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EVALUATION OF RATIONAL DRUG USE AND EFFICACY OF VARIOUS COMBINATIONS OF ANTIHYPERTENSIVE DRUGS COMMONLY PRESCRIBED FOR THE MANAGEMENT OF HYPERTENSION IN CKD PATIENTS AT T TERITARY CARE HOSPITAL

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Keywords:

Antihypertensive drugs, Rational drug use, Tertiary care hospital, Calcium channel blockers, Beta-blockers

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ABSTRACT: To evaluate the rational drug use and efficacy evaluation of various combinations of Antihypertensive drugs commonly prescribed for the management of hypertension in CKD patients at tertiary care hospitals. This is an observational and comparative study. A randomized trial was carried out in 300 patients after obtaining the consent for 1 year in a tertiary care hospital in Mahabubnagar. The data collection form was prepared and used. This form mainly contains the patient's demographic details and medication chart with diagnosis. Also, prescription pattern of the patient, daily usage of antihypertensive. Antihypertensive, antacids and anti-diabetics were the most prescribed drugs. A substantial number of drugs prescribed to patients with CKD were not appropriately adjusted. Inappropriate prescribing was associated with ADRS, and drug interactions. In the study, six antihypertensive combinations were observed in that CCB's were the most frequently prescribed drug category in patients with HTN and CKD.

INTRODUCTION: Chronic kidney disease occurs when one suffers from gradual and usually permanent loss of kidney function over time. This happens gradually, usually over months to years. The term "renal" refers to the kidney, so another name for kidney failure is "renal failure. Mild kidney disease is often called renal insufficiency [1]. Chronic kidney disease (CKD) is defined as persistent kidney damage accompanied by a reduction in the glomerular filtration rate (GFR) and the presence of albuminuria [2].

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HTN has been reported to occur in 85% to 95% of patients with CKD (stages 3-5) [3]. The relationship between HTN and CKD is cyclic in nature. Progressive renal disease can exacerbate uncontrolled HTN due to volume expansion and increased systemic vascular resistance.

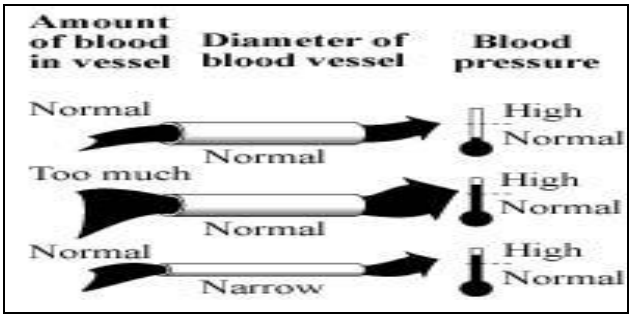

FIG. 1: HYPERTENSION CAN RESULT FROM TOO MUCH FLUID IN NORMAL BLOOD VESSELS OR FROM NORMAL FLUID IN NARROW, STIFF, OR CLOGGED BLOOD VESSELS

Multiple guidelines discuss the importance of lowering blood pressure (BP) to slow the progression of renal disease and reduce cardiovascular morbidity and mortality [4-6]. However, in order to achieve and maintain adequate BP control, most patients with CKD require combinations of antihypertensive agents; often, up to three or four medication classes may need to be employed [7].

Goals of Therapy: Patients with nondiabetic and diabetic CKD should have a target BP goal of <130/80 mm Hg[4-6]. Ultimately, the rationale for lowering BP in all CKD patients is to reduce renal and cardiovascular morbidity and mortality. Maintaining BP control and minimizing proteinuria in patients with CKD and HTN is essential for the prevention of the progression of kidney disease and the development or worsening of CVD.

Recent literature suggests that BP targets in diabetic and nondiabetic CKD may need to be individualized based on proteinuria. Some trials have failed to show a reduction in cardiovascular or renal outcomes in diabetic and nondiabetic patients with CKD when a BP target of <130/80 mmHg is achieved compared to lowering BP to <140/90 mm Hg [8, 9] However, patients who have proteinuria are less likely to experience a decline in renal function, kidney failure, or death when the lower BP target is achieved [8, 10]. Future guidelines may likely include a lower BP goal, <130/80 mmHg, for patients with proteinuria but maintain a goal of <140/90 mm Hg for patients without proteinuria.

Rational Drug use: Irrational use of Medicines is a global phenomenon. Rational use of drugs may be defined as: Patients receive medications appropriate to their clinical needs, in doses that meet their requirements, for an adequate period of time, and at the lowest cost to them and their community. Overuse, polypharmacy, and incorrect use of drugs are the most common drug use problems today.

Irrational use of drugs may result due to various reasons, including prescribing errors and over-the-counter drugs. Irrational use of medicines may lead to serious negative health and economic consequences. Many irrational drug combinations are available in the Indian market. Proper implementation of rational drugs will improve the quality of life and result in better community healthcare [11].

Treatment: According to the updated 2014 Eighth Joint National Committee (JNC-8) guidelines on HTN, evidence from clinical trials indicate that antihypertensive medications (blood pressure medication) should be initiated in patients less than 60 years old if the systolic blood pressure is persistently >140 mmHg and the diastolic blood pressure is persistently >90 mm Hg despite non-pharmacologic therapy. If a patient is 60 years old and older, antihypertensive therapy should be initiated if the systolic blood pressure is >150 mmHg and the diastolic blood pressure is >90 mm Hg [12, 13].

All hypertensive patients should be counseled on the appropriate lifestyle modifications needed to help lower blood pressure. Evidence has shown that societies with an average sodium intake (more than 2.3 grams per day) have a greater number of patients diagnosed with HTN. High amounts of sodium intake lead to increased volume in the bloodstream. This places increased pressure on the heart to pump blood throughout the body. As a result, blood pressure can become elevated [13-15]. The American Heart Association (AHA) recommends limiting sodium intake to less than 1500 mg per day (1.5 grams). Since most dietary salt is found in packaged and processed foods, limiting their intake and finding healthier alternatives is beneficial for blood pressure reduction.

Restrictive diets, like the Dietary Approaches to Stop Hypertension (DASH) diet, have been found to help lower blood pressure. The DASH diet emphasizes a food plan high in fruits, vegetables, whole grains, poultry, and fish while limiting sweets, sugar-sweetened beverages, and red meat. Furthermore, the DASH diet recommends that men restrict alcohol intake to two or fewer drinks a day and women to one or less. This recommendation is based on evidence indicating that patients who excessively drink alcohol have had a higher incidence of high blood pressure than those who drink alcohol in moderation. In addition to dietary modifications, exercise is recommended [16].

Both aerobic exercise and resistance training have been shown to lower blood pressure and improve overall cardiovascular health. Examples of aerobic exercise include walking, jogging, swimming, and biking. The AHA recommends an average of 40 minutes of moderate to vigorous-intensity aerobic exercise three to four times a week to help lower blood pressure [17].

Pharmacological therapy is initiated if nonpharmacologic treatment is ineffective in managing high blood pressure. Initial pharmacological therapy for HTN includes thiazide diuretics, long-acting calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs). Blood pressure goals for HTN are specific to a patient's age and comorbid diseases. It is important to note that these goals are updated from those previously recommended in past guidelines (Seventh Joint National Committee Guidelines) [12-14]. Agents that not only lower BP but also reduce proteinuria are recommended as first-line therapy for most patients with CKD and HTN; data indicate there may be significant long-term benefits in both cardiovascular and renal outcomes when proteinuria is decreased [9].

Several classes of antihypertensive agents may have a role in the treatment of CKD and HTN. Agents that target the renin angiotensin aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), are generally considered first-line antihypertensive therapy for this patient population. The following are the various antihypertensive drugs [18].

ACE-Is and ARBs: ACE-Is block the conversion of angiotensin I to angiotensin II and the degradation of bradykinin. It seems likely that the accumulation of bradykinin leads to persistent dry cough, a recognized side effect which occurs in 5 to 20% of patients on ACE-Is. Angioneurotic edema can occur with ACE-Is and ARBs, although the relative frequencies and mechanism are unclear. ARBs act by competitively antagonizing the interaction between angiotensin II and angiotensin receptors and were first introduced as an alternative to ACE-Is in patients who had an ACE-I induced cough.

Drug Combinations: ACE-Is and ARBs are valuable adjuncts to diuretics for treating high BP and vice versa. Co-administration of beta-blockers and calcium channel blockers with ACE-Is or ARBs is also acceptable.

Diuretics: Salt and water retention are major factors contributing to high BP in CKD patients and to morbidity and mortality through systemic or pulmonary edema. Thus, diuretics potentially have an important role in controlling hypertension in this clinical setting.

Drug Combinations: Thiazides are often one of the first 2 or 3 drugs used for BP lowering in CKD, particularly if there is edema or if ACE-Is or ARBs have already been prescribed. Thiazides are known to potentiate the effect of other antihypertensive agents, particularly ACE-Is and ARBs, and may also reduce the risk of hyperkalemia. The inclusion of thiazides in fixed-dose combinations with other antihypertensives is convenient for patients and may improve compliance.

Beta-blockers: All beta-blockers effectively reduce BP; other issues may influence whether they are appropriate in a given patient and which specific drug is chosen since beta-blockers vary widely in their pharmacology.

Drug Combinations: Beta-blockers have often been combined with diuretics; there are no theoretical reasons why beta-blockers should not be combined with ACE-Is or ARBs.

The combination of atenolol or bisoprolol (which accumulate in CKD patients) with bradycardia-inducing drugs such as nondihydropyridine calcium-channel blockers is not recommended. The combination of lipophilic beta-blockers (which cross the blood-brain barrier) with other centrally acting drugs such as clonidine may lead to drowsiness or confusion, particularly in the elderly.

Calcium Channel Blockers: The major subclasses are the dihydropyridines (*e.g.,* amlodipine, nifedipine, and lercanidipine), the non-dihydropyridine benzothiazepines (*e.g.,* diltiazem) and the phenylalkylamines (*e.g.,* verapamil). Dihydropyridines tend to be more selective for vascular smooth muscle Vasodilatation with less action on the myocardium.

Accordingly, the side effects may include fluid retention and ankle edema, which can be problematic in patients with CKD. Dizziness, headache, and redness of the face are also common side effects.

Non-dihydropyridines directly affect the myocardium, including the sinoatrial and atrioventricular nodes, and reduce the heart rate and cardiac-muscle contraction.

Drug Combinations: Fluid retention, seen particularly with dihydropyridines, can be problematic in patients with CKD, such that avoiding other vasodilators may be sensible. Combining non-dihydropyridines such as verapamil and diltiazem with beta-blockers can lead to severe bradycardia, particularly in patients with advanced CKD if drugs such as atenolol and bisoprolol, (that accumulate in CKD) are used.

Centrally Acting Alpha-agonists: Centrally acting alpha-agonists cause vasodilatation by reducing sympathetic outflow from the brain. The main agents in use are methyldopa, and clonidine. They are valuable as an adjunct therapy for hypertension in CKD patients.

Drug Combinations**:** The combination of alpha-agonists with thiazides is probably advantageous in reducing vasodilatation-induced fluid retention. Combination with other antihypertensive drugs is usually trouble-free, but caution is advised if the agents have similar side effects.

Alpha-blockers: Alpha-adrenergic blockers selectively act to reduce BP by causing peripheral vasodilatation. Prazosin, doxazosin, and terazosin are the alpha-blockers most commonly used in treating hypertension. Alpha-blockers are an adjunctive treatment for elevated BP in CKD patients in whom ACE-Is, ARBs, diuretics, calcium-channel blockers, and beta-blockers have failed or are not tolerated. Alpha-blockers are not considered a first-line choice because of the common side effects of postural hypotension, tachycardia, and headache.

Drug Combinations: There is little data about alpha-blocker combinations with other BP-lowering drugs. Vasodilatation can lead to peripheral edema, so diuretics are commonly combined with alpha-blockers, although the efficacy of this maneuver has not been studied. Alternatively, a non-selective beta-blocker can be used.

Direct Vasodilators: Hydralazine and minoxidil act by directly causing vascular smooth-muscle relaxation and Vasodilation. Its side effects (*e.g*., severe fluid retention, headache, tachycardia, hirsutism, and pericardial effusion) limit its use to the most resistant cases.

Drug Combinations: Because of the side effects of fluid retention and tachycardia, direct vasodilators (especially minoxidil) are usually combined with a beta-blocker and loop diuretic.

MATERIAL AND METHODS:

Study Design: The study was observational study.

Source of Data and Materials:

- Patient consent form.
- Patient data collection form.
- Patient case note/prescription.

Inclusion Criteria:

- In patients of department of Nephrology and dialysis unit of SVS Hospital and Medical college.
- Male and female patients with no age restrictions.
- Patients with hypertension as a comorbid condition are included.

Exclusion Criteria:

- Patients who are not willing to give consent.
- Pregnant, Patients with comorbid other than listed in inclusion criteria.

Method of Data Collection:

- Data collection form
- Patient interview

Study Procedure: This is a comparative study where patients eligible are enrolled in the study after obtaining the consent. The data collection form will be prepared and used. This form mainly contains the patient's demographic details and medication chart with diagnosis. Also, the prescription pattern of the patient, daily usage of antihypertensive drugs percentage was calculated.

The study was conducted at SVS Medical College and hospital. All information relevant to the study was collected from the patients. The data was analyzed using a suitable method for statistical analysis.

RESULTS: During the 12 months of project work, 300 patients with hypertension and chronic kidney disease were observed at the tertiary care hospital, Mahabubnager.

TABLE 1: AGE DISTRIBUTION OF PATIENTS WITH HTN IN CKD

Age group	No. Of patients	Percentage (%)
20-30	34	11%
31-40	58	19%
41-50	86	29%
51-60	95	32%
61-70	27	9%

Among 300 patients, the highest incidence of hypertension was found in the age group of 51-60, and the lowest number of incidents were reported in the age group of 61-70. Among 300 patients observed in tertiary care hospitals, the above-average gender-wise incidence. Male incidence was found to be 69%, and female incidence was found to be 31%.

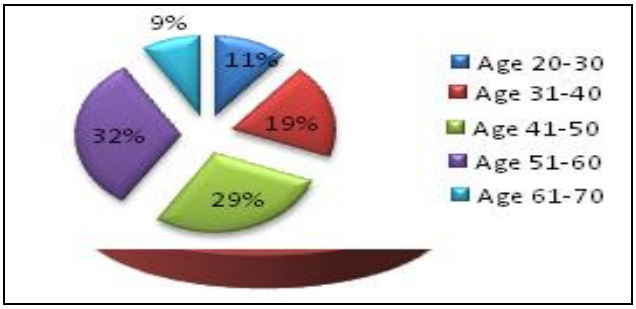

FIG. 2: AGE DISTRIBUTION IN HTN WITH CKD PATIENTS

TABLE 2: GENDER DISTRIBUTION OF PATIENTS WITH HTN IN CKD

Gender	No. of patients	Percentage (%)
Male	207	69%
Female	93	31%

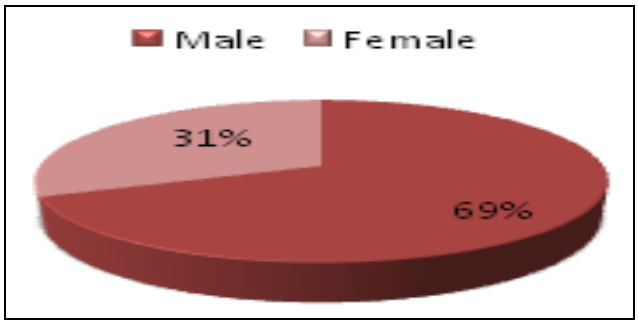

FIG. 3: % OF GENDER DISTRIBUTION IN HTN WITH CKD

TABLE 3: PERCENTAGE OF PATIENTS AT DIFFERENT SYSTOLIC BP RANGE

Hypertension Stage	Systolic Bp (Mm Hg)	No. of Patients	Percentage (%)
Mild	120-139 mm Hg systolic	96	32%
Moderate	140-159 mm Hg systolic BP	164	55%
Severe	≥60 mm Hg sytolic BP	40	13%

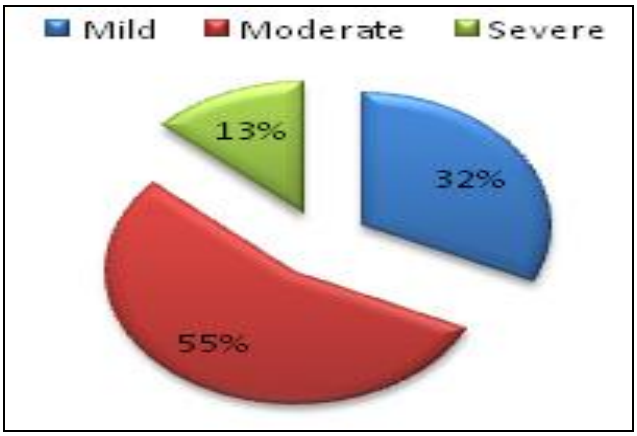

FIG. 4: PERCENTAGE OF PATIENTS AT DIFFERENT BP LEVELS

Among 300 patients, 96 patients have mild BP in a range of 120-139 mm Hg systolic, 164 patients have moderate BP in a range 140-159 mm Hg systolic, remaining 40 patients were observed with ≥60 mm Hg systolic BP.

TABLE 4: VARIOUS ANTIHYPERTENSIVE COMBINATIONS PRESCRIBED IN PATIENTS WITH HTN IN CKD

Antihypertensive combinations	No. of patients	Percentage (%)
ARB+CCB	22	7.30%
BB+CCB	50	16.60%
DU+ARB	41	14%
CCB	53	18%
CCB+BB+AB+AA	72	24%
CCB+DU+AB+AA	62	20.60%

From the data which was collected at tertiary care hospital, it was observed that among 300 patients, 22 patients were being prescribed an antihypertensive combination ARB's and CCB's, 50 patients were on BB and CCB combination therapy, 41 with DU and ARB's, 53 patients with CCB alone, 72 with CCB, BB, AB and AA, remaining 62 with CCB, DU, AB and AA combinations.

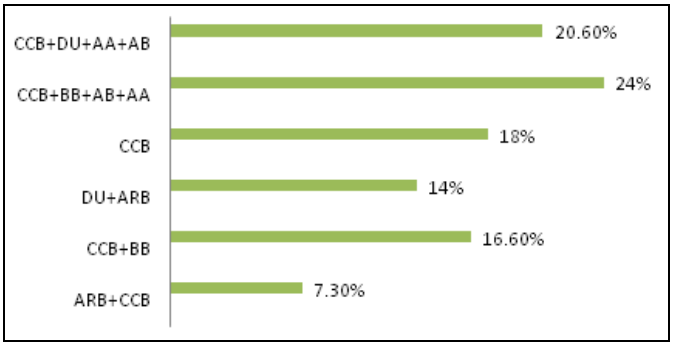

FIG. 5: PERCENTAGE OF VARIOUS ANTI-HYPERTENSIVE COMBINATIONS

TABLE 5: GFR LEVELS IN PATIENTS WITH HTN IN CKD

GFR (ml/min/1.73m2)	No. of patients	Percentage (%)
30-59	28	9%
15-29	230	74%
Less than 15	52	17%

From 300 patients 28 had GFR in range of 30-59, 230 were at GFR range of 15-29 and 52 patients were at GFR level below 15 which indicates severe loss of kidney function.

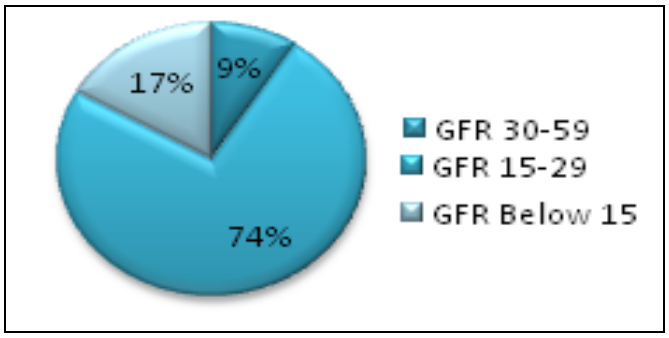

FIG. 6: PERCENTAGE OF PATIENTS AT DIFFERENT GFR LEVELS (ML / MIN / 1.73 M2

DISCUSSION: Among the study population, 207 (69%) were male, and 93 (31%) were female; the maximum number of patients were from the age group 51-60 years (31%) followed by the patients of age group 41-50 years (29%), age group 31-40(19%), 20-30(11%) and patients of >60 years (9%). Out of 300 patients, 96(32%) patients were at120-139 mm Hg systolic 164 (55%) at 140-159 mm Hg systolic BP, and 40(13%) had≥60 mm Hg systolic BP. Six various antihypertensive combinations were observed in the study in which ARB and CCB combination (7.30%), BB and CCB's (16.60%), DU and ARB (14%), CCB (18%), CCB, BB, AB, and AA, remaining (24%) and CCB, DU, AB and AA (20.60%). From 300 patients 9% patients were at GFR in range of 30-59 Ml/min/1.73 m^2, 74% patients were at GFR range of 15-29 Ml/min /1.73m^2 and 17% patients were at GFR below 15mlm/min/1.73m^2. Calcium channel blockers were the most commonly prescribed antihypertensive agents in patients with HTN and CKD at tertiary care hospitals. Dihydropyridines tend to be more selective for vascular smooth muscle Vasodilatation with less action on the myocardium. The combination of CCB's with beta-blockers provided adequate control of blood pressure in HTN and CKD patients and slowed the progression of CVD and CKD. CCB's alone was prescribed in most of the patients, which controlled BP effectively but CCB's and BB's combination was found to be more effective in moderate to severe hypertension, ARB's and CCB's are effective in controlling BP in CKD patients but was not frequently Prescribed at tertiary care hospital of Mahabubnagar. Diuretics are useful antihypertensives in controlling mild to moderate hypertension in CKD, it was found to be prescribed along with ARB's in initial stages of HTN and CKD patients. Alpha agonist /central sympatholytic agents and alpha-blockers were used in multiple antihypertensive therapy for controlling severe hypertension in CKD patients.

CONCLUSION: CCB's were most frequently prescribed drug categories in patients with HTN and CKD. CCB's and BB's combination therapy was found to be more effective in moderate to severe hypertension. CCB's, BB's, Alpha-blockers, and Centrally acting sympatholytics were prescribed multiple therapies in HTN and CKD patients for controlling severe hypertension in CKD.

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