Original Article

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Appropriateness of Sildenafil Prescribing in Pulmonary Hypertension with Valvular Heart Disease: A Single Centre Study

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Abstract

Oral sildenafil has proven efficacy in pulmonary hypertension in current clinical practice. However, there is a research gap in sildenafil prescribing among patients with valvular heart disease (VHD) and pulmonary hypertension (PH) in Malaysia. This study aimed to determine the appropriateness of sildenafil prescribing and rehospitalization rate in patients with corrected VHD and PH. This is a retrospective descriptive study using universal sampling with a calculated sampling size of 123. Patients who were diagnosed with VHD and PH in Hospital Serdang were recruited from 2014 - 2018. Patients' demographic and clinical characteristics were retrieved from Electronic Hospital Information System (eHIS) and recorded using a pre-designed data collection form. Appropriateness prescribing of sildenafil included appropriate dose(20mg to 80mg three times daily) and duration(total of eight weeks of sildenafil treatment that started before and continued after surgery). Rehospitalization is defined as any hospitalization within six months after surgery. Data were analyzed using descriptive and inferential statistics. From 123 patients (44.7% male, 55.3% female), 41% (n=51) and 61.8%(n=76) received appropriate dose and duration of Sildenafil respectively. Rehospitalization rate within six months after valve surgery was 55.3%(n=68). Univariate analysis showed that patients more than 65 years old (p=0.039), atrial fibrillation (AF) (p=0.04) and female (p=0.002) received appropriate prescribing of sildenafil. Only female patients and patients with AF were the predictors of appropriate prescribing of sildenafil. The role of sildenafil in VHD and PH remains unclear and needs further research in different perspectives such as short term and long-term duration with different doses.

Keywords: Appropriateness, Pulmonary Hypertension, Sildenafil, Valvular Heart Disease.

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1. Introduction

Pulmonary hypertension (PH) can be defined as an increment of mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC) (1). According to ESC Guidelines 2015 (1), pulmonary hypertension was closely related to left heart disease (PH-LHD), and it was classified into group 2 PH with subgroup 2.3 referring to valvular heart disease (VHD) (2). Approximately 69% of patients with PH were found with LHD, and out of these patients, valve malfunction and diastolic dysfunction was the leading causes (3). Left ventricular

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dysfunction contribute to the increased mortality risk of patients with PH (3). The development of PH-LHD is associated with poorer prognosis (4). There will be a significant decrease in pulmonary arterial pressure (PAP) after successful correction of valve stenosis or regurgitation in most of the patients with VHD (4). The rapid fall in left atrial (LA) pressure leads to a decrease in PH's passive component (5). The subsequent progressive lowering in pulmonary pressures, occurring up to several months after the implant, decreases in the pulmonary arterial vasoconstriction (5). However, the hypertrophy in the arteriolar medium layer, once established, does not reverse, facilitating the appearance of residual or recurrent PH (5). Management of PH is very challenging, with high morbidity and mortality (6). Interventions in patients with VHD include transcatheter and surgical approaches; furthermore, periodic evaluation is required once the intervention has been done (7). If the symptoms persist, treatment is based on goal-directed medical therapy, either non-PAH specific drugs (e.g. beta-blocker, angiotensin-converting enzymes, diuretics and etc.) or specific PAH drugs (e.g. endothelin receptor antagonists and phosphodiesterase-5 inhibitors) (1). Phosphodiesterase-5 (PDE-5) is an enzyme present in high concentrations in the lungs and functions to degrade cyclic guanylate monophosphate (cGMP) produced after nitric oxide (NO) binds to soluble guanylate cyclase—this degradation of cGMP results in impaired pulmonary arterial vasodilation. The PDE-5 inhibitor sildenafil prevent the degradation of cyclic guanylate monophosphate (cGMP), thereby preserving endogenous NO bioavailability, thus producing acute and relatively selective pulmonary vasodilatation while avoiding the complications of inhaled NO (8). Sildenafil has been reported to be effective in improving hemodynamics, exercise tolerance, and symptoms in group 2 PH, however, there is still a lack of evidence to support the use of those drugs in daily practice (9, 10). Hence, Sildenafil was used as an off label drugs in managing PH with VHD (11).

In recent years, there has been growing concern about the increasing indiscriminate off-label use of pulmonary vasodilators for group 2 and 3 PH (6, 12). Thus, in providing pharmaceutical care to patients, high-value care is a goal for clinicians and health systems (6).

Drug-related morbidity and mortality are a significant health care concern in elderly and resulted in increased health care expenditure (13). Thus, World Health Organization introduced a systematic approach to minimize poor-quality and prescribing error. This six-step approach include define the patient's problem, state the treatment objective, select the appropriate treatment, initiate treatment with appropriate details, provide information, instructions and warnings to patients followed by monitor treatment regularly (14). Several studies (15-19) have been investigated the efficacy and safety of sildenafil with various doses, duration and different timing, either preoperative or postoperative, but none of these determined the appropriateness of sildenafil prescribing. Thus, our study was designed to determine the appropriateness of sildenafil prescribing, predictors of appropriateness of sildenafil prescribing and rehospitalization rate within six months after valve surgery.

2. Material and methods

2.1. Study Design

This was a retrospective descriptive study carried out in Serdang Hospital. Serdang Hospital is a multi-specialty hospital located in the state of Selangor, Malaysia. It is a well-known referral hospital in the Klang Valley area which provides cardiothoracic surgery with more than 13 years of experience. The study was registered under Ministry of Health (MOH) Malaysia with NMRR ID of 18-1939-42036. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Study Setting

Patients who underwent corrected VHD and developed PH after surgery from 1st January 2014 to 31st December 2018 in Hospital Serdang were retrieved from Electronic Hospital Information System (eHIS). Universal sampling method was used to select our study sample.

Patients with congenital pulmonary hypertension, pre-existing lung parenchymal disease, hepatic cirrhosis, coronary artery occlusive disease, currently taking inhaled nitric oxide, and New York Heart Association (NYHA) functional

class IV were excluded from the study.

2.3. Data collection

Patients' demographic, clinical characteristics and clinical outcomes were retrieved from the clinical notes, whereas medication history including tablet Sildenafil was identified via drug profile in eHIS. All the data collected were then recorded in a pre-designed data collection form. In order to protect patients' confidentiality, each patient was allocated an identifier number. Appropriate sildenafil prescribing was defined as the dose prescribed as recommended which was 20 mg to 80 mg three times a day whereas appropriate duration of therapy was eight weeks of treatment, starting before and continue after valve surgery. Clinical outcomes were defined as rehospitalization within six months after surgery. The criteria were developed with the agreement of cardiothoracic surgeons, pharmacists, and cardiac anesthetists.

2.4. Statistical Analysis

Data collected were analyzed using Statistical Package for Social Science (SPSS) software Version 25. All data obtained were subjected to descriptive analysis. Categorical data were reported in frequency and percentage. Pearson's Chi-square was used to study the association between categorical variables. Univariate logistic regression analysis was undertaken to determine the predictors of the appropriateness of sildenafil prescribing for each known or potential risk factors. The Wald test was implemented and the variables which considered significant if $p<0.25$ were included in the multivariate logistic regression analysis stage. A cut-off value of 0.25 is supported by literature (20). The data was expressed as 95% confidence interval (CI) and odds ratio(OR). A $p<0.05$ was considered statistically significant.

3. Results

A total of 123 adult patients with PH and VHD were involved in this study. Demographic and clinical characteristics data are shown in Table 1. Majority of patients aged less than 65 (n=103, 83%) had multiple valves involvement (n=88, 71.5%), whereas 28.5% (n=35) patients had single valve diseases (either mitral regurgitation, mitral stenosis, tricuspid regurgitation or atrial stenosis). Most of the patients were classified under NHYA Class II (46.3%) prior to valve surgery, with most common morbidities was hypertension (41.5%), followed by atrial fibrillation (26.8%). Diuretics and warfarin were the most common concomitant therapy taken by the patients other than sildenafil.

Table 1. Baseline characteristics of sildenafil prescribing.

	All(n=123)
Age (≤ 65 years old)	103 (83.7)
Gender, female, n (%)	68 (55.3)
Appropriate indication (%)	123 (100)
Co-morbidities (%)	
Atrial fibrillation	33 (26.8)
Hypertension	51 (41.5)
Diabetes mellitus	19 (15.4)
Ischemic heart disease	19 (15.4)
Asthma	12 (9.8)
Dyslipidaemia	18 (4.6)
Sildenafil dosage per day (%)	
30 mg	31 (25.2)
50 mg	24 (19.6)
60 mg	27 (21.9)
75 mg	27 (21.9)
Other	14 (11.4)
Duration of sildenafil therapy (%)	
Total of 8 weeks	76 (61.8)
Less than 8 weeks	20 (16.3)
More than 8 weeks	27 (21.9)

From 123 patients, 41% (n=51) and 61.8% (n=76) received appropriate dose and duration of Sildenafil respectively. Patients with co-morbidities of hypertension and atrial fibrillation were having high percentage (40.7% and 31.9%) of inappropriate sildenafil prescribing. Only 71.9% patients with multiple valves diseases received appropriate sildenafil prescribing (Table 2). Hospitalization rate within six months after surgery was found to be 55.3% (n=68).

On univariate analysis, the prevalence of receiving appropriate prescribing of sildenafil was higher in patient more than 65 years old (p=0.039) and in female (p=0.002). Furthermore, patient with atrial fibrillation as co-morbidities also showed a

Table 2. Criteria of the appropriateness in sildenafil prescribing

	All (n=123)	Sildenafil prescribing		p Value
		Appropriate (n=32)	Inappropriate (n=91)	
Age (≤ 65 years old)	103 (83.7)	23 (71.9)	80 (87.9)	0.034
Gender, female, n (%)	68 (55.3)	10 (31.3)	58 (63.7)	0.01
Co-morbidities (%)				
Atrial fibrillation	33 (26.8)	4 (12.5)	29 (31.9)	0.033
Hypertension	51 (41.5)	14 (43.8)	37 (40.7)	0.76
Diabetes mellitus	19 (15.4)	5 (15.6)	14 (15.4)	0.974
Ischemic heart disease	19 (15.4)	4 (12.5)	15 (16.5)	0.592
Asthma	12 (9.8)	2 (6.3)	10 (11)	0.437
Dyslipidaemia	18 (4.6)	2 (6.3)	16(17.6)	0.119
Types of valve severity				
Single valve	35 (28.5)	9 (28.1)	26(28.6)	-
Multiple valves	68 (55.3)	23 (71.9)	65 (71.4)	-
NYHA Classification				
I	18(14.6)	3(9.4)	15 (16.4)	0.315
II	57(46.3)	19(59.4)	38 (41.8)	
III	48(39.0)	10(31.3)	38 (41.8)	
Concomitant medications				
Diuretics	104 (84.6)	28.7 (87.5)	76 (83.5)	0.592
Vitamin K Antagonist	80 (65)	18 (56.3)	62 (68.1)	0.225
Cardiac glycoside	34 (27.6)	9 (28.1)	25 (27.5)	0.943
Calcium channel blocker	10 (8.1)	3 (9.4)	7 (7.7)	0.764
Nitrates	1(0.8)	1 (3.1)	0 (0)	0.09

higher prevalence in getting appropriate prescribing of sildenafil (p=0.04). Based on multivariable regression analysis, only female patient and patients with atrial fibrillation were found to be independently related to the prevalence of receiving appropriate prescribing of sildenafil (Table 3).

4. Discussion

Gender as a risk factor of VHD remains unclear. Podolec et al. (21) reported that elderly women were more prone to suffer from degenerated valvular heart disease. Our study showed a predominance of female with a percentage of 55.3% which was consistent with the recent epidemiological registries oversea. Walker et al. (21) reported that that the ratio of female to male is 4:3 among total PAH group (22). In addition, the NIH registry showed that females were 1.8 times more likely to be affected by PAH comparing to male (23). It might be due to changes in estrogen level in female which damage the right ventricle and influence the development of pulmonary vascular disease (24). In regards with age, most of the patients was less than 65 years old which was different from most of the registries which showed increasing proportion of elderly patients aged >70 years (25). Hypertension (23.5%) and atrial fibrillation (17.2%) were the most common co-morbidities faced by our patient prior to study. There are a few prospective studies which confirmed high incidence of atrial arrhythmias in patients with PH (26). The mainstay of atrial fibrillation is the progressive fibrosis of the atria and hence structural remodeling (27). As regards with the concomitant therapy prior to study, most of our patients were taking diuretics as a symptomatic treatment for fluid overload and warfarin for atrial fibrillation.

Our study showed that only 26% of the patients was receiving appropriate prescribing of sildenafil. Female patients and those with atrial

Table 3. Risk factors associated with the appropriateness of sildenafil prescribing.

Characteristics			95% CI	
ID	HR	P value	Lower	Upper
Univariate				
<65 years old	(Ref)			
≥65 years old	0.35	0.039	0.13	0.95
Male	(Ref)			
Female	3.87	0.002	1.6	9.1
Single type of VHD	(Ref)			
Combination types of VHD	1.02	0.96	0.42	2.5
NYHA Class I	(Ref)			
NYHA Class II	0.76	0.705	0.18	3.15
NYHA Class III	1.9	0.157	0.78	4.6
Hypertension	0.881	0.76	0.39	1.99
Atrial Fibrillation	3.274	0.04	1.05	10.2
Asthma	1.86	0.44	0.38	8.9
Diabetes Mellitus	0.982	0.982	0.32	2.98
Ischemic Heart disease	1.38	0.593	0.422	4.52
Dyslipidemia	3.2	0.136	0.693	12.7
Diuretics	0.724	0.724	0.221	2.3
Vitamin K Antagonist	1.67	0.228	0.73	3.79
Cardiac glycoside	0.96	0.943	0.395	2.375
Calcium channel blocker (CCB)	0.806	0.765	0.195	3.32
Nitrate	0	1	0	0
Multivariate				
Age	0.445	0.154		
Gender	0.304	0.013		
NYHA Class II	0.548	0.447		
NYHA Class III	1.30	0.6		
Atrial Fibrillation	0.26	0.036		
Dyslipidaemia	0.286	0.147		
Warfarin	0.85	0.74		

fibrillation (AF) were more likely to receive appropriate prescribing of sildenafil. Drug-related problems can lead to morbidity and mortality, as well as increased health care expenditure. This can be avoided by encouraging appropriate prescribing among health care professionals. Based on our study, only female patient and patients with atrial fibrillation were found to be independently related to the prevalence of receiving appropriate prescribing of sildenafil. Older patients with larger left atria (LA) dimensions and lower left ventricle ejection fraction (LVEF) are more prone to the development of AF (28). Thus, patient with valvular AF were prescribed with vitamin K antagonists(VKA) (e.g. warfarin) for the prevention of thromboembolism (23). An effective oral antithrombotic therapy with VKA in patients with mechanical heart valves requires regular monitoring of INR. A single INR target is preferable for each patient and the acceptable range is 0.5 INR units on each side of the target. Specific INR target reduces the possibility of patients having INR values persistently near the upper or lower range which might cause increased risk of bleeding or ccoagulation (29). During the INR clinic follow up, the dose of sildenafil will be reviewed and ad-

justed to optimum dose too by prescriber during follow up. This shall explain why patients with AF three times were more likely to receive appropriate prescribing of sildenafil compared to the patients without AF.

4.1. Strengths and limitations of study

There was lack of study regarding the role of sildenafil in VHD and PH. Thus, our study can be served as a preliminary study. There are some limitations to this study. There was lack of standard indicator for monitoring of patients on Sildenafil as not all the patients involved have data regarding 6 Minute Walk Test (6 MWT) and pulmonary arterial pressure (PAP).

5. Conclusion

The study showed that 41% (n=51) and 61.8%(n=76) of our patients received appropriate dose and duration of Sildenafil respectively. 55.3% of patients were readmitted back to hospital within six months after surgery. Only female patients and patients with AF were predictors of receiving appropriate prescribing of sildenafil. Further research in different perspectives such as short term and long-term duration with ranges of dose have to be done to establish the use of Sildenafil in VHD and PH.

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Conflict of Interest

The authors have no conflict of interest.

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