The impact of ramipril on kidney function parameters in the chronic kidney disease patient with hypertension

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ABSTRACT
The administration of angiotensin converting enzyme inhibitors had gained popularity owing to their efficacy and safety in chronic kidney disease (CKD) patients. However, it is certainly necessary to look into the impact of the ramipril in kidney impaired individuals. We had enrolled 190 CKD with hypertensive patients based on the exclusion and inclusion criteria. The elder patients constituted to have a major share in the CKD population on ramipril therapy. From the study, it was found that the high costly brand was chosen the most and least cost was preferred only for 2 patients. The glomerular filtration rate (GFR) and serum creatinine, the major determinants of kidney function, had a small relationship with the dose of ramipril. However, the antihypertensive drug showed to have a favorable impact on patients overall treatment outcome. It is vital to evaluate the amount of protein in urine in case of a CKD patient. The easiest and cost effective technique, the dipstick urine protein test was done. The test value was found to be 1+ (30mg/dl) for majority of the patients and only 2 patients were observed with more than 1000 mg/dl. The ability of ramipril to reduce the progression of CKD can be attributed to the pooling of the data in +1 (30mg/dl) range.

INTRODUCTION
The angiotensin system related agents such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are one among the first line option to normalize the blood pressure in chronic kidney disease patients (CKD). Apart from their benefit in hypertension, the ACE inhibitors also have positive effects on the kidney function (Doggrell, 2001). This had been attributed by the improvement in kidney urine flow and reduction in urine protein (Kunz et al., 2008). There is an increased awareness and treatment of hypertension among CKD patients. Each of the antihypertensive agents is roughly equally effective in lowering the blood pressure, producing a good antihypertensive response in 30 to 50 percent of patients. Joint National Committee (JNC) 8 recommends to initiate a renin-angiotensin-aldosterone system (RAAS) inhibitor, thiazide diuretic or a calcium channel blocker (CCB) for improving the blood pressure (BP) in CKD patients. Among them, angiotensin converting enzyme inhibitors or angiotensin receptor blockers were most frequently used drug as monotherapy followed by CCBs, diuretics and beta blocker. Controlled blood pressure (BP) in normal...
levels can prevent worsening of kidney function. The HOPE and EUROPA trails depict the efficacy of ramipril when compared to placebo. Apart from BP control, progression of CKD is another important aspect that needs cautions. The angiotensin system inhibitors can normalize the BP in hypertension with suppression of the CKD progression. The studies on ACE inhibitor doses and their impact on proteinuria (a determinant of kidney function) suggesting that the amount of dose necessary for their benefits are likely to vary among patients. So, we had performed a study to analyse the impact of ramipril on kidney function test and the changes it can produce when administered to CKD patients.

**METHODOLOGY**

The prospective observational study was conducted from October 2018 to August 2019 at the nephrology department of KIMS Al Shifa hospital, the tertiary care referral hospital. The ethical committee approval and informed consent was obtained.

The CKD patients with hypertension on commonly administered ACE inhibitors – ramipril therapy were followed up for three consecutive consultations. Also, patients with acute kidney injury, unconscious or those with serum creatinine greater than 3.5mg/dl are excluded from the study. Direct patient interview, discussion with physician, medical record database and prescription were the sources for retrieval brands, dose and frequency of ramipril administered to the CKD patients. The kidney function parameters assessed was glomerular filtration rate, serum creatinine and urine protein. For that, blood and urine samples were collected on the patient’s three hospital visits and their value were noted.

The data collected was spread into an excel sheet which was then statistically analyzed by the same platform. The regression analysis was done to relate the clinical parameters with ramipril.

**RESULTS AND DISCUSSION**

The renal protection and slowing the progression of kidney impairment is the mainstay of concern in CKD patients. We had obtained 190 CKD patients with co-existing hypertension, who was on ramipril therapy. The ramipril was administered to 125 geriatric, 64 adult and 1 pediatric patient as shown in Figure 1.

The age group above 60 years are heavily prevalent to CKD when we analyzed the epidemiological results conducted in various countries (Mallappallil et al., 2014).

![Figure 1: The CKD patient category distribution](image1)

![Figure 2: Different brands of ramipril administered to the CKD patients](image2)

![Figure 3: The distribution of different doses of ramipril administered to patients](image3)

![Figure 4: The mean GFR and mean serum creatinine of CKD patients in 3 consultations](image4)
Table 1: Cost of different brands of Ramipril administered to the CKD Patients

| S. No. | Manufacturer | Brand name | Dose | Cost per 15 tablets |
|--------|--------------|------------|------|-------------------|
| 1.     | Sanofi       | Cardace    | 1.25mg | Rs 80           |
|        |              |            | 2.5mg  | Rs 83             |
|        |              |            | 5mg    | Rs 131            |
|        |              |            | 10mg   | Rs 286            |
| 2.     | Lupine       | Ramistar   | 1.25mg | Rs 84             |
|        |              |            | 2.5mg  | Rs 82             |
|        |              |            | 5mg    | Rs 130            |
|        |              |            | 10mg   | Rs 308            |
| 3.     | Micro Lab    | Hopace     | 1.25mg | Rs 38             |
|        |              |            | 2.5mg  | Rs 54             |
|        |              |            | 5mg    | Rs 123            |
|        |              |            | 10mg   | Rs 170            |

The Drug - Ramipril

In Figure 2, Cardace was the most common brand (73.6%), this was followed by Ramistar (17.3%) and least prescribed was Hopace, which had been the brand of choice for 2 patients. The physician also prescribed generic ramipril for 15 (7.8%) of CKD patients. But, there was no generic medicine in the hospital. Hence, the pharmacist chose the available brand stocked in the pharmacy.

The brand Hopace by Micro Lab had the least cost when we compared with Ramistar and Cardace. It was also observed that all the prescribed brands are available in 1.25mg, 2.5mg, 5mg and 10 mg. The cost distribution is shown in Table 1.

The clinical trial conducted to assess the efficacy of ramipril in kidney disease patients depicted that, a small dose of ramipril (1.25mg daily therapy) even though had limited effect on improving symptoms of hypertension, had the ability to preserve the kidney function (Doggrell, 2001). The most preferred dose in our study was 1.25 mg, opted for 107 (56.31%)
patients and among them 92 were given once daily dose and 15 with twice daily regimen. Two patients were given half of 1.25mg tablet. The practice of splitting the tablet into multiple portions and this might not produce the intended action. It may lead to underdosing or over dosing, which causes harm than benefit. Hence, such practice should not be promoted.

The dose strength of 2.5 mg was then preferred for patients, which constituted 19.47% (once daily therapy) and 4.21% (twice daily therapy). 5mg once daily was considered for 23 patients and 10 mg was the highest dose prescribed for the CKD patients based on our study criteria. The ramipril dose distribution is portrayed in Figure 3.

For hypertensive patient without CKD, the American College of Cardiology and American Heart Association (ACC/AHA) recommends to begin with 2.5 mg once daily therapy and then dose increment can be done, if the patient has no better response after 2 to 4 weeks of initiation. The maximum dose of ramipril is 20mg once daily or can be divided into two doses (Whelton et al., 2018). However, for CKD patients, the dose can be started with 1.25 mg once daily, titrated as tolerated to the desired effect and the maximum dose is 5 mg.

Glomerular Filtration Rate and Serum Creatinine
The Glomerular filtration rate (GFR), serum creatinine and urine protein are the prime determinants of renal function. It is vital to check those parameters in all the CKD patients. This would put light to the progression of the CKD, the improvement of the patient’s condition and the effectiveness and safety of the therapy initiated.

The GFR is defined as the cumulative filtration of nephron of both the kidneys. The glomeruli are the portion of nephrons which filters about 180 L of urine per day. The GFR range between 120 to 130ml/min/1.73m², this is influenced by age, gender and body mass index. The male population has a 10ml/min/1.73m² more GFR than female (Stevens et al., 2006). From Figure 4, we obtained the mean of GFR during the three consultations to be 38.1, 38.9 and 39.5 ml/min/1.73m², respectively. The pooled data of CKD patients, when interpreted revealed that, the 1.5 % of CKD patients with GFR between 15 to 60ml/min/1.73m² would progress to end stage renal disease within a year. However, only 0.5% of patients shifted from a GFR greater than 60 to less than 60ml/min/1.73m² in a year (Hsu et al., 2004; Fox, 2004).

The serum creatinine in health individuals should be around 0.9-1.3 mg/dl in male and 0.7-1.1mg/dl in case of female (Jones et al., 1998; Bakris and Weir, 2000). The mean serum creatinine observed in three consultations was 1.9mg/dl, 1.7mg/dl, 1.8mg/dl.

Urine Protein with Dipstick test
The urine protein can be detected and roughly quantified with dipstick test. The amount of albumin can be obtained; however, it would be relevant to assess the albumin to creatinine ratio also by means of urine sample. The results of dipstick test for protein are graded as negative, trace and 1+ to 4+ based on the amount of protein in urine. Most of our patients had dipstick value of 1+ (30 mg/dl), followed by 2+ (100 mg /dl), then 3+ (300 mg/dl) and 2 patients had 4+ value (greater than 1,000 mg/dl). This data was retrieved during their 3 consecutive consultations as shown in Figure 5.

The dipstick urine protein test even though can be performed easily, has their limitation. Most of the CKD patients with urine protein between 30 to 300mg/dl showed false negative results. Also, the test cannot detect globulin or parts of globulin (Lafayette et al., 1996). This is serious matter of concern because early detection and management of kidney impairment is the best way to prevent complications. This could be done, only if the accurate results are obtained. For identifying the nephrotoxic immunoglobulin, we need to go for sulfosalicylic acid test.

The Multiple Risk Factor Intervention Study compared individual values of dipstick protein results with combined GFR along with dipstick protein results and it was found that the hazard ratio was high for the latter (Ishani et al., 2006). Thus progression of CKD to end stage renal disease can be confirmed by low GFR and high dipstick proteinuria value.

Numerous studies had been done to quantify the influence of renin-angiotensin system (RAS) inhibitors in nullifying the proteinuria. The benefits of the agent on protein excretion can be dependent on their ability to correct the intra-glomerular pressure in CKD patients (Yoshioka et al., 1987). Nephrin is an essential module of the podocyte slit pore membrane and also contribute to the glomerular filtration barrier. The angiotensin 2 reduces the pore membrane and also contribute to the glomerular filtrate barrier. The nephrotoxic immunoglobulin, we need to go for sulfosalicylic acid test.

The Multiple Risk Factor Intervention Study compared individual values of dipstick protein results with combined GFR along with dipstick protein results and it was found that the hazard ratio was high for the latter (Ishani et al., 2006). Thus progression of CKD to end stage renal disease can be confirmed by low GFR and high dipstick proteinuria value.
of protein urine, ramipril was found to favorably decrease proteinuria (Remuzzi et al., 1997).

**Relation of glomerular filtration rate with ramipril dose**

From the Figure 6, the slope of the line was found to be 1.79, 1.93, 1.94 for the first, second and third consultations, respectively and the corresponding coefficient of determination was obtained as 0.023, 0.030, and 0.032, respectively. These value implies that, the GFR can be increased by 1.79 to 1.94 ml/min/1.73m² in each increase in dose of ramipril. The graph also clarifies that, the propensity of the ramipril’s dose to modify the GFR was only 2 to 3%.

**Relation of serum creatinine with ramipril dose**

The slope of the curve plotted with respect to data obtained on 1st, 2nd and 3rd consultation was -0.80, -0.090 and -0.108, respectively. The coefficient of determination was 0.03, 0.049 and 0.06 with the above mentioned curves, respectively (Figure 7). Thus, we can conclude that for each increase in dose of ramipril, there may be a decrease in the serum creatinine by 0.80 to 0.108 and this association was small (6-3%).

**Discontinuation of ramipril therapy**

Apart from hypertension and CKD, ramipril can also be administered for heart failure. The efficacy of the agent in all those conditions had been proved in studies. The drug is widely prescribed agent because of their high patient tolerability. Despite few side effects, they are safe to be administered and do not alter the lipid and glucose (Izzo and Weir, 2011; Taylor et al., 2011).

Figure 8 show that, we had small number of population (5%) who discontinued the therapy and that too only for a day. Fever was the major reason behind the transient stoppage of the therapy and other reasons was elevation in serum potassium and serum creatinine.

Some studies indicate the acute increment observed in serum creatinine with ramipril administration within the 2 months after treatment initiation. This gets stabilized gradually and the renal preservation was observed in later times. This association was identified in patients with serum creatinine more than 1.4 mg/dl. Hence, the drug should be stopped and an alternative agent should be initiated, when the serum creatinine is above 30 percent from the normal range within two months of ACE inhibitor therapy.

**CONCLUSION**

The angiotensin system related agents administered for hypertension also can influence the kidney function. Angiotensin converting enzyme inhibitors apart from their chance to induce dry cough had generated favorable impact for chronic kidney disease patient. Even in CKD patient without hypertensive, the introduction of ramipril can reduce the progression of the disease and improve their life expectancy.

**Conflict of Interest**

The authors declare that there is no conflict of interest for this study.

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