Impact of Intensified Pharmaceutical Interventions in Medication Adherence in Chronic Kidney Disease Patients

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ABSTRACT
Aim: The study aims to evaluate the medication adherence behavior of individuals by using validated questionnaire and to enhance the adherence by using various cost effective interventional methods which likely have a greater effect on the health of patients with chronic diseases than any improvement in specific medical therapies. Method: The prospective interventional study was carried out for a period one year. The participants selected from the outpatients of nephrology department in a 750-bedded tertiary care hospital in the Malabar region of south India. Patients were provided with a standard validated modified Morisky eight item questionnaire and self-reporting questionnaire assessing medication adherence before and after intervention. The intervention mainly in the form of patient counseling and patient information leaflet was carried out using a proper management plan and with the help of physician and feedback information was collected. Results: Statistically significant association exist between medication adherence before and after intervention (p <0.001). Medication adherence behavior of study subjects has a significant association with age, sex, education and stage of chronic kidney disease. Pharmaceutical interventions impart a significant improvement in the medication adherence behavior. Cost of the treatment, low family income and drug therapy burden have been reported as a main reason for non-adherence. Individual patients have their own preferences for dosage form, frequency of administration, food time etc. Conclusion: The study suggests that the periodic counseling by clinical pharmacist at regular intervals can improve the medication adherence by improving awareness and removing the misconceptions about the disease and therapy.

Key words: CKD, Medication adherence, Drug therapy, Patient counseling and Patient information leaflet, Renal disease.

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INTRODUCTION

Medication adherence can be defined as a condition in which a patient’s medication taking behavior coincides with the intention of health advice he or she has been given. Good medication adherence is important to obtain desired therapeutic outcome where as low adherence is considering to be one of the major reasons that not only decreases desired therapeutic outcome but also increases financial burden in individual patients and healthcare system. When it comes to chronic diseases, medication adheres is the key link between treatment and outcome. In case of both developing and developed countries chronic kidney disease, (CKD) which can be defined as an increase in serum creatinine concentrations greater than 1.2 to 1.5mg/dl, is one of the major public issues. Anemia, secondary hyperparathyroidism, renalosteodystrophy, hypertension and hyperlipidemia, metabolic acidosis, and several other comorbidities involving malnutrition, pruritus and uremic bleeding are can occur as associated with CKD.¹ These patients are also at increased risk of cardiovascular disease (CVD) such as coronary heart disease (CHD), cerebrovascular disease, peripheral vascular disease, and heart failure. As there is no defined gold standard for measuring adherence so far, it makes difficult not only to carry out the research involving such topics but also comparison of results with other similar researches. Large number of prescribed medicines and frequent dosing changes may contribute to decreased adherence which in turn can lead to drug related morbidities. In case of CKD major goals are to slow down the disease progression and prevent the related complications through careful monitoring. For this adherence to the treatment regimen is necessary. Increased morbidity and mortality in developing countries is mainly due to poor adherence to the therapy regimens.² The study aims to evaluate the medication adherence behavior of individuals by using validated questionnaire and to enhance the adherence by using various cost effective interventional methods which likely have a greater effect on the health of patients with chronic diseases than any improvement in specific medical therapies.

MATERIALS AND METHODS

This prospective interventional study of one-year duration was conducted in the nephrology department of a tertiary care hospital of Malabar region in South India. A pilot study was carried out to find out the patient’s response and attitude towards the study. The study was conducted in 3 phases. In the initial stage, pre-interventional, approximately 950 patients consulted in the department 163 patients were selected based on inclusion-exclusion criteria and informed consent was taken for the study after filtered in pursuance of inclusion exclusion criterions. Nephrology outpatients those underwent the treatment of chronic kidney disease, both male and female patients, who are willing to participate in the study were included in the study while pregnant patients, patients with co morbidity conditions like psychiatric illness, cognitive impairment and malignancy, patients of non-Indian origin, patients who provide incomplete information about drug use and patients on the initial stages of CKD (stage 1 and 2) excluded from the study. CKD stage 1 and stage 2 patients excluded because these patients don’t have any long term therapy
with medicines. Modified Morisky 8 item Questionnaire (MMQS-8) was used to assess the medication adherence of the patients and a Self-reporting questionnaire in a format of objective type to be filled by patient/bystander was prepared to gather information regarding patient education, living status, family support, availability of medicines, cost of treatment, awareness about disease condition, knowledge about medicines, economic burden medication taking behavior etc. Cranach's χ used for internal validation of MMQS-8 and the self-reporting questionnaire used were validated by experts using test-retest method. During interventional period medication adherence of the patients were classified in to low, medium and high. Based on the overall medication adherence pattern pharmaceutical interventions like patient counseling and patient information leaflets containing general outline information about CKD and importance of medicines were prepared and provide to individual patients. A feedback form was designed and developed to collect information from subjects regarding their preferences and attitude towards treatment. Telephonic interview was done when necessary. In post intervention phase the individuals were further evaluated for measuring the medication adherence and compared with the previously obtained score. Feedback form was given to the study subjects and information was collected. The collected data were analyzed categorized and entered Ms. Excel format. According to the formulae: 
\[ n = Z^2 \times P \times Q \] 
\[ d = \text{error of estimates (9%)} \] 
\[ Q = 1 - P \] 
\[ P = \text{rate of prevalence (50%)} \] 
\[ n > 2 \times Z^2 \times P \times Q / d^2 \] 

Where \( n \) is minimum sample size for the study was 116, 
Where \( Z = \text{confidence coefficient (95%)} \) 
Where \( P = \text{rate of prevalence (50%)} \) 
Where \( Q = 1 - P \) 
Where \( d = \text{error of estimates (9%)} \)

Different tools were used to perform statistical analysis of various data 'Chi square test' for association of qualitative variables under study, 'Independent student t test' for comparison of demographics details, ANOVA techniques were used for comparison of various parameters, 'Co-relation and regression' analysis was used for quantitative variables and 'Paired t test' was performed for comparison of variables.

Outline of Study Methodology

PREINTERVENTION PERIOD (3 months)  
- Enrollment study subject (163)  
- Data collection (Patient records, Morisky medication adherence scale, Self-reporting questionnaire)  
- Monitoring

INTERVENTION PERIOD (4 months)  
- Development of interventional programs (Patient information leaflet and patient counseling)  
- First review  
- Implementation of interventional programs

POSTINTERVENTIONAL PERIOD (3months)  
- Second review  
- Reevaluation of medication adherence (Feedback form and morisky medication adherence scale.)  
- Statistical analysis (Chi square test, Independent students t test, ANOVA and Paired t test)

RESULTS

During the study approximately 950 patients visited Nephrology outpatient department, among them 165 patients selected and enrolled in the study based. Amidst these 163 patients, 14 (8.58%) were ≥ 76-year-old, highest number of patients 65 (39.87%) belongs to range 61-75, 46 (28.22%) patients in range of 46-60. 27 (16.56%) patients were in group of 31-45, 10 (6.13%) in group of 16-30 and only 1 (.61%) were in range of 0-15. The correlation between age and adherence, before and after intervention was studied using Karl-Pearson coefficient of correlation and it is find out that there is a significant positive correlation between age and adherence before and after intervention (p<0.05). As age advances, the score obtained by the individuals was also increasing, indicating that medication adherence was decreasing as age increases (Figure 2a and 2b). In male patients (n = 91) and in female patients (n = 72), there is a statistically significant improvement in high level adherence and low-level adherence after intervention (p< 0.001). But comparing to female patients, male patients shows more improvement in medication adherence after the interventional studies (Figure 1).

Considering educational status none of the patients were illiterate. 57.05% people had high school education. 4.97% were graduates. Only 5.52% have secondary education. About 13.44% have lower primary education and 1.22% has technical education or equivalent. Patients with high school education show higher improvement in medication adherence after the interventional studies (Figure 1). Considering education status none of the patients were illiterate. Comparatively a very few study subjects have a social history of smoking, alcohol or both 12.8.8%, 4.29%, 6.134% respectively. Out of these163 study subjects, 48% were in stage 5 of CKD, 32% in stage 4 of CKD and remaining 20% were in stage 3 of CKD. None of the study subjects were in stage 1 or 2 of CKD. Majority of the study population, 75.46%, shows medium level of adherence followed by 15.95%, shows low adherence and remaining 8.5% exhibits high level of adherence. After intervention there is a reduction in medium (56.44%) and low level (0.613%) of adherence and increase in high level adherence (42.94%) exhibits a statistically significant improvement in medication adherence (p<0.001). Also, comparing to other stages, patients at CKD stage 5 shows more improvement in medication adherence (Table 1). Among total study subjects only n=111 (68%) patients preferred both

Figure 1: Association of Gender and Adherence. 
In male patients (n= 91), there is a statistically significant improvement in high level adherence after intervention (p< 0.001).

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improvement in adherence behavior of patients who supports both type of intervention (Figure 4) but when comparing the intervention preference and change in adherence behavior, medication adherence of the study subjects who preferred patient counseling (n=32) have better improvement (Figure 3). Patients under study reported various factors as reason for non-adherence. Among the reasons, majority suggest cost of the drug (77.91%) as a reason for non-adherence was low family income (77.3%) was also a reason for poor adherence. It is followed by various other reason for non-adherence such as taste or size of dosage form (60.12%), poor awareness about importance of medicines (44.78%) and lack of family support (33.35%). A very few people (16.56%) suggest side effects of drug as a reason for non-adherence. Majority of the patient population n= 119(73.06%) preferred to take tablets and capsules. About n= 40 (23.53%) was ready to take all type of dosage form, whereas none of them prefer to take liquid dosage forms. About 60.73% of patient population suggested once daily dose as a more acceptable frequency for drug administration.

There is a significant association exist between medication adherence before and after intervention (p <0.001). In medium and low level of adherence there is significant reduction after intervention (p < 0.001). There is significant increase in high level of medication adherence after intervention (p <0.001)

**Table 1: MEDICATION ADHERENCE at VARIOUS STAGES of CKD (before and after intervention).**

<table>
<thead>
<tr>
<th>MMQS - 1</th>
<th>CKD - 3</th>
<th>CKD - 4</th>
<th>CKD - 5</th>
<th>MMQS - 2</th>
<th>CKD - 3</th>
<th>CKD - 4</th>
<th>CKD - 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>5</td>
<td>1</td>
<td>8</td>
<td>HIGH</td>
<td>21</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>MEDIUM</td>
<td>42</td>
<td>60</td>
<td>31</td>
<td>MEDIUM</td>
<td>26</td>
<td>47</td>
<td>19</td>
</tr>
<tr>
<td>LOW</td>
<td>0</td>
<td>12</td>
<td>4</td>
<td>LOW</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>47</td>
<td>73</td>
<td>43</td>
<td>TOTAL</td>
<td>47</td>
<td>73</td>
<td>43</td>
</tr>
</tbody>
</table>

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**Table 2: Association of Education with Adherence.**

<table>
<thead>
<tr>
<th>Education</th>
<th>Adherence</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP</td>
<td>HIGH</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>MEDIUM</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>LOW</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>HIGH</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>UP</td>
<td>MEDIUM</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>LOW</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>HIGH</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>HS</td>
<td>MEDIUM</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>LOW</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>HIGH</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>HSS</td>
<td>MEDIUM</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>LOW</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>HIGH</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DIPLOMA</td>
<td>MEDIUM</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>LOW</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>HIGH</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>DEGREE</td>
<td>MEDIUM</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>LOW</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

A statistically significant improvement can be seen in patients at all level of education (p<0.001).

**Figure 2a: Association between Age and Adherence before Intervention.**

**Figure 2b: Association between Age and Adherence after Intervention.** There is a significant positive correlation between age and adherence before and after intervention (p<0.05). As age advances, the score obtained by the individuals was also increasing, indicating that medication adherence was decreasing as age increases.

**DISCUSSION**

The study was intended to assess and improve medication adherence of the CKD patients in various stages and the study showed that pharmaceutical interventional programs like patient counseling and patient information leaflet programs while remaining patients selected either patient counseling n= 32 (20%) or leaflet n=20 (12%) as their preference. There is a statistically significant improvement in adherence behavior of patients who supports both type of intervention (Figure 4) but when comparing the intervention preference and change in adherence behavior, medication adherence of the study subjects who preferred patient counseling (n=32) have better improvement (Figure 3). Patients under study reported various factors as reason for no adherence. Among the reasons, majority suggest cost of the drug (77.91%) as a reason for no adherence was low family income (77.3%) was also a reason for poor adherence. It is followed by various other reason for non-adherence such as taste or size of dosage form (60.12%), poor awareness about importance of medicines (44.78%) and lack of family support (33.35%). A very few people (16.56%) suggest side effects of drug as a reason for non-adherence. Majority of the patient population n= 119(73.06%) preferred to take tablets and capsules. About n= 40 (23.53%) was ready to take all type of dosage form, whereas none of them prefer to take liquid dosage forms. About 60.73% of patient population suggested once daily dose as a more acceptable frequency for drug administration.

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was 57.24±15.493, which is slightly greater than that of study conducted\(^6\) (51±16.7). There is a prevalence of male patients (60.4%), whereas in study conducted\(^1\) it was 62.7%. Chronic renal failure is categorized in to five different stages based on GFR values. As the disease progress severity of the disease also increases. Patients from stage 1 and 2 were not included in the study as they don’t have long term therapy, but the progression of disease mainly prevented by lifestyle modifications. Majority of patients (44.78%) were on stage 4, followed by 28.83% and 26.38% on stage 3 and stage 5 respectively. Medication adherence behavior of study patients were analyzed using MMQS- 8 item scale which categorizes adherence behavior into three groups low adherence, medium and high adherence. Here, majority of sample 75.46% have medium adherence 5.95% have low adherence and 8.5% have high adherence before the implementation of pharmaceutical interventional programs with a mean MMQS score of 5.77±1.642 and these results were contradictory with the results of the study conducted\(^4\) in which the adherence percentage of study subjects were 51.3%, 29.7% and 19.0% in high, medium and low level of adherence respectively. This contradiction in the adherence percentage was due to the lack of awareness, poor knowledge about proper usage of medicine, economic problem, treatment cost etc. After implementation of pharmaceutical care programs like patient counseling and patient information leaflet patient in high level of adherence increased to a percentage of 42.94 and patients in low level adherence and medium level adherence decreased to a percentage of 56.44 and 0.613 respectively and the mean MMQS score have been changed to 3.81±1.279. This relative change in the adherence behavior indicates an improvement in the medication adherence behavior that occurred as a result of effective pharmaceutical care programs. Extensive studies on adherence behavior of patients at different stages of renal failure were rare and hence a comparison at different aspects was not possible. Within the study patients at stage 5 of CKD exhibits a little more improvement than the other two stages. But results were in contradiction with study conducted.\(^3\) To a certain extent medication adherence behavior was influenced by gender of patient. The improvement in adherence behavior of male patients was found to be greater than that of females. This difference may be due to difference in educational status, poor family support and awareness, priorities among individuals etc. Level of education have a great impact on adherence behavior, patients with high school education shows good improvement in medication adherence than others which is like study conducted.\(^4\) A significant positive correlation (z= 0.376) exist between age and adherence. As age increases adherence behavior of study subjects decreases. This was in contradiction with study conducted,\(^7\) in which they concluded that adherence behavior decreases as age decrease. Among the two intervention programs individual study subjects prefer to choose an intervention or both. About 68% of patients suggested both patient counseling and information leaflet as an effective method whereas 20% suggested patient counseling and 12% suggested leaflet respectively. Within these preference patients supporting patient counseling exhibits more significant improvement in medication adherence which is same as that of the results of study conducted.\(^8\) In the current study, many patients reported more than two factors as a reason for non-adherence. About 77.9% of patients reports cost of treatment as reason for non-adherence. Similar observations were also reported in studies conducted.\(^9\) In present study 76.7% of study population reported burden of medication as a reason like the study conducted.\(^10\) As Medicines are available in different dosage form they can also influences medication adherence behavior of the patients. About 73.06% of patients prefer to take tablet and capsules as their option because of ease of consumption also time and frequency of administration have influenced the medication adherence behavior of patients, 60.73% of patients prefer once daily dosing at food time (60.75%) which is Similar to study conducted.\(^11\)

**CONCLUSION**

This study explores the impact of a pharmaceutical care based programme for improving the medication adherence in patients with chronic renal failure. Impact of patient counseling was higher in improving the medication adherence. Education and age have great influence on medication adherence.
adherence. Ranging from CKD stage 3 to 5, the adherence behaviors of study subjects were different. As stage of CKD progress, the adherence behaviors of study population were increasing. Various factors were reported as a reason for non-adherence. The treatment cost and low family income were the major reason for non-adherence. Along with these, availability of drug, side effect, taste and size of dosage form, burden of therapy etc. were also reported as reason for non-adherence.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CHD: Coronary Heart Disease; CKD: Chronic Kidney Disease; CVD: Cardio Vascular Disease; MMQS-8: Modified Morisky 8 item Questionnaire; GFR: Glomerular Filtration Rate.

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