A STUDY ON THE ANALYSIS OF PRESCRIBING PATTERN, SAFETY AND EFFECTIVENESS OF IRON-ERYTHROPOIETIN COMBINATION OVER ERYTHROPOIETIN MONOTHERAPY IN CHRONIC KIDNEY DISEASE PATIENTS WITH HAEMODIALYSIS

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ABSTRACT
Treatment of anaemia in chronic renal failure with exogenous recombinant human erythropoietin (rHuEpo) is well established. The objective of this prospective observation study was to evaluate anemia management protocol in haemodialysis patient using intravenous erythropoietin and iron. The sample population were patients with CKD undergoing haemodialysis. A total of 110 patients were supposed to be included with in the study, with 55 each for erythropoietin monotherapy and for combined erythropoietin and iron therapy. Due to COVID 19 pandemic situation only a sample size of 80 were achieved from which 40 of them were under erythropoietin monotherapy (control) and remaining 40 of them were administered with both erythropoietin and iron together(test). The primary outcome was proportion of patient on combined therapy of iron and erythropoietin achieved normal haemoglobin values more rapidly (p= 0.000008 for Group 1 and p= 0.00002 for group 2). A non-significant decrease on erythropoietin dose was observed in 17.5% of patients receiving both erythropoietin and iron together, while 20% of patients among those receiving erythropoietin monotherapy was observed with increased dose of erythropoietin. Combination therapy provided a remarkable increase in quality-of-life enjoyment and satisfaction to the patient. Upon prescribing pattern analysis cardiovascular drugs contributed
most to the prescription while genitourinary drugs and respiratory system drugs were the least prescribed ones. Hypertension was the most prominent side effect that almost 85% of total study population experienced followed by weakness, headache, and shortness of breath. Upon medication adherence evaluation 7% of people were observed with high adherence level and 5% of them with the least adherence. The study demonstrated that the combined use of iron and erythropoietin in patient with CKD undergoing haemodialysis may result in comparable Hb levels, reduced erythropoietin dose requirement and improved quality of life of the patient.

KEYWORDS: Haemodialysis, Erythropoietin, Medication adherence, Genitourinary, Hypertension.

INTRODUCTION
Chronic Kidney Disease (CKD) is defined as the reduction in GFR and/or urinary abnormalities or structural abnormalities of the renal tract. With the advancement of kidney failure and severe impairment of the organ’s function, dangerous levels of waste and fluid may rapidly build up in the body. The treatment aims at stopping or slowing down disease progression which is done by controlling its underlying cause. CKD affects nearly 10% of the population in Western Countries with the highest influence in some ethnic minority population and in females. The incidence significantly increases with age and is almost inevitable in persons of 80 years of age. Social deprivation is often associated with a higher prevalence of CKD. Patients with CKD were usually unrecognized due to difficulties in measuring the GFR in the past and their health needs were largely unmet. With the advent of simple techniques to estimate GFR, a huge population of CKD patients were identified. The National Guidance on the management of CKD, published in the year 2008 includes management in primary and secondary care. CKD differs from Acute Kidney Disease by virtue of the different spectrum of causes and chronicity. However, patients with AKD may not recover renal function fully and may be left with residual CKD. CKD is classified into 5 stages based on severity which in turn is dependent on the level of GFR.\(^1\)
Altered mineral metabolism contributes to anemia, bone disease, cardiovascular disease, and other clinical problems in these patients. Hence management of CKD involves the management of all comorbid conditions such as:

- Fluid and electrolyte balance
- Potassium homeostasis
- Iron and erythropoietin for anemia
- Phosphate binders
- Vitamin D therapy
- Antihypertensive agents
- Antihyperlipidemic
- Dietary supplements.\textsuperscript{[2]}

Anaemia in CKD is caused due to decreased production of erythropoietin by progenitor cells of kidney. Plasma concentration of erythropoietin increases in individuals with normal kidney function as Hb or Haematocrit declines. In contrast, there is no correlation between degree of anaemia and concentration of erythropoietin in anaemic ESRD patients. The result is a Normochromic, Normocytic Anaemia. Additional factors leading to development of anaemia in CKD are decreased RBC life span in the presence of uraemia, blood loss from regular laboratory testing, iron deficiency and blood loss with haemodialysis. Signs and symptoms include weakness, paleness, fatigue and shortness of breath.\textsuperscript{[3]}

<table>
<thead>
<tr>
<th>stage of CKD</th>
<th>GFR rate</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90ml/min + haematuria/proteinuria Or structural damage</td>
<td>Kidney damage with normal or increased GFR</td>
</tr>
<tr>
<td>2</td>
<td>60-89ml/min + proteinuria/haematuria or structural damage</td>
<td>Slight decrease in GFR with other evidence of kidney damage</td>
</tr>
<tr>
<td>3a</td>
<td>45-59ml/min</td>
<td>Moderate reduction in GFR with or without evidence of kidney damage</td>
</tr>
<tr>
<td>3b</td>
<td>30-44ml/min</td>
<td>Moderate reduction in GFR with or without evidence of kidney damage</td>
</tr>
<tr>
<td>4</td>
<td>13-29ml/min</td>
<td>Severe reduction in GFR</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15ml/min</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

**Figure 1: Stages of CKD.**
Treatment mainly includes IRON and ERYTHROPOIETIN. The first step in treating anaemia low iron levels. Iron pills may help improve iron and Hb level. Treatment with erythropoietin stimulating agents are important in CKD therapy and is initiated when Hb levels are below 10 g/dl and the reasonable goal is an increase in Hb level > 1g/dl over 2 weeks after initiating therapy, then the ESA dose should be reduced by 25 % to 50 %. Benefits of ESA are avoidance of blood transfusion, improvement in anaemia related symptoms and patient’s quality of life. Healthcare providers should not use ESA when the patients Hb level is greater than 12 g/dl, as it increases blood viscosity and cardiovascular risks.\textsuperscript{[4]}

PRESCRIBING PATTERN - explain the extent and profile of drug use, trends, quality of drugs and thereby promotes rational use of drugs.\textsuperscript{[5]}

**MATERIALS AND METHOD**

**Study Design:** Single centered hospital based Prospective Observational Study

**Study Population:** The study population includes patients who receive erythropoietin monotherapy as well as erythropoietin- iron therapy in the department of nephrology during the study period and who satisfies the Inclusion and exclusion criteria.

**Study Site:** The proposed study was conducted in the Department of Nephrology, Pushpagiri Medical College Hospital, Thiruvalla.

**Study Period:** 6 months after getting the approval from Institutional Ethical Committee (PCP/E3/01B/01/2019)

**INCLUSION CRITERIA**

- IP/OP patients in nephrology ward.
- Both male and female patients.
- Those who give consent voluntarily to participate in the study.
- Adult patients with age above 18 years.
- Patients diagnosed with CKD \{stage 3 -5\} who are undergoing haemodialysis
- Patients prescribed with either 1) Erythropoietin monotherapy 2) Iron supplements and erythropoietin.

**EXCLUSION CRITERIA**

- Patients who are not willing to give consent.
- Pregnant and lactating women.
• Patients with any other malignancies.
• Patient with anticipated death, transplant within next 6 month.

STUDY PROCEDURE
• A prospective observational study was conducted in the department of Nephrology at Pushpagiri medical college hospital on the above topic.
• The study commenced after approval from the Institutional Ethical Committee.
• A written informed consent was obtained from the patient or care giver.
• Baseline Demographics, Hemodialysis - Related Data, Erythropoietin Dose and Frequency, Hemoglobin levels were collected.
• Information about the patient ‘s present medications, comorbidities were collected.
• Occurrence of side effect was determined by direct observation and by monitoring vitals.

AIMS AND OBJECTIVES
Aim
“To analyse the prescribing pattern, safety and effectiveness of iron erythropoietin combination over erythropoietin monotherapy in chronic kidney disease patients with haemodialysis. {Stage 3-5}”.

Objective
• To evaluate the prescribing pattern of patients included in the study.
• To compare the effectiveness of combined use of iron-erythropoietin therapy over erythropoietin monotherapy on 1) Erythropoietin dose 2) Haemoglobin levels
• To assess the side effect prevalence of both the therapy.

RESULTS AND DISCUSSION
This study was done to analyse prescribing pattern and effectiveness of iron erythropoietin combination over erythropoietin monotherapy in chronic kidney disease patients with haemodialysis. It was a 6 months study in which patients were recruited based on inclusion and exclusion criteria. Patients diagnosed with CKD are included in the study. Medications were classified into different groups using Anatomic Therapeutic Chemical (ATC) classification.
A predesigned pro forma was used for the purpose of data collection. The comparison on effectiveness of iron erythropoietin over erythropoietin monotherapy was done by comparing Hb levels of respective patients.

**Age:** Majority of patients belongs to the category of 65 and above, that is of 45%. This is followed by other age groups, 55-64(27.5%), 45-54(18.75%), 35-44(5%). Least number of patients were from the category of 25-34 of age with a percentage of 3.7. It was found that increasing age was also a susceptibility factor for developing CKD.

**Gender:** In study, 73.75% of study population constituted of males whereas 26.25% was constituted by females.

**Social Habits:** 60% of population had no history of alcoholism and smoking. 10% had a history of alcoholism and 4% of them with smoking. 25% had history of both alcoholism and smoking. It was found that history of social habits contributed very scarcely to the development of CKD.

**Study of Prescribing Pattern of Drugs:** Hypertension was the most common co-morbidity (81%) observed in the study population followed by Type 2 diabetes (35%) and Gastrointestinal disorders (35%) and the least commonly found co-morbidity was Pancreatitis (1.25%).

The most prescribed drug in study population was found to be cardiovascular drugs (32%), this is followed by blood and blood forming agents (15%), food supplements and nutrients (10%), antithrombotic (9%), drug for GI disorders (7%), binding agents (6%) and diabetic agents (6%). Other drugs included those acting on nervous system (4%), antibiotics (4%) and musculoskeletal drugs (3%). Least commonly prescribed drugs were genitourinary drugs (2%) and respiratory system drugs (2%).
In this study 17.8% of patients were prescribed with CCB and diuretics. 44% of total prescribed CCB is constituted by cilnidipine. Torsemide contributed 61% of total diuretics that is being prescribed to the patients and 15.5% of patients were prescribed with beta blockers of which carvedilol was the most commonly prescribed drug (30%).

About 13.5% of prescription included vasodilators. Among those, isosorbide dinitrate was the highest prescribed drug. As per this study, 5.4% of study population was prescribed with antianginals, of which ivabradine was the highest prescribed and 29% was contributed by other cardiovascular drugs.
In this study major blood and blood forming agents were iron, erythropoietin, and folic acid, of which Erythropoietin was highest prescribed (65%). Food supplements and nutrients contributed 10% of total drugs prescribed, of which vitamins contributed the highest (59%).

About 9% of the prescription had anti-thrombotic agents. Aspirin (54%) was the major drug prescribed and 7% of patients were prescribed with drugs for GI disorders. Pantoprazole constituted the bulk of such prescription.

Among binding agents, a significant portion of 66% was contributed by calcium acetate. Other drugs in this group were k bind and sevelamer HCL.

In this study 6% of prescription had anti-diabetic drug. Insulin was the highest prescribed drug (79%) and drug acting on nervous system constituted around 4% of total prescription. The most prescribed drug acting on nervous system was antiepileptic drugs (36%).

Levofloxacin was the most commonly prescribed drug among anti-infectious. drug acting on musculoskeletal system constituted around 3% of total prescription. The most prescribed drug among them was febuxostat (88%). Among the drugs acting on genitourinary system, BPH
and urologicals were prescribed. BPH drugs composed a major portion and it was around 90%.

In this study, major respiratory system drugs prescribed were salbutamol (25%), xanthenes (33%), LTRAs (17%), anticholinergics (8%), and acetylcysteine (17%).

**COMPARISON OF ERYTHROPOIETIN MONOTHERAPY AND ERYTHROPOIETIN - IRON COMBINATION**

- **COMPARISON BASED ON EFFECT OF BOTH THERAPY ON Hb LEVELS.**

Patients on erythropoietin monotherapy had shown slight decrease in Hb levels than normal. Patients who underwent treatment with both erythropoietin and iron was observed with a noticeable increase in Hb levels. Some of the patients even managed to attain a normal level. It shows that combination therapy is having a positive effect on Hb levels of the patients rather than a monotherapy.

**Table 1: Distribution of Haemoglobin Levels Among Study Population.**

<table>
<thead>
<tr>
<th>TABLE SHOWING MEAN OF Hb VALUES IN BOTH GROUPS</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>GROUP 1</td>
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<tr>
<td></td>
</tr>
<tr>
<td>GROUP 2</td>
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<td></td>
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</tbody>
</table>

**Figure 3: Distribution of Haemoglobin Levels Among Study Population.**
**Comparison Based on Erythropoietin Dosage:** 17.5% of patients among those receiving both erythropoietin and iron together experienced a decrease in erythropoietin dose, while 20% of patients among those receiving erythropoietin monotherapy experienced an increase in erythropoietin dose. It is evident that patients on combination therapy show more effectiveness in treatment than those receiving a mono therapy.

### Table 2: Comparison Based On Change In Erythropoetin Dosage.

<table>
<thead>
<tr>
<th>Change in dose</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Change in dose</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase</td>
<td>8</td>
<td>20</td>
<td>Increase</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Decrease</td>
<td>2</td>
<td>5</td>
<td>Decrease</td>
<td>7</td>
<td>17.5</td>
</tr>
<tr>
<td>No Change</td>
<td>30</td>
<td>75</td>
<td>No Change</td>
<td>32</td>
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<tr>
<td>Total</td>
<td>40</td>
<td>100</td>
<td>Total</td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

**Figure 4: Comparison Based on Change in Erythropoetin Dosage.**

**Side Effect Prevalence:** Hypertension is the most prominent side effect that almost 85% of the total study population experienced. 77.5% suffered from weakness. Headache and shortness of breath was observed in 70% and 40% of patients. It was followed by swelling (25%), pain/irritation at injection site (20%), clot at the site of injection (5%)
CONCLUSION

From the results obtained, we conclude that the combination therapy using Iron and Erythropoietin produced statistically significant improvement in the objectives of parameter-erythropoietin dose, Hb levels and quality of life after five months, than that obtained with monotherapy using erythropoietin alone for 5 months.

Thus, combination therapy of Iron and erythropoietin over erythropoietin monotherapy were more preferred in CKD patients with haemodialysis. The overall prescribing pattern of patients were studied, and cardiovascular drugs were most prescribed. The side effect profile and medication adherence were also evaluated.

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REFERENCES


