Evaluation of the effect of sildenafil in hemodialysis patients with pulmonary Hypertension.

Thesis

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List of abbreviations

Full Term	Abb.
6-minute walk test	6MWT
ATP-binding cassette sub-family A member 1	ABCA1
ATP-binding cassette sub-family G member 1	ABCG1
Autosomal Dominant Polycystic Kidney Disease	ADPCKD
asymmetric dimethylarginine	ADMA
Acute myocardial infraction	AMI
Area under the curve	AUC
Arteriovenous	AV
Arteriovenous fistula	AV
Coronary artery calcium score	CACS
Cyclic adenosine monophosphate	cAMP
Cyclic guanosine monophosphate	cGMP
cardiac troponin I	cTnI
cardiac troponin T	cTnT
Coronary artery disease	CAD
Chronic kidney disease	CKD
Creatinine clearence	Cr CL
maximum (or peak) serum concentration	Cmax
Cardiac magnetic resonance imaging	CMRI
Cardio vascular	CV
Cerebrovascular accident	CVA
Cardiovascular disease	CVD
Congestive heart faliure	CHF
Cytochrome P3A4	CYP3A4

List of abbreviations

Cytochrome P2C9	CYP2C9
Electron beam computed tomography	EBCT
Ejection fraction	EF
Estimated pulmonary artery pressure	e PAP
Erythropoiesis stimulating agent	ESA
End stage renal disease	ESRD
Fibroblast growth factor 23	FGF-23
Glomerular filtration rate	GFR
Glomeruloneohritis	GN
Guanosine triphosphate	GTP
Hemodialysis	HD
Heart failure	HF
Hemoglobin	HGB
Human immunodeficiency virus	HIV
High sensitivity C-reactive protein	HsCRP
High seneitivity troponin I	HsTnI
Interleukin 6	IL-6
Interleukin 10	IL-10
Kidney Disease Outcomes Quality Initiative	KDOQI
Left atrium	LA
Left ventricle	LV
Left ventricular dilatation	LVD
Left ventricular diastolic dysfunction	LVDD
Left ventricular hypertrophy	LVH
Left ventricular Mass index	LVMI
Mean blood pressure	MBP
Mean pulmonary artery pressure	mPAP
mammalian target of rapamycin	mTOR
Normal hematocrit trial	NHT
Pulmonary artery systolic pressure	PASP
Pulmonary artery wedge pressure	PAWP

List of abbreviations

Pulmonary hypertension	PH
phosphodiesterase enzyme	PDE
Pulmonary embolism	PE
Protein kinase A	PKA
Protein kinase G	PKG
Parathyroid hormone	PTH
Pentroxin 3	PTX3
Pulmonary vascular disease	PVD
Pulmonary vascular resistance	PVR
Right atrium	RA
Renin-angiotensin-aldosterone system	RAAS
Right atrial end systolic area	RA ES A
Right heart catheterization	RHC
Recombinant Human Erythropoietin	rHuEpo
Right ventricle	RV
Right ventricular end diastolic basal diameter	RV ED BD
Right ventricular function	RVF
Tricuspid annulus plane systolic excursion	TAPSE
Urea reduction ratio	URR
Sudden cardiac death	SCD
Scavenger receptor, class B type1	SR-B1
Segmental wall motion abnormality	SWMA
Tissue Doppler imaging	TDI
Total iron binding capacity	TIBC
Tall like receptor 4	TLR4
Transferretin saturation	TSAT
Vascular smooth muscle cell	VSMC
Wood Unit	WU

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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% .

Aim of the work: To evaluate the effect of sildenafil on pulmonary artery pressure and 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.

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 patients 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, it is diagnosed when the mean pulmonary artery pressure exceeds 25 mmHg measured during right heart catheterization or when the pulmonary artery wedge pressure is over 15 mmHg and pulmonary vascular resistance is more than 3 WU***(Reque et al,. 2016)***

PH is a progressive condition characterized by ongoing endothelial dysfunction and pulmonary vascular remodeling. World Health Organization (WHO) has classified PH into five groups; group 1 which is idiopathic or due to hereditary conditions, group 2 that describes PH due to left heart disease including diastolic dysfunction, group 3 which is related to lung disease and/or hypoxia, group 4 is thromboembolic lung disease and group 5 that include multiple unclear factors and most importantly; chronic renal failure on dialysis. ***(Pabst et al,. 2012)***

Based on echocardiographic studies, prevalence of PH among chronic hemodialysis patients is 19% reaching up to 70% ***(Xu et a,l. 2014).***

Pathophysiology of PH in hemodialysis patients is multifactorial and can be explained primarily by pulmonary arterial vasoconstriction and increased pulmonary vascular resistance that occur due to metabolic and hormonal changes, along with volume overload, arteriovenous access and anemia that increase the pulmonary artery pressure (PAP) due to their effect on cardiac output. Pulmonary artery calcification caused by secondary hyperparathyroidism and the profound endothelial dysfunction in this category of patients may also has a role ***(Abassi et al,. 2006).***

Uraemic toxins, Inflammation as increases in pro-inflammatory monocytes, mast-cell proliferation, T-lymphocyte dysfunction, and decreased T-regulatory cells which result in an immune dysfunction in CKD with an increase in circulating inflammatory mediators causes an increase in oxidative stress resulting in endothelial dysfunction .Patients with CKD have elevated levels of vasoconstrictors such as endothelin-1 and angiotensin II and reduced levels of endogenously produced vasodilators such as nitric oxide (NO) . This imbalance of vasoactive peptides can directly affect pulmonary vascular tone and might mediate an increase in pulmonary vascular resistance causing PH. (***Kawar B et al., 2013)***

Although Right Heart Catheterization is the exploratory choice for pulmonary hypertension, transthoracic echocardiography is the recommended non-invasive modality in its screening and evaluation ***(Barst et al. 2004)*** especially that PH seems to be reversible in hemodialysis patients after temporary closure of arteriovenous fistula and after renal transplantation and thus, transthoracic echocardiography should be used for screening and early detection of PH among hemodialysis patients***.(Reque et al. 2016)***

PH associated reduced capacity of the right heart to maintain adequate left heart filling pressures in the face of intermittent dialytic fluid removal could contribute to the intradialytic myocardial stunning, ischemia and myocardial fibrosis has been recently described. Since pro-arrhythmogenic myocardial remodeling is considered a major contributor to sudden cardiac death in the HD population, such a pathway is potentially of therapeutic importance.***(Burton et al., 2009)***

Pharmacological treatments options currently are endothelin receptor antagonist, Ca channel blocker, prostacyclin analogues whether oral or subcutaneous and finally phosphodiesterase inhibitor. Treatment options in patients with

PH focus on symptomatic management of the disease, including improving breathlessness on exertion, chest pain and syncope. Lung transplantation is the only curative treatment available if pharmacological means fail***(Zimner-Rapuch et al. 2013)***

Sildenafil is a phosphodiesterase inhibitor that can exert a nitric oxide-mediated vasodilation effect, so it's considered one of the preferred agents especially in hypoxia induced pulmonary hypertension, can achieve pulmonary vasodilation by enhancing sustained levels of cyclic guanosine monophosphate (cGMP) and nitricoxide***.(Di Lullo et al,. 2013)***Metabolism of sildenafil occurs primarily by hepatic cytochrome P450 enzymes yielding one active metabolite with a potency of approximately 50% of the parent drug. Patients with creatinine clearance less than 30, and with hepatic cirrhosis have reduced clearance of sildenafil.

Its pharmacokinetics is altered when the creatinine clearance is less than 30 ml/min thus, dose should be adjusted in hemodialysis patients, and since it's not dialysable, it can be taken before, during and after hemodialysis session. Sildenafil over dosage may cause cardiovascular adverse effects (with flushing, vertigo and headaches) and, most of all, a risk for hypotension and coronary insufficiency, especially if the patient