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Is Sildenafil Citrate a safe and effective treatment for Pulmonary Hypertension in adults?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the requirement For

The degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: To determine whether or not the Phosphodiesterase inhibitors drug Sildenafil Citrate is safe and effective treatment for Pulmonary Hypertension in adults

STUDY DESIGN: reviewed primary research materials published in English language between 1996 and 2009

DATA SOURCES: Randomized, controlled, double-blind clinical trials found using OVID, MEDLINE, and Cochrane data bases

OUTCOME MEASURED: trials measured 6-minute walking distance improvement, hemodynamic measurements to assess vascular resistance, peak VO₂

RESULTS: two randomized trials included in this review showed Sildenafil is effective in treating PAH. The trials showed patients had an improvement their 6-minute walking distance, quality of life improvement, and decreased vascular resistance. A trial conducted by Shim et al was inconclusive needing further research as it is one of the only trials that tried to determine the effect of Sildenafil in patients who are undergoing cardiac surgery

CONCLUSIONS: Sildenafil provides symptomatic relief with little side effects in patients suffering from PAH. Two of the researches showed that sildenafil did have an efficacy in treating PAH by decreasing vascular resistance.

KEY WORDS: Sildenafil, Viagra, pulmonary hypertension, pulmonary arterial hypertension

INTRODUCTION

Pulmonary Hypertension is a very rare disease that is caused by an increase in pressure in pulmonary arteries. CDC reported in 2002 Pulmonary artery hypertension (PAH) was the cause of 15,668 deaths and 260,000 hospitalizations in the U.S. PAH affects primarily older women; however, it is seen in both male and female of all ages and races⁵. Prior to 1995 the life expectancy of person with PAH was 3years since then average life expectancy has improved due to better treatment options. The invention and use of pulmonary artery catheters (Swan-Ganz) have enabled clinicians to diagnose and treat PAH by measuring the pulmonary capillary pressure and thereby determining the pulmonary vascular resistance. This created the opportunity for early diagnosis/treatment and as a result prolonging life expectancy for those diagnosed.

Normally the average pulmonary artery pressure is 25 mmHg at rest or 30 mmHg during physical activity. The world health organization divides PAH into five categories. The first category contains causes of PAH that have unknown origin, inherited, congenital or from HIV infection. Second group consist of PAH with heart disease. Third is PAH that coexist with lung diseases such as COPD. Fourth deals with PAH caused by blood clotting diseases such as pulmonary emboli polycythemia, or sickle cell anemia and fifth group includes causes such as Sarcoidosis, Langerhans cell Histiocytosis, or tumor. In general, group one is considered primary PAH and those from 2nd -5th are secondary causes of PAH.

Patients with PAH present with exertional dyspnea, fatigue on exertion, light headedness/weakness due to hypoxia and if leg edema develops it is often a sign of right sided heart failure. If PAH is not diagnosed and treated early, patients are more likely to develop Cor-Pulmonale. Normally, pressure in the pulmonary arteries is low allowing the RV to pump blood in to the lungs with little effort. However, in patients with PAH due to narrowing of the

pulmonary artery the RV has to compensate by using forceful contractions in order to overcome pulmonary artery resistance which leads to RV enlargement. Moreover, PAH increases RV susceptibility to ischemic injury and patients with right sided heart failure are at high risk for pulmonary embolism. Definite diagnosis of PAH is made by pulmonary catheterization (swanz ganz cath) by measuring pressure in the RV and the pulmonary artery. However, exercise oximetry is a helpful diagnostic method as well. A fall in oxygen saturation without a history of lung parenchymal disease is a strong indication for pulmonary vascular disease. In addition Chest x-ray can be used to detect cardiomegaly and Echocardiography is used to detect RV and LV function and valvular insufficiency.

Arteries and lesions in the arterioles are the cause of the hypertension. Pulmonary endothelial dysfunction that leads to impaired production of vasodilators, such as nitric oxide, Prostacyclin, and over-expression of vasoconstrictors, such as Endothelin-1. These disease process lead to narrowing of the arteries. There are three classes of medications that are currently approved by the FDA. They are Prostacyclin (PGI₂) analogues (Epoprostenol, Treprostinil, and Iloprost), Endothelin Receptor Antagonists (ERA) (Bosentan, Ambrisentan, and Sitaxsentan) and Phosphodiesterase inhibitors (PDEI) (Sildenafil, Tadalafil)⁴. Other treatments include, Anticoagulants, diuretics, Digoxin, supplemental oxygen, OR calcium-channel blockers. If medication fails, Lung transplant is considered. The initial therapy of choice depends on cause of disease. Patients with Positive vasodilator response and WHO class I-III can be managed by CCB. Those with Negative vasodilator response or WHO class II or III are initiated with ERA or PDEI treatment.

Objective:

The objective of this systematic review is to determine whether or not the Phosphodiesterase inhibitors drug Sildenafil Citrate is safe and effective treatment for Pulmonary Hypertension in adults

METHODS:

The studies used for this review were selected based on the following criteria. The patient population was over the age of 18 and suffering from PAH. The intervention used was oral Sildenafil. The treatment groups were compared to placebo groups who received water pills. The outcomes measured were improvement of exercise capacity, improvement of 6minute walk, quality of life, hemodynamic measurements, and prevention of RVHF; all of these can qualify as patient oriented evidence that matter (POEM). All the three studies were randomized double blind, placebo-controlled

In research conducted by Shim et al, Fifty three patients with scheduled valvular heart surgery and systolic RV pressure >50mmHg and pulmonary pressure >30mmHg were enrolled into the trial. Participants were randomly divided and given 50mg Sildenafil (n=26) or Placebo-30ml sterile water (n=27) 10minutes before induction of anesthesia. Ten minutes before and five minutes after induction of anesthesia and 30 and 60 minutes after medication hemodynamic measurements were calculated. Badesch et al run a 12-week study on 278 PAH patients with 84 subset of patients with connective tissue disease (CTD-PAH) with mean Pulmonary pressure >25mmHg and pulmonary artery wedge pressure <15mmHg at rest. Patients were randomly assigned into treatment and placebo groups. Those in treatment groups received Sildenafil at doses of 20mg TID, 40mg TID, or 80mg TID. Exercise capacity, Hemodynamic Measures and

WHO functional class and tolerability were assessed at week 4, 8 and 12 weeks. Patients were excluded if they had a 6-minute walk distance (6MWD) of ≤ 100 m or ≥ 450 m.

Thirty four patients over the age of 18 who have chronic Heart failure despite standard HF therapies with secondary PAH (arterial pressure over 25mmHg) were enrolled in Lewis et al trial. Patients were randomized to 12-weeks treatment of Sildenafil (25-75mg orally TID) or placebo. Medication was initiated at 25mg then titrated up to 75mg TID over the course of every 2 weeks. Cardiopulmonary exercise testing was done before and after treatment in order to measure peak VO₂. 22-gauge catheter was placed in the radial artery for continuous measurement of mean arterial pressure and blood gas measurements were done at 1-minute intervals during cardiopulmonary exercise. Cardiac output at rest and during exercise was measured using Fick Oxygen technique.

Key words used in searches were Pulmonary Hypertension, pulmonary arterial hypertension, pulmonary hypertension, Sildenafil, Viagra. All articles were published in an English language in peer-reviewed journals. This author personally did the article search in OVID Medline and Cochran database. Inclusion criteria were: patients over the age of 18, randomized, POEM, RCT's, articles published between 1996 and the present and not used in any prior meta-analysis or systematic review publications. Exclusion criteria were: Patients under 18y.o, Disease-oriented evidence (*DOE*) trials, studies published before 1996, and articles used in prior meta-analysis or systematic review publications

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Shim, 2006 (1)	Double blind RCT	53	Mean age 53-57	Pts with concomitant pulmonary hypertension undergoing valvular surgery with pulmonary arterial pressure greater than 30mmHg	Pts w/ preexisting lung parenchymal disease, coronary artery occlusive disease, hepatic or renal disease, TR of at least 2, or NYHA functional class of at least 3, and pts taking nitrates were excluded.	7	50mg Oral Sildenafil given 10min before anesthesia
Badesch, 2007 (2)	Randomized, double blind, placebo-controlled study	278	Mean 50-56	Pts w/ Connective tissue disease, >18yo	Pts w/ 6-minute walk distance (6MWD) of ≤ 100 m or ≥ 450 m	5	Oral Sildenafil in three dose groups (20, 40, 80 Mg tid)
Lewis, 2007 (3)	Randomized, double blind, placebo-controlled study	34	Mean age 54-62	>18 y.o. w/ , LVSD and NYHA class II to IV CHF despite standard HF therapies. Pts w/ secondary PH pressure >25 mm Hg	Pts w/ a noncardiac limitation to exercise, provokable ischemia, hemodynamic instability, or ongoing nitrate therapy	3	Oral Sildenafil 25-75mg 3xday

OUTCOMES MEASURED

Pulmonary hypertension causes right ventricular failure. If pulmonary hypertension rises, RV is susceptible to ischemic injury. So the done by Shim et al tried measured systolic pulmonary arterial pressure (SPAP), MPAP, Central venous pressure, RV ejection fraction, RV end-systolic/diastolic volume index, and pulmonary vascular resistance index. In Badesch et al

study the outcomes were measured using exercise capacity from base line and hemodynamic measurements (mPAP, mean right atrial pressure (mRAP), cardiac output, and pulmonary vascular resistance (PVR)).

Lewis et al measured Oxygen uptake (VO_2), carbon dioxide output (VCO_2), and respiratory exchange ratio, cardiac output, systemic vascular resistance and PVR at rest and during exercise. Right atrial, pulmonary arterial and pulmonary wedge pressure were measured while patient was upright on bicycle or sitting during cardiopulmonary exercise. Also, 6minute walk distance was measured at baseline, 6weeks and at 12week 6-min walk distance and mean pulmonary arterial pressure was calculated. After completion of these measurements, patients were given a questionnaire (21 questions to assess their quality of life) with scores ranging from 0-5 for each question and. Measured VO_2 during exercise and at rest using Fick oxygen Technique.

RESULTS

All three of the articles presented double blinded, randomized control trials. Shim et al addressed the effects of Sildenafil citrate on patients with PAH who were undergoing vascular heart surgery. The study had 53 participants with mean age of 57 for control groups and mean age of 53 for control groups. Ratio of male to females was equal in both control and treatment groups. Badesch et al conducted research on 278 patients with PAH and 84 subgroup of patients with CTD-PAH. Of the 278 patients, 94 completed the study. Majority of the patients were women, patients with scleroderma and those in factional category III. Most common non-dose related sildenafil side effects noted among patients were Headache and epistaxis. During the trial, 5 patients dropped out of the treatment group. Three patients died (cause of death: MI, PE,

Urosepsis) and two patients discontinued due to lower leg edema and cirrhosis of the liver. None of these deaths were attributed to treatment with sildenafil.

Lewis et al studied thirty four patients with LVSD in NYHA class II-IV with PAH were enrolled in trial for 12 weeks. These participants had previously shown 2-4% increase in peak VO₂ after one time treatment of Sildenafil. In total, four patients withdrew from trial (two from each group) and no deaths occurred. One patient from treatment group withdrew after elective implantation of cardiac resynchronization device and second one due to ventricular tachycardia with syncope. In placebo group, one patient withdrew due to pruritis and another due to worsening HF. As with Badesch et al trial, the most common side effect noted in this trial was headache. About 41% of patients treated with sildenafil complained of Headache. In addition, at the end of the trial fewer patients in the treatment groups were hospitalized compared to those in placebo group (P=0.046).

The data in shim et al study was presented in Continuous data form using χ^2 test. At T0 there was no significant hemodynamic variables difference from baseline between control and treatment groups. At T30, SPAP, MPAP, and PVRI were significantly lower in sildenafil group compared to control groups; moreover, SPAP and MPAP at T30 were significantly lower in sildenafil group compared to baseline values. At T0 hemodynamic values are similar between all groups with no statistical significance (SPAP: $P=0.07$; MPAP: $P=0.087$; PVRI: $P=0.09$). There was little total significant difference between control and treatment groups with the exception of PVRI. P value for PVRI was statistically significant difference between treatment group and placebo group (P=0.04)

Patients in Badesch et al treated with Sildenafil showed had an increase in 6minute walking distance compared to control groups after 12weeks of treatment with a mean increase of

55m at the end of week 12. After 12 weeks of treatment the treatment group with 20mg had a mean increase of 42m and those treated with 40mg had an increase of 36m and with 80mg of Sildenafil there was an increase of 15m. Patients in treatment group showed an improvement in WHO functional class following the 12-week treatment. Patients treated with 80mg of Sildenafil had 42% changes, greater than the other two treatment groups. This data were converted from “continuous data” form to “Dichotomous” data. Experimental event rate (EER) was 42%; this is the percentage of patients who showed an improvement after treatment with 80mg of Sildenafil. The Control event rate (CER) was 5%, meaning the % of patients who showed an improvement in controlled group. From this numbers RRR and ARR were calculated. An absolute risk reduction (ARR) of 0.37 and the Relative risk reduction (RRR) was 7.4. the number needed to treat (NNT) was 2.7. Hemodynamic measurements only showed improvement in only those treated with 20mg TID achieved a statistical significant change with $P < 0.01$ of mPAP and $p < 0.05$ of PVR

Measured exercise capacity of patients by measuring their peak VO₂. Patients treated with Sildenafil had VO₂ increase from 12.2 ± 0.7 to 13.9 ± 1.0 mL/kg/ min with $P = 0.02$; while vo₂ did not change in placebo group. In addition patients in treatment groups had greater change in their peak VO₂ from base line compared to control group. Another variable measured was cardiac output. Patients treated with medication had an increase in CO. the increase in Peak VO₂ in treatment group lead to an improvement in PVR ($p = 0.002$) and RV ejection fraction ($p = 0.01$). patients had improved EEF at rest and peak exercise ($p = 0.03$; $p = 0.04$ respectively); while no change was observed in placebo group at the end of 12 weeks resting PVR ($20 \pm 6\%$; $P = 0.02$) and in PVR/SVR ($-16 \pm 6\%$; $P = 0.01$) indicating sildenafil has a selective vasodilator effect. Patients in intreatment groups had also an increase in their 6MWD by 62m ($p = 0.004$). The study

also measured patients quality of life by using a questioniar. NYHA class improved in 53% of sildenafil treatment patients while only 7% improved in placebo group ($p=0.045$). Patients receiving medication saw a reduction in N-terminal BNP levels at week 12 compared to placebo ($p=0.11$).

DISCUSSION

Sildenafil is the only FDA approved Phosphodiesterase inhibitor to PAH. Phosphodiesterase Inhibitors works by slowing the metabolism of intracellular cGMP. cGMP is activated by NO and Prostacyclins leading to relaxation of vascular smooth muscle. Sildenafil is marketed under trade name Revatio for PAH and Viagra for erectile dysfunction. It peaks an hour after first ingestion and has 3.7 hours of half life. It is associated with Headache and Visual blurriness. Two trials by Levi et al and Badesch et al showed a statistically significant improvement in outcomes they measured. In these studies, Sildenafil treatment improved exercise capacity, Hemodynamic measurements and improved patients' functional class in Patients with CTD-PAH compared to placebo group. Also Systolic heart failure patients with PAH that were enrolled in sildenafil treatment group had an improved exercise capacity, 6-minute walking distance, improved quality of life and decreased hospital admission. However, trial conducted on patients that were undergoing valvular heart surgery did not show statistically significant difference between treatment and control groups. The most important clinical significant of this trial was to determine the effect of sildenafil on homodynamic measurements because this measurements directly reflect PAH. There by decreased pulmonary pressure can preserve coronary perfusion leading to decreased complications due to RV ischemia and subsequent RV dysfunction. Limitations of these three trials were their small sample size (it

ranged from 34-53), short duration of trial period with the longest being 12wks and none of the trials included comprehensive long-term treatment follow-up. Small sample sizes may be good for limiting sample variables; however, larger data sizes give a more concrete and strong correlations.

CONCLUSION

Although, treatment with sildenafil did not show efficacy in patients undergoing vascular surgery, the other two studies done on CTD-PAH and Systolic heart failure patients showed Sildenafil is effective in improving 6-MWD, quality of life and hemodynamic measurements. Furthermore, compared to medications used for PAH, Sildenafil has fewer numbers of side effects. The dilatory effect of Sildenafil leads to decreased vascular pressure which in turn increases cardiac output and EF. The increase in cardiac output and EF has direct effect on improving patients' quality of life by decreasing dyspnea, fatigue and other symptoms. All the studies measured atrial pressure to determine the effects of sildenafil; however, atrial pressure depends on different variables. Larger study with larger number of participants that run longer period of time is needed to show long term benefits and complications. Future researches in this arena should focus on how sildenafil compares to other drugs that treat PAH. How it differs and how its potential benefits compare to other drugs. These studies focused primarily on hemodynamic measurements. It would be interesting to include patient feedback through surveys on their quality of life improvement.

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