EVALUATION OF THE EFFECT OF SILDENAFIL IN HEMODIALYSIS PATIENTS WITH PULMONARY HYPERTENSION

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ABSTRACT:

Background*: Pulmonary hypertension (PH) is one of the fatal and progressive conditions in ESRD patients, its prevalence among hemodialysis patients ranging from 19% to 70% and it is responsible for 50% of mortality rate.*

Aim of the Work: *To evaluate the effect of sildenafil on pulmonary artery pressure and six minute walk test (6MWT) in hemodialysis patients with pulmonary hypertension and detection of safety and optimum dose of the drug.*

Patients and Methods: *Prospective, Placebo Controlled, clinical trial involving 60 ESRD patients with pulmonary hypertension from January to May 2019.*

Results: *Group 1 (20 patients) received 25 mg sildenafil, group 2 (20 patients) received 50 mg sildenafil and group 3 (20 patients)who received placebo for 3 months .There was significant increase in mean of 6 MWT after treatment among group 1 and 2 but there is non-significant change among placebo group.*

Estimated pulmonary artery pressure (e PAP) mean after treatment showed significant decrease among group 1,2 and 3.

In group 1 there was 4 patients with mild PH , 13 with moderate , 3 with severe PH after treatment 5 patients downgraded from moderate to mild and 2 patients downgraded from severe to moderate .In group 2 there was 8 patients with mild PH, 6 patients with moderate and 4 patients with severe PH after treatment 4 patients downgraded from moderate to mild PH and 2 patients downgraded from severe to moderate PH . In group 3 only one patient downgraded from moderate to mild PH.

Conclusion: *Our clinical trial confirmed efficiency of 50mg and 25mg sildenafil on improving e PAP and functional exercise capacity in ESRD patients with PH.*

Key words: *clinical trial, pulmonary hypertension, ESRD, sildenafil.*

INTRODUCTION:

Pulmonary hypertension (PH) is one of the fatal and progressive conditions in (ESRD) patients its prevalence in hemodialysis patients ranges from 19% to 70%. Sildenafil is a phosphodiesterase inhibitor widely used in treatment of PH .Despite the potential burden of pulmonary hypertension in hemodialysis patients, such agent like sildenafil has limited studies about optimum dose, safety and long term efficacy

in ESRD patients on hemodialysis with pulmonary hypertension.

AIM OF THE WORK

To evaluate the effect of sildenafil on pulmonary artery pressure and (6MWT) in hemodialysis patients with pulmonary hypertension. Also detection of safety of sildenafil in hemodialysis patients and Finding out sildenafil's optimum dose for hemodialysis patients with pulmonary hypertension.

PATIENTS AND METHODS:

This study was conducted between January and May of 2019 on 60 hemodialysis patient in Ain Shams University Hospitals divided randomly into 3 groups: group 1 (20 patients) received 25 mg sildenafil for 3 months group 2 (20 patients) received 50 mg sildenafil daily for 3 months and group 3 (20 patients) who received placebo for 3 months.

We excluded any patient on current treatment of pulmonary hypertension (prostacyclin analogues, endothelin receptor antagonists or phosphodiesterase inhibitors). We also excluded any patient with heart diseases (congestive heart failure, ischemic heart disease, congenital heart disease),Lung diseases (chronic obstructive pulmonary disease, pulmonary thromboemboli or tumor, interstitial lung diseases, sleep apnea, pulmonary fibrosis, Sarcoidosis), systemic diseases (scleroderma, systemic lupus erythematosus, portal hypertension),human immunodeficiency virus (HIV) infection .

All patients after written informed consent approved by the ethical committee have been included into our registry and subjected to the following:

Every patient in the study was subjected to full history taking and clinical examination with special attention to symptoms of pulmonary hypertension.

I. ***Transthoracic echocardiography*** Was done at the begging of the study and after three months in mid-week non-dialysis day, the patients was assessed regarding:

- Change in ePAP via Doppler echocardiography pulmonary artery pressure calculated using the modified Bernoulli equation: PAP =tricuspid systolic jet (TR) + (10-15) mm Hg (estimated right atrial pressure: 15 mm Hg in dilated right atrium and 10 mmHg in normal or slightly enlarged right atrium). PH was defined as a systolic PAP > 35mmHg
- Right ventricular examination: Assessment of right ventricular functions by TAPSE (Tricusped annulus plane systolic excursion), tricuspedregerge (TR), estimated PASP, RV end-diastolic basal diameter, .RA end-systolic area, ejection fraction and left ventricle mass index (LVMI)

II. ***Exercise capacity assessment by 6MWT:*** The test was performed along a long, flat, straight, enclosed corridor with a hard surface. The test (6MWT) was done for every patient at the begging of the study (6MWT 1) and after 3 month of receiving the medication (6MWT 2).

Management: Group 1 (20 patients) received 25 mg sildenafil daily for 3 months group 2 (20 patients) received 50 mg sildenafil daily for 3 months and group 3 (20 patients) who received placebo daily for 3 months .

Follow up including:

patients improved or deteriorated, compliance and appearance of any drug side effect.

The collected data was revised, coded, tabulated and introduced to a PC using

Statistical package for Social Science (SPSS 25). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

RESULTS:

Basic demographic baseline data between the 3 study groups

	Group 1 (n=19) (25 mg)	Group 2 (n=18) (50mg)	Group 3 (n=19) (placebo)	p value
Age (years)	52.6±10.8	45.5±12.1	52.2±7.0	.07
Gender: Male Female	 12 (65%) 7 (35%)	 9 (50%) 9 (50%)	 12 (63%) 7 (37%)	 .59
Vascular access: Cath AVF	 4 (21%) 15 (79%)	 5 (28%) 13 (72%)	 5 (26%) 14 (74%)	 .84
Duration of HD(years)	4 ± 4	2 ± 1	2.5 ± 3	.004
BMI	29.4 ±4	29.7 ±4.6	30 ±4	.91
MBP (mmHg)	89.3 ± 14	96.2±9.3	96.4 ±11.2	.201
Dry WT(kg)	82.4 ±15	85.9 ±13	85.7 ±11.7	.95
Pulse(b/min)	75.8 ±6.6	80 ±7	78 ±6.1	.32

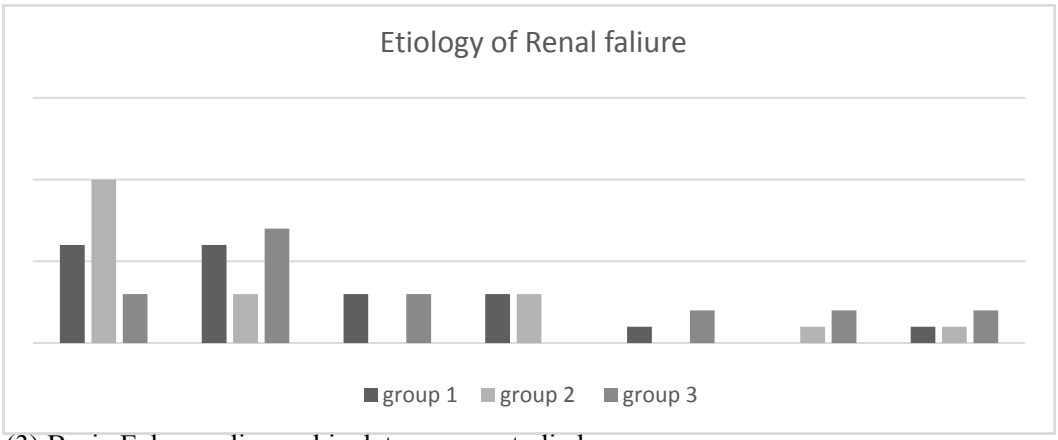


Table (3) Basic Echo cardiographic data among studied groups

	Group 1 25mg	Group 2 50 mg	Group 3 Placebo	p value
EF	55 ±8.6	59 ±11	58 ±5	.26#
LVMI	93.8 ±12	93.1 ±14	92 ±11	.75#
RV ED BD	34.7 ±3.5	35.3 ±4.4	35 ±3	.88#
RA ES area	15.9±1.8	16.3 ±1.9	15.9 ±1.9	.59#
e PAP 1	49.4 ±7.7	48.7 ±11.5	47 ±8.1	.8#
TR : -ve Mild Moderate Severe	10 (50%) 7 (35%) 2 (15%) 0 (0%)	12 (66%) 5 (28%) 1(6%) 0 (0%)	11 (58%) 7 (37%) 1 (5%) 0 (0%)	.89##
RVF : normal impaired	16 (84%) 3 (16%)	14 (78%) 4 (22%)	14 (74%) 5 (26%)	.72##

There was no significantly statistical difference between the 3 groups regarding EF, LVMI, right ventricular end diastolic basal diameter, right atrial end systolic area, ePAP, tricuspid regurge and right ventricular function.

Comparison between 6MWT pre and post intervention

	Group 1 25 mg	Group 2 50mg	Group3 Placebo	p value
6 MWT 1	171 ±45	214 ±58	175 ±39	.06
Sig. bet. grps	p1= .24, p2=.93, p3=.064			
6 MWT 2	205 ±57	258 ±59	182 ±49	.001
Sig. bet. grps	p1= .027, p2=.45, p3=.001			
p value	.00	.00	.15	

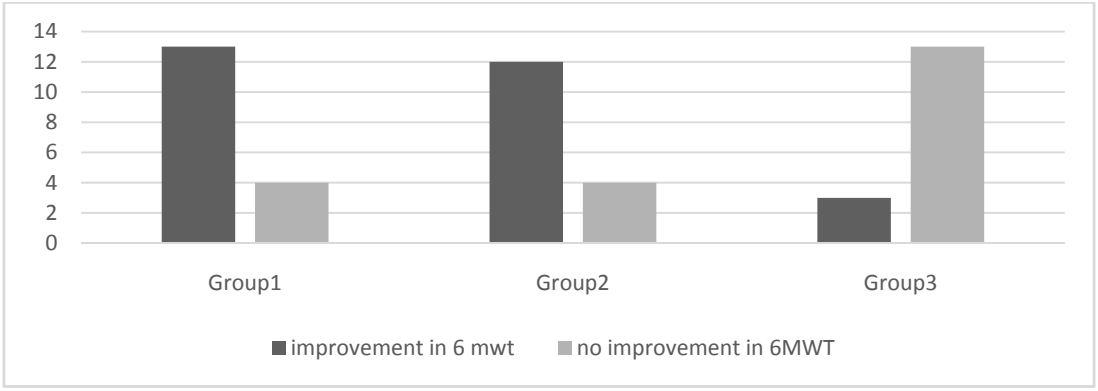
p1: p value for comparing group 1 and group 2 / p2: p value for comparing group 1 and group 3
p3: p value for comparing group 2 and group 3

Shows significant increase in mean of 6 MWT after treatment among group 1 and 2 but there is non- significant change among placebo group. There was no significant differences between the 3 groups regarding basal means of 6 MWT. A significantly statistical difference between three groups after treatment (*P<0.01) as post Hoc test results* was statistically significant increase in 6MWT2 in group 2 in comparison to group 1 of *(P<0.05*), there was also statistically high significant increase in 6MWT 2 in group 2 (50mg) in comparison to group 3 (placebo) *(P< .001.*

Improvement in 6 MWT in the 3 group post treatment

	Group 1 25mg	Group 2 50mg	Group 3 Placebo	P value
Improvement on 6MWT (Change ≥30 meters)	13 (76%)	12 (75%)	3 (19%)	.001
No improvement in 6 MWT	4 (24%)	4 (25%)	13 (81%)	.001

There was significant increase in improvement on 6MWT post treatment in both group 1 (76%) and group 2 (75%) versus group 3 with only (19%) improvement in 6MWT.



Comparison between e PAP pre and post intervention

	Group 1 25 mg	Group 2 50mg	Group3 Placebo	p value
ePAP1	48 ±9	43.5 ±16	48.5 ±12	.804
Sig. bet. grps	p1= .98, p2=.80, p3=.88			
ePAP2	42 ±9	39 ±15	44.5±8	.251
Sig. bet. grps	p1= .97, p2=.28, p3=.37			
pvalue	.00	.00	.00	

p1: p value for comparing group 1 and group 2 / p2: p value for comparing group 1 and group 3

p3: p value for comparing group 2 and group 3

e PAP mean change in each group after treatment with significant decrease among group 1, 2 and 3.There were no statistically significant difference between the 3 studied groups regarding e PAP1 before and e PAP2 after the intervention

Comparison between grading of severity of PH in the 3 study group pre and post treatment

	Group1		Group2		Group3	
	pre	Post	pre	post	pre	post
Mild ePAP=25-40	4 (20%)	11 (53%)	8 (45%)	12 (67%)	7 (37%)	8 (42%)
Moderate ePAP 41-55	13 (65%)	8 (42%)	6 (33%)	4 (22%)	11 (58%)	10 (53%)
Severe ePAP >55	3 (15%)	1 (5%)	4 (22%)	2 (11%)	1 (5%)	1 (5%)

In group 1 there was 4 patients with mild PH, 13 with moderate, 3 with severe PH, after treatment 5 patients downgraded from moderate to mild and 2 patients downgraded from severe to moderate .In group 2 there was 8 patients with mild PH, 6 patients with moderate and 4 patients with severe PH, after treatment 4 patients downgraded from moderate to mild PH and 2 patients downgraded from severe to moderate PH. In group 3 only one patients downgraded from moderate to mild PH.

There was correlation between e PAP and right ventricular end diastolic basal diameter (r=.60, p<.001), right atrial end systolic area (r=.45 , p<.001) which both has positive correlation with increased e PAP in pulmonary hypertension.

6 MWT done in the start of the study show negative correlation with only age (r=-.42, p<.001) as patient with older age seems to score less in the 6 MWT.

DISCUSSION:

Despite the potential burden of pulmonary hypertension in hemodialysis patients(prevalence ranges from 19% to 70%)[1], such agent like sildenafil has no studies about optimum dose, safety and long term efficacy in ESRD patients on hemodialysis with pulmonary hypertension. Through our reviewing of literature there was no prior study emphasizing and studying the drug and its effect on ESRD patients with PH.

Basic characteristics:

A comparison of demographic data between the 3 study groups demonstrated no significantly statistical difference between the 3 groups regarding age, sex, vascular access, BMI, dry weight, MBP and pulse. The only statistical significant difference was in duration of HD which was longer in group 1

All basic echocardiographical data showed no statistically significant difference between the 3 study groups regarding EF, LVMI, right ventricular end diastolic basal diameter, right atrial end systolic area, e PAP, tricuspid regurge and right ventricular function.

Change in e PAP:

There was significant decrease in e PAP in all groups after treatment. In group 1 ePAP after treatment recorded mean of (42±9) with significant decrease in relation to ePAP before treatment *(p<.00).* Group 2 after treatment ePAP mean was (39±15) with *(p<.00).* Group 3 ePAP post treatment mean was (42±9)and *(p=01).*

There was significant decrease in e PAP in all groups after treatment. In group 1 ePAP after treatment recorded mean of (42±9) with significant decrease in relation to ePAP before treatment (p<.00). Group 2 after treatment ePAP mean was (39±15) with (p<.00). Group 3 ePAP post treatment mean was (42±9) and (p=01).

In comparison to Galié *et al., (2005)*[2]in his placebo-controlled study, he assigned 278 patients with symptomatic pulmonary arterial hypertension with no renal impairment to placebo or sildenafil (20, 40, or 80 mg) orally daily for 12 weeks. All sildenafil doses reduced the mean pulmonary-artery pressure (P=0.04, P=0.01, and P<0.001, respectively) in relation to placebo .

Hemodynamic variables are related to survival in patients with pulmonary arterial hypertension[3]. It has been suggested that there is possible reverse remodeling of pulmonary vascular changes with both prostanoids and endothelin-receptor antago-nists, on the basis of their antiproli-ferative properties, and this may also explain the effects seen with sildenafil[4].

Change in 6MWT*(functional assessment of patients with pulmonary hypertension):*

There was no statistically significant difference between 3 groups regarding the 6MWT done at the begging of the study between the 3 groups p value was non-significant (p=.06).

There was statistically significant increase in 6MWT done after treatment in group 1 *(p<.001).* Group 2 also had significant increase with mean of *(p<.001).*However group 3 (placebo) shows no statistically significant difference *(p=.15).*

We compared the effect of different doses of sildenafil on 6MWT, we reported that group 2 (receiving 50mg sildenafil) showed significant increase in (6MWT) in comparison to group 1 (receiving 25mg sildenafil) *(p<0.05)* and highly significant increase in comparison to group 3 (receiving placebo) *(p<.001).*

Our results agreed with Galié *et al., (2005)* who found that the distance walked in six minutes (6MWT) increased from baseline in all sildenafil groups for 20, 40, and 80 mg of sildenafil, respectively *(P<0.001)* in comparison to placebo.[2]

The six-minute walking test is an independent predictor of death in patients with pulmonary arterial hypertension and has been used as the primary end point in most clinical trials involving patients with pulmonary arterial hypertension. [5]

We observed in the our study positive correlation between e PAP and right ventricular end diastolic basal diameter *(r=.60)(p<.001)* in our study group in agreement with Seo and Lee, (2018) study who observed that the RV dilates in response to increased PAP and that enlarged RV can predict mortality in patients with pulmonary disease and pulmonary arterial hypertension (PAH) .[6]

There was also positive correlation between e PAP and right atrial end systolic area (*r=.45) (p<.001)* in study group. That was consistent with a study conducted by Querejetaet al., (2015) who stated that patients with PH also had significantly larger

RA area compared with controls (15.0±4.7 cm^2 versus 8.5±1.4 cm^2, $P<0.001$)[7].

Although in our study group 2 (receiving 50mg sildenafil) showed better results and increase patient's functional exercise capacity there were 2 drop out through study due to drug related side effects the first one suffered from persistent hypotension after one weak from using medication and the second drop out from this group suffered from persistent headache after one month of treatment.

Side effects of sildenafil were reported to be nausea, hypotension, headache, palpitation, flushing, and angina in a study conducted on a Fifty-five hemodialysis patients above 18 years suffering from erectile dysfunction, A Single 50-mg sildenafil tablet was prescribed for each patient[8].

Group 1 (receiving 25 mg sildenafil) showed statistically significant improvement in ePAP and 6MWT without any side effects in any patient in this group.

Conclusion: Our clinical trial confirmed efficiency of 50mg and 25mg sildenafil on improving e PAP and functional exercise capacity in ESRD patients with pulmonary hypertension. Although dose of 50 mg daily is more effective in both decreasing ePAP and increasing functional exercise capacity (measured by 6MWT) dose of 25mg daily showed no side effect in such patients.

Limitations: Relatively small number of patients and it was a single center study

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تاثير عقار السيلدنافيل على ارتفاع ضغط الدم في الشريان الرئوي في مرضى الاستصفاء الدموي المصابين

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الخلفية: يعد مرض ارتفاع ضغط الشريان الرئوي من اخطر الامراض في مرضى الفشل الكلوي المزمن واكثرها فتكا حيث يتراوح معدل الاصابة به من ١٩% حتى ٧٠% في مرضى الغسيل الدموي .

الهدف : تقييم تاثير عقار السيلدنافيل على ضغط الدم بالشريان الرئوي و التحسن الاكلينيكي في مرضى الغسيل الدموي الذين يعانون من ارتفاع ضغط الدم في الشريان الرئوي وتحديد الجرعة المثلى ومدى امان عقار السيلدنافيل على مرضى الغسيل الدموي

المرضي والطرق: كانت هذه تجربة سريرية على ٦٠ من مرضى الغسيل الدموي المصابين بارتفاع ضغط الشريان الرئوي من يناير ٢٠١٩ إلى مايو ٢٠١٩.

النتائج :تم تقسيم المرضى الى ٣ مجموعات المجموعة الاولى تلقت تركيز ٢٥مجم من السيلدنافيل المجموعة الثانية تلقت تركيز ٥٠ مجم من السيلدنافيل و المجموعة الثالثة تلقت عقار وهمي لمدة ٣ شهور

تم رصد تحسن ملحوظ في متوسط اختبار المشي لست دقائق في المجموعة الاولى و الثانية في اخر الدراسة ولم يلاحظ اي تحسن في المجموعة الثالثة .

لوحظ انخفاض في متوسط ضغط الشريان الرئوي في المجموعات الثلاثة ولكن في المجموعة الاولى تبين وجود ٤ مرضى يعانون من ارتفاع ضغط الشريان الرئوي من الدرجة البسيطة و ١٣ من الدرجة المتوسطة و٣ من الدرجة الشديدة وبعد العلاج تحول ٥ من المرضى من الدرجة المتوسطة للدرجة البسيطة ومريضين من الدرجة الشديدة للدرجة المتوسطة بينما في المجموعة الثانية تبين وجود ٨ مرضى يعانون من ارتفاع ضغط الشريان الرئوي من الدرجة البسيطة و ٤ من الدرجة المتوسطة و٣ من الدرجة الشديدة وبعد العلاج تحول ٤ من المرضى من الدرجة المتوسطة للدرجة البسيطة ومريضين من الدرجة الشديدة للدرجة المتوسط . في المجموعة الثالثة لم يتحسن سوى مريض واحد انتقل من المجموعة المتوسطة للبسيطة

خاتمة: أكدت تجربتنا السريرية فعالية عقار السيلدنافيل بجرعتيه ٢٥ مجم و ٥٠ مجم في تحسين ضغط الشريان الرئوي وتحسين القدرة الاكلينيكية الوظيفية لدى مرضى الفشل الكلوي المزمن المصابين بارتفاع ضغط الشريان الرئوي