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Blood Pressure Monitoring in Hemodialysis Patients With or Without Renin Angiotensin Aldosterone System (RAAS) Inhibitors: A Comparative Study

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ABSTRACT

Cardiovascular complications are the prime cause of morbidity and mortality in patients with end-stage renal disease leading to haemodialysis. Most of these patients have hypertension, and adequate control of blood pressure is challenging due to the multifactorial aetiology. The present study aims to evaluate the efficacy of RAAS and Non-RAAS inhibitors that can provide better control of blood pressure and improve the quality of life in haemodialysis patients. A Prospective observational study was carried out on the patients who attended the Haemodialysis unit of KIM's hospital and the study was conducted for 6 months; data on antihypertensive drugs and blood pressure control (pre-dialysis and post-dialysis) were recorded and analyzed. The mean and deviated pre and post systolic blood pressure of patients receiving RAAS inhibitors were found to be 150.6 $\pm$ 13.4 & 162 $\pm$ 20.9 and the diastolic pre and post blood pressure was found to be 83.3 $\pm$ 13.7 & 87.2 $\pm$ 11. The mean and deviated pre and post-systolic blood pressure of patients receiving Non-RAAS inhibitors were found to be 152.04 $\pm$ 15.2 & 161.6 $\pm$ 24.2 and the diastolic pre and post-blood pressure were found to be 83.6 $\pm$ 13.7 & 86.1 $\pm$ 7.8 as well. The study concluded the efficacy of RAAS and Non-RAAS inhibitors in the management of hypertension in haemodialysis patients have shown similar results.

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INTRODUCTION

Hypertension is common worldwide. It was estimated that 26% (972million) of the world's population has high blood pressure, and its prevalence is expected to increase to 29% by 2025, mainly driven by growth in developing countries. The high prevalence of hypertension places a great health burden on the population [1]. Hypertension is common in dialysis patients and affects more than 80% of the final stages. People with kidney disease have inadequate blood pressure (BP) control. A vague association was seen between pre-dialysis blood pressure and cardiovascular mortality. Blood pressure in dialysis patients has been shown to be recorded using home blood pressure measurements. Haemodialysis patients are more closely associated with mortality and cardiovascular disease [2]. The incidence of hypertension during repeated haemodialysis (HD) remains high and is associated with high morbidity and mortality. The

frequency of hypertension was determined by monitoring blood pressure (BP) at the starting, and ends of dialysis. Hypertension is defined as systolic blood pressure (SBP) greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg (DBP) in at least two measurements. It compared the hypertensive dialysis group and the non-hypertensive group. The incidence of arterial hypertension was 69.35% (86/124). The mean age was 57.15 years and the sex ratio was 1.2. On echocardiography performed in 64.5% of patients, the cardiac ejection fraction of arterial hypertension with left ventricular hypertrophy was high at 80% and the mean ejection fraction was 62% [3].

Systolic and diastolic blood pressure is associated with damage to target organs, including vascular stiffness. High and low SBP or DBP levels are associated with poor outcomes in dialysis patients.

The occurrence of isolated systolic hypertension was found in the 5D CKD stage population. Clinical Solutions Management of BP inter dialysis should be based on SBP and DBP rather than arterial blood pressure.

Recent guidelines from the National Institutes' Kidney Disease Outcomes Quality Initiative suggest: BP before and after HD should be 140/90 and 130/80 mm Hg [4].

Kidney

The kidneys are brown, bilateral bean-shaped organs located at the back of the abdomen. Their main function is to filter and remove waste products from the blood and balancing water and electrolytes in the body.

Metabolites and excess electrolytes are excreted by the kidneys in the urine. Urine is carried from the kidneys to the bladder through the ureters.

It leaves the body through the urethra, which in women extends up to the perineum and in men through the penis [5]. Some kidney functions include:

1. Control of extracellular fluid volume
2. Monitor the inorganic electrolyte concentration in the extracellular fluid.
3. Regulation of osmotic pressure of the extracellular fluid.
4. Removal of metabolites
5. Toxin removal
6. Maintaining acid-base balance
7. Production of hormones and enzymes.

Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) or chronic renal failure (CRF) is a term that encompasses impaired kidney function of all degrees, from critically impaired to mild, moderate, and severe chronic kidney failure. In the United States, Kidney disease is the 9th foremost cause of death. The National Kidney Research Institute (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) introduced the definition and classification of CKD in 2002. Since then, KDOQI and the International Commission on Improvement of Renal Performance (KDIGO) have updated these recommendations. The guidelines define CKD as renal impairment or reduced glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m2 for at least 3 months [6]. Stages are classified as G1-G5, based on the e GFR, and A1-A3 based on the ACR (albumin: creatinine ratio) as detailed in Figure 1 [7].

Renin Angiotensin Aldosterone System (RAAS)

RAAS is a complex system involved in the regulation of arterial BP and regulates sodium, potassium, and blood volume, and influences the vascular tone and sympathetic nervous system. Renin is an enzyme stored in JG cells whose secretion is modulated by intra renal and extra renal factors. Intra renal factors kike like decreased renal blood flow, increase sympathetic stimulation, increase macula densa signal, and extra renal factors like sodium, potassium, and chloride. When renin enters the bloodstream, it can act on its target, angiotensinogen. Angiotensinogen is produced by the liver and continuously circulates in the plasma. Then rennin cleaves angiotensinogen to angiotensin I which is physiologically inactive but acts as a precursor to angiotensin II. The transformation of angiotensin II to angiotensin I is catalyzed by an enzyme called angiotensin. ACE is mainly found in the vascular endothelium of the lungs and kidneys. Angiotensin II has receptors like angiotensin II type 1 (AT1) and angiotensin II type 2 (AT2).

AT1 is located in the brain, kidney, myocardium, adrenal glands, peri vasculature and helps in mediating responses critical to cardiovascular and kidney function. AT2 is located in the adrenal medulla, brain, and uterus and its stimulation doesn't help in the regulation of BP. Angiotensin II is a vasoconstrictor and elevates the BP with two mechanisms that are pressure and volume effects and synthesize aldosterone from the adrenal cortex which eventually increases the plasma volume, TPR, and finally BP [8].

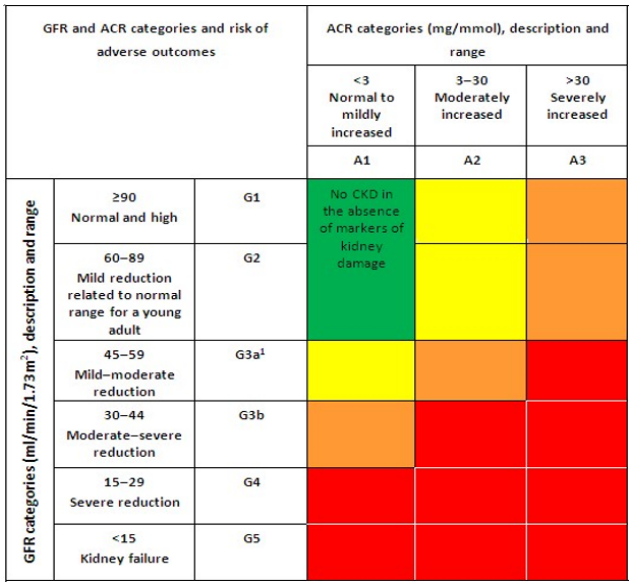

Figure 1: Classification of CKD Stages

Renin-Angiotensin-Aldosterone System Inhibitors (RAAS)

It includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and direct renin inhibitors and are useful drugs for the treatment of high blood pressure as they have fewer side effects. Figure 2 represents the inter-relationship between the kidney, angiotensin II, and regulation of blood pressure is depicted. Renin secretion by juxtaglomerular cells in afferent arterioles is regulated by three main factors that convert angiotensinogen to angiotensin. The main sites of action of major antihypertensive agents are included:

1. ACE inhibitors (ACEi);
2. Angiotensin II receptor blockers (ARB);
3. Direct rennin inhibitors

Non RAAS Inhibitors:

1. βeta-blockers;
2. Calcium channel blockers;
3. Alpha blockers;
4. Vasodilators

Need for the Study

1. Hypertension is seen in most of the dialysis patients on haemodialysis and studies have shown that it is not well controlled.
2. Owing to the fact that the dialysis population does not have appropriate guidelines to address this important issue.
3. Even at presently available data, disease awareness is low among both the general public and healthcare authorities.
4. Studies have shown that antihypertensive medication use in dialysis patients has been limited.
5. To identify the incidence of hypertension and the types of anti-hypertensive used in haemodialysis patients.
6. This study was targeted to compare two different lines of treatment in hypertensive patients undergoing haemodialysis for better perception of indication, efficacy, and benefits of RAAS and Non-RAAS inhibitors and therefore improving the quality of life (QOL).
7. Along with this study, we intend to take note of parameters, patient condition, co-morbidities, and ADRS involved in them.
8. Giving a general panorama of past-to-present literature.
9. The comparative response of RAAS and Non-RAAS inhibitors belonging to different classes in improving the quality of life in haemodialysis patients with hypertension was determined.
10. The choice of treatment and selection can be optimized by measuring the impact of RAAS and Non-RAAS Inhibitors.

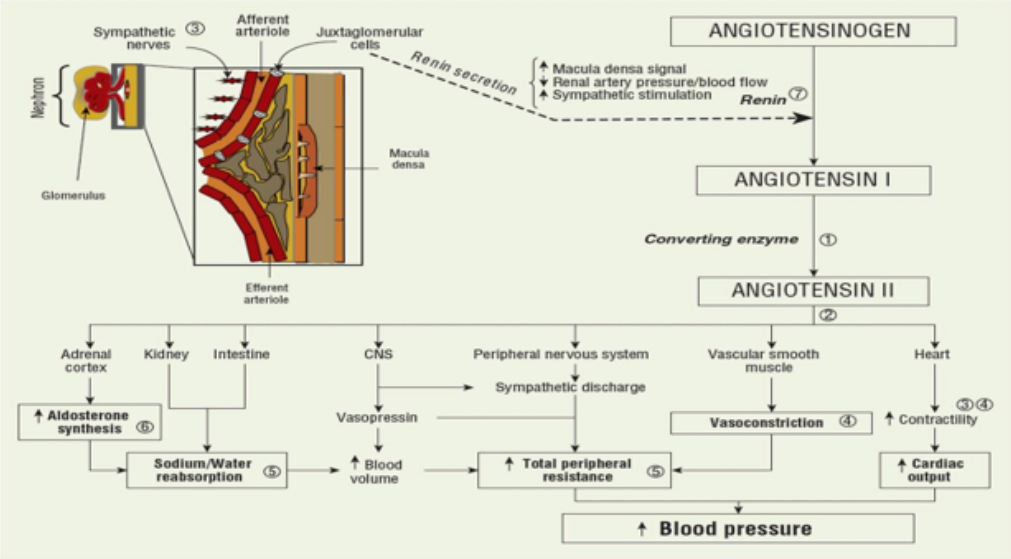

Figure 2: The Renin–Angiotensin–Aldosterone System (RAAS)

Aim

To evaluate the efficacy of RAAS & Non – RAAS inhibitors in the management of hypertension in haemodialysis patients.

Objective

Primary Objective

1. The main objective is to know the most effective line of treatment in the management of hypertension in haemodialysis patients.

Secondary Objective

1. To determine the possible adverse drug reaction occurring during the haemodialysis session.
2. To compare the effectiveness of RAAS and Non-RAAS Inhibitors in increasing the quality of life in haemodialysis patients with hypertension thus allowing the influence of treatment options providing better therapy.

METHODOLOGY

Study Site

This study was conducted in the department of the Nephrology dialysis unit, Krishna institute of medical sciences (KIMS) hospital Secunderabad.

Study Design

This is "A Prospective Comparative Study".

Study Period

This study was conducted for 6months.

Sample Size

Minimum of 100 patients.

Study Criteria

Inclusion Criteria

1. Adults ($\geq$18 years of age).
2. Patients giving consent.
3. Haemodialysis patients.
4. Patients with co-morbidities.

Exclusion Criteria

1. Pregnant and lactating women.
2. Patients with alarming symptoms during hemodialysis.
3. Renal transplantation.
4. Peritoneal dialysis patients.
5. CKD stage 1, 2, 3 & 4.

Data Collection

1. All the relevant and necessary data will be collected from patient records, lab reports, and prescriptions.
2. Communicating with healthcare professionals and also with patient attenders.
3. Primary parameters to be collected: Blood pressure, ADR report.

4. Secondary parameters to be collected: Heart rate, dry weight.

Statistical Analysis

1. Results are presented as mean ± S.D.
2. The demographic and other baseline characteristics of the patients (e.g. age, gender, etc) are summarized.
3. Mean was used to compare the baseline and post-treatment values for each variable.
4. Adverse events experienced by the patients during the course of the study were appropriately summarized and tabulated.

Ethical Considerations

This research was carried out under the basic principles defined in the International Conference on Harmonization "Guidance for Good Clinical Practice" and the principles enunciated in the Declaration of Helsinki. This prospective comparative study was conducted after the protocol and the informed consent form (ICF) were reviewed and approved by the KIMS Ethics committee, KIMS Scientific Review/Research Committee at a convened meeting held on 09/04/2021. The detailed procedure followed in this study has been described in the approved protocol "Comparative Study of Blood Pressure Monitoring in Haemodialysis Patients with Or without Renin Angiotensin Aldosterone System (RAAS) Inhibitors. The purpose of the study, details of the procedures involved, and potential risks that may be encountered during the study were lucidly explained to the subjects in the vernacular language and non-technical terms. After the subjects attended the oral presentation and had thoroughly read the informed consent form, formal written consent was obtained from all the patients before they were enrolled in the study.

RESULTS

A total number of 100 Subjects with End-Stage Renal Disease (ESRD) on haemodialysis were screened according to the inclusion and exclusion criteria out of which 82% & 18% were found to be male and female respectively. In which, 50 Subjects with Hypertension on haemodialysis receiving RAAS Inhibitors were compared with another 50 Subjects with Hypertension on haemodialysis receiving NON-RAAS Inhibitors were enrolled in the study represented in Figure 3.

Out of 50 patients receiving RAAS Inhibitors, 78% & 22% were found to be male & female respectively. Out of 50 patients receiving non-RAAS inhibitors, 86% were males and 14% were females. The ADRs of patients receiving RAAS and Non-RAAS Inhibitors during haemodialysis, where 64% of the subjects shows no ADR's and 14% with hypotension, cramps 8%, rash and edema 4%, fatigue 3%, shortness of breath (SOB) 2%, and blood clot 1%. The patient compliance was 80% of patients were feeling well 8% with pain at the injection site and 4% are with rashes at the injection site.

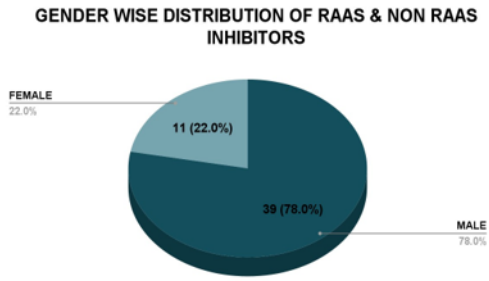

Figure 3: Gender-Wise Distribution

Demographic and Other Baseline Characteristics of RAAS Inhibitors

This study was conducted on the Indian population. Out of 50 patients, the mean age receiving RAAS inhibitors was 63.74 years which was redistributed by age represented in Figure 4. The mean and deviated pre and post systolic blood pressure of patients receiving RAAS inhibitors were found to be 150.6 ± 13.4 & 162 ± 20.9 and the diastolic pre and post blood pressure was found to be 83.3 ± 13.7 & 87.2 ± 11.0 as well. At the baseline, the dry weight and the heart rate were found to be 2.2 ± 0.5 & 76 ± 9 represented in Table 1. The patients were also divided on a gender basis where the male and the female ratio were found to be 78% & 22% distributive represented in Figure 5.

Demographic and Other Baseline Characteristics of Non-RAAS Inhibitors

This study was conducted on the Indian population. Out of 50 patients, the mean age receiving non-RAAS inhibitors was 63.74 years which was redistributed by age: young adults 4%, middle-aged 8%, and older age 38% represented in Figure 6. The mean and deviated pre and post-systolic blood pressure of patients receiving Non-RAAS inhibitors were found to be 152.04 ± 15.2 & 161.6 ± 24.2 and the diastolic pre and post-blood pressure were found to be 83.6 ± 13.7 & 86.1 ± 7.8 as well. At the baseline, the dry weight and the heart rate were found to be

Table 1: Demographics and Baseline Characteristics of the Patients Receiving RAAS Inhibitor

Parameters	Mean ± S.D	
Age	63.7 ± 14.4	
Male	39 (78%)	
Female	11 (22%)	
Dry weight	2.2 ± 0.5	
Heart rate	76 ± 9	
Blood pressure		
	Pre-SBP	150.6 ± 13.4
	Pre-DBP	83.3 ± 13.7
	Post-SBP	162 ± 20.9
	Post-DBP	87.2 ± 11.0

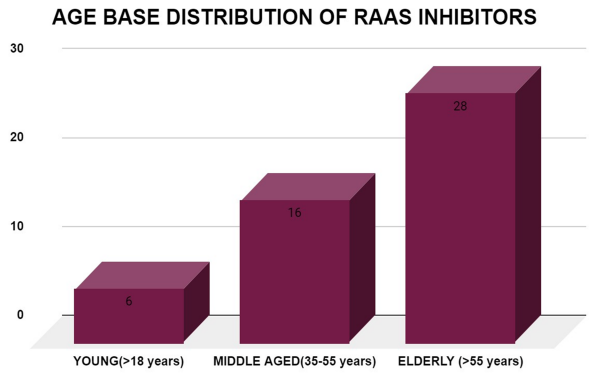

Figure 4: Distribution of Age Based on RAAS Inhibitors

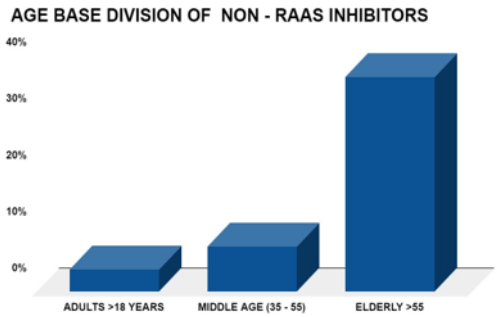

Figure 6: Distribution of Age Based on Non-RAAS Inhibitors

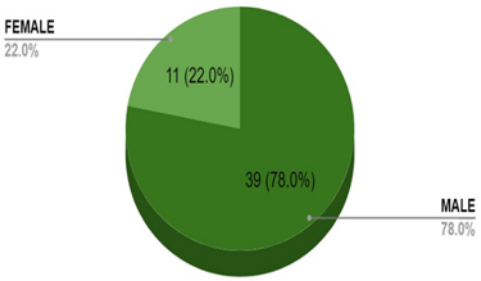

Figure 5: Distribution of Age

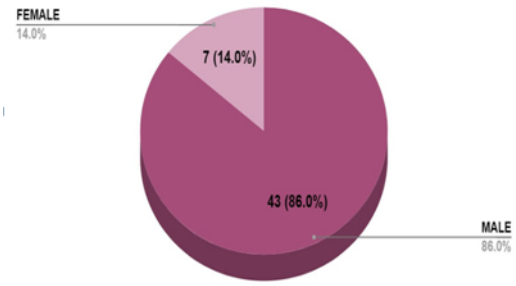

Figure 7: Distribution of Gender Based on Non-RAAS Inhibitors

2.73 ± 0.8 & 82 ± 10.7 represented in Table 2. The patients were also divided on a gender basis where the male and the female ratio were found to be 86% & 14% distributive represented in Figure 7.

Comparison of Blood Pressure With and Without RAAS Inhibitors During Haemodialysis

The average pre and post-systolic blood pressure (SBP) of patients receiving RAAS and Non-RAAS inhibitors were found to be 150.6 & 152.04; 162.08 & 161.62. The diastolic blood pressure (DBP) was 83.34 and 83.68; 87.26 and 86.12 correspondingly represented in Figure 8.

Adverse drug reaction observed during haemodialysis was represented in Figure 9.

DISCUSSION

Hypertension is common in dialysis patients and affects more than 80% of the final stages. People with kidney disease have inadequate blood pressure (BP) control. A vague association was seen between

Table 2: Demographics and Baseline Characteristics of the Patients Receiving Non-RAAS Inhibitor

Parameters	Mean ± S.D	
Age	66.6 ± 11.3	
Male	43 (86%)	
Female	7 (14%)	
Dry weight	2.73 ± 0.8	
Heart rate	82 ± 10.7	
Blood Pressure		
	Pre-SBP	152.04 ± 15.2
	Pre-DBP	83.6 ± 13.7
	Post-SBP	161.6 ± 24.2
	Post-DBP	86.1 ± 7.8

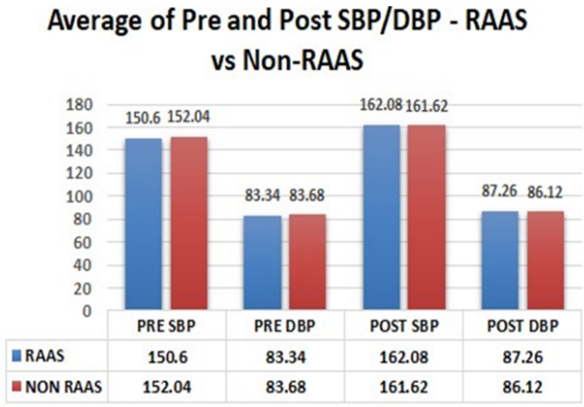

Figure 8: Adverse Drug Reaction Observed During Haemodialysis

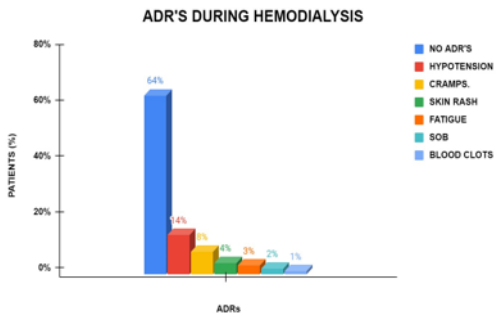

Figure 9: ADR'S During Haemodialysis

pre-dialysis blood pressure and cardiovascular mortality. Blood pressure in dialysis patients has been shown to be recorded using AMBP measurements. Haemodialysis patients are more closely associated with mortality and cardiovascular disease. The incidence of hypertension during repeated haemodialysis (HD) remains high and is associated with high morbidity and mortality. The frequency of hypertension was determined by monitoring blood pressure (BP) at the 15 minutes interval during 4 hours dialysis. Hypertension is defined as systolic blood pressure (SBP) greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg (DBP) in at least two measurements. It is estimated that 1 in 5 men between the ages of 66 and 75, 1 in 4 women, and half of the population aged 75 and older have chronic kidney disease (CKD) and affects 10% of the world's population and kills more than a million people each year, has become a major public health problem. Anti-hypertensive drug therapy in dialysis patient is as follows: ACEIs, angiotensin-II receptor blockers (ARBs), calcium channel blockers (CCBs), α-blocker, β-blocker, Diuretics, Direct vasodilators, and mineral corticoid receptor antagonists (MRAs).

Reviewing literature suggested that ESRD needs dialysis or kidney transplant and studies have manifested that the class of antihypertensive use in dialysis patients is not clear and there were many research gap regarding the use of RAAS and Non-RAAS inhibitor and among both the treatment which was a better line of treatment was a conflict of interest. Fact shows that the dialysis population does not have appropriate treatment guidelines. The main objective of our study was to compare the effectiveness of RAAS and Non-RAAS Inhibitors in increasing the quality of life in haemodialysis patients with hypertension thus allowing the influence of treatment options providing better therapy. This study was conducted in the department of the Nephrology dialysis unit, Krishna institute of medical sciences (KIMS) hospital Secunderabad and is a Prospective Comparative study conducted for 6months. A total number of 100 Subjects with End-Stage Renal Disease (ESRD) on haemodialysis were screened according to the inclusion and exclusion criteria out of which 82% & 18% were found to be male and female respectively. In which, 50 Subjects with Hypertension on haemodialysis receiving RAAS Inhibitors were compared with another

50 Subjects with Hypertension on haemodialysis receiving NON-RAAS Inhibitors. Out of 50 patients receiving RAAS Inhibitors, 78% & 22% were found to be male & female respectively. Out of 50 patients receiving non-RAAS inhibitors, 86% were males and 14% were females.

The ADRs of patients receiving RAAS and Non-RAAS Inhibitors during haemodialysis, where 64% of the subjects shows no ADR's and 14% with hypotension, cramps 8%, rash and edema 4%, fatigue 3%, shortness of breath (SOB) 2%, and blood clot 1% The patient compliance was 80% of patients were feeling well 8% with pain at the injection site and 4% are with rashes at the injection site. The mean and deviated pre and post systolic blood pressure of patients receiving RAAS inhibitors were found to be 150.6 $\pm$ 13.4 & 162 $\pm$ 20.9 and the diastolic pre and post blood pressure was found to be 83.3 $\pm$ 13.7 & 87.2 $\pm$ 11.0 as well. At the baseline, the dry weight and the heart rate were found to be 2.2 $\pm$ 0.5 & 76 $\pm$ 9. The patients were also divided on a gender basis where the male and the female ratio were found to be 78% & 22% distributive. The mean and deviated pre and post-systolic blood pressure of patients receiving Non-RAAS inhibitors were found to be 152.04 $\pm$ 15.2 & 161.6 $\pm$ 24.2 and the diastolic pre and post-blood pressure were found to be 83.6 $\pm$ 13.7 & 86.1 $\pm$ 7.8 as well. At the baseline, the dry weight and the heart rate were found to be 2.73 $\pm$ 0.8 & 82 $\pm$ 10.7. The patients were also divided on a gender basis where the male and the female ratio were found to be 86% & 14% distributive. The average pre- and post-systolic blood pressure (SBP) of patients receiving RAAS and Non-RAAS inhibitors were found to be 150.6 & 152.04; 162.08 &161.62. The diastolic blood pressure (DBP) was 83.34 and 83.68; 87.26 and 86.12 correspondingly.

CONCLUSION

By summarizing the statistical data of our study, we have observed that the pre & post systolic and diastolic blood pressure has shown no major difference in both the treatment groups during the four hourly haemodialysis where the pre and post average blood pressure of RAAS and Non-RAAS (Renin angiotensin aldosterone system) Inhibitors were found to be 151/83 - 162/87: 152/84 - 162/86 (PRE BP: POST BP) respectively. The study concluded the efficacy of RAAS and Non-RAAS inhibitors in the management of hypertension in haemodialysis patients have shown similar results.

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The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

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