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Administration of sildenafil citrate not able to reduced hs-CRP on erectile dysfunction patient at Doctor Soetomo Hospital, Surabaya, Indonesia

I Gusti Ngurah Pramesemara[1,2*], Rossy Sintya Marthasari[1,2], Rezia Octarina[1,2], Ahmad Ricardo Syukur Silalahi[1,2], Judie Hartono[1,2], Tjahjo Djojo Tanojo[1,2]

ABSTRACT

Background: Phosphodiesterase type-5 (PDE5) inhibitors was the first choice for the oral treatment of erectile dysfunction because of its ability to prevent endothelial dysfunction and restored erectile function properly. However, the inflammatory parameter such as hs-CRP can be used to assess the performance of PDE5 inhibitors as well as clinical questionnaires, IIEF-5, and EHS. So that, this study aims to determine the effect of PDE5 inhibitors administration such as sildenafil citrate 50 mg per day can decrease the value of hs-CRP, as well as increased the IIEF-5 and EHS at Dr. Soetomo General Hospital.

Methods: A true clinical experimental studies used pretest and posttest control group design were carried out among 20 patients during 4 weeks. In the next 2 weeks, the crossover was conducted among respondents for the washout period whereas divided into 2 groups, control (K1 and K2) and treatment (P1 and P2). Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 16.0 software for Windows.

Results: The average age of group K1 and P2 was 51 ± 12.07 years old whereas 48.60 ± 15.40 years old in group P1 and K2. The research was conducted in Andrology Clinic of Doctor Soetomo Hospital in Surabaya during June to November 2017. The research data were not normally distributed, then analyzed by two-tail T-group tests and Wilcoxon test at significance level α=0.05. The results showed that PDE5 inhibitors did not decrease the hs-CRP significantly ($p>0.05$), but increased EHS ($p<0.05$) and increased IIEF-5 ($p<0.05$) significantly.

Conclusion: This study concluded that the administration of sildenafil citrate per day by oral increased the EHS and IIEF-5, but not able to reduced hs-CRP in patients with erectile dysfunction significantly.

Keywords: erectile dysfunction, PDE5 inhibitor, sildenafil citrate, hs-CRP, IIEF-5, EHS

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[1]Andrology Department, Doctor Soetomo General Hospital, Surabaya, Indonesia
[2]Biomedicine Department, Medical Faculty of Airlangga University, Surabaya, Indonesia

*Corresponding to:
I Gusti Ngurah Pramesemara; Andrology Department, Doctor Soetomo General Hospital, Surabaya, Indonesia; i.gusti.ngurah.pramesemara-2016@fk.unair.ac.id

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INTRODUCTION

Erectile dysfunction is a disease that frequently occurs with a significant negative impact on the quality of man's life.[1] Some literature mentioned the incidence of erectile dysfunction cases ranging from 15% to over 50% and increases with age.[2] Erectile dysfunction is a good predictor for cardiovascular disease, because of erectile dysfunction and cardiovascular disease have the same mechanism, namely the endothelial damage. The dysfunction of cavernous endothelial cells is a central mechanism in erectile dysfunction. The ischemic condition will disrupt the relaxation process of the erectile tissue who mediated by endothelial cell.[3] Endothelial cells have important roles in the regulation of vascular tonus and permeability, coagulation and fibrinolysis, inflammatory and immunological reaction, and cell growth.[4]

The diagnosis of erectile dysfunction can be confirmed from anamnesis, physical examination, and laboratory investigations. In addition, it is also known the International Index of Erectile Function questionnaire with 5 questions (IIEF-5) and Erection Hardness Score (EHS) with 4 grading scale that is useful for screening and assessing the treatment response of erectile dysfunction.[5] The treatment of erectile dysfunction is to restore the patient's ability to erect, so can improve the quality of patient's life. There were strongly evidenced that PDE5 inhibitors were effective and safe in the treatment of erectile dysfunction, a first-line oral treatment for erectile dysfunction, regardless of the various etiologies.[2] One of the well-known PDE5 (phosphodiesterase-5) inhibitor is sildenafil citrate. PDE5 inhibitors had a positive impact on the endothelial cell's health. It was a fact that the incidence of myocardial infarction was lower in patients who received sildenafil citrate compared placebos.[1]

Chronic inflammatory conduct endothelial dysfunction and improve the level of high sensitivity

CRP (hs-CRP). This condition causes the artery walls more rigid and become one of the risk factors for erectile dysfunction event.[6] hs-CRP increased has been confirmed to correlate with vasculogenic erectile dysfunction, and it can be measured with IIEF-5 and EHS questionnaire.[7] Those paradigms increase the interest of researchers mainly to evaluate the inflammatory marker, hs-CRP, which is important in erectile dysfunction. Therefore, this study aims to determine the effect of oral sildenafil citrate per day to the hs-CRP levels, as well as the score of the IIEF-5 and EHS.

METHODS

A true clinical experimental study with crossover and pretest-posttest control group design were enrolled among patients with erectile dysfunction in this study at Androgologi Airlanga Dr. Soetomo General Hospital, Surabaya Indonesia from June-November 2017. The sample size calculated based on Pudjirahardjo's and to anticipate the drop out was 20 peoples, divided into 2 groups (control and treatment). The crossover was carried out in the middle of the study and after 2 weeks of washout period. The inclusion criteria were the age of 25-75 years old, married, and still living with his wife, and willing to sign an informed consent. While the exclusion criteria were contained psychogenic or other non-organic disorder, physical trauma history of the genital region and active chronic inflammatory diseases, also was used immunosuppressant drugs and PDE5 inhibitor before.

The independent variables in this study were oral PDE5 inhibitor, Sildenafil citrate 50 milligrams, given every day for the treatment group, and given placebo for the control group. While the dependent variables were 2) IIEF-5 scores divided into mild (17-21), mild-moderate (12-16), moderate (8-11), and high (5-7); 2) EHS scores were divided into four scales: the penis is completely hard and fully rigid (4), the penis is hard enough for penetration but not completely hard (3), the penis is hard but not enough for penetration (2), and the penis is larger but not hard (1); 3) hs-CRP serum levels were increased in line with the inflammatory process and described the condition of endothelial dysfunction.

The research materials were 50-milligram sildenafil citrate capsule and placebo capsule. For examination of hs-CRP biomarkers, blood samples of subjects will be sent to the laboratory that was invited to cooperate. Research instruments used in this study are included a glove, 5 ml syringes, and needles, alcohol swab, blood storage tubes for the examination of hs-CRP, IIEF-5 questionnaire, and EHS tools. The sample determination as a control group (K) or treatment group (P) was done using double-blind randomization. Samples were required to sign an action approval letter, Informed Consent, and Information for Consent after being given counseling and explanation about the research.

The treatment of oral sildenafil citrate 50 mg once daily in group I and placebo capsule in group II for 4 weeks begin since the first day. After that, the washout period was conducted for 2 weeks to eliminate the effects of previous treatment and crossover the group. Group I got a placebo and group II got oral sildenafil citrate capsule 50 mg once daily for 4 weeks.

Data were analyzed using a statistical analysis software with the Statistical Package for the Social Sciences (SPSS) version 16.0 Program for Windows by mean and standard deviation, independent T-test, percentage, and significant value less than 0.05 considered statistically significant.

RESULTS

The baseline characteristic of respondents is depicted in Table 1. The average age of respondents in Group K1 and P2 was 51±12.07 years old and P1 and K2 approximately 48.60 ± 15.40 years old. The EHS and IIEF-5 score in both groups were 2 and 13. In Addition, the hs-CRP value was about 0.16 ± 0.06 mg/l in K1 and P2 group as well as 0.44 ± 0.47 mg/l in P1 and K2 group (Table 1).

The Data of EHS, IIEF-5, and hs-CRP level in the treatment group (P1) and control group (K1) or after the crossover (P2 and K2) both pretest and posttest data were tested for normality using Shapiro-Wilk test with the result that not all the data were normally distributed ($p<0.05$) as shown in Table 2. The homogeneity assessment using the Levene test was also found that not all data homogeneous ($p<0.05$) as shown in Table 2.

A two-tail T-test for both groups (control and treatment) and non-parametric tests were tested by Wilcoxon test before and after crossover or washout with all results show $p<0.05$ as shown in Table 3 and Table 4. This result indicates that variables which the P-values are less than 0.05 need to be further assessed using a non-parametric test such as the Wilcoxon test as mentioned in Table 4.

Nonparametric test using Wilcoxon was carried out to assess the pretest and posttest results between control and intervention group in before and after the washout period (Table 4). The findings suggest that EHS and IIEF-5 score were significantly different in the treatment group, before or after the washout period, compared to control ($P<0.05$). However, there was no significant difference between pretest and posttest results in the hs-CRP examination among groups ($P>0.05$) (Table 4).

Table 1. Baseline characteristics of research subjects

Characteristics	n	Age (years)	EHS	IIEF-5	hs-CRP (mg/l)
Group					
K1 and P2	10	51 ± 12.07	2	13	0.16 ± 0.06
P1 and K2	10	48.60 ± 15.40	2	13	0.44 ± 0.47

EHS: Erection Hardness Score; IIEF-5: International Index of Erectile Function-5; hs-CRP: high-sensitivity C-reactive protein.

Table 2. Normality and Homogeneity-test among groups

Group	n	P1	P2	Levene Test
EHS				
Pre-Test				
K1 and P2	**10**	0.000	0.000	0.394
P1 and K2		0.036	0.000	
Post-Test				
K1 and P2	**10**	0.004	0.022	0.548
P1 and K2		0.000	0.000	
IIEF-5				
Pre-Test				
K1 and P2	**10**	0.132	0.514	0.171
P1 and K2		0.086	0.017	
Post-Test				
K1 and P2	**10**	0.003	0.490	1.000
P1 and K2		0.561	0.846	
hs-CRP				
Pre-Test				
K1 and P2	**10**	0.144	0.093	0.865
P1 and K2		0.007	0.084	
Post-Test				
K1 and P2	**10**	0.000	0.114	0.614
P1 and K2		0.000	0.320	

P1: before crossover; P2: after crossover; P-value less 0.05 was statistically significant; EHS: Erection Hardness Score; IIEF-5: International Index of Erectile Function-5; hs-CRP: high-sensitivity C-reactive protein.

DISCUSSION

In line with the function of PDE5 inhibitor on demand which can maintain an erection by increasing Nitric Oxide (NO) and inhibiting cGMP formation through inhibition of phosphodiesterase enzyme, once daily sildenafil citrate can be considered because of its ability to increase IIEF-5 score, including EHS. Although the half-life of sildenafil citrate is quite short, the impression of increased erectile function was still well-rated by the study subjects.[8]

Sildenafil citrate is a first-generation, effective, mass-produced oral PDE5 inhibitor, and can be well-tolerated by the body.[8] It has long been thought about the possibility of long-term sildenafil citrate with a lower dose for the treatment of erectile dysfunction. This idea is based on the fact that on-demand therapy does not provide clinical benefit after the drug is not used and once-daily use for more spontaneous sexual activity.[9]

As it is known that sildenafil citrate is a PDE5 inhibitor which has a half-life of about 4 hours. The time to reach a maximum concentration is about 0.83 hours and the maximum concentration in the blood is 327 ng/ml. Another PDE5 inhibitor similar to Sildenafil Citrate is a Vardenafil type. While Tadalafil achieved maximum concentration after 2 hours with a longer half-life, about 17.5 hours and the maximum concentration in blood was 378 ng/dl.[10]

Animal studies indicate daily sildenafil citrate administration for the treatment of endothelial dysfunction and oxidative stress associated with insulin resistance. Other studies have been conducted in humans with good efficacy and safety efficacy from long-term sildenafil citrate during night hours to improve spontaneous erection in men.[9]

Low doses of sildenafil citrate 25 mg three times daily in the long term have been studied with the presence of increased endothelial function in patients with diabetes mellitus, even up to one month after discontinuation of its use. In addition to this information, many patients are satisfied with long-term sildenafil citrate treatment which mainly associated with increased sex drive.[11]

There was no significant difference between the control group hs-CRP compared with the treatment group. The short half-life of sildenafil citrate could cause the results compared to other PDE5 inhibitor drugs, coupled with the compliance factor of the study subjects because each subject did not necessarily have a habit of taking medication at the same hour and there are variations in the medicinal habits among different subjects.

Several previous studies that used sildenafil citrate and reviewing hs-CRP did show different results. The study of Aversa *et al.* showed a 20% decrease in hs-CRP in the group given Sildenafil citrate.[9] But research conducted by Grover-Paes *et al.* concluded that there was no difference between before and after given Sildenafil citrate due to its relatively short time of therapy, 4 weeks. The result of the meta-analysis showed that administration of Sildenafil Citrate was able to decrease endothelin-1, but did not decrease hs-CRP.[12] Successful studies showing significantly reduced hs-CRP were studies that used Tadalafil 5 mg for 12 weeks.[13]

A hs-CRP is protein produced by the liver and is a marker of infection, inflammation, endothelial dysfunction, and metabolic syndrome. In the case of erectile dysfunction found hs-CRP increases with the degree of erectile dysfunction. In severe erectile dysfunction, hs-CRP is about 0.46 mg/dl. In moderate erectile dysfunction is about 0.30 mg/dl and in mild erectile dysfunction is about 0.09-0.13

Table 3. Independent T-test of EHS, IIEF-5, and hs-CRP Variable Results

Groups	N	Mean±SD	*P-value*
EHS			
(Before *Cross-over*)			
P1		2±0.47	0.688
K1	20	2±0.74	
P2		2±0.57	0.000
K2		4±0.52	
(After *Cross-over*)			
P1		3±0.52	0.090
K1	20	2±0.47	
P2		2±0.47	0.000
K2		4±0.53	
IIEF-5			
(Before *Cross-over*)			
P1		13±3.37	0.894
K1	20	13±3.24	
P2		21±1.83	0.000
K2		14±3.47	
(After *Cross-over*)			
P1		15±1.48	1.000
K1	20	15±2.65	
P2		2±0.47	0.000
K2		4±0.53	
hs-CRP			
(Before *Cross-over*)			
P1		0.44±0.47	0.270
K1	20	0.16±0.56	
P2		0.31±0.37	0.623
K2		0.29±0.31	
(After *Cross-over*)			
P1		0.16±0.09	0.850
K1	20	0.17±0.08	
P2		0.20±0.14	0.577
K2		0.17±0.12	

P1: Pre-test in the treatment group; P2: post-test in the treatment group; K1: Pre-test in control group; K2: Post-test in control group; EHS: Erection Hardness Score; IIEF-5: International Index of Erectile Function-5; hs-CRP: high-sensitivity C-reactive protein.

mg/dl. The initial data on hs-CRP subjects involved varied from 0.06 mg/dl to 1.4 mg/dl.[3]

In addition, hs-CRP has been a marker for erectile dysfunction that plays a role in endothelial dysfunction and atherogenic. The hs-CRP level primarily responds to long-term tadalafil therapy. So in the initial subjects with high hs-CRP levels, it certainly showed a weak response to tadalafil and other PDE5 inhibitors.[3]

Also, inter and inter-individual biases were inevitable in this study. hs-CRP itself is not a specific marker. Any inflammatory condition may increase hs-CRP. Although at the beginning of the study, the selection of subjects was in accordance with inclusion criteria, but over time, inflammation or other changes in the subject itself were unavoidable. Besides each change and process in the individual body has the potential to convert hs-CRP up to 175%, so often hs-CRP is advised to be measured at least 10 times the measurement to avoid bias within that individual, in addition to the hs-CRP measurements suggested for regular and uniform time.[3] The aforementioned earlierwas the reason why it cannot be completely fulfilled in research using human subjects.

CONCLUSION

Oral administration of sildenafil citrate every day not able to reduced hs-CRP in patients with erectile dysfunction.

ETHICAL CLEARANCE

This research has got the information of ethical clearance, no. 168/Panke.KKE/III/2017 from the Health Research Ethics Committee of Doctor Soetomo General Hospital Surabaya.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript

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AUTHOR CONTRIBUTION

I Gusti Ngurah Pramesemara is responsible for data gathering and concept of study. Rossy Sintya Marthasari, Rezia Octarina, and Ahmad Ricardo Syukur Silalahi are responsible as supervisors and data analysis. Judie Hartono and Tjahjo Djojo Tanojo are responsible as supervisors and English improvement.

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Table 4. Wilcoxon Test on EHS, IIEF-5, and hs-CRP

Group	n	Average		Difference	%Enhancement	p
		Pretest	Posttest			
EHS (score)						
K1		2	2	0	0	0.564
K2	20	3	2	-1	-33	0.046
P1		2	4	2	50	0.004
P2		2	4	2	50	0.004
IIEF-5 (score)						
K1		13	14	1	8	0.428
K2	20	15	14	1	8	0.318
P1		13	21	8	62	0.000
P2		14	21	7	50	0.000
hs-CRP (mg/l)						
K1		0.16	0.21	0.05	31	0.220
K2	20	0.16	0.21	0.05	31	0.083
P1		0.43	0.31	0.12	27	0.240
P2		0.17	0.17	0.0	0	1.000

P1: before crossover; P2: after crossover; P-value less 0.05 was statistically significant; EHS: Erection Hardness Score; IIEF-5: International Index of Erectile Function-5; hs-CRP: high-sensitivity C-reactive protein.

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