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THESIS DISSERTATION

COMPARISON OF ANTIHYPERTENSIVE EFFECT OF MOXONIDINE VERSUS CLONIDINE IN RENAL FAILURE PATIENTS.

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INTRODUCTION

High Blood Pressure

Blood pressure is the force of blood pushing against blood vessel walls as the heart pumps out blood, and high blood pressure, also called hypertension, is an increase in the amount of force that blood places on blood vessels as it moves through the body. Factors that can increase this force include higher blood volume due to extra fluid in the blood and blood vessels that are narrow, stiff, or clogged(1).

High blood pressure can damage blood vessels in the kidneys, reducing their ability to work properly. When the force of blood flow is high, blood vessels stretch so blood flows more easily. Eventually, this stretching scars and weakens blood vessels throughout the body, including those in the kidneys.

If the kidneys' blood vessels are damaged, they may stop removing wastes and extra fluid from the body. Extra fluid in the blood vessels may then raise blood pressure even more, creating a dangerous cycle.

High blood pressure is the second leading cause of kidney failure . In addition, the rate of kidney failure due to high blood pressure increased 7.7 percent from 2000 to 2010.

CKD

Kidneys carry out the complex system of filtration in our bodies - excess waste and fluid material are removed from the blood and excreted from the body(2).

In most cases, kidneys can eliminate most waste materials that our body produces. However, if the blood flow to the kidneys is affected, they are not working properly because of damage or disease, or if urine outflow is obstructed, problems can occur.

Functions of kidney include:

-Regulation of blood ionic composition[3]

-Regulation of blood pH

-Regulation of blood volume

-Regulation of blood pressure

-Maintenance of blood osmolarity

-Production of hormones

-Regulation of blood glucose level.

Kidney failure:

Kidney failure occurs when your kidneys lose the ability to filter waste from your blood sufficiently. Many factors can interfere with your kidney health and function[2], such as:

- toxic exposure to environmental pollutants or certain medications
- certain acute and chronic diseases
- severe dehydration
- kidney trauma

Your body becomes overloaded with toxins if your kidneys can't do their regular job. This can lead to kidney failure and even be life-threatening if it's left untreated.

Chronic kidney disease[2] (CKD), also called chronic kidney failure, outline the gradual loss of kidney function. When CKD reaches an advanced stage, dangerous levels of fluid, electrolytes and wastes can build up in our body.

In the early stages of the disease, you may have few signs or symptoms. Treatment for chronic kidney disease focuses on slowing the progression of the kidney damage, usually by controlling the underlying cause. Chronic kidney disease can progress to end-stage kidney failure, which is fatal without artificial filtering (dialysis) or a kidney transplant.

Stages

Changes in the GFR rate can assess how advanced is the kidney disease, stages of kidney disease are classified as follows:

- Stage 1 – Kidney damage with normal or increased GFR ≥90ml⁄min.
- Stage 2 – Kidney damage with mild reduction in GFR (60-89ml⁄min).
- Stage 3 – Kidney damage with moderate reduction in GFR (30-59ml⁄min).
- Stage 4 – Kidney damage with severe reduction in GFR (15-29ml⁄min).
- Stage 5 - GFR rate is lower than 15ml⁄min and renal failure has occurred.

Majority of patients with chronic kidney disease rarely progress beyond Stage 2. It is important for kidney disease to be diagnosed and treated early for serious damage to be prevented.

Causes:

Progressive kidney damage is the result of a chronic disease (a long-term disease)[2], such as:

- Diabetes
- Hypertension (high blood pressure)
- Obstructed urine flow – Due to an enlarged prostate, kidney stones, or a tumor.
- Kidney diseases – including polycystic kidney disease, pyelonephritis, or glomerulonephritis.
- Kidney artery stenosis
- Certain toxins - including fuels, solvents (such as carbon tetrachloride), and lead (and lead-based paint, pipes, and soldering materials).
- Fetal developmental problem - if the kidneys do not develop properly in the unborn baby while it is developing in the womb.
- Systemic lupus erythematosus.
- Malaria and yellow fever
- Medications - NSAIDs (non-steroidal anti-inflammatory drugs), such as aspirin or ibuprofen.
- Illegal substance abuse - such as heroin or cocaine.
- Injury - a sharp blow or physical injury to the kidney(s)

Five types of kidney failure

There are five different types of kidney failure[4]:

- Acute pre-renal kidney failure

Insufficient blood flow to the kidneys can cause acute pre-renal kidney failure. The kidneys can't filter toxins from the blood without enough blood flow. This type of kidney failure can usually be cured once you and your doctor determine the cause of the decreased blood flow.

- Acute intrinsic kidney failure

Acute intrinsic kidney failure can be caused by direct trauma to the kidneys, such as physical impact or an accident. Causes also include toxin overload and ischemia, which is a lack of oxygen to the kidneys.

The following may cause ischemia:

severe bleeding.

shock.

renal blood vessel obstruction.

glomerulonephritis.

- Chronic pre-renal kidney failure

When there isn't enough blood flowing to the kidneys for an extended period of time, the kidneys begin to shrink and lose the ability to function.

- Chronic intrinsic kidney failure

This happens when there is long-term damage to the kidneys due to intrinsic kidney disease. Intrinsic kidney disease is caused by a direct trauma to the kidneys, such as severe bleeding or a lack of oxygen.

- Chronic post-renal kidney failure

A long-term blockage of the urinary tract prevents urination. This causes pressure and eventual kidney damage.

Pathophysiology of kidney disease

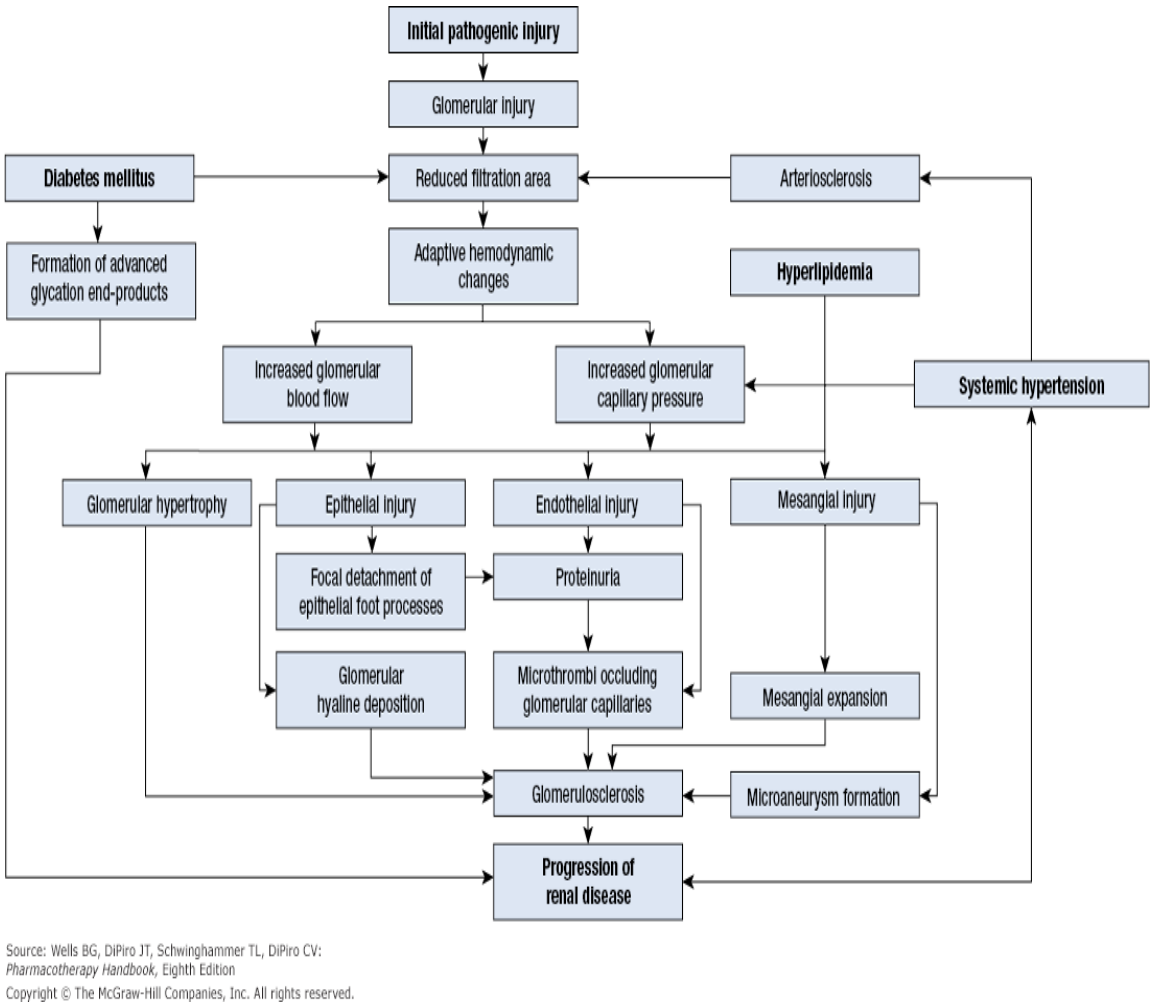


Figure1: Pathophysiology of kidney disease.

Symptoms:

Signs[4] and symptoms of kidney disease are often nonspecific, as kidneys are highly adaptable and able to compensate for lost function, signs and symptoms may not appear until irreversible damage has occurred. Some of the signs and symptoms of kidney disease may include:

- Sleep problems
- Loss of appetite
- Nausea and vomiting
- Fatigue and weakness
- Muscle twitches and cramps
- Swelling of feet and ankles

- Persistent itching
- Chest pain, if fluid builds up around the lining of the heart
- Shortness of breath, if fluid builds up in the lungs
- High blood pressure (hypertension) that's difficult to control

Risk factors:

Factors that may increase your risk of chronic kidney disease include:

- Diabetes
- High blood pressure
- Heart and blood vessel (cardiovascular) disease
- Smoking
- Obesity
- Family history of kidney disease
- Abnormal kidney structure
- Older age[3]

Complications:

Chronic kidney disease can affect almost every part of your body. Potential complications may include:

- Fluid retention, which could lead to swelling in your arms and legs, high blood pressure, or fluid in your lungs (pulmonary edema)
- A sudden rise in potassium levels in your blood (hyperkalemia), which could impair your heart's ability to function and may be life-threatening
- Heart and blood vessel (cardiovascular) disease
- Weak bones and an increased risk of bone fractures
- Anemia
- Decreased sex drive, erectile dysfunction or reduced fertility
- Damage to your central nervous system, which can cause difficulty concentrating, personality changes or seizures
- Decreased immune response, which makes you more vulnerable to infection
- Pericarditis, an inflammation of the saclike membrane that envelops your heart (pericardium)
- Pregnancy complications that carry risks for the mother and the developing fetus
- Irreversible damage to your kidneys (end-stage kidney disease), eventually requiring either dialysis or a kidney transplant for survival.[3]

Prevention:

- To reduce your risk of developing kidney disease[4]:
- Follow instructions on over-the-counter medications. Taking too many pain relievers could lead to kidney damage and generally should be avoided if you have kidney disease. Ask your doctor whether these drugs are safe for you.
- Maintain a healthy weight.This involves increasing daily physical activity and reducing calories.
- Don't smoke. Cigarette smoking can damage your kidneys and make existing kidney damage worse. If you're a smoker, talk to your doctor about strategies for quitting smoking.
- Manage your medical conditions with your doctor's help. If you have diseases or conditions that increase your risk of kidney disease, work with your doctor to control them.

Diagnosis

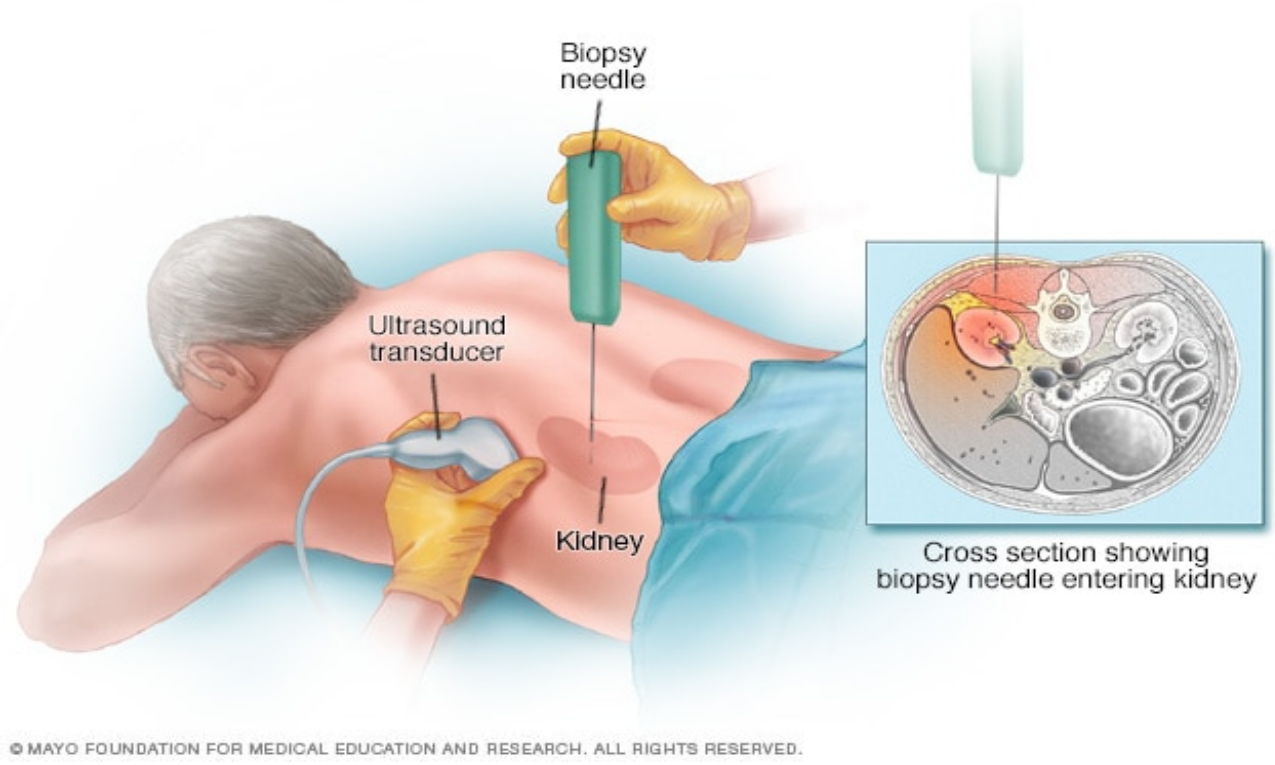


FIGURE 2: Biopsy of kidney

For kidney disease diagnosis, you may need certain tests and procedures, such as:

- Blood tests. Kidney function tests look for the level of waste products, such as creatinine and urea, in your blood.
- Urine tests. Analyzing a sample of your urine may reveal abnormalities that point to chronic kidney failure and help identify the cause of chronic kidney disease.
- Imaging tests. Your doctor may use ultrasound to assess your kidneys' structure and size. Other imaging tests may be used in some cases.

- Removing a sample of kidney tissue for testing. Your doctor may recommend a kidney biopsy to remove a sample of kidney tissue. Kidney biopsy is often done with local anesthesia using a long, thin needle that's inserted through your skin and into your kidney. The biopsy sample is sent to a lab for testing to help determine what's causing your kidney problem.

- Chest X-ray - the aim here is to check for pulmonary edema (fluid retained in the lungs).

- Glomerular filtration rate (GFR) - GFR is a test that measures the glomerular filtration rate - it compares the levels of waste products in the patient's blood and urine. GFR measures how many milliliters of waste the kidneys can filter per minute. The kidneys of healthy individuals can typically filter over 90 ml per minute.

Treatment:

There is no current cure for chronic kidney disease[5]. However, some therapies can help control the signs and symptoms, reduce the risk of complications, and slow the progression of the disease.

- Kidney transplant

Depending on the underlying cause, some types of kidney disease can be treated. Often, though, chronic kidney disease has no cure.

Treatment usually consists of measures to help control signs and symptoms, reduce complications, and slow progression of the disease. If your kidneys become severely damaged, you may need treatment for end-stage kidney disease.

- Treating the cause

Your doctor will work to slow or control the cause of your kidney disease. Treatment options vary, depending on the cause. But kidney damage can continue to worsen even when an underlying condition, such as high blood pressure, has been controlled.

- Treating complications

Kidney disease complications can be controlled to make you more comfortable. Treatments may include:

o High blood pressure medications. People with kidney disease may experience worsening high blood pressure. Your doctor may recommend medications to lower your blood pressure — commonly angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers — and to preserve kidney function. High blood pressure medications can initially decrease kidney function and change electrolyte levels, so you may need frequent blood tests to monitor your condition. Your doctor will likely also recommend a water pill (diuretic) and a low-salt diet.

o Medications to lower cholesterol levels. Your doctor may recommend medications called statins to lower your cholesterol. People with chronic kidney disease often experience high levels of bad cholesterol, which can increase the risk of heart disease.

o Medications to treat anemia. In certain situations, your doctor may recommend supplements of the hormone erythropoietin, sometimes with added iron. Erythropoietin supplements aid in production of more red blood cells, which may relieve fatigue and weakness associated with anemia.

o Medications to relieve swelling. People with chronic kidney disease may retain fluids. This can lead to swelling in the legs, as well as high blood pressure. Medications called diuretics can help maintain the balance of fluids in your body.

o Medications to protect your bones. Your doctor may prescribe calcium and vitamin D supplements to prevent weak bones and lower your risk of fracture. You may also take medication known as a phosphate

binder to lower the amount of phosphate in your blood, and protect your blood vessels from damage by calcium deposits (calcification).

o A lower protein diet to minimize waste products in your blood. As your body processes protein from foods, it creates waste products that your kidneys must filter from your blood. To reduce the amount of work your kidneys must do, your doctor may recommend eating less protein. Your doctor may also ask you to meet with a dietitian who can suggest ways to lower your protein intake while still eating a healthy diet.

o Your doctor may recommend follow-up testing at regular intervals to see whether your kidney disease remains stable or progresses.

Treatment for end-stage kidney disease:

If your kidneys can't keep up with waste and fluid clearance on their own and you develop complete or near-complete kidney failure and /or when the kidneys are functioning at less than 10-15 percent of normal capacity. Measures used so far - diet, medications, and treatments controlling underlying causes - are no longer enough.

The kidneys of patients with end-stage kidney disease cannot keep up with the waste and fluid elimination process on their own - the patient will need dialysis or a kidney transplant in order to survive and at that point, you need dialysis or a kidney transplant.

Most doctors will try to delay the need for dialysis or a kidney transplant for as long as possible because they carry the risk of potentially serious complications.

- Kidney dialysis

This is the removal of waste products and excessive fluids from blood when the kidneys cannot do the job properly any more. Dialysis has some serious risks, including infection.

There are two main types of kidney dialysis. Each type also has subtypes. The two main types are:

o Hemodialysis: Blood is pumped out of the patient's body and goes through a dialyzer (an artificial kidney). The patient undergoes hemodialysis about three times per week. Each session lasts for at least 3 hours.

Experts now recognize that more frequent sessions result in a better quality of life for the patient, but modern home-use dialysis machines are making this more regular use of hemodialysis possible.

o Peritoneal dialysis: The blood is filtered in the patient's own abdomen; in the peritoneal cavity which contains a vast network of tiny blood vessels. A catheter is implanted into the abdomen, into which a dialysis solution is infused and drained out for as long as is necessary to remove waste and excess fluid.

- Kidney transplant

A kidney transplant is a better option than dialysis for patients who have no other conditions apart from kidney failure. Even so, candidates for kidney transplant will have to undergo dialysis until they receive a new kidney.

The kidney donor and recipient should have the same blood type, cell-surface proteins and antibodies, in order to minimize the risk of rejection of the new kidney. Siblings or very close relatives are usually the best types of donors. If a living donor is not possible, the search will begin for a cadaver donor (dead person)[5].

Potential future treatments:

Regenerative medicine holds the potential to fully heal damaged tissues and organs, offering solutions and hope for people who have conditions that today are beyond repair.

Regenerative medicine approaches include:

- Boosting the body's natural ability to heal itself
- Using healthy cells, tissues or organs from a living or deceased donor to replace damaged ones
- Delivering specific types of cells or cell products to diseased tissues or organs to restore tissue and organ function

Lifestyle and home remedies:

As part of your treatment for chronic kidney disease, your doctor may recommend a special diet to help support your kidneys and limit the work they must do. Ask your doctor for a referral to a dietitian who can analyze your current diet and suggest ways to make your diet easier on your kidneys.

Depending on your situation, kidney function and overall health, your dietitian may recommend that you:

- Avoid products with added salt. Lower the amount of sodium you eat each day by avoiding products with added salt, including many convenience foods, such as frozen dinners, canned soups and fast foods. Other foods with added salt include salty snack foods, canned vegetables, and processed meats and cheeses.
- Choose lower potassium foods. Your dietitian may recommend that you choose lower potassium foods at each meal. High-potassium foods include bananas, oranges, potatoes, spinach and tomatoes. Examples of low-potassium foods include apples, cabbage, carrots, green beans, grapes and strawberries. Be aware that many salt substitutes contain potassium, so you generally should avoid them if you have kidney failure.
- Limit the amount of protein you eat. Your dietitian will estimate the appropriate number of grams of protein you need each day and make recommendations based on that amount. High-protein foods include lean meats, eggs, milk, cheese and beans. Low-protein foods include vegetables, fruits, breads and cereal
- Patients with chronic kidney disease typically need to take a large number of medications.
- **Treatments include:**

o Anemia treatment

Hemoglobin is the substance in red blood cells that carries vital oxygen around the body. If hemoglobin levels are low, the patient has anemia.

Some kidney disease patients with anemia will require blood transfusions. A patient with kidney disease will usually have to take iron supplements, either in the form of daily ferrous sulfate tablets, or occasionally in the form of injections.

o Phosphate balance

People with kidney disease may not be able to eliminate phosphate from their body properly. Patients will be advised to reduce their nutritional phosphate intake - this usually means reducing consumption of dairy products, red meat, eggs, and fish.

o High blood pressure

High blood pressure is a common problem for patients with chronic kidney disease. It is important to bring the blood pressure down to protect the kidneys, and subsequently slow down the progression of the disease.

o Skin itching

Antihistamines, such as chlorpheniramine, may help alleviate symptoms of itching.

o Anti-sickness medications

If toxins build up in the body because the kidneys don't work properly, patients may feel sick (nausea). Medications such as cyclizine or metaclopramide help relieve sickness.

o NSAIDs (non -steroidal anti-inflammatory drugs)

NSAIDs, such as aspirin or ibuprofen should be avoided and only taken if a doctor recommends them[5].

Complications:

If the chronic kidney disease progresses to kidney failure, the following complications are possible:

- anemia
- central nervous system damage
- dry skin or skin color changes
- fluid retention
- hyperkalemia, when blood potassium levels rise, possibly resulting in heart damage
- insomnia
- lower sex drive
- male erectile dysfunction
- osteomalacia, when bones become weak and break easily
- pericarditis, when the sac-like membrane around the heart becomes inflamed
- stomach ulcers
- weak immune system

Prevention:

- Managing the chronic condition

Some conditions increase the risk of chronic kidney disease (such as diabetes). Controlling the condition can significantly reduce the chances of developing kidney failure. Individuals should follow their doctor's instructions, advice, and recommendations.

- Diet

A healthy diet, including plenty of fruits and vegetables, whole grains, and lean meats or fish will help keep blood pressure down.

- Physical activity

Regular physical exercise is ideal for maintaining healthy blood pressure levels; it also helps control chronic conditions such as diabetes and heart disease. Individuals should check with a doctor that an exercise program is suited to their age, weight, and health.

- Avoiding certain substances

Including abusing alcohol and drugs. Avoid long-term exposure to heavy metals, such as lead. Avoid long-term exposure to fuels, solvents, and other toxic chemicals.

Clonidine:

Description:

Clonidine, an imidazoline-derivative hypotensive agent is a centrally-acting α_2-adrenergic agonist. It crosses the blood-brain barrier and acts in the hypothalamus to induce a decrease in blood pressure. It may also be administered as an epidural infusion as an adjunct treatment in the management of severe cancer pain that is not relieved by opiate analgesics alone.It may be used for differential diagnosis of pheochromocytoma in hypertensive patients.

Other uses for clonidine include:

- prophylaxis of vascular migraine headaches
- treatment of severe dysmenorrhea
- management of vasomotor symptoms associated with menopause
- rapid detoxification in the management of opiate withdrawal
- treatment of alcohol withdrawal used in conjunction with benzodiazepines
- management of nicotine dependence, topical use to reduce intraocular pressure in the treatment of open-angle and secondary glaucoma and hemorrhagic glaucoma associated with hypertension used in the treatment of attention-deficit hyperactivity disorder[(6)].

clonidine also exhibits some peripheral activity.

Dose:

Initial: 0.1mg 2times daily.

Maintance: 0.2-0.6mg /day.

Maximum:.2.4mg/day

Indication:

- May be used as an adjunct in the treatment of hypertension,
- Also used as an epidural infusion as an adjunct treatment in the management of severe cancer pain that is not relieved by opiate analgesics alone,
- Used for differential diagnosis of pheochromocytoma in hypertensive patients.
- prophylaxis of vascular migraine headaches,
- treatment of severe dysmenorrhea,
- management of vasomotor symptoms associated with menopause,
- rapid detoxification in the management of opiate withdrawal,
- treatment of alcohol withdrawal used in conjunction with benzodiazepines,
- management of nicotine dependence,
- topical use to reduce intraocular pressure in the treatment of open-angle and secondary glaucoma and hemorrhagic glaucoma associated with hypertension,
- treatment of attention-deficit hyperactivity disorder (ADHD).

Pharmacodynamics:

Clonidine is an α-adrenergic agent that acts specifically on α_2-receptors. α_2-receptors regulate a number of signaling pathways mediated by multiple G_i proteins, $G\alpha_{i1}$, $G\alpha_{i2}$, and G&alpha$_{i3}$. Stimulation of α_2-receptors

mediates effects such as inhibition of adenylyl cyclase, stimulation of phospholipase D, stimulation of mitogen-activated protein kinases, stimulation of K^+ currents and inhibition of Ca^{2+} currents. Three G-protein coupled α_2-receptor subtypes have been identified: α_{2A}, α_{2B}, and α_{2C}. Each subtype has a unique pattern of tissue distribution in the central nervous system and peripheral tissues. The α_{2A}-receptor is widely distributed throughout the central nervous system; it is found in the locus coeruleus, brain stem nuclei, cerebral cortex, septum, hypothalamus, and hippocampus. α_{2A}-receptors are also expressed in the kidneys, spleen, thymus, lung and salivary glands. The α_{2C}-receptor is primarily expressed in the central nervous system, including the striatum, olfactory tubercle, hippocampus and cerebral cortex. Low levels of the α_{2C}-subtype are also found in the kidneys. The α_{2B}-receptor is located primarily in the periphery (kidney, liver, lung and heart) with low levels of expression in the thalamic nuclei of the central nervous system. The α_{2A}- and α_{2C}-receptors are located presynaptically and inhibit the released of noradrenaline from sympathetic nerves. Stimulation of these receptors decreases sympathetic tone, resulting in decreases in blood pressure and heart rate. Sedation and analgesia is mediated by centrally located α_{2A}-receptors, while peripheral α_{2B}-receptors mediate constriction of vascular smooth muscle. α_{2A}-Receptors also mediate essential components of the analgesic effect of nitrous oxide in the spinal cord. Clonidine stimulates all three α_2-receptor subtypes with similar potency. Its actions in the nervous system decreases blood pressure in patients with hypertension and decreases sympathetic overactivity in patients undergoing opioid withdrawal. Clonidine is also a potent sedative and analgesic and can prevent post-operative shivering in intensive and post-operative care. Its use in differential diagnosis of pheochromocytoma owes to the fact that hypertension in patients with pheochromocytoma is refractory to antihypertensive treatment with clonidine[6].

Absorption:

Well absorbed following oral administration. Bioavailability following chronic administration is approximately 65%.

Volume of distribution

Not Available

Protein binding

20-40%, primarily to albumin

Metabolism

Hepatic. Metabolized via minor pathways.The major metabolite, *p*-hydroxyclonidine, is present in concentrations less than 10% of those of unchanged clonidine in urine. Four metabolites have been detected, but only *p*-hydroxyclonidine has been identified

Route of elimination

Not Available

Half life

6-20 hours; 40-60% is excreted in urine unchanged, 20% is excreted in feces. Less than 10% is excreted by *p*-hydroxyclonidine.

Clearance

Not Available

Toxicity

Oral LD_{50} is 150 mg/kg in rat and 30 mg/kg in dog. Symptoms of overdose include constriction of pupils of the eye, drowsiness, high blood pressure followed by a drop in pressure, irritability, low body temperature, slowed breathing, slowed heartbeat, slowed reflexes, and weakness.

Mechanism of Action

Clonidine works by stimulating alpha receptors that are located throughout the brain and spinal cord as well as other organs throughout the body such as the kidneys, liver, lungs, and heart.

Stimulation of the receptors in the hypothalamus causes signals to be sent that keep blood vessels relaxed, which allows the blood pressure to drop. Signals are sent to other parts of the brain to prevent the release of noradrenaline (hormone that increases the heart rate and constricts blood vessels),which may decreases the blood pressure and heart rate.

The alpha receptors throughout the body are stimulated by clonidine, causing the muscles that make up the walls of our internal organs and blood vessels to relax. This allows the blood pressure throughout the body to decrease.

Clonidine also used to relieve pain. This also involves stimulation of the alpha receptors, specifically the receptors on the spinal cord. When they are stimulated, the receptors send signals that block the feeling sensation throughout the spinal cord and these sensation-blocking signals will continue from the spinal cord out through the nerves that branch off from the spinal cord. Every area of the body served by the nerves will have the sensation of feeling blocked so that pain cannot be detected. This includes the brain, which is why clonidine can be used to relieve your migraines[7].

Moxonidine

Description

Moxonidine is a new-generation centrally acting antihypertensive drug approved for the treatment of mild to moderate essential hypertension. It may have a role when thiazides, beta-blockers, ACE inhibitors and calcium channel blockers are not appropriate or have failed to control blood pressure[6]. In addition, it demonstrates favourable effects on parameters of the insulin resistance syndrome, apparently independent of blood pressure reduction.

Dose:

Initial:0.2mg/day.

Maintance:0.4mg/day.

Maximum:0.6mg/day.

Renal dose:0.2-0.4mg/day if Cr CL is30-60ml/min.

Indication

For the treatment of mild to moderate essential or primary hypertension. Effective as most first-line antihypertensives when used as monotherapy

Pharmacodynamics

Antihypertensive agent whose site of action is the Central Nervous System (CNS), specifically involving interactions with I1- imidazoline and alpha-2-adrenergic rececptors within the rostral ventrolateral medulla (RSV).

Mechanism of action

Stimulation of central alpha 2-adrenergic receptors is associated with sympathoadrenal suppression and subsequent reduction of blood pressure. As this class was further explored it was discovered that sympathoadrenal activity can also be suppressed by a second pathway with a newly discovered drug target specific to imidazolines. Specifically, moxonidine binds the imidazoline receptor subtype 1 (I1) and to a lesser extent αlpha-2-adrenoreceptors in the RSV causing a reduction of sympathetic activity, reducing systemic vascular resistance and thus arterial blood pressure.

Moreover, since alpha-2-adrenergic receptors are considered the primary molecular target that facilitates the most common side effects of sedation and dry mouth that are elicited by most centrally acting antihypertensives, moxonidine differs from these other centrally acting antihypertensives by demonstrating only low affinity for central alpha-2-adrenoceptors compared to the aforementioned I1-imidazoline receptors[7].

Absorption

90% of an oral dose is absorbed with negligible interference from food intake or first pass metabolism, resulting in a high bioavailability of 88%.

Volume of distribution

1.8±0.4L/kg.

Protein binding

About 10% of moxonidine is bound to plasma proteins.

Metabolism

Biotransformation is unimportant with 10-20% of moxonidine undergoing oxidation reactions to the primary 4,5-dehydromoxonidine metabolite and a guanidine derivative by opening of the imidazoline ring[7].

The antihypertensive effects of these 4,5-dehydromoxonidine and guanidine metabolites are only 1/10 and 1/100 the effect of moxonidine

Oxidation on either the methyl group (pyrimidine ring) or on the imidazole ring of moxonidine results in the formation of the hydroxylmethylmoxonidine metabolite or the hydroxymoxonidine metabolite. The hydroxymoxonidine metabolite can be further oxidized to the dihydroxy metabolite or it can lose water to form the dehydrogenated moxonidine metabolite, which itself can be further oxidized to form an N-oxide. Aside from these Phase I metabolites, Phase II metabolism of moxonidine is also evident with the presence of a cysteine conjugate metabolite minus chlorine . Nevertheless, the identification of the hydroxymoxonidine metabolite with a high level of dehydrogenated moxonidine metabolite in human urine samples suggests that dehydrogenation from the hydroxy metabolite to the dehydrogenated moxonidine metabolite represents the primary metabolic pathway in human].

The cytochromes P450 responsible for the metabolism of moxonidine in humans have not yet been determined .

Ultimately, the parent moxonidine compound was observed to be the most abundant component in different biological matrices of urinary excretion samples, verifying that metabolism only plays a modest role in the clearance of moxonidine in humans.

Route of elimination

Elimination is nearly entirely via the kidneys with a majority (50 -75%) of overall moxonidine being eliminated unchanged through renal excretion. Ultimately, more than 90% of a dose is eliminated by way of the kidneys within the first 24 hours after administration, with only approximately 1% being eliminiated via faeces[7].

Half life

Plasma elimination half- life is 2.2 - 2.3 hours while renal elimination half- life is 2.6-2.8 hours.

Clearance

Administered twice daily due to short half -life .

However, lower dosage adjustments and close monitoring is necessary in elderly and renal impairment patients due to reduced clearance. In particular, the exposure AUC can increase by about 50% following a single dose and at steady state in elderly patients and moderately impaired renal function with GFR between 30-60 mL/min can cause AUC increases by 85% and decreases in clearence to 52 %.

Toxicity

Contraindicated due to known hypersensitivity to an ingredient (Physiotens tablets contain lactose), heart failure, severe renal impairment, < 16 years old, >75 years old, bradycardia, severe bradyarrhythmia, sick sinus syndrome, second or third degree atrioventricular block, malignant arrhythmias.

Used with caution in patients with history of severe coronary artery disease (CAD), unstable angina, angioneurotic edema.

Pregnancy Category B3:Avoid use during pregnancy (inadequate data in pregnant woman) and lactation (maternal blood stream transfer to breast milk shown) unless benefit clearly justifies risk.

Lack of specific therapeutic experience in cases of intermittent claudication, Raynaud's disease, Parkinson's disease, epileptic disorders, gluacoma, and depression suggest moxonidine should not be used in such instances .

Carcinogenicity and genotoxicity does not appear significant.

Concurrent administration of other hypotensives or sedative and hypnotics can enhance the hypotensive effect and intensify sedation respectively.

Avoid concurrent Tricyclic Antidepressant (TCA) use to avoid reduction of monoxidine efficacy.

Generally well tolerated with dry mouth and headache the most common adverse effects

Symptoms of overdose correlate with pharmacodynamicproperties:hypotension, sedation, orthostatic dysregulation, bradycardia, dry mouth with no specific counter- treatment known[7].

REVIEW OF LITERATURE

Suresh V Sagarad[6]***et al;*** **(2013):** conducted a study on "Prospective Real world experience of Moxonidine use in Indian Hypertensive patients-Prescription beyond current guidelines."In this study they focus on the use of Moxonidine. A prospective study conducted in which male and female patient with hypertension above 18 year's was selected and patient from op clinic with hypertension also were enrolled.There demographics with co-morbid illness of all patients were recorded. Patient's prescription and anti -hypertensive medications were also analysed and as a result a total of 990 patients were eligible during study period. Moxonidine were used in 4.5% patient's. One group with resistant hypertension and another group with intolerance to conventional first line drug. Moxonidine was given to resistant hypertension and renal failure patient's only. From this it was concluded that patients generally receive medication in accordance with recommendation and guidelines. Small but significant proportion of patient's may require use of Moxonidine to control high blood pressure.

Maria I Pikilidou [7]***et al;*** **(2013):** conducted a study on "The Effect of anti-hypertensive drugs on Chronic kidney disease A Comprehensive review." From a randomized clinical trial and epidemiological evidence data identified hypertension as second most risk factors for CKD. CKD progress over years and early diagnosis and

control of hypertension is important. In this study it was found out that a variety of anti-hypertensive drugs can be used in treatment of hypertension. In this the first choice of drug was renin angiotensin system inhibitors(enalapril,captopril).Other classes of drug including CCB (Amlodipine,verapamil),beta blockers (metoprolol,atenolol,nebivolo),Diuretics,aldosterone receptor blockers, alpha blockers and centrally acting antihypertensives (clonidine,moxonidine) etc,were used for treating hypertension . So they concluded that anti-hypertensive therapy should be obtained for optimal blood pressure control and variety of drugs are available.So every drug that effectively lowers hypertension is believed to be renoprotective.

Carinepoppe[8]***et al;*** **(2012):** conducted a study on "Improving Quality of life in patients with CKD:influence of acceptance and personality." In this study they are evaluating whether acceptance of disease contributes to better physical and mental health related quality of life (PHQL and MHQL) and also impact of personality characteristics on acceptance of PHQL and MHQL.A cross sectional study conducted on 99 patients from OP clinic and had mean duration of CKD of 10.81 years and mean GFR by diet modification in renal disease. Regression analysis revealed that acceptance had a significant positive contribution of PHQL and MHQL. They conducted that acceptance is an important positive variable in accounting for HQL and provide a better understanding of psychological determinants of HQL in CKD.

G.J.A. MACPHEE[9]***et al;(*****2012),** conducted astudy on "A comparison of thehaemodynamic and behaviouraleffects of moxonidine and clonidine in normotensive subjects."Randomised double-blind placebo controlled crossover study inhealthy normotensive patients.9 patients were selected and given single oral doses of moxonidine(200 mcg),clonidine (200 mcg) and placebo.Both active drugs significantly reduced blood pressure as comparedwith placebo.The hypotensive effect of clonidine was significantly greater. Moxonidine produced less adverse effects than clonidine, an equivalent hypotensive response was not demonstrated in normal subjects.

P.R. WILKINSON[10]***et al; (*****2012)**:conducted a study on"A Comparative Trial of Clonidine, Propranolol and Placebo in the Treatment of Moderate Hypertension." A double-blind cross over trial between clonidine, propranolol anda placebo in patients with moderate hypertension has been performed.32 patients completed the study which consisted of three treatmentperiods in random order of 3 months each.Both clonidine and propranolol was equipotent in reducing blood pressure.But clonidine has more side effect.

Maria CaroliaCruz[11]***et al;*** **(2011**): conducted a study on "Quality of life in patients with chronic kidney disease.| Here 155 patents with stage 1-5 kidney disease and 36 hemodialysis were studied. Quality of life rated using SF-36 and functional status by karnofsky performance scale. It was found that QOL decreases in all stages of kidney disease. A reduction in physical function was observed in different stages of kidney disease. Individuals with high educational level displayed high physical component where as men and those with high income presented with better mental status. Older patients performance was worse on physical status where better on mental status .From this concluded that QOL s decreased in Renal patients in early stages of disease.

STEFANOS ZENIOS[12]***et al;*** **(2005):** conducted a study on "Health-related quality of life and estimates of utility in chronic kidney disease." In this study 205 persons with CKD and CKD stages 4 and 5 were tested two to eight times over two years with help of Kidney Disease Quality of Life Short Form 36 (KDQOL-36TM), Health Utilities Index (HUI)-3, and Time Trade-off (TTO) questionnaires .The relations among estimated glomerular filtration rate(e-GFR),and changes in health related quality of life and utility overtime were estimated using mixed effect regression models. From this mean scores on the KDQOL-36TM , HUI-3, and TTO suggested considerable loss of function and well-being in CKD relative to population norms. On cross-sectional analysis, lower levels of kidney function were associated with significantly lower scores on the SF-12 Physical Health Composite , the Burden of Kidney Disease subscale and the Effects of Kidney Disease subscale of the KDQOL-36TM. Kidney function was significantly associated with the TTO and global HUI-3 utility although these

associations were attenuated after adjustment for diabetes. From this concluded that Health-related quality of life and estimates of utility are distressingly low in persons with CKD. Self-reported outcomes should be considered when evaluating health policy decisions that affect this population.

Gerry Ligtenberg[13]***et al; (*****2004):** conducted a study on "Moxonidine Normalizes Sympathetic Hyperactivity in Patients with Eposartan-Treated Chronic Renal Failure." In this study 42

patients were taken in which 22 patients are controlled and 11 stable patients with CRF, MSNA, BP and baroreceptor sensitivity were measured in the absence of antihypertensive drugs (except diuretics) during chronic eposartan therapy (600 mg for 6wk)and in 9 patients after moxonidine (0.2mgfor6wk) was added. BP, heart rate and MSNA were higher in patients than in 22 controls. After six weeks BP, Heart rate, MSNA were reduced with eposartantreatment.But addition of moxonidine to eposartan treatment further reduced BP, Heart rate, MSNA. The addition of moxonidine to angiotensin II antagonist treatment might be appropriate in reducing sympathetic hyperactivity.

B. N. C. Prichard1[14]***et al;(*****2003):**conducted a study on "Dose Relation of Blood Pressure Reduction with Moxonidine: Findings from Three Placebo- and Active-Controlled Randomized Studies." In this study three placebo-controlled trials in which 461 patients were selected and divided into 3 groups and blood pressure lowering effect of moxonidine with that of enalapril was compared.In all 3 groups enalapril reduce BP more than placebo and showed equivalence with moxonidine. Single dose of moxonidine 0.2-0.6mg reduced dose dependent, clinically relevant, statistically significant decrease in SiBP.

Farsang C[15]***et al;*** **(2001):** conducted a study on "Moxonidine clinical profile" .Moxondine is a selective I1 receptor agonist used for hypertension .It act by inhibiting increased sympathetic tone and increases natriuresis and decrease blood pressure .So a daily dose of 0.2-0.6mg helps to reduce blood pressure in patients with mild to moderate hypertension. Various studies have been done and in a placebo controlled 6 week study 0.2-0.4mg moxonidine decreases both SBP and DBP and another double blinded randomised study for 8 weeks was conducted in 47 hypertensive patients and effect of moxonidine compared with enalapril 5-10mg and placebo. As compared to placebo, moxonidine and enalapril significantly decreases blood pressure. In a 6 months study 20 hypertensive patient with LVH was selected and also septum thickness was evaluated. 20 patients were given 0.6mg and 8 patients were given 0.4mg and 4 patients were given 0.2mg.After 9 months BP ,LVH and septum thickness decrease gradually. From this study it was concluded that moxonidine have several beneficial effect and is very useful in treatment of hypertension.

R.Wolf[16]***et al;*** **(2000),** conducted a study on"The Treatment of Hypertensive patients with a calcium antagonist or moxonidine: A Comparison." In this study Antihypertensive potency & tolerability of nifedipine&moxonidine in 229 patients where studied with primary hypertension.Screening phase of 7 days followed by a 21 day single blind placebo run & 26week active treatment phase.Initially patients received 0.2 mg moxonidine or 20mg nifedipine once a day. After 4 week dose was doubled. Both drugs are equieffective in treatment of hypertension 0.2mg moxonidine once a day is equal to 20mg/day nifedipine. Doubling of dose increased the responder rate to approximately 80%.The adverse event profile of moxonidine was better than nifedipine in the study.

Rene Roland Wenzel[17]***et al;*** **(2000):** conducted a study on "I1 imidazoline agonist Moxonidine decreases sympathetic nerve activity and blood pressure in hypertensives."Moxonidine is a I1 imidazoline receptor agonist that reduces blood pressure in hypertensives and inhibits central sympathetic activity. In this study 0.4mg moxonidne orally given to 8 volunteres to evaluate muscle sympathetic nerve activity and heart rate, bp. 24 hour blood pressure profile and hormone plasma level in 25 untreated hypertensives. In a double blinded placebo-controlled study.It resulted that moxonidie decreases muscle sympathetic nerve activity in both healthy volunteres and hypertensives. Plasma NE also decreasesd but epinephrine and renin level did not change .Also there is decrease in SBP and DBP who has given moxonidine and heart rate decrease in healthy

subjects in hypertensives. plasmalevel,LDL,HDL and total cholestrol were not influenced by drug. It was concluded that moxonidine decreases SBP and DBP by inhibiting central nervous sympathetic activity. So new drug suitable for treatment of hypertension and cardiovascular diseases with increased sympathetic nerve activity.

OBJECTIVES AND METHODOLOGY

AIM

To determine the antihypertensive effect of moxonidine versus clonidine in renal failure patients.

OBJECTIVE

1) To compare and estimate the antihypertensive effect of moxonidine versus clonidine in renal failure patients .
2) To estimate the Quality of life in Renal failure patients.

METHODOLOGY

STUDY DESIGN

A prospective observational follow up study.

SAMPLE SIZE

120 patients.

$2(SD)^2 (Z_\alpha+Z_\beta)^2$ where, SD -standard deviation

Δ^2 Z- mean sum

STUDY POPULATION

Renal Failure patients from stage 1-5

STUDY SITE

Department of Nephrology, Pushpagiri Medical College Hospital, Thiruvalla.

STUDY PERIOD

The study period was 6 months. The study was carried out after getting approval from Institutional Ethics Committee

STUDY CRITERIA

INCLUSION CRITERIA

- Patient with blood pressure ranging from 140/90mmHg.
- All Renal Failure patients
- IP/OP patients.
- Those who are able to give informed consent.

EXCLUSION CRITERIA

- Those who are unable to give informed consent.
- Current alcoholic patients.
- Pregnant women.
- Pediatric patients.

BRIEF PROCEDURE

A prospective observational study was conducted in Department of Nephrology at Pushpagiri Medical College Hospital on the topic "Comparison of Antihypertensive effect of Moxonidine Versus Clonidine in Renal Failure Patients".

The entire study was carried out only after getting approval from Institutional Ethics Committee. The selection of patients were based upon the inclusion and exclusion criteria.

All patients were provided with a brief introduction regarding the study and the confidentiality of the data. A written Informed Consent was obtained from the patient or care-giver.About 120 patients were selected. Patients data collection form was used for recording demographic details of the patients. It was a 6 month study in which blood pressure was recorded before and after treatment with drugs and after 3months of follow up.

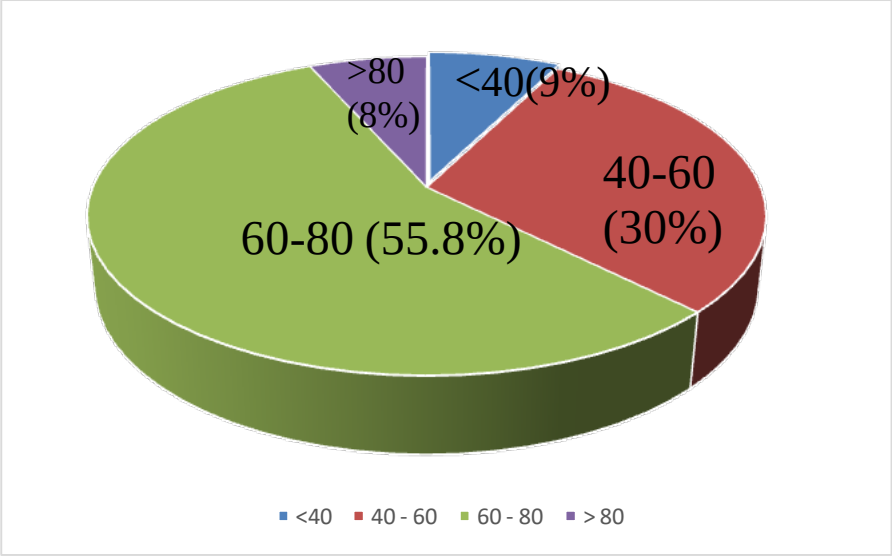
Quality of life score was obtained using KDQOL- SF 36 questionnaires and Standard WHO questionnaires were used to monitor the adverse effect. Finally analyzed the results,

RESULTS

TABLE1: DISTRIBUTION OF PATIENTS BASED ON AGE

AGE	Frequency	Percent	Valid Percent	Cumulative Percent
<40	9	7.5	7.5	7.5
40 – 60	36	30.0	30.0	37.5
60 – 80	67	55.8	55.8	93.3
> 80	8	6.7	6.7	100.0
Total	120	100.0	100.0	

FIGURE3: DISTRIBUTION OF PATIENTS BASED ON AGE



In this study population majority of patients comes under 60-80 age group,30%comes under age group40-60,6.5%comes under the age group>80 &7.5 % comes under <40 age group.

TABLE 2: DISTRIBUTION OF PATIENTS BASED ON GENDER

GENDER		Frequency	Percent	Valid Percent	Cumulative Percent
	Male	78	65.0	65.0	65.0
	Female	42	35.0	35.0	100.0
	Total	120	100.0	100.0	

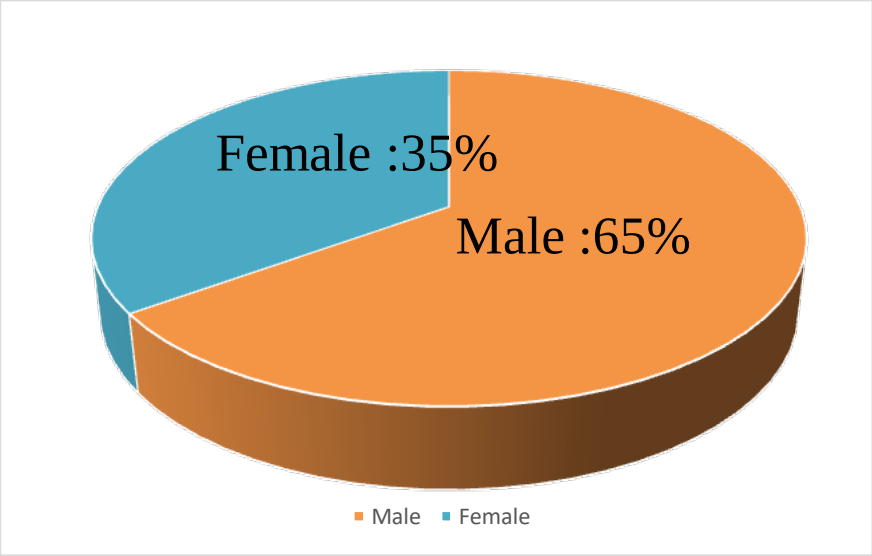


FIGURE 4: DISTRIBUTION OF PATIENTS BASED ON GENDER

In this study population 65% are males & 35% are females.

TABLE 3: DISTRIBUTION OF PATIENTS BASED ON MARITAL STATUS

MARITAL STATUS	MARITAL STATUS	Frequency	Percent
Unmarried	Unmarried	**4**	**3.3**
Married	Married	**116**	**96.7**
Total	Total	**120**	**100.0**

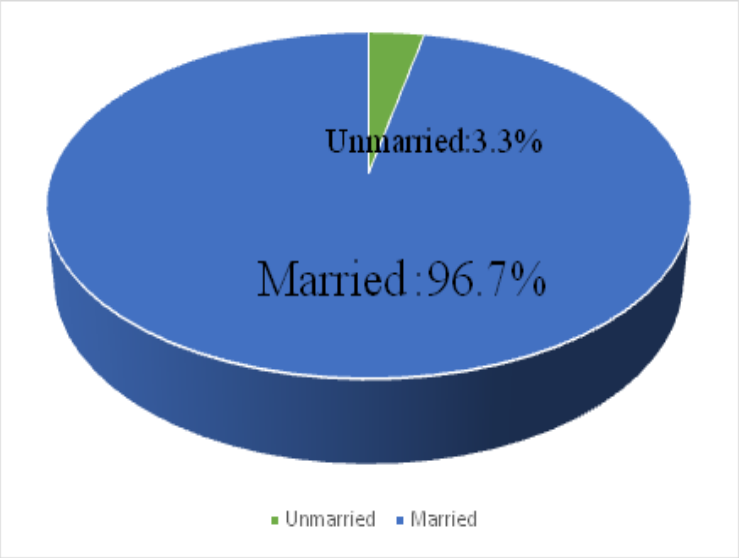


FIGURE 5: DISTRIBUTIN OF PATIENTS BASED ON MARITAL STATUS

TABLE 4: DISTRIBUTION OF PATIENTS BASED ON HISTORY OF ALCOHOLISM

Alcoholism	Frequency	Percent
No	**61**	**50.8**
Yes	**59**	**49.2**
Total	**120**	**100.0**

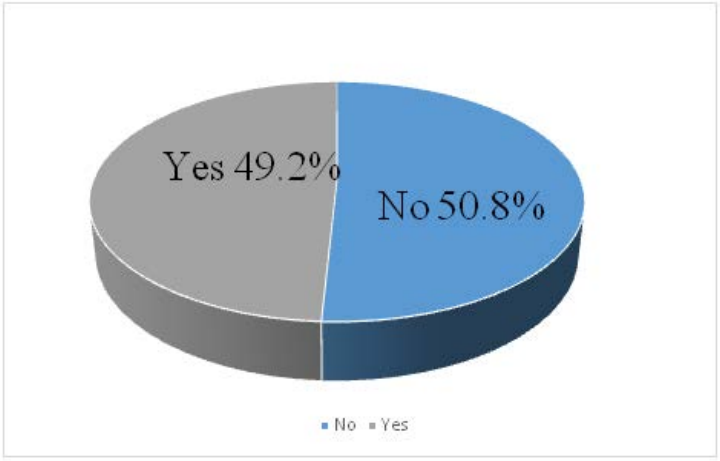


FIGURE 6: DISTRIBUTION OF PATIENTS BASED ON HISTORY OF ALCOHOLISM

In this study population about 59% are alcoholics & 61% are non alcoholics.

TABLE 5: DISTRIBUTION OF PATIENTS BASED ON HISTORY OF SMOKING

SMOKING	Frequency	Percent
No	73	60.8
Yes	47	39.2
Total	120	100.0

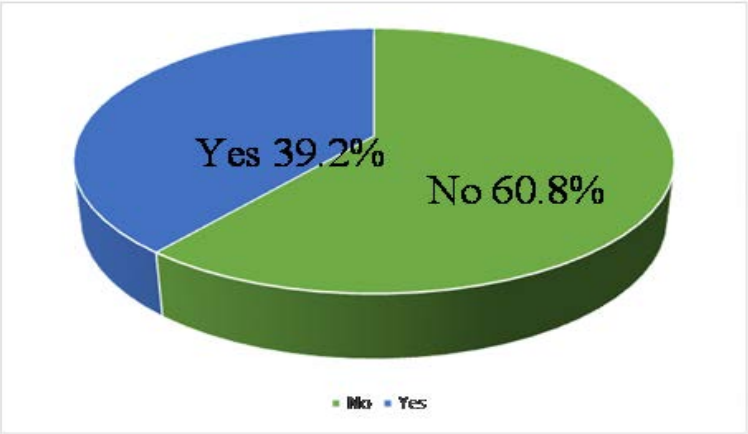


FIGURE 7: DISTRIBUTION OF PATIENTS BASED ON HISTORY OF SMOKING

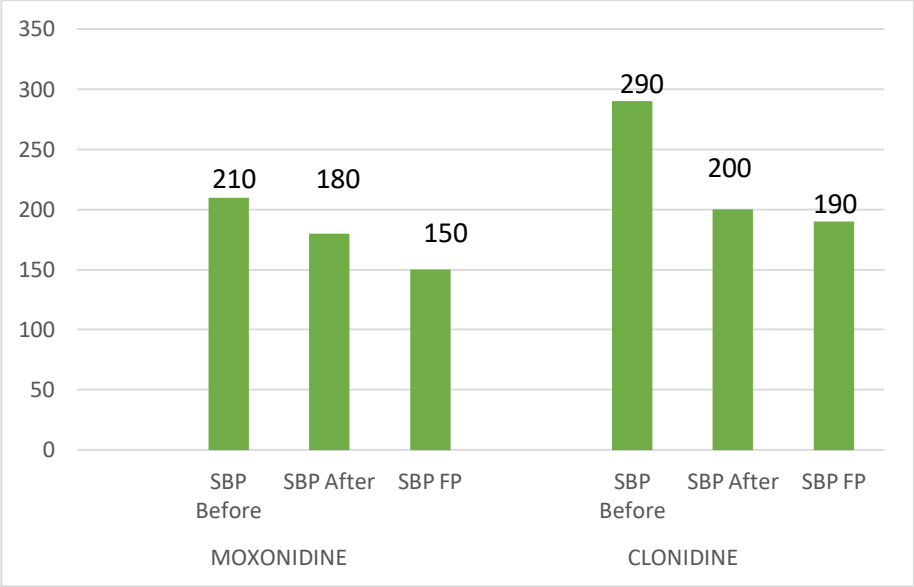
In this study population about 47% are smokers & 73% are non smokers.

ANTIHYPERTENIVE EFFECT OF DRUGS

TABLE 6: EFFECT OF DRUGS ON SYSTOLIC BLOOD PRESSURE

Drug	Parameter	Maximum	Mean	SD
Moxonidine	SBP Before	210	182.00	15.817
	SBP After	180	142.03	11.495
	SBP FP	150	128.67	7.471
Clonidine	SBP Before	290	179.33	28.515
	SBP After	200	153.33	16.292
	SBP FP	190	141.33	18.997

FIGURE 8: EFFECT OF DRUGS ON SYSTOLIC BLOOD PRESSURE



Systolic blood pressure indicates highly significant difference before and after treating with drugs.

EFFECT OF DRUGS ON DIASTOLIC BLOOD PRESSURE

TABLE 7: EFFECT OF DRUGS ON DIASTOLIC BLOOD PRESSURE

Drug	Parameter	Maximum	Mean	SD
Moxonidine	DBP Before	120	95.67	14.656
	DBP After	100	80	9.206
	DBP FP	90	73.33	7.739
Clonidine	DBP Before	150	96	13.55
	DBP After	100	87.33	8.995
	DBP FP	100	84.83	8.129

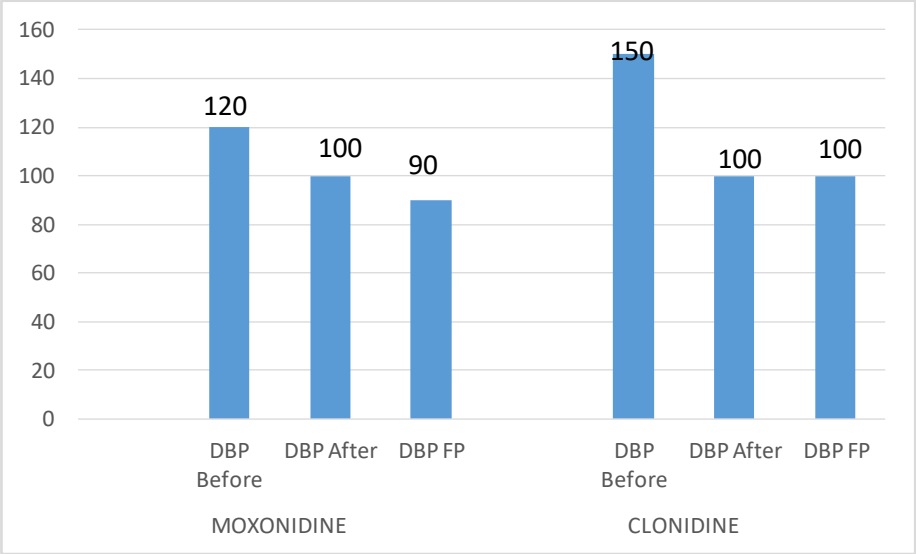


FIGURE 9: EFFECT OF DRUGS ON DIASTOLIC BLOOD PRESSURE

Diastolic blood pressure indicates highly significant difference before and after treating with drugs.

TABLE 8: EFFECT OF DRUGS ON QUALITY OF LIFE

Drug	Parameter	Maximum	Mean	SD
Moxonidine	QOL Before	64	37.87	12.868
	QOL After	90.1900	72.85	9.227
Clonidine	QOL Before	79	41.70	16.198
	QOLAfter	85	100.26	9.43

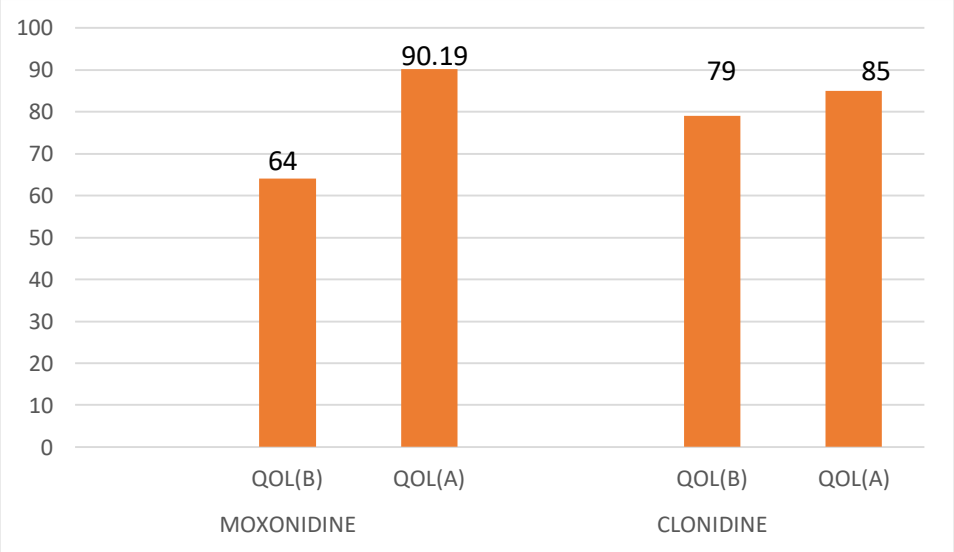


FIGURE10: EFFECT OF DRUGS ON QUALITY OF LIFE

Quality of life indicates a highly significant difference before and after treating with drugs.

TABLE 9: COMPARISON OF ANTIHYPERTENSIVE EFFECT AND QUALITY OF LIFE OF PATIENTS BEFORE AND AFTER TREATMENT WITH MOXONIDINE AND CLONIDINE.

PARAMETER	MEAN		SD		P value
	Moxonidine	Clonidine	Moxonidine	Clonidine	
BP BEFORE	182	179.33	115.817	28.515	0.58
SBP AFTER	142	153	11.49	16.29	0.000
SBP FP	128.67	141.33	7.471	18.97	0.000
DBP BEFORE	95.67	96	14.656	13.55	0.332
DBP AFTER	80	87.33	9.206	8.99	0.000
DBP FP	73.33	84.83	7.739	8.129	0.000
QOL BEFORE	37.87	41.70	12.868	16.19	0.548
QOL AFTER	72.85	182	9.227	9.21	0.000

DISCUSSION

The patients who have satisfied the inclusion criteria where included in the study. A total of 120 patients were included in the study.

Age Group: In this study majority of patients comes under the 60-80 age group 67%), 36% comes under the age group of 40-60,9% comes under less than 40 age group and 8% comes under more than 80 years of age.

Gender: In this study 65% are male patients and 35% are female patients.

Marital status: In this study 96.7% patients are married and 3.3% patients are unmarried.

Social habits: In this study 49.2% patients have history of alcoholism and rest 50% are non -alcoholics. In this study 39.2% patients have history of smoking and rest 60.8% are non-smokers.

In this study blood pressure of the patients were monitored during the study period. Follow upwas conducted after3 months and their blood pressure was monitored. The patients had high blood pressure before the treatment and their blood pressure was reduced significantly during the treatment with the drugs as there p value shows a significant difference between the pairs (<0.05)

The quality of life of the patient was measured using KDQOL SF 36 questionnaire. They showed a poor quality of life before the treatment but quality of life score improved significantly during the treatment phase.

The ADR of drugs were measured using WHO standard questionnaire.Both drugs showed a possible reaction and a more number of patients exhibited ADR when treated with Clonidine (45 out of 60) as compared to that of Moxonidine(27 out of 60).

SUMMARY

A Prospective observational study on Comparison of Antihypertensive drug on CKD patients and effect of drug treatment on quality of life was assessed using KDQOL SF 36 which was carried out in Department of Nephrology, Pushpagiri Medical College Hospital Thiruvalla. Sample size consisted of 120 patients .The main objective of study was to determine which antihypertensive drug is more effective for CKD patients and also to determine the quality of life of patients after treating with drugs.

- In this study population majority of patients have age group of 60-80 years.
- In this study out of 120 patients 59(49.2%) are alcoholics and 47(39.2%) are smokers
- In this study population the systolic blood pressure of patients before and after treatment and during follow up have a significant difference as the p-value is less than 0.05.
- In this study population the diastolic blood pressure of patients before and after treatment and during follow up have a significant difference as the p- value is less than 0.05.
- In this study population total SF 36 score before and after treatment with drugs moxonidine and clonidine have significant difference between the pairs.
- In this study more number of patients exhibited ADR when treated with Clonidine (45 out of 60) as compared to that of Moxonidine(27 out of 60).

CONCLUSION

To date, CKD remains an incurable disease and hypertension is the leading cause and / or seconds most risk factor for CKD. In this study primary objective was to focus the blood pressure reduction in patients with renal failure by comparing the antihypertensive action of Moxonidine and clonidine respectively. The secondary

objective was to assess quality of life in CKD patients before and after the therapy. The quality of life was determined using KDQOL SF 36 questionnaire.

Our study confirms that the drug Moxonidine showed better result in reduction of blood pressure and improved the quality of life in patients who were on therapy with Moxonidine when compared to Clonidine. The drug Moxonidine also showed less adverse drug reaction when compared to that of Clonidine. Hence this study concluded that the newer antihypertensive drug Moxonidine is the best drug in CKD patients for the control of blood pressure and to improve the quality of life.

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