo group before and 12 weeks after treatment. CCS, Canadian Cardiovascular Society.

at the Iranian Registry of Clinical Trials (IRCT) with the approval number IRCT20220223054103N1. The link to access it in IRCT is https://www.irct.ir/trial/62181

Inclusion

In order to identify eligible patients, the Yazd Cardiovascular Disease Registry (YCDR) system and Medical Heart Record (MeHR) system reviewed all coronary angiography reports from April 2021 to September 2022 at Yazd Afshar Hospital. In order to qualify, patients were required to have a confirmed diagnosis of primary CSFP through coronary angiography and exhibit typical angina pectoris with a Canadian Cardiovascular Society (CCS)[24] classes II–IV.

The diagnosis of CSFP was based on the calculation of the Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) in each of the three territories of the coronary arteries according to Gibson's standard criteria.[25] Right coronary arteries (RCAs) were marked by the first branch of the posterolateral branch artery. The point of division at the apex indicated the territory of the left anterior descending arteries (LAD). Left circumflex arteries (LCXs) were demarcated by the longest obtuse marginal artery (OM). In the case of nondominant RCA, the last branch leaving the atrioventricular groove was considered, whereas in the case of dominant LCX, the last OM branch before the posterior descending branches was considered. For the LAD artery, by dividing the TFC by 1.7, the Corrected TFC (CTFC) was calculated, and CTFCs greater than 27 in any territory were thought to be suggestive of CSFP.[26]

Exclusion criteria

Contraindication to sildenafil or use of drugs that interact with sildenafil, history of myocardial infarction or percutaneous coronary intervention or coronary artery bypass graft, valve surgery, obstructive coronary artery disease (CAD) (stenosis above 40%), age younger than 30 years or older than 70 years, uninterpretable coronary angiography, uncontrolled hypertension, migraine headache, coronary aneurysm or ectasia or any diagnosed reasons of secondary CSFP, no-reflow, spasm or dissection, heart failure, valvular disease, or left ventricular ejection fraction less than 50%.

Sample size

We employed the subsequent formula to determine the sample size, taking into account the assessment of functional capacity as our major outcome, which has been identified as the most significant index in predicting mortality, both in individuals with cardiovascular disease and those without it.[27]

$$n = \frac{2(\sigma^2)(z_{\alpha/2}+z_{\beta})^2}{\Delta^2} = \frac{2(3.5^2)(1.96+0.84)^2}{2.3^2} = 36.31 \approx 36$$

$\sigma = Standard\ \ deviation$

$\Delta = Effect\ \ Size$

$Z_{\alpha/2} = Z - score\ for\ siginifact\ level\ of\ 0.05\ \ which\ \ is\ 1.96$

$Z_{\beta} = Z - score\ for\ desired\ power\ of\ 80\%\ \ which\ \ is\ 0.84$

z_{α}>:mi>t:mi>h>

Based on the study of Myers *et al*,[27] we used an SD of 3.5 and an effect size of 2.3, resulting in a sample size of 36. Out of all coronary angiography reports between April 2021 and September 2022, only 196 reports were diagnosed with CSFP, and only 20 individuals met the study's inclusion and exclusion criteria and were included in the final evaluation. Therefore, the study was redesigned as a pilot trial involving 20 individuals. We reassessed the study's power by applying the following formulas:

Table 2 The investigated indices before and after treatment in sildenafil and placebo groups

Parameters	Sildenafil	Placebo
1 min heart rate recovery		
Baseline (mean±SD)	16±8.4	25.1±8.3
After three months (mean±SD)	19.2±9.9	22.8±9.8
Change (median (IQR))	−0.5 (−4.5 to 8.2)	−1 (−5.2 to 0.2)
P value	0.84	0.2
Maximum heart rate		
Baseline (mean±SD)	149±17.8	140.7±12.1
After 3 months (mean±SD)	161±11.2	140.1±10.7
Change (median (IQR))	8.5 (0.7 to 26.2)	1 (−11.0 to 8.0)
P value	0.046	0.95
Resting systolic blood pressure		
Baseline (mean±SD)	123.9±14.8	127.6±12.5
After 3 months (mean±SD)	111±10.8	117.6±15
Change (median (IQR))	−14.5 (−20.7 to −4.5)	−6.5 (−23.7 to 2.5)
P value	0.005	0.083
Resting diastolic blood pressure		
Baseline (mean±SD)	74.9±12.1	76.9±8.3
After 3 months (mean±SD)	70.6±7.1	78.9±7.1
Change (median (IQR))	−4.0 (−10.5 to 3.0)	0 (−2.5 to 7.5)
P value	0.11	0.50
Corrected QT interval (ms)		
Baseline (mean±SD)	410.8±30.7	426.2±42.5
After 3 months (mean±SD)	389.8±38.3	429.2±34.7
Change (median (IQR))	−120 (−295 to 25)	75 (−62.5 to 175)
P value	0.058	0.44
Functional capacity (METs)		
Baseline (mean±SD)	9.9±3.1	9.56±2.1
After 3 months (mean±SD)	13.1±3.3	9.63±2.4
Change (median (IQR))	3.1 (1.1 to 4.1)	−0.5 (−1.9 to 2.4)
P value	0.008	0.94
Duke score		
Baseline (median (IQR))	3.0 (0.0 to 9.0)	7 (−1.5 to 9.25)
After 3 months (median (IQR))	9.5 (7.75 to 15)	8 (1.5 to 11.25)
Change (median (IQR))	5.5 (1.0 to 9.2)	−0.5 (−2.0 to 4.2)
P value	0.01	0.95

METs, metabolic equivalents.

The Z− table indicated that the cumulative probability of -0.491 *is approximately* 0.3121

$$Power = 1 - \beta = 1 - 0.3121 = 0.6879 \rightarrow \approx 68.8\%$$

Randomisation

We used a four-block randomisation method and sealed envelope web software (https://www.sealedenvelope.com[28]) to randomly assign patients to treatment and placebo groups. To conceal the group allocation, the letters A and B were shown, and each letter was randomly assigned to either the treatment or placebo group. The number of 5 makeups of the A|B treatment group was randomised in a block of four using sealed envelope web software. The assigned treatment was written on separate papers and placed in envelopes numbered 1–20, which were sealed. These procedures were performed by an identified individual, and none of the other researchers were involved.

Allocation concealment

A trained nurse allocated the treatment to the patients immediately after the doctor's visit. The nurse opened an envelope for each patient and administered the corresponding treatment from the medications named A or B. Both sildenafil and placebo drugs were blue-round pills that were packed in coded containers to hide the identity of the prescribed drug. Finally, patients were randomly assigned in a 1:1 ratio to receive either 50 mg of sildenafil (Rouz Darou, Tehran, Iran) or a placebo once daily. It is important to note that there were no changes to the patient's previous medications, and only drugs containing nitroglycerin compounds were discontinued.

Assessment, treatment and follow-up

Prior to providing treatment, patients had a comprehensive baseline assessment that included interviews, physical examinations, ECGs, echocardiography and ETT. The clinical interview and physical examination involved recording demographic information, symptoms, primary clinical presentation, medical history of CAD risk factors, medications, body mass index, classifying chest pain according to CCS,[24] reviewing the patient's medical records, and measuring blood pressure with a sphygmomanometer (Omron, Osaka, Japan). Exercise tests were conducted on all patients using treadmills (Track Master, Kansas, USA) and the Bruce protocol[29] until symptoms became limiting. The exercise test parameters, including functional capacity measured as METs,[30] DTS,[31] maximum heart rate (HR) and HR recovery, were extracted and recorded.

$$DTS = Exercise\ Time - (5 \times ST\ Deviation) - (4 \times Excercise\ Angina)$$

Excercise Angina: None = 0 | Not Limiting = 1 | Excercise Limiting = 2

A 12-week monitoring period was conducted with monthly visits to assess medication adherence, side effects, symptoms and CCS class. A telephone number allowed patients to contact a cardiology specialist 24 hours a day, and they could report any complications or new symptoms. In addition to the cardiologist, an expert nurse was accountable for providing follow-up care and providing 30 pills per month during their next visit. Additionally, she kept a manual record of how patients took medicine,

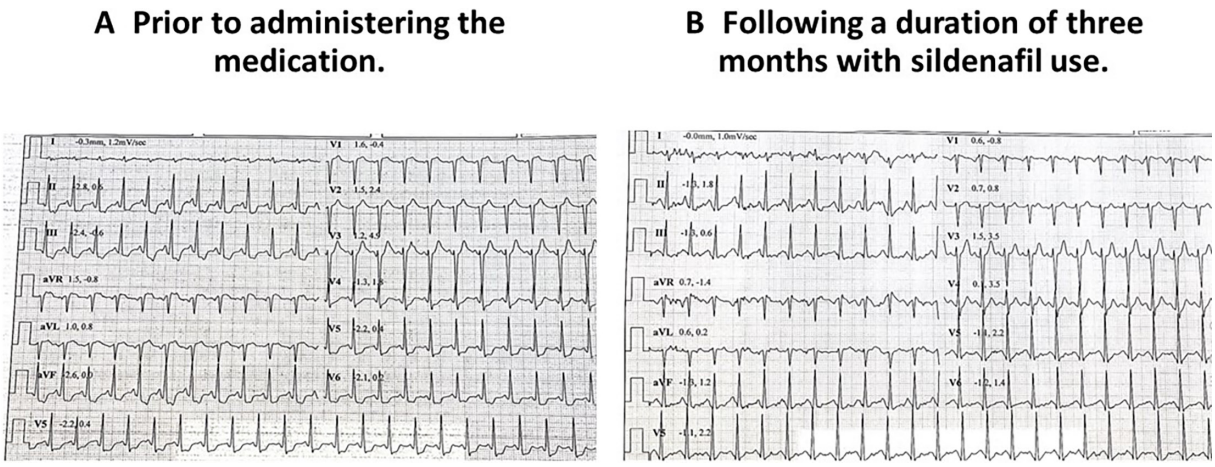


Figure 3 ECG recordings of a male participant who had coronary slow flow phenomenon and was enrolled in the sildenafil group.

how many pills they took, the side effects and their adherence. After 3 months of follow-up, all patients underwent another exercise test, and their parameters were recorded.

Outcome measurement

Patient outcomes were assessed by a cardiologist who was unaware of treatment allocations. The primary endpoints were changes in DTS, attained METs, improvement in clinical manifestations and CCS class from baseline to week 12. Major adverse cardiovascular events, arrhythmia and rehospitalisation due to acute coronary syndrome were the secondary objectives.

Statistical analysis

The data were analysed by using SPSS V.20 software (IBM, Chicago, USA). Quantitative data were expressed as mean and SD while categorical data were expressed as frequency and percentage. Given the restricted size of the sample, we employed non-parametric tests, which are more reliable when dealing with small samples. Mann-Whitney U test was employed to compare quantitative factors at baseline between the intervention and placebo groups, whereas the Wilcoxon signed-rank test was used to compare quantitative variables across each group during the intervention. The difference in the quantitative variables across groups during the intervention was reported using the median and IQR. χ^2 test was used to analyse categorical data.

RESULTS

Patient characteristic

From April 2021 to September 2022, a total of 196 patients were diagnosed with CSFP through angiography. Based on the inclusion and exclusion criteria, 20 eligible patients were randomly assigned to two groups in a 1:1 ratio to receive Sildenafil or a placebo. All patients were followed up for 12 weeks (figure 1). The basic characteristics of the two groups are shown in table 1. With the exception of HRs in the ECGs and 1 min HRs recovery in the ETT, there were no notable disparities between the intervention and placebo groups at the beginning of the study. The average age of the patients was 49 years, with 65% being male.

Changes in severity of angina and blood pressure

After 12 weeks of treatment, all receivers of sildenafil achieved a state of being asymptomatic during regular physical activity (CCS I). Whereas just 40% of the recipients in the placebo group achieved the same level of improvement (p=0.011) (figure 2).

Furthermore, the administration of sildenafil led to a decrease in systolic blood pressure, with a median drop of −14.5 (IQR: −20.7 to −4.5, p=0.005). However, this reduction was not statistically significant in the placebo treatment (table 2).

Changes in ECG and ETT parameters

After 12 weeks, the sildenafil group exhibited a median DTS improvement of +5.5, with an IQR of +1.0 to +9.2 and p value of 0.005. In contrast, the median change of DTS in the placebo group was −0.5, with a range between −2.0 and +4.2, and a p value of 0.95. Concurrently with these improvements, the sildenafil group experienced an improvement in functional capacity (median: +3.1, IQR: +1.1 to +4.1, p=0.008) and maximum HR during exercise testing (median: +8.5, IQR: +0.7 to +26.2, p=0.046). In contrast, the placebo group lacked any noticeable rise in these measures (table 2).

Our findings indicate that sildenafil led to a reduction in the QT interval when compared with the placebo group ((median: −120, IQR: −295 to +25) vs (median: 75, IQR: −62.5 to +175)). However, it is important to note that this reduction in the sildenafil group did not reach statistical significance (p=0.058 vs p=0.44) (table 2).

Figure 3 demonstrates the resolution of ST depression in a male participant from the sildenafil group during the third stage of exercise testing after 3 months of using sildenafil.

Adverse events

Both groups adhered to their drug regimens completely. No cardiovascular death, arrhythmia or myocardial infarction occurred during follow-up. Within the placebo group, a single patient was readmitted to the hospital due to acute chest discomfort, but no patients in the sildenafil group required readmission. Tolerable headaches were experienced by one patient in the sildenafil group after taking sildenafil for half an hour, but they completely cleared up after 2 weeks. Another patient who took sildenafil had transient episodes of facial flushing lasting 10 min, which resolved spontaneously without requiring any intervention.

DISCUSSION

The current study is the first known investigation of the effects of PDE-5 inhibitors on primary CSFP. Our findings indicate that sildenafil has several benefits in primary CSFP, including symptom improvement, blood pressure reduction and enhanced exercise test parameters like DTS, functional capacity and maximum HR. Furthermore, our investigation found no notable adverse effects of the intervention, indicating that sildenafil's advantages may outweigh its potential hazards in CSFP.

Mechanism

Several theories have been proposed to elucidate the pathophysiology of primary CSFP. The first theory focuses on endothelial dysfunction and increased vasomotor tone, particularly in the microvasculature, which can lead to impaired blood flow.[2] By inhibiting PDE-5, sildenafil effectively impedes the breakdown of cGMP, thereby augmenting smooth muscle relaxation in response to nitric oxide. Nitric oxide plays a pivotal role in influencing vascular tone[19] and serves as an indicator of endothelial dysfunction.[32] Notably, Denardo *et al* have presented compelling evidence supporting the potential of PDE-5 inhibitors to ameliorate microvascular coronary dysfunction.[33] Another hypothesised theory for impairing blood flow in primary CSFP involves platelet dysfunction and inflammation.[2] A study by Semen *et al* has demonstrated that sildenafil contributes to a reduction in oxidative stress and modulation of fatty acid composition, implying anti-inflammatory effects.[22] Furthermore, Yang *et al* demonstrated that sildenafil effectively inhibits neointimal formation and platelet aggregation through cGMP-dependent protein kinase.[34] Collectively, these findings strongly suggest that sildenafil holds promise in addressing all facets of the hypotheses posited for CSFP.

Exercise tolerance test

The current pilot study indicates that sildenafil has the capacity to positively affect performance metrics of ETT. In a longitudinal research conducted by Myers *et al*, it was shown that individuals without cardiovascular problems who died had a lower maximal HR compared with those who lived, following a follow-up period of 6.2±3.7 years.[27] Moreover, after adjusting for age, functional capacity emerged as the most influential factor in predicting mortality, both among those without cardiovascular disease and those with the condition.[27] Furthermore, in a comprehensive study involving 6619 patients from 2 distinct cohorts, Salokari *et al* identified the DTS as an indicator strongly linked to cardiovascular mortality among individuals subjected to exercise testing.[35] Notably, the authors assert the superiority of functional capacity as a predictor in this context.[35] Therefore, sildenafil could play a promising role in reducing the risk of cardiovascular mortality in CSFP.

Blood pressure

Previous studies have provided data indicating that hypertension could serve as an independent risk factor for primary CSFP.[20 36] The present investigation found that sildenafil reduced systolic blood pressure by the median of −14.5 (−20.7 to −4.5) mm Hg. A decrease in blood pressure leads to a decrease in cardiac afterload, reducing the workload on myocytes and perhaps resulting in a decrease in the onset of symptoms. The finding that all individuals in the sildenafil group achieved a CCS class of I provides evidence in favour of this theory. In addition, a dose-response meta-analysis revealed that every 10 mm Hg rise in blood pressure is associated with a 5% increase in cardiovascular events and a 2% increase in all-cause mortality.[37] This indicates that the reduction in blood pressure achieved through the use of sildenafil in this study was not only statistically significant but also clinically significant.

QT interval

Previous studies found that primary CSFP patients have a longer QT interval, which is a sign of an increased risk for ventricular arrhythmias and cardiovascular mortality.[5 7] Sildenafil has the potential to modulate the tone of cardiac autonomic nerves, improving the dispersion of ventricular repolarisation and reducing the risk of cardiac arrhythmias.[5] However, the decrease in QT interval in the current study was at the marginal threshold of non-significance (p=0.058); this could be attributed to the small sample size in our investigation.

Recommendation for future research

The present study represents the first investigation of the efficacy of sildenafil in primary CSFP. We suggest that future research should assess the effectiveness of this medication in a larger sample size and over a longer duration to obtain more reliable results and examine long-term adherence to the treatment. Furthermore, conducting a comparison between this medicine and other alternatives such as calcium channel blockers, beta-blockers, ACEI and vasodilators will aid in determining the most advantageous treatment option.

Strength and limitation

It is important to acknowledge the following strengths of the present study: The use of precise randomisation

and allocation concealment methods, combined with the implementation of triple blinding, effectively minimises the potential for bias. In addition, we performed a comprehensive evaluation of the impact of sildenafil on CSFP by evaluating both exercise test parameters and the symptoms exhibited by patients.

This study has several limitations. The small number of participants reduces the statistical power and also limits the ability to find potential adverse cardiac events and side effects of sildenafil. The follow-up did not include coronary angiography; therefore, it is unclear whether the clinical effects and improvement in ischaemia observed with sildenafil are only due to improved coronary blood flow. Moreover, we were unable to compare sildenafil with other drugs that have been used in the past for CSFP treatment.

Conclusion

Current study findings suggest that a daily low dose of sildenafil could be a valuable therapeutic option for patients with the primary CSFP by reducing chest pain, improving functional capacity and enhancing the DTS without any significant side effects.

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Contributors AA, SS and AE were involved in the conception, design and conduct of the study and SMN analysed the data. AE, SRM and EA were involved in interpretation of the results and writing the first draft of the manuscript. All authors edited, reviewed and approved the final version of the manuscript. AE is the corresponding author and guarantor of this work and, as such, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The trial has been approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, with the ethical approval number being SSU.REC.1401.002 and conducted based on the Declaration of Helsinki on medical research. In addition, all participants in the trial obtained written informed consent prior to their involvement.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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