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Prospective Study On Effectiveness and Usage Pattern of Erythropoiesis Stimulating Agents In Patients With Anaemia Of Chronic Kidney Disease

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ABSTRACT

Chronic Kidney Disease (CKD) characterized by progressive decline in Glomerular Filtration Rate (GFR), is major public health issue associated with morbidity and mortality. Anaemia is one of the most common problems causing morbidity in patients with CKD while they are on dialysis. Erythropoietin is a major advance in the management of anaemia in CKD which stimulates erythropoiesis by increasing proliferation and maturation of erythroid progenitors and thereby treats anaemia. Prescribing pattern, effectiveness and cost of erythropoietin therapy in patients with chronic kidney disease. This was a Prospective and Observational study conducted for 06 months after obtaining IEC from Apollo Multi-Specialty Hospital, Bengaluru. Patients were enrolled based on enrolment criteria. Data were analysed using suitable statistical tool. Of 152 patients enrolled, 77 (50.65%) patients were in the age group ≥ 60 years, second generation ESAs was mostly prescribed 119(78.28%) than third 01(0.65%) and first 32(21.05%). Significant increase in Haemoglobin, RBC, PCV was observed. We have demonstrated that ESAs were prescribed majorly in Nephrology compared to medicine department. Second generation ESAs were prescribed mostly, darbepoetin alfa 40mcg were preferred over other doses. The changes in Hb, PCV and RBC were significant suggesting ESAs as effective. The side effects reported were less, common and mostly unrelated to ESAs. Based on these finding, we suggest that ESAs is prescribed majorly in Nephrology and is effective and safe in managing anaemia of CKD.

Keywords: Erythropoietin therapy, Erythropoietin Stimulating Agents, Chronic Kidney Disease, Anaemia, cost analysis.

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INTRODUCTION

Chronic kidney disease occurs when the renal reserve is lost and there is irreversible damage to about 75% of nephrons. When the kidneys are damaged, waste products and fluids can build up in the body which can cause swelling in the ankles, vomiting, weakness, poor sleep and shortness of breath. There is reduction in the glomerular filtration rate and /or urinary abnormalities or structural abnormalities of the renal tract. [1] CKD is categorized by the level of kidney function, based on GFR, into stages 1 to 5, with each increasing number indicating a more advanced stage of the disease, as defined by a declining GFR. Stage 1 (>90 ml/min), stage 2 (60-89 ml/min), stage 3a (45-59 ml/min), stage 3b (30-44 ml/min), stage 4 (15-29 ml/min) and stage 5 (<15 ml/min).[2] CKD is a common condition affecting up to 10% of the population in Western societies and is more common in some ethnic minority populations and in females. The incidence increases exponentially with age such that some degree of CKD is almost unavoidable in persons over 80 years of age. Social deprivation is also associated with a higher prevalence of CKD.[3]

Anaemia is common consequence in people with CKD stages 4 and 5 which is defined as haemoglobin (Hb) concentration below 13.0g/dl for adult males and postmenopausal women, and Hb below 12.0g/dl for pre-menopausal women (world health organization, 1968) [2]. The fall in haemoglobin level is a slow, insidious process accompanying the decline in renal function. A normochromic, normocytic pattern is usually seen with haemoglobin levels falling to around 8 g/dl by end stage renal disease.

Anaemia in CKD is a major cause of fatigue, breathlessness at rest and on exertion, lethargy and angina. Patients may also complain of feeling cold, poor concentration and reduced appetite and libido. Several factors contribute to the pathogenesis of anaemia in CKD, including shortened red cell survival, marrow suppression by uraemic toxins and iron or folate deficiency associated with poor dietary intake or increased loss, for e.g., from gastro-intestinal bleeding. However, the principal cause is damage of peritubular cells leading to inadequate secretion of erythropoietin, which is produced mainly, although not exclusively, in the kidney. Erythropoietin is the main regulator of red cell proliferation and differentiation in bone marrow.

The normochromic, normocytic anaemia of CKD does not respond to iron or folic acid unless there is a coexisting deficiency. Traditionally, the only treatment available was to give red blood cell transfusions, but this is time-consuming, expensive, an infection risk, may lead to fluid and iron overload and promotes antibody formation, which may give problems if transplantation is subsequently attempted.[1]

Therefore, Erythropoietin therapy is preferred for managing anaemia of CKD and Iron supplementation is necessary to replete iron store. As oral iron therapy is often inadequate, Parenteral iron therapy is preferred which improves response to erythropoietic therapy and reduces the dose required to achieve and maintain target indices.[2]

Classification of erythropoietin stimulating agents (based on generation).[4]

1. First generation ESAs (e.g. Epoetin alfa, Epoetin beta)
2. Second generation ESA (e.g. darbepoetin alfa)
3. Third generation ESA {e.g. Continuous erythropoietin receptor Activator (CERA)}

Classification of ESAs (based on duration of action) [5]

1. Short acting ESAs (e.g. Epoetin Alpha, Epoetin Beta)
2. Long acting ESAs {e.g. Darbepoetin alfa, pegylated Continuous Erythropoietin Receptor Activator (CERA)}

CKD is a worldwide public health problem and Anaemia is an independent risk factor for cardiac disease and mortality in CKD patients. Anaemia was present in 90.39% of CKD patient while 25.53% had an Hb of <7g/dl. The prevalence of anaemia increased from stage 3 (66.6%) to stage 5 (94.7%). Erythropoietin deficiency is the most significant cause of anaemia in CKD.[4,6,7]

The high prevalence of CKD, the attendant need for anaemia treatment with ESA, high risk associated with inappropriate prescribing of ESAs and the high costs associated with anaemia treatment in CKD calls for a more structured approach on the use of Erythropoietin stimulating agents. In this study, we investigated prescribing pattern, effectiveness, interactions, side effects and cost of erythropoietin stimulating agents, in patients with anaemia of CKD.

MATERIALS AND METHOD

Subject selection:

Inclusion criteria:

- All CKD patients along with anemia and prescribed with ESAs
- Both outpatients and inpatients
- Patients aged < 18 years
- Patients who were medically stable with CKD in predialysis period and while undergoing chronic haemodialysis therapy for at least 3 months

Exclusion criteria:

- Pregnancy and Lactating women
- Non - anaemic CKD Patients

Study design:

The Prospective and Observational study was conducted in the Medicine and Nephrology department of Apollo Multi-Specialty Hospital and Research Centre, Bengaluru from November 2018 to April 2019 for a period of 6 months after taking IEC approval. A total of 152 patients who satisfied the study criteria and consented for the study were enrolled.

Information like the medication information (name, dose, frequency, route, Class etc.), patient details (name, age, and sex), socioeconomic parameters, past medical history, disease diagnosed and duration of treatment were obtained from patient's case notes, physicians and nurses' notes, treatment chart, laboratory reports and progress report charts.

For patients who were prescribed with erythropoiesis stimulating agents, the prescribing pattern was assessed based on departments as well as generation of ESAs used. Therapeutic data such as name of drugs, its generation, department, doses, and route of administration and duration were collected and documented in a suitably designed data collection form. The laboratories values like Hb, PCV and RBCs were noted at the time of admission from laboratories reports and followed up for the changes after ESAs administration during the study. The changes in those parameters were noted and effectiveness of ESAs were analysed. Probable drug interactions of drugs with ESAs were identified by using the software like Lexicomp and Micromedex. Natures of interaction were evaluated with regard to onset, severity and documentation. Side effects were identified and noted by conducting follow up of progress notes and laboratory investigation reports of patients. Cost of each brand of ESAs prescribed in each patient were obtained and cost of therapy was calculated based on the cost per dose and its frequency of administration per week. The cost per week were then calculated for cost per month and then the costly and cheapest ESA were identified.

Descriptive statistical analysis has been carried out to analyse the data. Chi-Square test has been used to find the significance of study parameters on categorical findings among different groups. The statistical software called SPSS (IBM) version 1.0 was used for the analysis. Microsoft Word and Excel are used to generate tables and graphs respectively.

RESULTS AND DISCUSSION

The study of usage pattern is a component of medical audit for which monitoring, evaluation and modification required in the prescribing practices of prescribers is necessary to achieve rational and effective and cost-efficient medical care. It is therefore important to define prescribing and identify irrational prescribing habits to drive a remedial message to the prescribers.

Of 152 patients involved in the study, the majority of the patients were male (70.39%) and female patients (29.60%) were less in number (Figure 1). Similar findings were found in a study conducted by P Ansuman Abhishek et al and Iain C Mac Dougall et al.[3,8]Among patients of various age groups studied, 5.26% patients were in the age group of 30-39 years, 21.05% patients were in between 40-49 years, 23.02% were from the age group of 50-59 years and 50.65% of subjects were from the age group of >/=60 years (Figure 2). Majority of patients were in the age group of >/=60 years which means the prevalence of renal failure and anaemia is high in geriatric age group. Similar findings were seen in other study conducted by Bajait C S et al.[9] Hence, it indicates the major necessity of ESAs in the elderly.

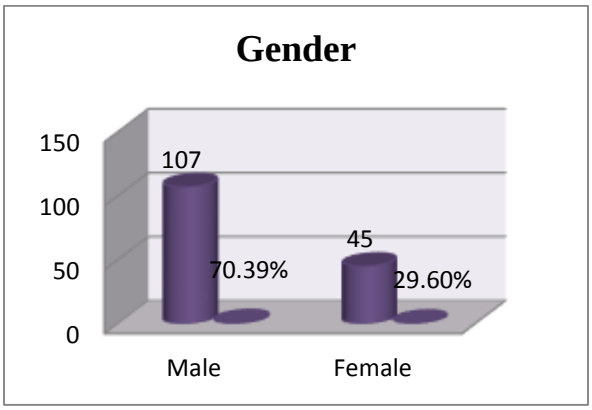

Figure 1: Gender distribution of patients enrolled in the study.

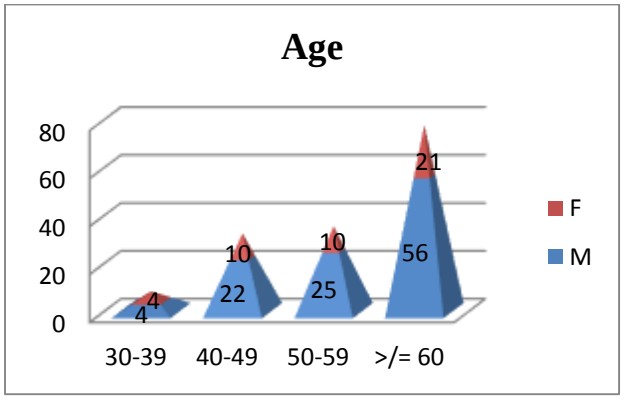

Figure 2: Age distribution of patients enrolled in the study.

ESAs prescribing pattern evaluation:

The department wise distribution of all patients shows that the patients receiving or prescribed with ESAs are high in Nephrology department as renal failure induced anaemia is the major cause for indication of ESAs. Among 152 patients evaluated for the use of different generation ESAs, we found that the order of usage of ESAs were second generation ESAs (78.28%) > first generation ESAs (21.05%) > third generation ESAs (0.65%) (Table 1). Similar findings were found in one more study by Fuller D.S. et al.[10] Most of patients were prescribed with darbepoetin alpha

(78.27%) than epoetin alpha (21.03%). Darbepoetin alfa 40 mcg was prescribed majorly (65.13%) which reveals that, darbepoetin alpha 40 mcg is preferably prescribed among all other doses (Table 2).

Among 152 patients enrolled in study, 91.44% patients were prescribed with subcutaneous route and 8.55% with intravenous. Similar findings were found in the other study conducted by Piergiorgio Messa et al. Hence, it reveals that the preferred route for ESAs is Subcutaneous over intravenous because of several advantages such as 20-30% reduction in dose requirement, ease of administration and non-requirement of venous access. Intravenous route is used as an alternative according to the needs of the patient and availability of the formulation. [11] In the evaluation of rate of administration or frequency in 152 patients, the order was found to be once a week (85.52%) – Males are receiving more frequently than females > twice a week (5.26%) = monthly once (5.26%) – Males dominate females > monthly twice (3.94%) – males and females receive with equal frequency. It revealed that ESAs were prescribed mostly as once a week and males were receiving more frequently than females. Similar findings were found in the other study conducted by Jerry Seigel et al.[12] The distribution of drugs per prescription revealed that majority (50.65%) of patients were receiving 9-12 drugs per prescription and the average number of drugs per prescription was 9.60. Similar findings were found in the other study conducted by Sourav Chakraborty et al. [13]

Table 1: Distribution of generation of ESAs prescribed

Drug generation	Name of the drug	Male	Female	Total	Percentage
First	Epoetin alpha	21	11	32	21.05
Second	Darbepoetin alpha	86	33	119	78.28
Third	Continuous erythropoietin receptor activator	00	01	01	0.65
Total		**107**	**45**	**152**	**100**

P=0.70, Non-Significant, Chi-Square test

Table 2: ESAs dose distribution

Drug Name	Dose	Male	Female	Total	Percentage
Epoetin alpha	4000U	8	7	15	9.86
	5000U	0	2	2	1.31
	10,000U	13	2	15	9.86
Darbepoetin alpha	40mcg	68	31	99	65.13
	60mcg	13	2	15	9.86
	80mcg	2	0	2	1.31
	100mcg	3	0	3	1.97
Continuous Erythropoietin Receptor Activator	80mcg	0	1		0.65
Total		**107**	**45**	**152**	**100**

P=0.51, Non-Significant, Chi-Square

ESAs effectiveness evaluation:

Among 152 patients, the evaluation of Hb gives the information about effectiveness of therapy before and after administration of ESAs and the data showed that the significant rise (average rise of 0.69g/dl) in Hb in both males and females after using ESAs (Table 3). The evaluation of RBC for effectiveness of therapy before and after administration of ESAs showed significant rise (average rise of $0.33*10^{12}$/Cmm in males and $0.43*10^{12}$/Cmm in female patients) in RBC level, after using ESAs (Table 3). The evaluation of PCV for effectiveness of therapy before and after administration of ESAs revealed significant rise in PCV (average rise of 2.82% in males and 2.23% in female patients) after using ESAs (Table 3). Similar findings were found in the other study conducted by Michael Jones et al. [14]

Table 3: Distribution of changes seen in the laboratory parameters of the patients.

Gender	Haemoglobin			RBC			PCV		
	Bef	Aft	Outcome (Increased)	Bef	Aft	Outcome (Increased)	Bef	Aft	Outcome (Increased)
Male	9.56	10.25	0.69	3.71	4.04	0.33	31.14	33.96	2.82
Female	9.20	9.89	0.69	3.28	3.71	0.43	30.91	33.14	2.23

Bef: -before, Aft: - after, RBC: - Red Blood Cell, PCV: - Packed Cell Volume

Side effects assessment:

Of 152 patients, the evaluation of side effects revealed that 19 (12.50%) patients had hypertension among which 13 are males and 6 are females. This implies that the occurrence of ADR with ESAs is less common and are safer. Similar findings were seen in the other study conducted by Tilman B Drueke et al. [15]

ESAs cost evaluation:

The cost evaluation of given brands was done on the basis of total number of subjects using a particular brand and average cost per unit dose. Therefore, the overall or average cost burden on the given population with respect to extent of usage was considered. On the basis of this consideration, it was found that cresp was preferably accepted in most of the patients with respect to cost. But when the average cost per unit was considered, it was understood that the cheapest among all is zyrop (Rs.1263.83) and NeoRecormon was the costliest brand (Rs.7965.75) (Figure 3).

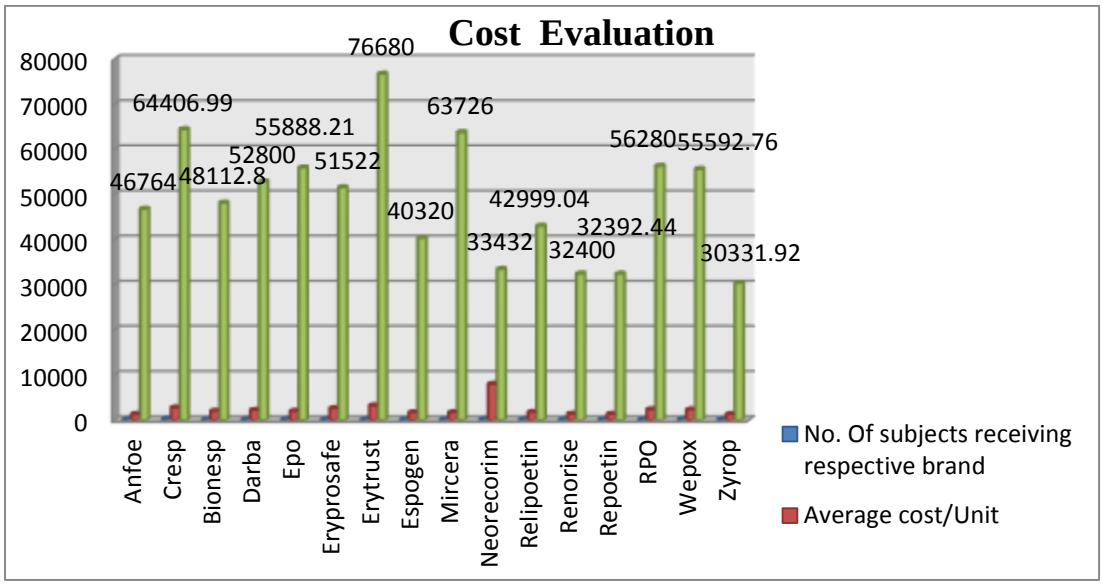

Figure 3: - Cost distribution of different prescribed ESAs brands

CONCLUSION:

We have demonstrated that ESAs were prescribed majorly in Nephrology department compared to medicine department. Second generation ESAs were prescribed mostly, darbepoetin alfa 40mcg were preferred over other doses. The changes in Hb, PCV and RBC were significant suggesting ESAs as effective. The side effects reported during this study were less, common and mostly unrelated to ESAs. Based on these finding, we suggest that ESAs is prescribed majorly in Nephrology and is effective and safe in managing anaemia of CKD. However, further studies are needed in order to examine adverse drug reactions of ESAs, quality of life and exercise capacity following ESAs therapy and effect of iron profile and frequency of haemodialysis in effectiveness of ESAs therapy.

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