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Original Article

ADAPTABILITY OF CLINICAL PHARMACIST LED INTERVENTIONS IN THE MANAGEMENT OF ANEMIA OF CHRONIC RENAL DISEASE: OPTIMIZING CARE

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ABSTRACT

Renal anemia is a common comorbidity in chronic kidney disease (CKD) patients, typically treated with erythropoiesis-stimulating agents (ESAs) like erythropoietin. However, both over- and under-treatment are prevalent. In 2008, the Pharmacy Council of India introduced the Pharm.D course to enhance pharmaceutical care in clinical settings. While extensive studies in other countries highlight the benefits of clinical pharmacists' interventions, Indian research on this topic is limited. This prospective randomized controlled trial included CKD patients not on dialysis, with serum creatinine levels of 2-6 mg/dL and hemoglobin (Hb) levels below 12 g/dL. Participants were divided into three subgroups based on baseline Hb levels: < 10 g/dL (Group I), 10-12 g/dL (Group II), and >12 g/dL (Group III). ESAs and iron supplements were adjusted to maintain Hb levels of 10-12 g/dL. Quality of life was assessed using the Short Form Health Survey-36 questionnaire. Out of 448 participants, those in the pharmacist intervention group showed a significant shift towards Group II by the trial's end, compared to the control group. The study demonstrated a significant improvement in quality of life and physical performance, particularly for those in Group II, indicating that maintaining Hb levels at 10-12 g/dL is optimal for Indian CKD patients. This trial exemplifies the profound impact clinical pharmacists can have on patient care, highlighting their crucial role in improving healthcare outcomes through active participation and targeted interventions in clinical settings.

KEYWORDS: Chronic Kidney Disease, Anemia Management, Clinical Pharmacists Intervention, Pharmaceutical Care.

1. Introduction

Chronic Kidney Disease (CKD) is long standing disease where patients often suffer from anemia. Erythropoiesis Stimulating Agents (ESA) are thought to be extremely effective in treating anemia, and the treatment recommendations for target Hemoglobin (Hb) levels have been set in several countries based on prior clinical trials [1-3]. The large randomized controlled trial known as 'Correction of Hemoglobin and Out-comes in Renal Insufficiency' (CHOIR) study found that higher Hb (13.5 g/dL) target group had increased risk for adverse outcomes, such as death, myocardial infarction, hospitalization for congestive heart failure, and stroke, compared to the lower Hb (11 g/dL) group, indicating the target would be maintained for 11.0 - 12.0 g [4]. Additionally, a meta-analysis of studies that suggested a target hemoglobin level for CKD patients revealed a considerably greater risk of mortality and uncontrolled blood pressure in the higher Hb group [1]. As a result, anemia recommendations published in 2007 by the "National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NFK-KDOQI)" indicated that target Hb values should not exceed 13.0 g/dL [5].

In India alone, the prevalence of CKD ranges from 13 to 15.04%, and recent data from the International Society of Nephrology's Kidney Disease Data Centre study disclosed an average prevalence of 17% [6-7]. Recent assessments demonstrated that CKD affects over 10 percent of the population as a whole around the globe, accounting for > 800 million people [8]. The emergence of new symptoms and other concurrent problems often rises as CKD progresses from early to late stages. The common objective of CKD and ESRD patients' care teams composed of Physicians, Nurses, Dieticians, and Clinical Pharmacists is to manage the comorbid diseases whilst still preventing the progression of the disease. Clinical Pharmacists, being experts in pharmacotherapy, are involved in patient care and liaise with other medical experts to meet the need of

pharmacotherapy optimization. Ideally, this happens through a proactive rather than a reactive strategy and data from previous worldwide studies have shown that the involvement of clinical pharmacists in multiple healthcare areas enhances patient outcomes and care [9-10]. In 2008, Pharmacy Council of India introduced a Pharm.D course in view of pharmaceutical care in real clinical setting. There are extensive studies available in other countries related to the applicability of clinical pharmacists' intervention in pharmaceutical clinical care, whereas the studies showcasing the importance of Pharmaceutical Care conducted in Indian scenarios are limited, especially the clinical pharmacists' role. Hence, the current study was carried out in order to address the need for clinical intervention by Clinical Pharmacists in Pharmaceutical Care in Indian origin by employing the scenario of anemia treatment and health-related quality of life outcomes in CKD patients.

2. Materials and Methods

This was a prospective randomized, single-cantered, open-label, parallel-assigned study which was conducted in BGS Global Hospitals, Kengeri, Bengaluru, India and was approved by Institutional Ethics Committee (ECR/128/ Inst/KA/2013). This was a time-bound study in which the sample size was chosen arbitrarily based on inpatient admits for over 12 months of period. The CKD patients above 18 years, who were not on dialysis, with serum creatinine levels falling within 2-6 mg/dL and hemoglobin levels less than 13.0 g/dL, were included in the study. Patients who were on dialysis, with comorbidities such as uncontrolled hypertension (above class III on the JNC 8 classification), congestive heart failure, malignancy, blood disease or active bleeding, and study drugs allergy were excluded from the study. The eligible participants were randomly assigned to either the experimental group receiving pharmacists' care or the control group not receiving pharmacists' care by 1:1 using shuffled tokens. Participants were then divided into three groups in both control and study groups based on baseline hemoglobin levels. Group I consisted of patients whose hemoglobin level was < 10 g/dL, Group II: 10 – 12 g/dL, and Group III: > 12 g/dL. Based on the study group participants' baseline hemoglobin levels, clinical pharmacists' provided recommendations to the physicians for the adjustment of erythropoietin dose. For iron-deficient participants, based on ferritin and Transferrin Saturation (TSAT) levels, recommendations were made for the administration of an iron preparation. The iron preparation (iron sucrose) at 40 mg was administered I.V. once a week to patients with ferritin and TSAT values of less than 60 ng/ml and 20%, respectively. To maintain the hemoglobin levels in the respective subgroups the dosage of ESA was adjusted. Aside from the study requirements, iron supplements were administered to both the groups to maintain serum transferrin saturation of >20% or serum ferritin of >100 ng/mL. Blood pressure objectives for treatment were systolic of <130 mmHg and diastolic of < 80 mmHg. Detailed guidelines are shown in Fig. 1.

The Pharmacists' clinical management included five pivotal activities: providing drug information on renal anemia to physicians; compiling guidelines for proper use of recombinant human erythropoietin and iron in collaboration with physicians; medication use evaluations based on laboratory data; ADR detection and management; proposing plans to change prescriptions based on medication use evaluations; providing disease, treatment, and lifestyle modification information to the patients. The primary outcomes were the change in hemoglobin levels following the Clinical Pharmacist's intervention and an improvement in health-related quality of life in CKD-anemic patients. The secondary outcome was occurrence of adverse events which indicated the safety of the study.

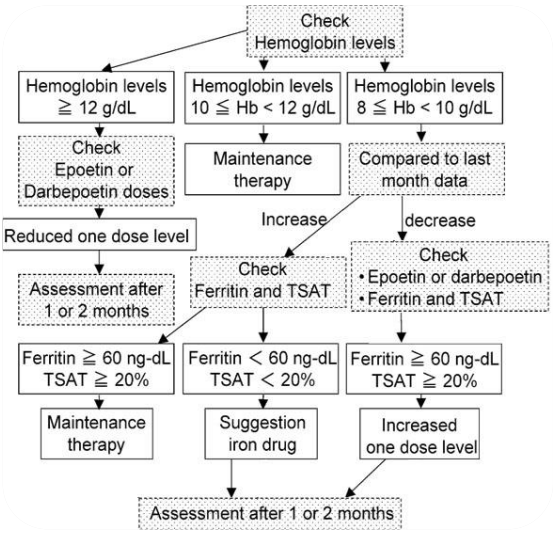

Fig. 1. Guidelines on Pharmacists' evaluation criteria for adjusting the dosage of Erythropoiesis Stimulating Agents

Upon obtaining the informed consent form from the participants, the data was collected which included demographic details, clinical history and progress throughout the study proceedings. Quality of life was assessed at baseline and 3, 6, and 12 months using Short-Form health survey (SF-36) version 2 form (Quality Metric's Health Outcomes™ Scoring Software 5.0). All the data were analyzed using a SPSS software to detect a significant level of two-sided probability of <0.05 in comparing variables between two groups.

3. Results

The study included a total of 448 CKD patients with Hb levels of < 13 g/dL, and with serum creatinine of 2.0 - 6.0 mg/dL; none of them were receiving dialysis. They were randomized into study and control arm by 1:1 which comprised of 224 patients in each group. The flow of participants is represented in a flow-chart (Fig. 2). The baseline characteristics of each group of participants are summarized in Table 1.

The primary aim was to maintain the hemoglobin levels <12.0 g/dL which was considered as safe and target levels advised by several previous trials for CKD patients. Clinical Pharmacists' attempts to maintain target Hb levels through various activities were documented as a trend change in the number of patients in each subgroup. The change of participants between the subgroups is summarized in Table 2 and 3. There was a statistically significant change in the pharmacists' intervention at the end of the study (p-0.03) compared to control group. The number of patients in study group decreased in Groups I and III while increasing in Group II. The control group resulted in change of participants to either low Hb group (<10 g/dL) or to high Hb group (>12 g/dL), whereas the study group improved

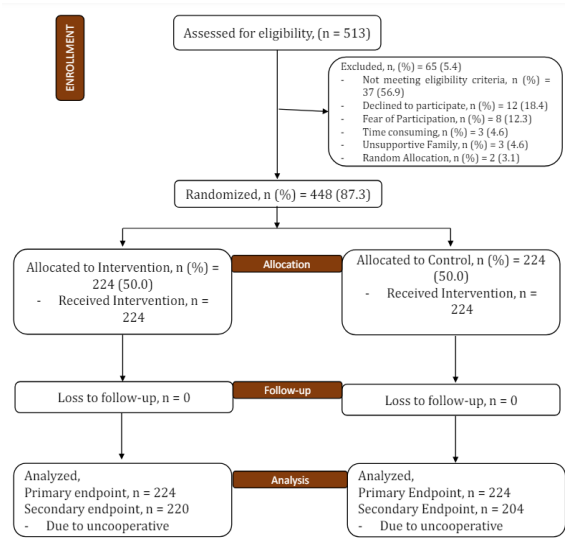

Fig. 2. The Flow of Events of the study participants

Table 1. Demographics and baseline characteristics of participants of each group.

Charcteristics	Study Group	Control Group
Age (Years), Mean ± SD	63.2 ± 8.7	62.7 ± 12.1
Gender, n (%)		
Male	137 (61.1)	143 (63.8)
Female	87 (38.9)	81 (36.2)
Comorbidities, n (%)		
Hypertension	184 (82.1)	171 (76.3)
Diabetes Mellitus	156 (69.6)	145 (64.7)
Cardiovascular Diseases	83 (37.0)	79 (35.3)
Bone disorders	17 (7.6)	13 (5.8)
Hemoglobin Levels (g/dL), Mean ± SD	9.3 ± 2.7	10.8 ± 2.2
Mean TSAT	23 %	27 %

considerably with Clinical Pharmacists' interventional treatments, demonstrating the significance of Pharmacist clinical interventions. The trend in change of participants among the groups has been picturized in Fig. 3. At baseline, the mean ± SD Hb values were not statistically significant between the study and control group (9.3 ± 2.7 g/dL and 10.8 + 2.2 g/dL), but the change towards the endpoint was statistically significant (11.44 ± 0.99 g/dL and 9.72 ± 1.56 g/dL with p = 0.001).

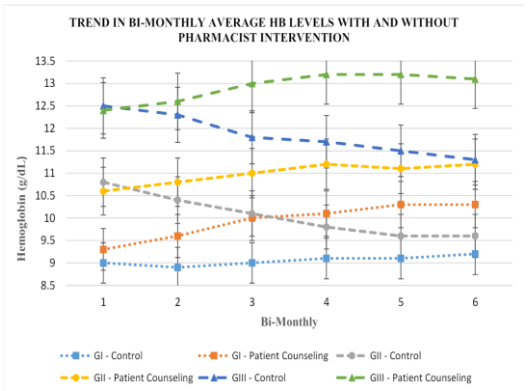

Fig. 3. Change of participants in each subgroup in both study and control groups.

Twenty-four patients were not cooperative to fill the questionnaire from 2nd visit, hence 424 participants (220 for the study and 204 for the control group) were included for the analysis in QoL Assessment. In the study group, the QoL scores improved in all eight domains of the SF-36V2 from baseline to endpoint. The greater improvement was observed in pharmacists' led intervention group compared to control group. The improvements were especially significant in vitality scores (P = 0.001), where the difference in percentage mean change between the two groups at endpoint was 11.47%. The participants who sustained in group II (Hb: 10 – 12 g/dL) had better quality of life index compared to other groups. The participants in the group I and III had lower mental wellbeing and general health compared to Group II. Table 4 summarizes the percentage mean score between the groups.

The adverse events were noticed in 11 patients among 224 patients in the control group and 11 patients among 224 patients in the study group. The odds ratios (95% CI) between the two groups for all adverse events with an occurrence rate of <5% was nearly 1. All the adverse events were infamous for ESA and there was no significant difference between groups in any components. During thestudy period, one patient with a high Hb group died of an alveolar haemorrhage resulting from the progression of underlying ANCA-related glomerulonephritis, so a causal relationship between death and the study medication was ruled out. Adverse events related to cancer occurred in two patients in each group who did not have a history of malignancy at baseline but a causal relationship between these events and the study medication was excluded.

Table 2. Number of CKD Patients with Group I, II & III of hemoglobin in both control and study groups at Start-up.

Pharmacist Management	Group I < 10 g/dL	Group II 10- 12 g/dL	Group III >12 g/dL
Control group	68	112	44
Study group	86	98	40

Table 3. Change in the Number of CKD Patients with Group I, II & III of hemoglobin with and without the Pharmacists intervention at the End Point.

Pharmacist Management	Group I < 10 g/dL	Group II 10- 12 g/dL	Group III >12 g/dL	P Value
Control group	89	93	42	0.001
Study group	52	152	20	

Table 4. The SF-36 v2 percentage mean score between the groups at baseline and Endpoint.

Scale	Baseline (Percentage Mean ± SD)		Endpoint (Percentage Mean ± SD)		P Value
	Study Group	Control Group	Study Group	Control Group	
Physical Functioning	42.23 ± 12.3	51.23 ± 11.36	63.86 ± 9.56	59.41 ± 5.36	0.01
Role-Physical	36.12 ± 5.83	31.56 ± 3.29	52.18 ± 9.32	51.98 ± 8.23	0.001
Pain	27.63 ± 9.18	32.53 ± 8.96	46.80 ± 15.23	41.29 ± 9.47	0.001
General Health	46.82 ±11.63	49.51 ± 10.32	61.29 ± 7.93	60.13 ± 9.56	0.001
Viltality	41.29 ± 8.36	42.20 ± 10.92	71.29 ± 10.89	59.82 ± 9.63	0.001
Social functioning	56.29 ± 21.30	53.89 ± 19.71	59.52 ± 10.23	55.83 ± 10.29	0.13
Role-Emotional	42.36 ± 10.69	45.28 ± 16.52	61.53 ± 11.29	62.69 ± 9.13	0.001
Mental Health	28.91 ± 10.23	35.63 ± 12.86	49.23 ± 8.63	51.87 ± 9.13	0.01

4. Discussion

The prevalence of CKD and the high cost of care when preventative efforts are not successfully implemented make it a significant public health problem in developing nations like India. Anemia is a prominent CKD characteristic linked to higher mortality rates. Recent clinical trials have shown higher morbidity and mortality linked to erythropoiesis-stimulating drugs, raising questions about the present care of patients with anemia in CKD [11,12]. For the past 25 years, ESA and iron treatment have been the cornerstones of managing anemia among individuals with chronic renal disease; blood transfusions have only been utilized when these therapies are unsuccessful or when there is an immediate medical necessity. The therapeutic impact is frequently jeopardized by drug side effects and patients' noncompliance with prescribed treatment regimens. As a result, pharmaceutical intervention becomes important in co-managing anemia in kidney disease patients.

In this study, the clinical recommendations were developed using evidence-based medicine and the assistance of nephrologists in making decisions about the advantages and risks of treatment in achieving the best possible patient care. In this study, iron replacement therapy began with less than 20% TSAT or 100 ng/dl ferritin. The Pharmacists have collaborated with the nephrology team as well as nurses to accomplish the activities. TSAT% and ferritin levels were the gold standard iron storage criteria used to routinely monitor and advise anemia therapy in CKD patients. However, iron storage levels may increase the risk of bacteremia in CKD patients receiving intravenous iron treatment. Furthermore, recurrent intravenous iron administration to CKD patients was linked to increased oxidative DNA damage, as measured by elevated blood levels of 8-hydroxy-2-deoxyguanosine [13]. These alterations were accompanied by elevated serum ferritin levels, suggesting that extra bodily iron reserves may play a role in oxidative stress. Specifically, the hyper-iron status must be closely monitored. As a result, it was decided to initiate the iron replacement therapy when TSAT was less than 20% or ferritin levels of 60 ng/dl.

In the current investigation, the average age was determined to be more than 60 years in both groups (63.2 in the study group and 62.7 in the control group). According to statistics, the vast majority of individuals with renal impairment are over 60 years old globally [14]. Contrarily, studies have shown that females are more likely than males to develop CKD [15], nevertheless, in this study, males outnumbered females. Despite the significant frequency of CKD in women, the majority of men are under nephrological medical care [16].

The most common co-morbid condition among CKD patients was observed to be diabetes mellitus, which was followed by hypertension in both groups. It is well documented that diabetes causes kidney damage because elevated blood sugar levels undermine the kidney's nephrons [17,18]. In addition, fluid overload, sympathetic overactivity, salt retention, endothelial dysfunction, and changes in the hormonal system that controls blood pressure are all impacted when the kidneys fail, which increases the prevalence of hypertension and vice versa [19].

The study showed that dosing techniques devised by pharmacists using realistic principles produces better results in clinical practice. Additionally, the development and implementation of renal anemia therapy regimens for CKD patients by chemists, nurses, and interdisciplinary groups have also been covered in other publications [20]. The primary goal of the trial was to determine if the clinical pharmacist intervention improved renal anemia by adjusting the dosing techniques along with the proper patient counselling to improve the medication adherence. A large number of the patients were in one of the groups of hemoglobin: <10 g/dL or >12 g/dL group at the beginning of the trial, but at the end of the study, owing to the intervention, the hemoglobin levels had improved, and were sustained in the 10–12 g/dL range. This was consistent with the research done by Marouf et al. [21]. Whereas, the participants in the control group tended to shift to lower and higher groups. As opposed to the control group, the pharmacist intervention group observed fewer side effects throughout the investigation, as well as enhancing the patient's quality of life. This trial indicated that clinical pharmacists are essential in managing renal anemia, particularly through optimizing erythropoiesis-stimulating agent (ESA) therapy and iron supplementation. They ensure appropriate dosing and titration of ESAs based on individual patient hemoglobin levels, reducing the risks of under- or over-treatment. Additionally, pharmacists monitor and evaluate patient responses to ESAs, adjusting therapy to minimize adverse effects. They also manage iron supplementation, ensuring adequate iron levels to

support erythropoiesis without causing iron overload. By providing comprehensive medication management and patient education, clinical pharmacists enhance the overall effectiveness and safety of renal anemia treatment in chronic kidney disease patients.

Additionally, based on the results of quality of life and physical examination of the participants, this research advises a hemoglobin level of 10-12 g/dl as a target for CKD patients. Furthermore, for patients with hemoglobin levels exceeding 12 g/dl the research suggests lowering the dosage or discontinuing ESA. There are number of flaws in this trial. Firstly, it was an open label study, which did result in loss of follow-up of patients. Secondly, it was conducted in a single centre, which owed to limited resources and variability. Thirdly, this was a time-bound study

5. Conclusions

This study demonstrates the crucial role of clinical pharmacists in managing anemia among Indian CKD patients. Pharmacist-led interventions significantly improved hemoglobin levels, maintaining them within the optimal range of 10-12 g/dL, which enhanced patients' quality of life and minimized adverse events. The targeted management strategies, including precise dosing and patient education, resulted in better clinical outcomes compared to standard care. This is merely an exemplification of how clinical pharmacists would profoundly enhance patient care. A pharmacist's active participation in clinical settings and interventions improves healthcare outcomes.

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Informed Consent Statement: The informed consent was obtained prior to the recruitment and voluntary participation was appreciated. Participants were free to deny and withdraw from the study at any point of time ensuring ethical conduct of the trial.

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Conflicts of Interest: The authors declare no conflict of interest.

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