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Prescribing Patterns and Adverse Drug Reactions in Pulmonary Hypertension: A Prospective Study

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ABSTRACT

Pulmonary hypertension is a chronic progressive disease demonstrates by the elevation of mean pulmonary arterial pressure (mPAP) it leads to morbidity and pre-mature mortality. The objective of the study to calculate the current methods of prescribing patterns, adverse drug reactions and medication adherence of those subjects. A prospective observational study was conducted a period of 6 months in a cardiology department, SVIMS. A total number of 30 subjects were involved in this study. According to patient information (patient's data, drug therapy and investigations) were used to elevate the other necessary data. The result of the data were calculated in Microsoft excel sheet. ADR's of drugs and medication adherence among the subjects were analysed. In our study 30 subjects were enrolled majority were males (57%) with average age of 37.5 years. There exists a significant relationship between the habits (smoking and alcoholism) and development of the disease. The therapy was given depending upon the type of PAH and condition of the patient. Males were more predominant than females. Adults were more prone to PAH. IPAH is the most common type. The number of drugs can be prescribed in an each prescription was three and among them one drug (sildenafil) was prescribed for pulmonary hypertension and others were used as supportive therapy. Most of the subjects have medium medication adherence.

1. Introduction

1.1 Definition

Pulmonary hypertension is defined as a class of clinical conditions present in abnormal elevations in the pulmonary circulation pressure. (Mean pulmonary artery pressure is higher than 25 mm of Hg at rest or 30 mm of Hg with exercise). PAH is progressive affecting disease in the arteries of the lungs [1].

1.2 Epidemiology

The prevalence of pulmonary hypertension in the regular population is unknown, because of the prolonged classification and multiple aetiologies. The Racial distribution of PAH was survey in REVIAL registries, the patient distribution was 72.8% Caucasians, 12.2% Americans, 8.9% Hispanics, 3.3% Asians and 2.8% others [2]. PAH shows female predominance compared to a female to male ratio 1.7:1 in NIH Registries [2]. Contemporary registries of PAH shows a female dominant distribution through the female to male ratio was significantly large in modern US based Registries, PHC registries-3:1, REVEAL registries-4.8:1, and Mayo registries-3.2:1[3, 4].

1.3 Classification

According to WHO measures pulmonary hypertension was divided into five major categories listed as below:

1. Pulmonary Arterial Blood Pressure
2. Pulmonary Venous Blood Pressure
3. Pulmonary Hypertension associated with disorders of the respiratory system or hypoxemia
4. Pulmonary Hypertension due to chronic thrombotic or embolic disease
5. Pulmonary Hypertension due to disorders directly affecting the pulmonary vasculature.

Newly updated classification

Since 1998, the major revisions of the class in Pulmonary hypertension have the disease based anatomical site and aetiology [5].

1. Pulmonary Arterial Blood Pressure
2. Pulmonary Hypertension Owing to Left Heart Disease
3. Pulmonary Hypertension Owing to Lung Diseases Or Hypoxia

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4. Chronic Thromboembolic Pulmonary Hypertension
5. Pulmonary Hypertension with Unclear Multifactorial Mechanism

1.4 Aetiology

I. Idiopathic cause.

II. Non - Idiopathic cause-

a) Connective tissue disorders (scleroderma and lupus).

b) Congenital heart disease - Eisenmengers (Left to right cardiac shunts)

c) Left Sided Valvular Heart Disease (Mitral Valve and Aortic Valve)

d) Respiratory Disorders (chronic obstructive pulmonary disease, Emphysema, pulmonary fibrosis and pulmonary emboli

e) Chronic liver disease (cirrhosis)

f) Blood Disorder, Sarcoidosis, Metabolic Disorder Glycogen Storage Disease

III. Others-

Gene mutation

Tumours

HIV Infection

Drugs: Methamphentamines

Toxins [6-8]

1.5 Pathophysiology

Pulmonary arterial hypertension is a associated with increase PVR resulting from a loss of vascular luminal cross-section, because of vascular re-modelling generated by excessive cell proliferation and reduced rate of apoptosis [9]. Pulmonary arterial hypertension is a characterized by several of arterial abnormalities including intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis, may separate the inflammation and plexiform arteriopathy. A patient may manifest all this lesions and distribution of lesions may be diffused [10]. It is characterized by endothelial dysfunction, a decreased ratio of apoptosis in pulmonary artery smooth muscle cell and thickened disordered in which it is more activation of adventitial metalloproteases. The multigenic disorder especially target receptor type 2 [BMPR-2] and action in like kinase-1 has been involved in the pathogenesis of FPAH. In the vascular lumen, the Pulmonary hypertension is demonstrated by platelets that should be depleted a serotonin and elevation of plasma serotonin. The pulmonary hypertension of , endothelial malfunction is evolved by the increased production of mitogenetic compounds such that endothelin, thromboxane and deficient production of vasodilators such as prostacycline [11]. In pulmonary hypertension there is an increased production of thromboxane A2 and deficient prostacycline leading to its thrombosis, proliferation and vasoconstriction. Endothelin-1stage is increased in Pulmonary hypertension and Decreased level of endothelial nitric oxide has been observed in Pulmonary hypertension as inactivated by PDE-5 [12]. Auto-antibodies and inflammatory infiltrates have been observed in some critical cases of pulmonary hypertension they suggest that inflammation may contribute the development and forms of pulmonary hypertension. The PASMC'S in pulmonary hypertension display an excessive proliferation of response to transforming the growth factor -beta and propensity to accumulate a unwanted cells is the exacerbated by unpaired smooth muscle cell apoptosis. In Pulmonary hypertension the adventitia is fragmented and permitting cell migration and creating mitogenic peptide such that tenoscin [13]. Histopatholagical parts were showed in Figure 1.

1.6 Clinical features

The sign and symptoms of pulmonary arterial hypertension in early stages that might not be notify for month or years. The disease progresses a symptoms become worse or bad. Image representation shows a clinical presentation was given in Fig 2.

- Chest pain
- Loud p2
- TR murmur.
- Dyspnea, initially while exercising and eventually at rest
- Cough
- Fatigue
- syncope
- Swelling in ankles, legs and eventually in abdomen
- Haemoptysis
- Cyanosis

1.7 Investigations

- Chest X-RAY: In pulmonary hypertension the enlargement of Right ventricular and pulmonary arteries are identified. It may vary show evidence of pulmonary lung or cardiac diseases.
- Ventilation – perfusion lung scan: It shows a several segmental or greater sized perfusion defects in thromboembolism
- Pulmonary Angiogram: Identify the suspicion of thromboembolism.
- Echocardiogram: Right ventricular and arterial enlargement are seen, RBBB, Right ventricular strain pattern.
- Trans Thoracic Echocardiogram: Identify the cardiac status.
- Pulmonary Function Test: Identify the COPD
- Arterial Blood Gas: Low pao2 and high pao2 in situation of parenchyma lung disease.
- Six-Minute Walk Test: Unexplained exercise induced de-saturation-

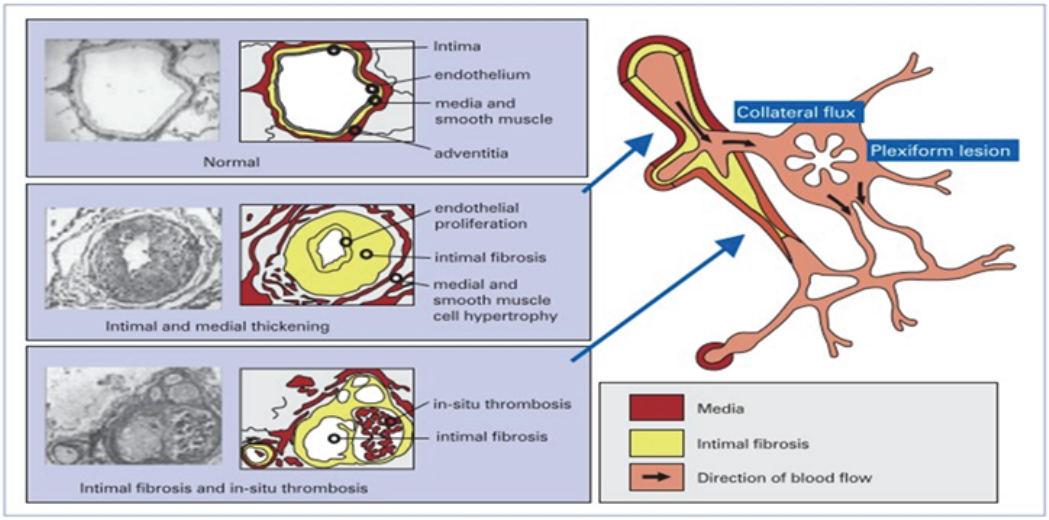

Figure 1: PAH: Histopathological Features

Figure 2: PAH: Clinical presentations

Pulmonary hypertension

- CT Chest: Identify parenchymal and mediastinal lesions.
- MRI: Find out cardiac anomalies.
- Radionuclide Ventriculography: Assesses Right ventricular and Left ventricular function.
- Right Heart Catheterisation: To confirm the Pulmonary hypertension and further management.

1. Accurate the measurement of pulmonary arterial pressure, cardiac output and Left ventricular pressure
2. Useful for drug testing with low acting pulmonary vasodilator can be treated with calcium channel blockers.

- Lung Biopsy: Histology confirmation of pulmonary vasculitis, veno-occlusive disease and interstitial lung disease

1.8 Management of PAH

A) Primary therapy

Primary therapy indicates the underlying cause of pulmonary hypertension. It includes oxygen, diuretics, digoxin and anticoagulant therapy.

- Diuretics: used to reduce fluid retention in pulmonary hypertension, diminishing the hepatic congestion and peripheral edema [14].
- Exercise: Low-level of exercise training can be improved exercise capacity, 6-minutes walk test, quality of life, World Health Organization functional class and high oxygen consumption [15]. Patients are also advised to avoid physical exertion or isometric exercises, as they can induce syncope [16].
- Oxygen: on flow oxygen administration remains the mainstay of therapy in group III pulmonary hypertension patients. Two large clinical trials studying patients with chronic obstructive pulmonary disease, the common cause of group III pulmonary hypertension, showed the continuous oxygen therapy reduced mortality, but the survival advantage did not appear until after 500 days of therapy [17, 18].
- Digoxin: It can improve the left ventricular ejection fraction in group III pulmonary hypertension patients with COPD and biventricular failure [20].

B) Anticoagulation Therapy-

Patients with pulmonary hypertension are vulnerable for thromboembolic disease because of sluggish blood flow, dilated right heart chambers, venous stasis and sedentary lifestyle in an already compromised pulmonary circulation. Various studies have shown that anticoagulation therapy indicated in patients with idiopathic pulmonary hypertension, hereditary pulmonary hypertension, and drug-induced pulmonary hypertension [21,22]. Patients who are with advanced pulmonary hypertension should receive anticoagulation therapy in the absence any contraindications [16]. A decrease of mortality with warfarin therapy was observed and finds in 5 out of 7 studies evaluating the effect of warfarin in patients with group I pulmonary hypertension [21].

Pharmacological treatment

Figure 3: It depicts an algorithm for the pharmacological treatment of pulmonary hypertension on the criteria of assessment disease severity. According to scenario, PDE5 inhibitors or endothelin receptor antagonists are normal initial therapies for patients who have undertaken mild to moderate pulmonary hypertension or for patients who are not more invasive therapies. Such that intravenous therapies with a prostacyclin analogue should be involved as a first-line therapy for patients with symptoms or for patients whose disease progresses on less invasive therapy. There are several approved agents for pulmonary hypertension, including Prostacycline and prostacycline analogues, Phosphodiestarase-5 inhibitors, a soluble guanylylcyclase stimulator and endothelin receptor antagonist, it should be improved the outlook dramatically. Although there is no cure for pulmonary hypertension, current pharmacologic therapies improve morbidity and mortality.

- Calcium-channel blockers: Calcium-channel blockers can be a effective treatment for patients with acute response to vasodilator testing. Long-acting nifedipine, diltiazem, and amlodipine they are the most commonly-used agents. Due to its potential for negative inotropic effects, verapamil should be avoided. Nifedipine up to 90 mg daily. diltiazem up to 720 mg daily [22].
- Prostacyclins: There are multiple prostanoids frequently available. Prostacycline [PGI2] activates cyclic adenosine mono phosphate [c-AMP] dependant pathways that mediatevasodilation.PGI2 also has antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation [23].
- Endothelin Receptor Antagonists: Endothelin receptor antagonists act as selectively blocking endothelin-A receptors or by dual blockage of endothelin-A and -B receptors, they constituted the first class of drugs in orally administered in pulmonary hypertension [21, 22]. Macitentan, a nonselective endothelin-A and -B receptor antagonist, has been increased tissue penetration and more sustained receptor blockade compared with bosentan 10 mg PO every day [27].
- Nitric oxide: Nitric oxide is a potent vasodilator of the pulmonary circulation, its act through the increase cyclic guanosine monophosphate and mainly result of degradation by PDE-5. Reduction in the expression of Nitric oxide synthase has describes a mechanism associated with the pathogenesis of pulmonary hypertension [28]. Currently, there are two therapeutic classifications of drugs interacting in the Nitric oxide pathway, it aiming to increase the direct action of cGMP, PDE-5 inhibitors, which decrease cGMP degradation and soluble guanylate cyclase stimulators, which increase cGMP production.

- Phosphodiesterase Type 5 Inhibitors: Sildenafil is currently approves a dose of 20 mg 3 times a day. Tadalafil is approved a dose of 40 mg once daily. The most common side effects of the PDE-5 inhibitors are headache, flushing, dyspepsia, myalgia, and epistaxis.
- Soluble Guanylate Cyclase Stimulators: Riociguat is a first class soluble guanylate cyclase stimulator. It directly stimulates the soluble guanylate cyclase independent of nitric oxide and increases the sensitivity of soluble guanylate cyclase to nitric oxide [29, 30]. The most common adverse events are syncope, headache, dyspepsia, peripheral edema and hypotension.Concomitant use of riociguat and PDE-5 inhibitors is contraindicated because of hypotension.

Surgeries:

- Atrial Septostomy: Atrial septostomy is conflicted as patients with severe pulmonary hypertension and right heart failure despite maximal medical therapy. Atrial septostomy conducts a shunt between the right and left atria, decreasing right ventricular filling, improving right ventricular function and increasing left ventricular filling space.
- Lung and Combined Heart and Lung Transplantation: Lung transplantation is end considered therapy option for all selected patients of pulmonary hypertension. Single lung transplantation, double lung transplantation and combined heart and lung transplantation have been performed worldwide in adults for the primary indication of pulmonary hypertension [31].
- Pulmonary Thromboendarterectom: Patients with chronic Thromboembolic Pulmonary Hypertension should have considered a pulmonary angiogram.

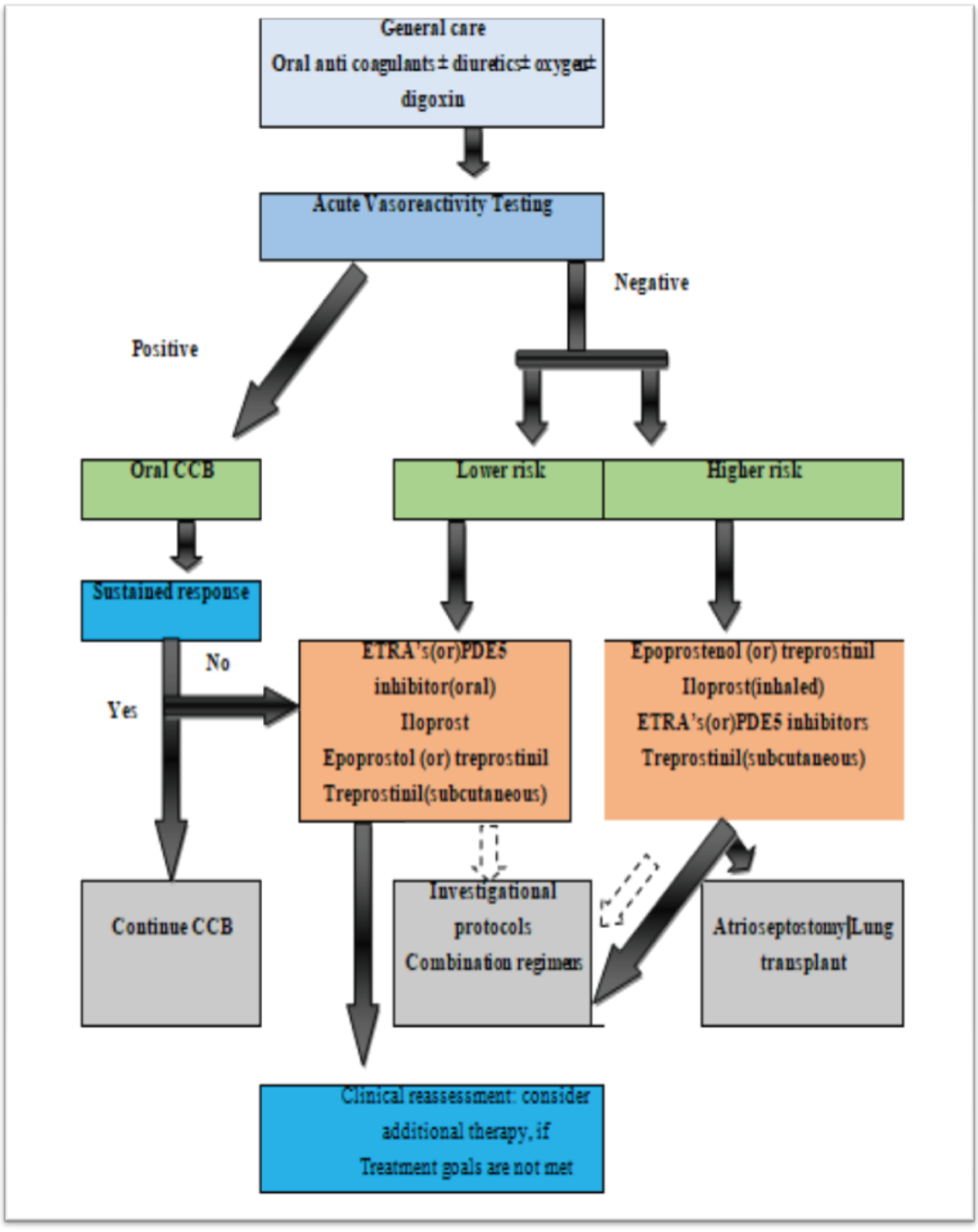

Figure 3: PAH: Pharmacological treatment Algorithm

2. Materials and Methods

A study of prescribing patterns and adverse drug reactions in pulmonary hypertension followed by materials and methods.

2.1 Study design

Prospective observational study

2.2 Study area

Department of Cardiology, SRI VENKATESWARA ISTITUTE OF MEDICAL SCIENCES (SVIMS), Tirupathi.

2.3 Duration of study

Study was conducted a period of 6 months from August 2018 – January 2019

2.4 Study Population

Patients who are taken consultation with doctor in outpatient department with the diagnosis of Pulmonary Hypertension in the Department of Cardiology, SVIMS.

2.5 Sample Size

30 pulmonary hypertension Patients

2.6 Inclusion Criteria

- Confirmed diagnosis for idiopathic pulmonary hypertension.
- Patients above 18 years of age
- Patients who are willing to participate

2.7 Exclusion Criteria

- Pregnant women
- Patients with other cardiac conditions like systemic hypertension and coronary heart disease.
- Patients with other co-morbid conditions like Renal disease, Hepatic disease and Neurological conditions

2.8 Study Materials

- Informed Consent Form [Annexure -I]
- Patient data collection Form [Annexure -II]
- ADR reporting Form [Annexure -III]
- Morisky medication adherence scale [Annexure-IV]

2.9 Method of Study

Patients who attended in cardiology department with diagnosis of pulmonary hypertension in the period from Aug 2018-Jan 2019 assessed prospectively using their Medical case sheets and prescriptions. The data was collected in patient data collection form- demographic details [Name, Age, Sex], Therapy [Name of the Drug, Dosage Form, Dose, route of administration, frequency], Lab investigations and Echo-graphic data. A study of prescribing patterns in pulmonary hypertension, all the patients included in the study and divided into two groups depending upon the age factor, gender. Different classes of drugs and as well as individual drugs prescribed for patients were calculated and presented in percentage. The average number of drugs in each prescription and the percentage of drugs prescribed by generic name were mentioned.

3. Results

3.1 Categorization based on gender

In our study population out of 30 subjects 17(57%) were males and 13(43%) were females

3.2 Categorization based on age

We categorized the patient to their age groups. The average age of total study population is 37.5. Out of 30 Subjects 8 (27%) of them were from age group 20-29 years, followed by 05 (17%) from 10-19 years, 05 (17%) from 30-39 years, 04 (13%) from 40-49 years, 04 (13%) from 50 - 59 years, 03 (10%) from 70-79 years, then finally 01 (3%) from 60-69 years.

3.3 Categorization based on social habits

Out of 30 subjects 6 (20%) were Alcoholism followed by 4 (13%) were Smoking, 4 (13%) were Alcoholism with Smoking then finally 5 (17%) were Quit [Alcoholism / Smoking]. In our study population 11 (37%) were Non Alcoholism & Smoking.

3.4 Categorization based on diagnosis

In our study the patients were diagnosed pulmonary artery hypertension through 2D Echo. In that we found various conditions, out of 30 subjects 19 (63%) were Idiopathic PAH, followed by 5 (17%) were VSD with PAH, 4 (13%) were ASD with PAH, finally 1 (3%) were ASD with Eisenmenger and VSD with Eisenmenger.

3.5 Prescribing patterns of drugs

Out of 30 subjects 24 [28%] were treated with Sildinafil, followed by 24 [28%] were treated with digoxin ,19[22%] were treated with Torsemide + spironolactone in combination, 7[8%] were treated with Acenocoumarol, 5[6%] were treated with Spironolactone + furosemide in combination then finally 2 [2%] were treated with following Metaprolol, Metolazone and Torsemide Table 1 Explains distribution based on commonly prescribed drugs among the total study population.

Table 1: Distributions Based on Commonly Prescribed Drugs

S.No	Prescribed Drugs	No. of prescriptions drugs *(N=85)*	% Percentage
1	Sildenafil	24	28
2	Digoxin	24	28
3	Torsemide+spironolactone	19	22
4	Spironolactone+furosemide	5	6
5	Acenocoumarol	7	8
6	Metaprolol	2	2
7	Metolazone	2	2
8	Torsemide	2	2

3.6 Distribution Based on Medication Adherence

Among prescribed class of drugs diuretics constitute 28(33%),then followed by phosphodiesterase inhibitors and cardiac glycosides24(28%),anticoagulants constitute 7(8%)and beta blockers constitute 2(2%). Table 2: Explains Distribution Based on Medication Adherence.

Table 2: Distribution Based on Medication Adherence

S.No	Class of Drugs	No.of drugs *(N=85)*	Percentage (%)
1	Phosphodiesterase Inhibitors	24	28
2	Cardiac Glycosides	24	28
3	Diuretics	28	33
4	Anticoagulants	7	8
5	Beta Blockers	2	2

3.7 Prescribing Pattern of Idiopathic PAH

In idiopathic PAH most of the subjects 7(37%) are prescribed with four drug therapy,5(26%) were prescribed with triple drug therapy,4(21%) were treated with five drug therapy,2(11%) were prescribed with double drug therapy, followed by 1(5%) prescribed with six drug therapy.

3.8 Prescribing Pattern of ASD with PAH

In ASD with PAH, 2(50%) were prescribed with triple drug therapy and 2(50%) were treated with quadrant drug therapy.

3.9 Prescribing Pattern of VSD with PAH

In VSD with PAH 2(40%) were treated with double drug therapy and 2(40%) were prescribed with four drug therapy, followed by 1(20%) were prescribed with triple drug therapy.

3.10 Prescribing Pattern of ASD with Eisenmengers

In ASD with Eisenmengers 1(100%) prescribed with triple drug therapy. Table 3: Explains distribution of type of therapy based on ASD with Eisenmengers on among the total study population.

Table 3: Distribution of Type of Therapy Based on ASD with Eisenmengers

S.No	Type of therapy	No. of Subjects(*N*=1)	Percentage (%)
1	Double Drug Therapy	0	0
2	Triple Drug Therapy	1	100
3	Four Drug Therapy	0	0
4	Five Drug Therapy	0	0
5	Six drug therapy	0	0

3.11 Prescribing Pattern of VSD with Eisenmengers

In VSD with Eisenmengers 1(100%) prescribed with quadrant drug therapy. Table4: Explains distribution of type of therapy based on VSD with Eisenmengers among the total study population.

Table 4: Distribution of Type of Therapy Based on VSD with Eisenmengers

S.No	Type of therapy	No. of Subjects(N=1)	Percentage (%)
1	Double Drug Therapy	0	0
2	Triple Drug Therapy	0	0
3	Four Drug Therapy	1	100
4	Five Drug Therapy	0	0
5	Six drug therapy	0	0

3.12 Adverse Drug Reactions

Sildenafil: In our study out of 24 subjects 17 patients were experienced Penile Erection

Digoxin: In our study out of 24 subjects 4 patients were experienced Gynaecomastia.

3.13 Medication Adherence

Out of 30 subjects 17(57%) were with medium adherence followed by 8(27%) were with high adherence and 5(17%) were with low adherence. Table 5 Explains distribution based on medication adherence among the total study population.

Table 5: Distribution Based on Medication Adherence

S.No	Type of Adherence	Male	Female	Total	Percentage (%)
1	HIGH	4	4	8	27
2	MEDIUM	9	8	17	57
3	LOW	4	1	5	17

4. Discussion

There is no data available on the prescribing patterns in PAH. This is the first study that describes the prescribing patterns of PAH in a tertiary care hospital, SVIMS. In our study we observed 17 (57%) were males and 13 (43%) were females. this is supported by a retrospective study done by Babu B, at Manipal University, India .their study revealed that out of 125 patients, male predominance (54%) with a median age of 60 was observed. In our study population the Mean ± SD of age was found to be 37.5± 17.43. Among 30 subjects we observed that most of the subjects were from age group of 20-29 which constitutes of 8(27%), followed by 5(17%) from 10-19 and 5(17%) from 30-39,4(13%) were from 40-49,4(13%) were from 50-59 ,3(10%) from 70-79 and 1(35) were from 60-69. Among the various categories of PAH, we observed 19 (63%) IPAH have the high incidence when compared to others with categories, Such as VSD with PAH, 4 (13%) were ASD with PAH, 1 (3%) were ASD with Eisenmenger and finally 1 (3%) were VSD with Eisenmenger. In PAH most commonly, prescribed drugs were sildenafil (28%) and digoxin (28%) followed by supportive therapy of diuretics and anticoagulants.

In IPAH

In our study we observed that most of the subjects with idiopathic PAH(37%) were treated with four Drug Therapy, compared to others therapies such as Triple Drug Therapy (26%) and five Drug Therapy (21%).

ASD with PAH

We observed that most of subjects with ASD with PAH 2(50%) were prescribed with triple and four drug therapy respectively.

VSD with PAH

Subjects with VSD with PAH 2(40%) were prescribed with double and four drug therapy respectively, then followed by 1(20%) were prescribed with triple drug therapy.

ASD with Eisenmenger's

Subjects with ASD with Eisenmenger's were 1(100%) prescribed with triple drug therapy.

VSD with Eisenmenger's

Subjects with VSD with Eisenmenger's were 1(100%) prescribed with triple drug therapy.

Medication Adherence

We observed that most of the subjects (57%) have medium adherence, followed by 8(27%) with high adherence and 5(17%) with low adherence. In our study we observed penile erection with Sildenafil in 17 patients and Gynacomastia with Digoxin in 4 patients during therapy.

5. Conclusion

Based on results we would like to conclude that males were more predominant than females. Adults were more prone to PAH. IPAH is the most common type. most of the IPAH patients were prescribed with four drug therapy, ASD with PAH patients were prescribed with triple and four drug therapy, VSD with PAH were prescribed with double and four drug therapy and ASD with Eisenmenger and VSD with Eisenmenger were prescribed with triple drug therapy..The average number of drugs prescribed per prescription was three and among them one drug (Sidenafil) was prescribed for pulmonary hypertension and others were used as supportive therapy. Most of the patients have medium adherence. In our study we observed penile erection with Sildenafil in 17 patients and Gynacomastia with Digoxin in 4 patients during therapy. As we have studied only 30 patients, these results may or may not be same. If we do in large sample size, so more studies with large sample size are needed to confirm the prescription patterns.

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Ethical Approval

We have obtained the patient's informed consent from every participant and our research protocol approval number was 802 given by Ethical committee.

Conflict of Interest

Authors declare that they have no conflict of interest.

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