

## Original Article

### Drug Utilization in Resistant Hypertension

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**Background :** Resistant Hypertension (RHT) is defined as a Blood Pressure (BP) that remains above 140/90 mmHg despite concurrent use of three antihypertensive agents of different classes taken at maximally tolerated doses, one of which should be a diuretic. Specifically, the triple combination of an Angiotensin-Converting Enzyme (ACE) inhibitor or Angiotensin Receptor Blocker (ARB), a long-acting Dihydropyridine Calcium Channel Blocker Amlodipine and a long-acting Thiazide-like diuretic is often effective and generally well tolerated.

**Aims and Objectives :** (1) To measure the prevalence of RHT at a Tertiary Care Hospital. (2) To identify the RHT related morbidity. (3) To identify the drug /drug combinations suggested in the treatment of RHT.

**Materials and Methods :** After IHEC approval a retrospective cross sectional clinical study was performed at General Medicine and Cardiology department using IP resistant hypertension case records for a period of 1 year January, 2018 to December, 2018 using Data collection tool and analyzed after calculating sample size using global prevalence rate 10.3%.

**Results :** Prevalence of RHT was 3.45%. The combination used predominantly was ACE inhibitor with a Diuretic and Beta blocker. Co-morbidity observed were Coronary Artery Disease [64%], Diabetes [57%], Dyslipidemia [22%], CKD [23%], Hypothyroidism [10%].

**Conclusion :** Majority of the RHT patients were on 3 or more drug therapy and CAD co-morbidity was high.

[J Indian Med Assoc 2023; 121(12): 21-3]

**Key words :** Resistant Hypertension, Diuretics, ACE Inhibitors, Comorbidity.

**R**esistant Hypertension (RHT) is defined as a Blood Pressure (BP) that remains above goal despite concurrent use of three antihypertensive agents of different classes taken at maximally tolerated doses, one of which should be a diuretic. True resistant hypertension requires that white coat hypertension and nonadherence to treatments have both been excluded as reasons for the uncontrolled BP<sup>1</sup>.

Resistant Hypertensions are at high risk for adverse cardiovascular events and hence fast reduction in BP is must. Obstructive sleep apnea, Renal parenchymal disease, Primary Aldosteronism, Renal artery stenosis, Cushing's disease, Aortic coarctation and Hyperparathyroidism are some of the reasons for resistant hypertension when a person even on regular drug treatment<sup>2</sup>.

#### Review of Literature :

Common approach is to treat RHT by sequentially combine agents with different mechanisms of action. Specifically, the triple combination of an Angiotensin-Converting Enzyme (ACE) inhibitor or Angiotensin

#### Editor's Comment :

- Resistant hypertension is an emerging disease.
- Physicians have to titrate one drug to the maximum dose then have to add the next drug.
- Hyperaldosteronism has to be checked for RHT patients.

Receptor Blocker (ARB), a long-acting Dihydropyridine Calcium Channel Blocker (CCB) Amlodipine and a long-acting thiazide-like diuretic is often effective and generally well tolerated. RHT are treated with at least three antihypertensive agents, including a diuretic (usually a thiazide, but loop diuretics are selected in patients with estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m<sup>2</sup>)<sup>3,4</sup>.

eGFR is an important clinical aid to apply diuretics in RHT. Thiazide-type diuretic (Hydrochlorothiazide), choice of therapy for patients who have an eGFR ≥30 mL/min/1.73 m<sup>2</sup>. Even after addition of Thiazides if persistent signs of hypervolemia (edema), the recommended drug is a loop diuretic<sup>5</sup> (Furosemide / Bumetanide/Torsemide). Hypokalemia is a more common problem in patients with resistant hypertension due to at least in part to higher aldosterone levels and can be treated with Spironolactone.

Patient preferences, drug side effects and compliance can help to select choice of drug treatment. A Vasodilating Beta Blocker, such as labetalol, carvedilol, or nebivolol may be preferred with tachycardia. To provide more antihypertensive benefit

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Received on : 14/02/2023

Accepted on : 16/03/2023

with fewer side effects compared with traditional beta blockers<sup>6</sup>.

Pseudo-resistant (seemingly resistant) hypertension is high BP that seems to be resistant to treatment, but other factors like Wrong medication or wrong dose, improper Medicines and supplements, Lifestyle factors, White-coat effect, Stiffening of the arteries, Inadequate measurement technique<sup>7</sup>.

The prevalence of RHT is unknown. Cross-sectional studies and hypertension outcome studies suggest, that it is not uncommon. National Health and Nutrition Examination Survey (NHANES) participants being treated for hypertension, only 53% were controlled to <140/90 mm Hg<sup>1</sup>. In a cross-sectional analysis of Framingham Heart Study participants, only 48% of treated participants were controlled to <140/90 mm Hg and less than 40% of elderly participants (>75 years of age) were at a goal BP<sup>8</sup>. Among higher-risk populations and, in particular, with application of the lower goal blood pressures recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) for patients with Diabetes Mellitus (DM) or Chronic Kidney Disease (CKD), the proportion of uncontrolled patients is even higher. Of NHANES participants with Chronic Kidney Disease (CKD), only 37% were controlled to <130/80 mm Hg<sup>9</sup> and only 25% of participants with diabetes were controlled to <130/85 mm Hg<sup>10</sup>.

RHT is called "refractory" when it remains uncontrolled on five or more antihypertensives of different classes including a diuretic and a Mineralocorticoid receptor antagonist<sup>11</sup>. When white coat or masked HTN is suspected, an ambulatory BP monitor can help. One study found that more than 37% of those with a diagnosis of RHT had normal BPs on ambulatory monitoring. Similarly, individuals with correctly calibrated BP cuffs can measure their BP at home to assist in the assessment of their usual BP. It is vital to obtain as accurate an assessment of BP as possible, certainly before a diagnosis of RH is diagnosed<sup>12</sup>.

Since prevalence of RHT is variable throughout country and globally due to many patient related factors and is a major barrier to stop avoidable cardiac and renal morbidity and mortality. Hence, this study has been planned to assess the prevalence and cardio renal complication with RHT.

#### AIMS AND OBJECTIVES

- (1) To measure the prevalence of RHT at a Tertiary Care Hospital.
- (2) To identify the RHT related morbidity.

(3) To identify the drug /drug combinations practiced in the treatment of RHT.

**Study Type** : A retrospective cross sectional clinical study.

**Study Location** : PSG IMSR General Medicine and Cardiology Departments, Peelamedu, Coimbatore.

**Study Populations** : SHT patients attending PSG IMSR General Medicine and Cardiology Departments, Peelamedu, Coimbatore.

**Sample size** :  $n = Z^2 P(1-P) / d^2$  Where n is the sample size, Z is the statistic corresponding to level of confidence, P is expected prevalence (that can be obtained from same studies or a pilot study conducted by the researchers) and d is precision (corresponding to effect size). The level of confidence usually aimed for is 95%, most researchers present their results with a 95% Confidence Interval (CI). Prevalence rate 10.3%<sup>13</sup>.

$$n = Z^2 pq / d^2$$

n = sample size and z = confidence level at 95% (std value 1.96)

p, q = variance of population

$$q = 1 - P$$

d = allowance error 5% and (Precision) d = 0.05  
Prevalence = 10.3%

$$p = 0.10$$

$$q = (1 - p) = 0.90$$

$$N = \frac{(1.96)^2 \times 0.10 \times 0.90}{(0.05)^2}$$

$$= \frac{0.3457}{0.0025} = 138.28$$

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$$n = 138$$

**Study Data** : Patients IP and OP records of PSG IMSR Hospitals Medicine and Cardiology departments, Peelamedu COIMBATORE.

**Study period** : January, 2018 to January, 2019

**Mode of data Collection** : Through data collection tool (attached)

IHEC Approval

#### MATERIALS AND METHODS

Analysis using suitable statistical method

Data collection using data collection tool and Documentation

General Medicine, Cardiology [resistant hypertension IP/OP case sheets cases record will be collected from MRD]

**Inclusion Criteria** : All patients attending General Medicine and Cardiology departments above 18 years with or without Co-morbidities and on antihypertensive treatment both IP and OP.

**Exclusion Criteria :** Patients admitted in other wards and on any other complications including HT emergency and urgency.

**Statistics :** Descriptive statistics.

**Results :** Prevalence of RHT was 3.45%. The combination used predominantly was ACE inhibitor with a Diuretic and Beta Blocker. Co-morbidity observed were Coronary Artery Disease [64%], Diabetes [57%], Dyslipidemia [22%], CKD [23%], Hypothyroidism [10%] (Tables 1-3).

Co-morbidity	Percentage
CAD	64%
Hypothyroidism	10%
Diabetes	57%
Dyslipidemia	22%
CKD	23%

Drug Combinations	No of patients
ACE I + Diuretic + Beta Blocker	64
ARB + Diuretic + Beta Blocker	22
CCB + Beta Blocker + Diuretic	9
CCB + ARB + Diuretic	5
CCB + ARB+ Alpha Blocker + Diuretic	8

Combination therapy	No of patients
No of patients on 3 drug therapy	100
No of patients on 4 drug therapy	33
No of patients on 5 drug therapy	5

### DISCUSSION

Prevalence of RHT was less (3.45%) when we compare to Global Prevalence Rate (10.3%). Even though we had reduced prevalence, the patients are not treated with maximum doses of drugs in combination therapy. Only those patients started with Thiazide Diuretics showed a greater reduction in BP in a month. But in many of them Thiazide are not given at the maximum dose (50 mg) The burden of Resistant Hypertension (RHT) is highest in patients with Chronic Kidney Disease (CKD) globally<sup>13</sup> but in our study Coronary Artery Disease was the main co-morbidity. New treatments for RHT are highly needed, considering the disastrous complications of the disease. Physicians must give full dose of one drug for Hypertension if patient not responded then only they have to switch over to next drug therapy for patient compliance and manual record of BP must be advised to every patient.

### CONCLUSION

Majority of the RHT patients were on 3 or more drug therapy and Coronary Artery Disease Co-morbidity was high. Prevalence of RHT was less (3.45%).

### ACKNOWLEDGEMENT

I express my deepest gratitude and sincere thanks to Dr K Bhuvaneshwari, MD, PGDBE, Professor and Head, Department of Pharmacology of PSG Institute of Medical Sciences & Research, for being my guide. It was her mentoring, valuable suggestions, guidance and constant encouragement in every step that has helped me to complete my research work.

I am thankful to my family members from my heart for unwavering confidence they have rendered on me throughout the study and encouraging me to complete my research work and they are my pillars of support.

I would like to thank all my Co-workers in this study.

**Conflict of Interest :** Nil

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