PATTERN OF USE OF VARIOUS ERYTHROPOIESIS STIMULATING AGENTS IN HEMODIALYSIS PATIENTS

Thesis submitted in partial fulfillment of the requirement for the Degree of Clinical Pharmacy and Pharmacy practice

By

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CERTIFICATION OF APPROVAL

This is to certify that MISS. ALANKAR MUKHERJEE bearing class Roll No- 001711403002 , Examination Roll No- M4PHC19002, Registration No- 140856 of 2017-2018, a candidate of Master of Pharmacy in Clinical Pharmacy and Pharmacy Practice, has submitted the project thesis entitled "PATTERN OF USE OF VARIOUS ERYTHROPOIESIS STIMULATING AGENTS IN HEMODIALYSIS PATIENTS" under our supervision at AMRI Hospitals, Dhakuria , Kolkata for partial fulfillment of requirement for the completion of M.Pharm.in Clinical Pharmacy and Pharmacy Practice".

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DECLARATION OF ORIGINALITY AND COMPLIANCE OF ACADEMIC ETHICS

I hereby declare that this thesis contains literature survey and original research work by the undersigned candidate, as part of her Master of Clinical Pharmacy and Pharmacy Practice studies. All information in this document have been obtained and presented in accordance with academic rules and ethical conduct. I also declare that as required by these rules and conduct, I have fully cited and referenced all materials and results that are not original to this work.

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Ref: AMRI -EC/AP-02/2017-18 **Date:04.10.18**

Dr.Arghya Majumdar

Subject: Ethics review of clinical research proposal

Protocol title: "A prospective observational study on the pattern of use of erythropoiesis stimulating agent among Hemodialysis patients in a tertiary care Hospital in Eastern India"

Study Site: AMRI Hospitals, Dhakuria.

Name of Student: Alankar Mukherjee

Dear Dr. Majumdar,

In the meeting held on **04.10.18**, the members of the ethics committee reviewed and discussed the protocol and other related documents of the above mentioned study:

The following members of the committee were present:

Prof. Santanu Kumar Tripathi (Chairman)
Dr. Arghya Majumdar (Member Secretary)
Mr. Atanu Ray Chaudhuri (Legal Advisor)
Dr. Avijit Bhattacharya (Clinician)
Dr. Subhra Dhar (Basic Medical scientist)
Dr.Ashok Kr Mondal (Clinician)
Ms.Anjali Ghosh (Social Scientist)
Ms. Sunita Sarkar (Community Representative)
Ms. Atashee Chatterjee Sinha (Philosopher)

The Thesis protocol, Data Collection Proforma were submitted and duly reviewed by Members of IEC present in the meeting:

(1) **Approval is hereby granted to the above mentioned study protocol and related documents in order to conduct the study in AMRI Dhakuria.**

(2) **The Committee should be informed:**
   (a) about the progress of the study every six months
   (b) about any Serious Adverse Events occurring in the course of the study within 24 hours of their occurrence, including their management and compensation etc
   (c) about any changes in the protocol and patient information/informed consent documents.

(3) **The final report of the study shall have to be submitted to the IEC in all cases, even when the study is abandoned for any reason.**

Prof.Santanu Kumar Tripathi
Chairperson
CHAIRMAN
INSTITUTIONAL ETHICS COMMITTEE

Dr.Arghya Majumdar
Member Secretary
MEMBER SECRETARY
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CONTENTS

ABSTRACT

Background:-Chronic kidney disease (CKD) is the advanced stage of kidney disease which slowly and eventually causes a loss of kidney function over a period of time counting from months to years. Chronic kidney disease has a high global prevalence and carries significant morbidity and mortality. The progress of CKD, anemia and erythropoietin deficiency is extremely common among patient undergoing hemodialysis. Iron and erythropoietin (EPO) have crucial role for RBC production in bone marrow, however due to CKD, Iron and erythropoietin (EPO) are unable to work properly hence, Erythropoiesis-stimulating agents are used which stimulates the bone marrow to make red blood cells. They are used to treat anemia due to end stage kidney disease. ESAs work like the human protein erythropoietin, which stimulates bone marrow to make red blood cells. Erythropoietin alpha and beta (Recombinant human erythropoietin) are the examples of highly effective short active ESAs. Darbepoietin (administered every two weeks) and *Epoetin* (administered once to thrice per week) are also very effective to maintain hemoglobin level in patients undergoing hemodialysis.

Objective:-The objective of the study was to assess the pattern of use of various erythropoiesis stimulating agents in hemodialysis patients in a tertiary care hospital in eastern India

Methodology: - Around 127 patients were evaluated along with the patients details for the assessment of the pattern of use of erythropoietin stimulating agents in hemodialysis patients in AMRI hospital,Dhakuria. All adult patients ≥ 18 years of age with diagnosis of CKD on HD were included. Patients were included if they were anemic and have received ESA alone or IV iron alone or ESA + IV iron treatment at least once during the study period. Patients were excluded if patients received ESA or IV iron for reasons other than anemia of CKD (for example, patients with cancer diagnosis, chemotherapy or radiotherapy). Data has been collected from the Hemodialysis unit database maintained by the hemodialysis unit of AMRI Hospitals and finally Statistical analysis of data was done using appropriate statistical tests SPSS statistical software.

Result: - There a total of 127 patients who received ESA during study period. 52.7 % patients received ESA and iron and 47.3 % received ESA, iron and blood transfusion. Males constituted the majority in both groups (73.1% and 58.3%). Comorbidities were assessed and compared between the two groups. Hypertension was the most prevalent comorbidity (97% and 86.7%) followed by diabetes (76.1% and 71.7%) in both groups. We also compared the presence of other cardiovascular, chronic liver disease and neurological diseases between the two groups. We evaluated the dialysis details of all patients irrespective of the group that they belonged. 92.1% were hypertensive and 74.0 % patients were diabetic. Details of kidney diseases could be assessed only in 51.3% of patients - 41.5% of these had glomerulonephritis and 29% had renal sclerosis and another 29% had nephrotic syndrome Patients received ESA+Iron+BT were further categorized under four groups namely cardio vascular disease(CVD) ,elderly patients

(>60years), diabetic patients and chronic liver disease (CLD)patients.Total number of patients in these category was 60.Out of these 60 patients 37% were elderly. 72% patients were in the categories of CVD and 72% patients were suffering from diabetes and nearly 49% patients were under CLD. Majority of patients (57.5%) underwent 3 dialysis per week (Figure 8). 37% of patients were undergoing dialysis for more than 2 years, 23.6% between 1 to 2 years, 29.1% between 6 - 12 months and 10.2% of patients for less than 6 months. Most dialysis (85.8%) were planned dialysis. We compared the change in the mean hemoglobin levels in the Epoeitin alfa and Darbopoeitin alfa groups at baseline, 3 months and 6 months after ESA use. The mean hemoglobin steadily increased in both the groups and this increase was statistically significant in both groups. The mean hemoglobin level was also significantly different between the two groups at the end of 6 months, and lastly the payer status were also compared.

Conclusion: - My study showed that elderly patients had more frequent need for blood transfusion. Erythropoetin & darbapoetin had equal efficacy increasing hemoglobin. However, darbaportin faired slightly better. This was more cost effective and caused less discomfort to patient. Patients with cardiovascular disease needed more blood transfusion as in their case Hb targets are higher. In chance liver disease more blood transfusion were needed as they frequently loose blood from their gut. In general compared to the past there is a pattern of more use of darbapoetin in tertiary care hospital today, irrespective of funding.

INTRODUCTION

Kidney or renal disease popularly known as nephropathy in medical sciences, is damage to kidney or a condition which results in disorder of the structure or function of kidney. Nephritis, nephrosis, loss of kidney function, kidney failure are few such examples of kidney diseases. Chronic kidney disease (CKD) is a kind of kidney disease which slowly and eventually causes a loss of kidney function over a period of time counting from months to years [1]. At the early stage of the disease no typical symptoms are observed; however with the progress of the disease swelling of legs, tiredness, loss of appetite, vomiting, confusion high blood pressure, bone disease, anemia and even heart failure could be the probable complication. Diabetes, Glomerulonephritis, Polycystic kidney disease, high blood pressure, renal neoplasiaare some of the causes of chronic kidney disease [1].

Chronic kidney disease prevalence

Chronic kidney disease has a high global prevalence and carries significant morbidity and mortality [2]. In 1990 and 2010 age-standardized maintenance dialysis incidence rates per million population were 125 and 240 respectively in North America; 80 and 135 respectively in East Asia; 75 and 140 respectively in Asia Pacific; 65 and 75 respectively in South Latin America; 40 and 65 respectively in Australia; 12 and 130 respectively in Central Europe; and 5 and 14 respectively in East Europe [2,3,4]. Chronic kidney disease is also a predominant public health problem in India The age-standardized prevalence per million population of maintenance dialysis in year 2010 in India was 1-9. The prevalence rates of chronic kidney disease vary from less than 1% to 13% in different region of our country. In some cases the prevalence value has

been reported to as high as 17% [2,5]. Parts of Andhra Pradesh Orissa and Goa have high chronic kidney disease of unknown etiology [4,6].Figure 1 shows the global prevalence of CKD.

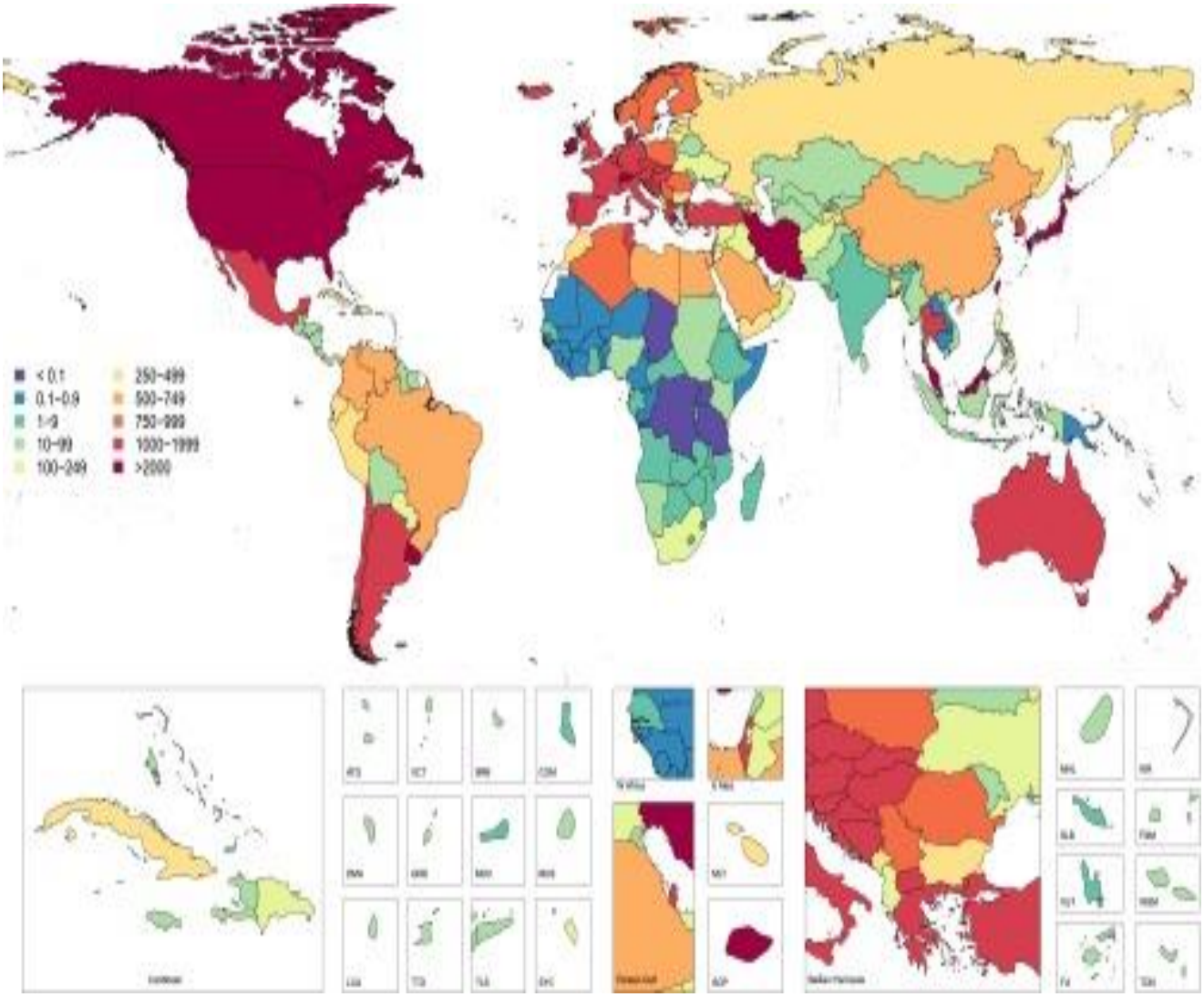


Figure 1 showing CKD prevalence globally. Age-standardized prevalence per million population of maintenance dialysis in year 2010 for 187 countries.

The United Nation Children Emergency Fund data showed that "28% Indian children have less than body weight of 2.5 kg and by birth suffer from hypovitaminosis A and have deficient nutrition leading to smaller kidney volume and lower glomerulus filtration rate at birth"[2,4]. Consanguinity and genetic inbreeding provides risk of congenital abnormalities of kidney and urinary tract and obstructive or reflux nephropathy. Neurotoxins such as heavy metals, plant toxins are also causing glomerular interstitial kidney diseases. Further, burden of hypertension and diabetes mellitus are the dreadful threats for chronic kidney disease conditions. A report suggest that over 50% Indian patients with advance chronic kidney disease had estimated glomerular filtration rate less than 15 ml per minute per 1.73 meter square [5].

As stated earlier along with the other associated complications anemia is one of the hallmarks of progressive chronic kidney disease (CKD).Anaemia is a medical condition in which total RBC account or hemoglobin level in blood is decreased than the normal value (hemoglobin 13-14 g/dl in male and 12-13g/dl in female and RBC in female is 4.2-5.4 million cells /microliter and in male it is 4.7-5.4 million cells /microliter) resulting lowered ability of the blood to carry oxygen [3,7]. Its symptoms include fatigue, weakness, tiredness, shortness of breathing, poor ability to exercise, increase thirst and even loss of consciousness. Association of anaemia with chronic kidney disease is a common complication leading to permanent or partial loss of kidney functions. Anaemia may develop at the early stage of chronic kidney disease and worsen with the progress of chronic kidney disease with patients having 20 to 50% of normal kidney function [8].

Iron and erythropoietin (EPO) have crucial role for RBC production in bone marrow [9].Availability of iron is regulated by the liver hormone hepcidin which controls dietary iron absorption and recycling of iron by macrophages from RBC [10]. In patients with chronic kidney disease hepcidin level becomes predominantly elevated due to reduce renal clearance and induction by inflammation ultimately causing iron restricted erythropoietin. Erythropoietin is a hormone produced by the kidney and it promotes production of RBC in the bone marrow (erythropoiesis) [10,11]. Figure 2 shows the role of erythrpoeitin in anemia of CKD. It is also known as hemopoietin or hematopoietin. This glycoprotein cytokinin is produced by the kidney in response to cellular oxygen deficiency. Chronic kidney disease leads to decreaseerythropoietin production in the kidney due to circulating uremic toxins inhibition of erythropoiesis, shortening RBC life span and enhanced of blood loss. Some of the other causes of anemia in CKD are deficiency of vitamin B12, folic acid and iron deficiency [11,12].

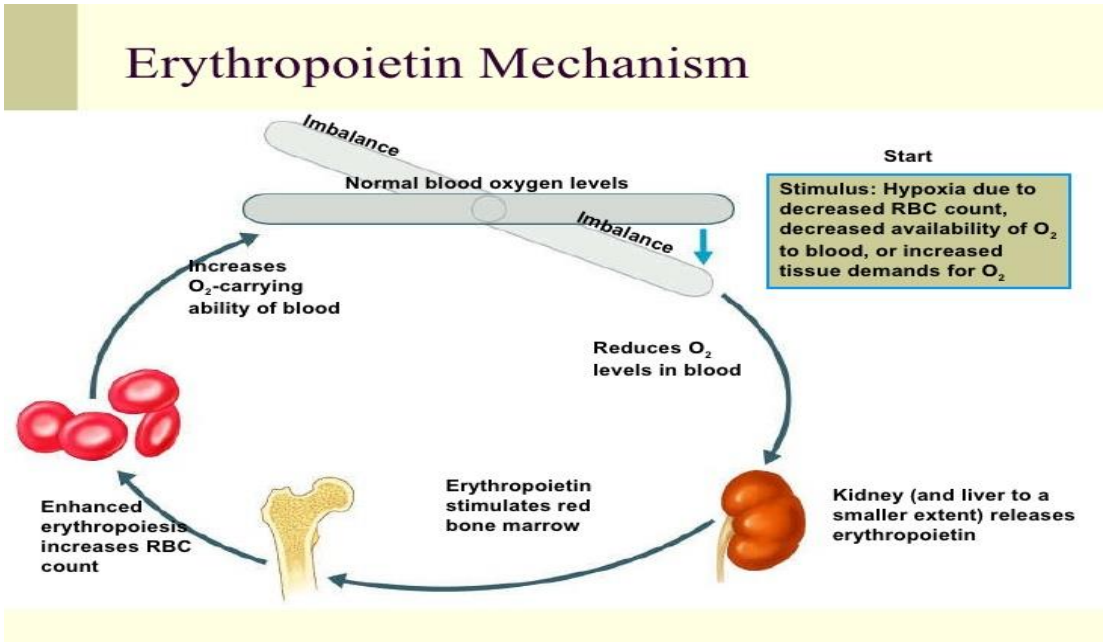


Figure 2 showing the role of erythrpoeitin in anemia of CKD (11)

The progress of CKD, anaemia is extremely common among patient undergoing hemodialysis. Screening and treatment of anaemia is a routine part of care for hemodialysis patients[13]. In severe anaemic condition in CKD, the patients are generally administered with erythropoiesis stimulating agents(ESAs) with the repletion of iron stores and correction of other causes of anaemia [13]. Erythropoiesis stimulating agents markedly improves lives of CKD patients who mostly suffered from severe transfusion dependent anaemia.

Erythropoeisis stimulating agents

Erythropoiesis-stimulating agents are medications which stimulates the bone marrow to make red blood cells. They are used to treat anemia due to end stage kidney disease. ESAs work like the human protein erythropoietin, which stimulates bone marrow to make red blood cells[13]. ***Erythropoietin alpha and beta*** (Recombinant human erythropoietin) are the examples of highly effective short active ESAs.***Darbepoietin*** (administered every two weeks)and***Epoetin*** (administered once to thrice per week) are also very effective to maintain hemoglobin level in patients undergoing hemodialysis [14].Darbepoetin was approved by the United States Food and Drug administration (US-FDA) in 2001 for the treatment of anemia in patients with CKD. Darbepoetin- alfais a re-engineered moiety of erythropoietin with five amino acids changes, resulting in the creation of two new sides of N-linked carbohydrate addition. It has serum half-life three times compared to epoetinalfa and beta [14]. It stimulates erythropoiesis by activation Epo receptor. In 2010 in India, Darbepoetinalfa was launched under a brand name “Cresp” by Dr. Reddy’s laboratories. Darbepoetinalfaadminiatration was found to effectively reduce need for blood transfusion in adults in CKD with stage 3 to stage 5 without little or any effect on mortality and quality of life [14].Erythropoiesis stimulating agents (ESAs) has now emerged as

an integral part of treating anemia in CKD patients with end stage renal disease undergoing dialysis. However, ESAs enhance the risk for death and serious adverse cardiovascular event in patients with CKD (cases of dialysis and non dialysis both) when targeting higher and hemoglobin versus lower hemoglobin concentrations [15]. Recombinant human erythropoietin products also provide risk for deep vein thrombosis in perisurgical patients receiving ESAs. Examples of some of the protein based ESAs [16] are shown in Table 1.

Epoetin Alfa	*brand names* Epogen® and Procrit® ; short acting
Darbepoetin alpha	*brand name*Aranesp®; intermediate acting
Epoetin beta	brand name NeoRecormon®; short acting
Epoetin Omega	brand name Epomax®; short acting
Epoetin Delta	brand name Dynepo®; short acting
CERA	brand name Mircera®;long acting pegylatedepoietin

Table 1 showing some of the protein based ESAs

A popular brand of ESAs is Mircera®. Mircera is marketed by the company 'Roche'. The average molecular weight of it is approximately 60 kilo Dalton. Methoxy polyethylene glycol-epoetin beta is made from erythropoietin by chemically linking the N- terminal amino group of ϵ-amino group of any lysine present in the protein with methoxy polyethylene glycol butanoic acid.

EPO mimetic agents are those drugs that mimic the action of EPO [17]. Hematite (trade name) is short peptide sequence that binds to and activates EPO receptor. It is used in case of erythropoietin (EPO) failure therapy as an ESAs [17].

Hemodialysis (Figure 3) patients may also have iron deficiency requiring intravenous iron supplements. Functional iron deficiency occurs due to an imbalance between iron demands of the erythroid marrow and delivering of iron by transferin (iron carrier protein in blood) [18]. However, some serious adverse reactions often occurs due to the rate administration of type of iron compounds and their careers. Sodium ferric gluconate and iron sucrose must be given by slow injection or infusion. Ferumoxytal is an encapsulated iron which can be administered by rapid injection, although its polysaccharide coating often produces adverse reaction. Ferric carboxymaltose, another encapsulated iron, can be administered in a large dose by rapid injection. Once ESAs have been started in patients they need more iron supply as ESAs makes more red blood cells faster [19].

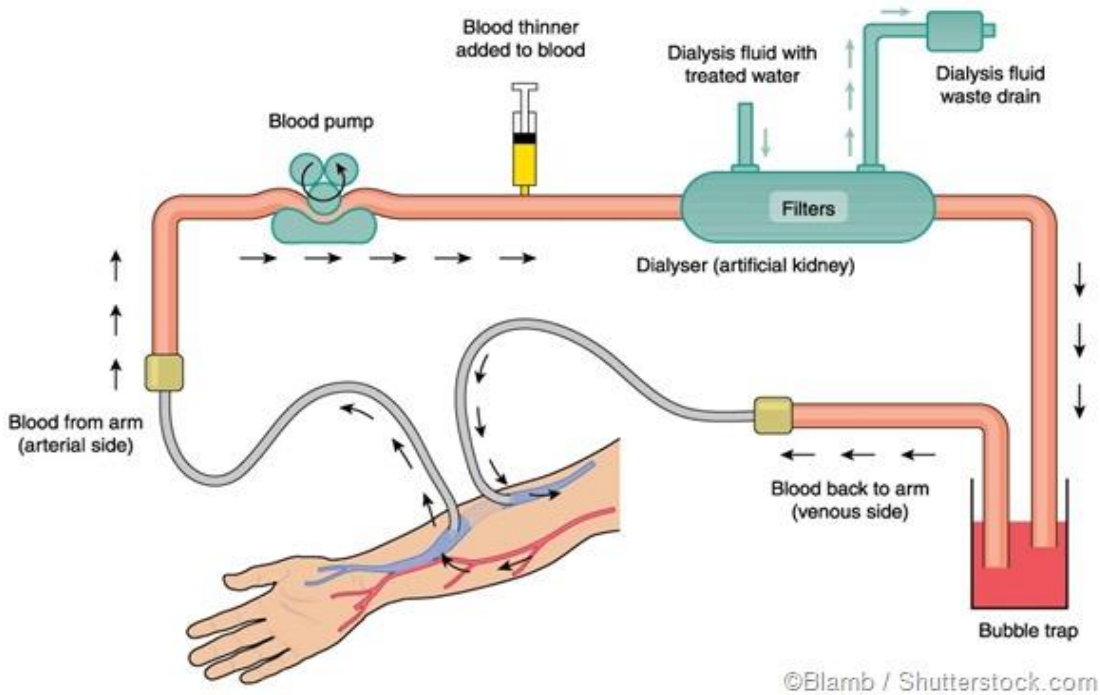


Figure 3: Dialysis process (taken from @Blamb/Shutterstock.com)

While taking ESAs, iron therapy helps to prevent iron deficiency. It reduces the amount of ESAs required and keeps the level of hemoglobin within the desired range [20]. The amount of iron and its route of administration required by a patient depend on the type of dialysis he or she receives. In case of peritoneal dialysis patient can take iron supplements orally or by intravenous route [21]. Oral iron formulations are generally sulphate, gluconate, fumerate or polysaccharide complex and parenteral intravenous formulations are iron dextran, gluconate, sucrose or ferric carboxymaltose, but in case of hemodialysis patient needs extra iron by intravenous route or a large iron dose may be injected through the dialysis machine or a small iron dose as a part of dialysis solution [22,23].

Although there are several such investigations related to the pattern of use of ESAs in dialysis patients suffering from CKD available in the western countries and their data base, there is a scarcity of Indian data related to the same context. Thus, the effort is given here to study the pattern of use of ESAs, patients' effectiveness and tolerability, complications and mode of payment by CKD patients. undergoing dialysis in the AMRI Hospitals, Dialysis unit, Dhakuria, Kolkata, India for a period of about one year.

LITERATURE REVIEW

Here we have attempted to review the literature related to CKD, anemia caused due to it and its therapy using various agents including ESAs.

Since the pioneering studies by ***Eschbach et al in 1987***, erythropoiesis-stimulating agents (ESAs) have become the mainstay of anemia therapy in chronic kidney disease (CKD) patients. The introduction of ESAs 25 years ago markedly improved the lives of many patients with CKD, who until then had severe, often transfusion-dependent anemia. However, randomized controlled trials demonstrate an increased risk for cardiovascular events such as stroke, thrombosis, and death at nearly normal hemoglobin concentrations and higher ESA doses in CKD. By contrast, kidney transplant recipients may represent a unique population of CKD patients who may benefit from ESA therapy. This review discusses potential mechanisms involving the erythropoietic and nonerythropoietic effects of ESA treatment and ESA resistance. Further research aimed at elucidating the causal pathways is strongly recommended. Given current knowledge, however, clinical practice should avoid disproportionately high dosages of ESAs to achieve recommended hemoglobin targets, particularly in those with significant cardiovascular morbidity or ESA resistance. The key to CKD anemia management will be individualization of the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm.[24]

Deicher et al. 2004 studied differentiating factors between the various erythropoiesis-stimulating agents. For treating anaemia in CKD, epoetin-δ is an approved agent produced by human cells that are genetically engineered to transcribe and translate the EPO gene under the control of an introduced regulatory DNA sequence. The erythropoietin analogue darbepoetin-α

carries two additional glycosylation sites, which permit a higher degree of glycosylation. Consequently, in comparison with the other epoetins, darbepoetin-α has a longer serum half-life and a higher relative potency, which further increases with extension of the administration interval. Dosage requirements of darbepoetin-α did not appear to differ between the intravenous and subcutaneous routes of administration. The less frequent administration of darbepoetin-α in comparison to the other epoetins reduced drug costs in the long term, but the variability in dosage or dosage frequency required within a single patient was high. Further, they concluded that the studies should be aimed at defining predictors of the individual demand for erythropoietic agents, thereby allowing nephrologists to prescribe a cost-effective, individualized regimen[25].

Recombinant human erythropoietin has been used for more than 20 years for the treatment of renal anaemia, with epoetin-alfa and -beta representing the common traditional preparations**.** ***Zrt et al 2007*** studied on Current issues in erythropoietin therapy of renal anemia. In praedialysed, transplanted or peritoneally dialyzed patients, erythropoiesis stimulating agents as suggested by the researchers should preferably be given subcutaneously both for economic and practical reasons. There are ongoing clinical trials with erythropoiesis stimulating molecules that can be administered by inhalation or per os. In their study, they suggested that the serum haemoglobin level should preferably not exceed 12 g/dl with the use of erythropoiesis stimulating agents. No cardiovascular protective effect of higher serum haemoglobin levels was demonstrated in two large clinical trials. Further well-designed studies are necessary to set evidence-based haemoglobin targets for erythropoiesis stimulating treatment. Arguments for a more widespread use of agents with extended duration include medical, financial and patient

satisfaction reasons. The release of new erythropoiesis stimulating agents may further simplify the treatment of renal anaemia[26].

In another study***Macdougall et al 2009*** assessed erythropoiesis-stimulating agents, iron products, and other novel anemia medications. Treatment for anemia came a long way since the first recombinant human erythropoietins were licensed for the management of anemia in chronic kidney disease. The first-generation epoetins were succeeded by the development and production of a longer-acting erythropoietin (EPO) analog, darbepoetinalfa, which allowed less frequent dosing, usually once weekly or once every 2 weeks. Another EPO-related molecule has been manufactured called Continuous Erythropoietin Receptor Activator with an even longer half-life. Two different biosimilarepoetins have already been licensed in Europe, one under 2 different brand names and one under 3 different brand names, and others may follow. They described that Hematide, a synthetic peptide-based EPO receptor agonist, interestingly, has no structural homology with EPO, and yet is still able to activate the EPO receptor and stimulate erythropoiesis. In conclusion, they stated that development of effective therapies for the treatment of anemia has been a highly active field, both scientifically and economically, over the last two decades[27].

Kalantar-Zadeh et al. 2009 described the predictors of hypo-responsiveness to erythropoiesis-stimulating agents in hemodialysis patients to improve anemia management and reduce hemoglobin variability. They conducted repeated measure and logistic regression analyses in a retrospective cohort of long-term HD patients to examine the association of iron markers and measures of renal osteodystrophy with ESA-responsiveness. The ESA-response

coefficient at the individual level, i.e., the least-confounded dose-response association, was separated from the population level, assumed to represent confounding by medical indication. The mean (±SD) ESA-response coefficients of the least to most responsive quartiles were 0.301±0.033, 0.344±0.004, 0.357±0.004, and 0.389±0.026 g/dL higher hemoglobin per 1,000 units/week higher ESA dose in each quarter, respectively. In this study, in long-term HD patients, low iron stores, hyperparathyroidism and high turnover bone disease were associated with significant ESA hyporesponsiveness[28].

Keown et al in the year 2010 showed in their Canadian Erythropoietin Study Group trial that Dialysis patients treated with Epoetinalfa showed improved anemia symptoms. The health-related quality of life (HRQOL) claims in the current Epoetinalfa label are based on the reanalysis of the exercise and physical function data from the Canadian Erythropoietin Study Group trial. The reanalysis was done to comply with the Food and Drug Administration's requirement of using statistical methods that are currently standard in evaluating clinical trial data. The Epoetinalfa-treated group showed a statistically significant improvement in the Kidney Disease Questionnaire symptom of fatigue in comparison with placebo. Additionally, the change in hemoglobin at 2 months was correlated with change in fatigue, energy, shortness of breath, and weakness, but had minimal effect on depression. These analyses confirm previously reported results, which indicate that treating hemodialysis patients with an erythropoiesis-stimulating agent improves HRQOL[29]

The European Renal Best Practice (ERBP), which are issued by ERA-EDTA, are suggestions for clinical practice in areas in which evidence is lacking or weak, together with

position statements on recently published randomized controlled trials, or on existing guidelines and recommendations. In 2009, the Anaemia Working Group of ERBP published its first position statement about the haemoglobin target to aim for with erythropoietin-stimulating agents (ESA) and on issues that were not covered by K-DOQI in 2006-07. This second position paper of the group follows the publication of the trial to reduce cardiovascular events with Aranesp therapy (TREAT) study. ***Locatelli et al 2010*** studied target haemoglobin to aim for treatment with erythropoiesis-stimulating agents as a position statement by ERBP following publication of the trial to reduce cardiovascular events with Aranesp therapy (TREAT) study. This multi-centre, placebo-controlled trial compared cardiovascular and renal outcomes in 4038 patients with type 2 diabetes, chronic kidney disease not on dialysis, and anaemia who were randomized to complete anaemia correction (haemoglobin target of 13 g/dL using darbepoetin alpha) or placebo (with a haemoglobin rescue value of 9 g/dL). Following the findings of the TREAT study, the Anaemia Working Group of ERBP maintains its view that 'Hb values of 11-12 g/dL should be generally sought in the CKD population without intentionally exceeding 13 g/dL' and that the doses of ESA therapy to achieve the target haemoglobin should also be considered. More caution was suggested when treating anaemia with ESA therapy in patients with type 2 diabetes not undergoing dialysis (and probably in diabetics at all CKD stages). In those with ischaemic heart disease or with a previous history of stroke, Locatelli et al suggested that the possible benefits should be weighed up against an increased risk of stroke recurrence, when deciding which Hb level to aim for[30].

Johansen et al., 2011 studied the impact of erythropoiesis-stimulating agents on fatigue in dialysis patients. They wanted to determine the level of benefits and risks associated with ESA

therapy on fatigue among both early-stage CKD patients and end-stage renal disease patients on dialysis. The study was a systematic review of the literature on fatigue in adults on maintenance dialysis therapy. The requirement for inclusion in the review was the measurement of fatigue before and after ESA treatment. Several different measures of fatigue were used in the studies. They concluded that partial correction of anemia with ESA results in improvement of fatigue among patients on dialysis, most strikingly in those patients with baseline Hb levels <10 g/dL[31].

Duong et al in the 2011 provided information regarding, mortality associated with dose response of erythropoiesis-stimulating agents in hemodialysis versus peritoneal dialysis patients. They examined the association between prescribed ESA dose and mortality in peritoneal dialysis (PD) and hemodialysis (HD) patients. They hypothesized that PD patients received lower ESA dose for the same achieved hemoglobin compared to HD patients and that ESA dose-mortality associations were different between PD and HD patients. They compared the prescribed doses of ESA between 139,103 HD and 10,527 PD patients treated in Da- Vita dialysis clinics from 7/2001 through 6/2006 and examined mortality-predictability of prescribed ESA dose and ESA responsiveness index (ESA/hemoglobin) in PD and HD with follow-up through 6/2007 using Cox regression models. In conclusion, they reported that between 2001 and 2006, most PD patients received substantially lower ESA dose for same achieved hemoglobin levels, and low ESA responsiveness was associated with higher mortality in both HD and PD patients[32].

Advances and clinical application of erythropoietin and erythropoiesis-stimulating agents were reported by ***Tanaka et al., 2012***. The use of recombinant human EPO (rhEPO)

dramatically changed management of anemic patients with chronic kidney disease and improved their quality of life. They stated that clinical benefit of normalization of anemia in pre-dialysis CKD by EPO therapy was controversial and large-scale, randomized-controlled trials did not favor normalization of anemia by EPO in improving cardiovascular as well as renal outcomes. They further opined that optimal EPO therapy should be determined based on the clinical context of individual patients[33].

Freburger et al 2012 studied changing patterns of anemia management in US hemodialysis patients. Erythropoiesis-stimulating agents and adjuvant intravenous iron have been the primary treatment for anemia in chronic kidney disease and later clinical and policy-related events have challenged the traditional paradigm, particularly in regard to erythropoiesis-stimulating agents. For each patient, monthly intravenous iron dose, erythropoiesis-stimulating agent dose, and hemoglobin values were determined. Data were summarized by calendar quarter and plotted for the entire sample and by demographic, clinical, and facility-level subgroups. Marginal means for those variables were computed to account for changes in patient characteristics over time. Quarterly iron use increased from 64% in 2002 to 76% in 2008. Mean quarterly iron dose increased from 500 mg in 2002 to 650 mg in 2008. Mean monthly erythropoiesis-stimulating agent dose (per quarter) increased from 2002 to 2006 and then declined. Mean hemoglobin values followed a pattern similar to erythropoiesis-stimulating agent dose. The same patterns in iron, erythropoiesis-stimulating agent dose, and hemoglobin were generally observed across demographic, clinical, facility, and geographic subgroups, with some important differences between subgroups, specifically race and dialysis vintage. They concluded that anemia management patterns have changed markedly between 2002 and 2008, with a steady increase in

intravenous iron use even after declines in erythropoiesis-stimulating agent dose and hemoglobin[34].

Goodnough et al 2013 in a study provided an update on erythropoiesis-stimulating agents. Erythropoiesis-stimulating agents (ESAs) have long been approved for the management of anaemia in a variety of clinical settings. Subsequently, a number of clinical trials were undertaken in which the haemoglobin end points were targeted to be maintained at normal or high-normal ranges, in an attempt to demonstrate improvements in long-term survival. For patients undergoing spine surgery, patients with cancer chemotherapy-induced anaemia and those with chronic kidney disease, adverse outcomes in these clinical trials were found, including death, thrombosis and/or cardiovascular events. They concluded that informed choice by patients for risks of ESA therapy as well as for blood transfusion should be part of the consent process for management of anaemia. Further, they stated that despite current regulations restricting ESA use, these agents are an effective treatment of anaemia, particularly for those who would be transfusion dependent without ESA therapy[35].

Anemia in chronic kidney disease worsens as glomerular filtration rates decline. The complications of severe anemia in this patient population contribute significantly to their overall morbidity with increased cardiovascular complications, decreased quality of life, and increased dependence on transfusions to maintain adequate hemoglobin levels. Erythropoietin-stimulating agents (ESAs) have revolutionized the treatment of anemia in this population, but there has been a great deal of controversy surrounding the quest for the ideal hemoglobin target. In addition, there are economic and practice management implications where anemia treatment is concerned.

One of the newest additions to the arsenal used to fight anemia in end-stage renal disease patients is peginesatide (Omontys), a synthetic, PEGylated, peptide-based ESA that acts by stimulating the erythropoietin receptor**.** ***Valliant et al in 2013*** studied on the managing of the dialysis patients who developed anemia caused by chronic kidney disease with a special focus on peginesatide. They concluded that role of peginesatide in the future treatment of anemia in chronic kidney disease remains uncertain, with new safety concerns being brought to attention as it emerges on the market[36].

Anne et al 2016 studied trends in anemia management in hemodialysis patients with cancer. However, anemia treatment patterns have not been described among end-stage renal disease (ESRD) patients undergoing hemodialysis with concurrent cancer, especially in the recent era of ESA-related safety concerns. They analyzed medicare data from a cohort of hemodialysis patients diagnosed with incident cancer and used multivariable generalized linear models to estimate trends and patterns in ESA use, iron use, transfusion use, epoetinalfa (EPO) dose, iron dose, and resulting hemoglobin levels (2000–2011). Anemia treatment patterns varied by demographic/clinical subgroups, especially among patients receiving chemotherapy, who required higher ESA use, EPO dose, and frequency of transfusions. Despite safety concerns about ESAs in both the ESRD and cancer populations, the proportion of hemodialysis patients with cancer who used ESAs between 2000 and 2011 remained extremely common. EPO dose and hemoglobin levels increased then decreased. Iron use, iron dose, and transfusions increased substantially[37].

End-stage renal disease, the last and most severe stage of chronic kidney disease, represents a major and rising concern for countries in Latin America, driven in large part by

aging populations and the near-epidemic rises in diabetes, obesity, and hypertension. This places a great clinical, economic, and social burden on the region's health systems. During the ISPOR 6th Latin America Conference held in Sao Paulo, Brazil, in September 2017, an educational forum debated on value-based decision making in the treatment of end-stage renal disease in Latin America. ***Brabata et al in 2018*** proposed End-Stage Renal Disease Models in the Americas for optimizing resources to achieve better health outcomes and summarized the current state and how to build strategies and implement actions to move to a more patient-centered, outcomes-based approach for renal care in the region, taken from the discussions in the conference and also from a literature review. Models of renal care used in Ontario (Canada), Colombia, and a Chilean hospital stress the importance of empowering and supporting patients and their families, allowing for a better coordination between primary care providers and specialists, providing financial incentives to health units, and establishing an entity that holds insurers and providers accountable for health outcomes and costs of treatment. The study used the framework of value-based health care for the evaluation of different dialysis options-peritoneal dialysis, hemodialysis, home dialysis, and so forth-and calls for the countries to adopt an integrated care model. They have emphasized that countries in Latin America need to recognize the chronic kidney disease challenge and develop health systems and efficient renal care models to be able to reduce the burden of the disease[38].

Nissenson et al. (2002) in a randomized, controlled trial of darbepoetinalfa for the treatment of anemia in hemodialysis patients showed some potential results. In their study, patients receiving epoetin therapy were randomized to continue epoetin administered intravenously (IV) three times weekly (n = 338) or change to darbepoetinalfa administered IV

once weekly (n = 169). The dose of darbepoetinalfa or epoetin was individually titrated to maintain hemoglobin concentrations within −1.0 to +1.5 g/dL (−10 to +15 g/L) of patients' baseline values and within a range of 9.0 to 13.0 g/dL (90 to 130 g/L) for up to 28 weeks (20-week dose-titration period followed by an 8-week evaluation period). The primary end point was change in hemoglobin level between baseline and the evaluation period (weeks 21 to 28). Mean changes in hemoglobin levels from baseline to the evaluation period were 0.24 ± 0.10 (SE) g/dL (2.4 ± 1.0 g/L) in the darbepoetinalfa group and 0.11 ± 0.07 g/dL (1.1 ± 0.7 g/L) in the epoetin group, a difference of 0.13 g/dL (95% confidence interval [CI], −0.08 ± 0.33 [1.3 g/L; 95% CI, −0.8 to 3.3]). This difference was not statistically significant or clinically relevant despite the reduced frequency of darbepoetinalfa administration. The safety profile of darbepoetinalfa was similar to that of epoetin, and no antibody formation to either treatment was detected. In conclusion, they stated that darbepoetinalfa maintained hemoglobin concentrations as effectively and safely as epoetin in patients with CKD, but with a reduced dosing frequency [39].

From the findings of another randomized comparative trial, ***Carrera et al . 2010*** described maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycol-epoetin beta versus darbepoetinalfa administered monthly. Haemodialysis patients (n = 490) on stable once weekly intravenous darbepoetinalfa were randomized to methoxy polyethylene glycol-epoetin beta once monthly or darbepoetinalfa every 2 weeks for 26 weeks, with dose adjustment for individual haemoglobin target (11–13 g/dL; maximum decrease from baseline 1 g/dL). Subsequently, patients entered a second 26-week period of once-monthly methoxy polyethylene glycol-epoetin beta and darbepoetinalfa. The primary endpoint was the

proportion of patients who maintained average haemoglobin≥10.5 g/dL, with a decrease from baseline ≤1 g/dL, in Weeks 50–53; the secondary endpoint was dose change over time. They reported that methoxy polyethylene glycol-epoetin beta maintained target haemoglobin more successfully than darbepoetinalfa at once-monthly dosing intervals despite dose increased with darbepoetinalfa [40].

To compare the efficacy and safety of ESAs (epoetinalfa, epoetin beta, darbepoetinalfa, or methoxy polyethylene glycol-epoetin beta, and biosimilar ESAs, against each other, placebo, or no treatment) to anaemia in adults with CKD, a meta-analysis was done by ***Palmer et al. 2014.*** They identified 56 eligible studies involving 15,596 adults with CKD. Risks of bias in the included studies was generally high or unclear for more than half of studies in all of the risk of bias domains we assessed; no study was low risk for allocation concealment, blinding of outcome assessment and attrition from follow-up. In network analyses, there was moderate to low confidence that epoetinalfa (OR 0.18, 95% CI 0.05 to 0.59), epoetin beta (OR 0.09, 95% CI 0.02 to 0.38), darbepoetinalfa (OR 0.17, 95% CI 0.05 to 0.57), and methoxy polyethylene glycol-epoetin beta (OR 0.15, 95% CI 0.03 to 0.70) prevented blood transfusions compared to placebo. In very low quality evidence, biosimilar ESA therapy was possibly no better than placebo for preventing blood transfusions (OR 0.27, 95% CI 0.05 to 1.47) with considerable imprecision in estimated effects. We could not discern whether all ESAs were similar or different in their effects on preventing blood transfusions and our confidence in the comparative effectiveness of different ESAs was generallyvery low. Similarly, the comparative effects of ESAs compared with another ESA, placebo or no treatment on all-cause mortality were imprecise. All

proprietary ESAs increased the odds of hypertension compared to placebo (epoetinalfaOR 2.31, 95%CI 1.27 to 4.23; epoetin beta OR 2.57, 95% CI 1.23 to 5.39; darbepoetinalfa OR 1.83, 95% CI 1.05 to 3.21; methoxy polyethylene glycol-epoetin beta OR 1.96, 95%CI 0.98 to 3.92), while the effect of biosimilar ESAs on developing hypertension was less certain (OR 1.18, 95%CI 0.47 to 2.99). They ultimately concluded that In the CKD setting, there was insufficient evidence to suggest the superiority of any ESA formulation based on available safety and efficacy data. Directly comparative data for the effectiveness of different ESA formulations based on patient-centred outcomes (such as quality of life, fatigue, and functional status) were sparse and poorly reported and current research studies are unable to inform care. All proprietary ESAs (epoetinalfa, epoetin beta, darbepoetinalfa, and methoxy polyethylene glycol-epoetin beta) prevent blood transfusions but information for biosimilar ESAs is less conclusive. Comparative treatment effects of different ESA formulations on other patient-important outcomes such as survival, MI, stroke, breathlessness and fatigue are very uncertain [41].

AIMS AND OBJECTIVES:

To assess the pattern of use of various erythropoiesis stimulating agents in hemodialysis patientsin a tertiary care hospital in eastern India.

STUDY RATIONALE

Patients with chronic kidney disease(CKD) often have anemia due to erythropoiesis stimulating agent (ESA)-erythropoietin (EPO) deficiency. They, therefore, need treatment with EPO. Newer formulations of EPO have been discovered now. Data is sparse in Indian patients with regards to pattern of use of these erythropoiesis stimulating agents in the present era.

METHODOLOGY

Study setting

This was a retrospective observational study which was carried out in the hemodialysis depratment of AMRI Hospitals, Dhakuria. The Dialysis department of AMRI Hospitals, Dhakuria is a state-of-art dialysis facilities and carries out dialysis on approximately 40 CKD patients per day.

Study period

The study has been carried out over a period of 10months starting from July 2018. to April 2019.All patients undergoing hemodialysis(HD) during the study period were eligible for the study.

Study population

Inclusion and exclusion criteria:

All adult patients ≥ 18 years of age with diagnosis of CKD on HD were included. Patients were included if they were anemic and have received ESA alone or IV iron alone or ESA + IV iron treatment at least once during the study period. Patients were excluded if patients received ESA or IV iron for reasons other than anemia of CKD (for example, patients with cancer diagnosis, chemotherapy or radiotherapy).

Data collection and analysis

Data has been collected from the Hemodialysis unit database maintained by the hemodialysis unit of AMRI Hospitals and updated by trained nurses regularly. All data were collected on a paper data sheet and uploaded in an electronic databases created in Excel format. Data's were cross checked for maintaining data accuracy.

Statistical analysis of data was done using appropriate statistical tests SPSS statistical software.

Variables

Variables that were collected include demographic data (age, sex, funding status - self-paid, insurance paid or corporate paid), cause of CKD (hypertension, diabetes, chronic glomerulonephritis, nephrotic syndrome, chronic, renal sclerosis), renal dialysis status , co-morbidities and frequency and duration of dialysis. Laboratory data include hemoglobin prior to ESA use and after ESA use. Medication data include whether patient is receiving ESA alone, ESA +Iron or Iron alone, type of ESA used-erythropoietin, derbapoetin, and frequency of ESA and dosing.

Ethical approval

Ethical approval was taken from the Ethics Committee of AMRI Hospitals, Dhakuria.

DATA SHEET

The following variables must be considered in the data sheet in order to carry out the study successfully.

Patient ID:

Age:

Sex:

CKD Cause:

Dialysis Status:

Frequency of dialysis per week:

Duration of dialysis per month:

<u>Comorbidities</u>

- Diabetes mellitus (DM)
- Hypertension(HTN)
- Cardio vascular diseases(CVD)
- Chronic Lung Disease(CLD)
- Neurological diseases

Immunosuppressive Therapy:

Medications

- Erythropoiesis stimulating agents (ESA): erythropoietin, darbepoetin ,CERA
- Iron
- ESA+ Iron
- ESA Dosage
- ESA Type
- ESA Frequency
- ESA Adverse Effect

Hemoglobin prior to ESA Use:

Hemoglobin after ESA use:

Funding Status:

RESULTS

There a total of 127 patients who received ESA during study period. 52.7 % patients received ESA and iron and 47.3 % received ESA , iron and blood transfusion (Figure 1). The mean age of patients differed significantly between groups (60.6 ± 10years vs. 59.1 ± 14, p = 0.0002). Males constituted the majority in both groups (73.1% and 58.3%), but there was no significant difference in the sex distribution in both groups (p=0.2) (Figure 2). The baseline characteristics of the patients recruited are described in Table 1.

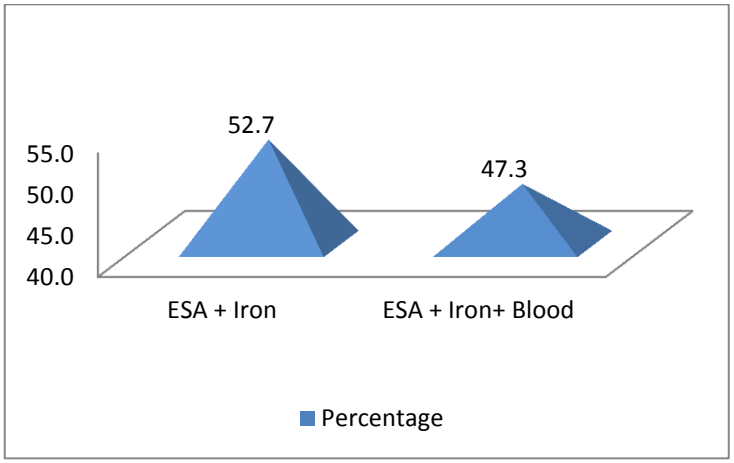


Figure 1: Pictorial depiction of total number of patients who received i) ESA + iron & ii) ESA + iron + Blood transfusion.

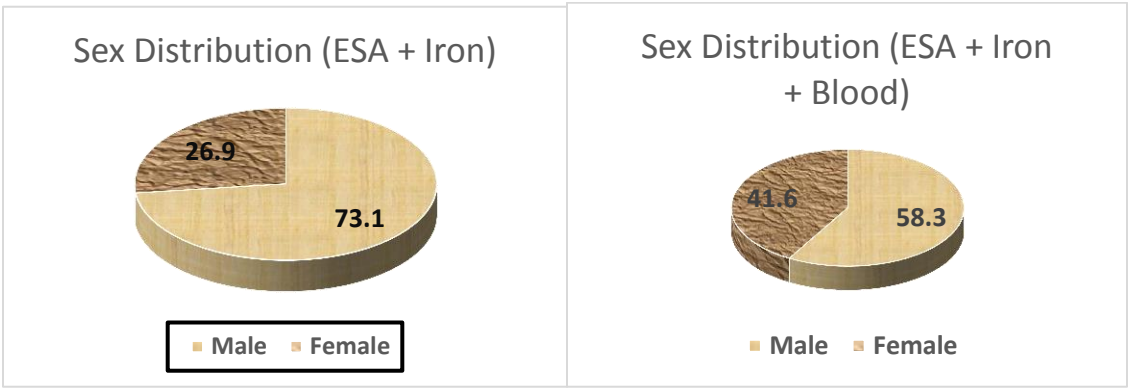


Figure2:Sex distribution of patients who received i) ESA + iron & ii) ESA + iron+ Blood (p=0.2)

Table 1- Describing the demographics of study population

Characteristics	ESA + Iron (n = 67)	ESA + Iron+ Blood (n=60)	p
Sex, n (%)			
Male	49 (73.1)	35 (58.3)	0.2
Female	18 (26.9)	25 (41.6)	
Age, mean ± SD	60.6 ± 10	59.1 ± 14	0.0002
Age group distribution (years) n(%)			
18 - 30	1(1.5)	1 (1.7)	0.005
31 - 50	8 (11.9)	20 (33.3)	
51 - 64	31 (46.3)	17 (28.3)	
≥ 65	27 (40.3)	22 (36.7)	

We looked at the age group distribution of patients in both groups. While majority in ESA+Iron group belonged to the 51 - 64 year age group (46.3%), elderly patients more than 65 years of age were seen more in the ESA+Iron+Blood transfusion group (36.7%). There was significant difference in receipt of ESA+Iron and ESA+Iron+Blood between age groups (p= 0.0005). (Figure 3)

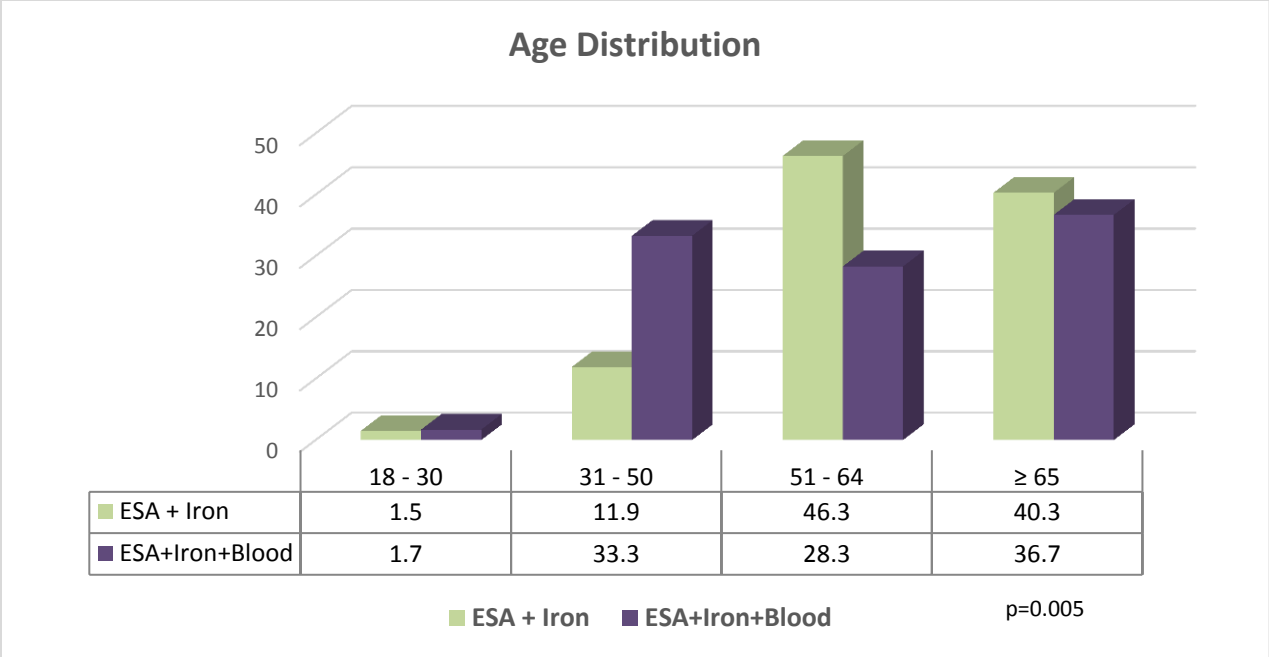


Figure 3: Graphical representation of the age group distribution for both the groups (ESA + Iron & ESA + Iron + Blood transfusion)

Comorbidities were assessed and compared between the two groups. Hypertension was the most prevalent comorbidity (97% and 86.7%) followed by diabetes (76.1% and 71.7%) in both groups. We also compared the presence of other cardiovascular, chronic liver disease and neurological diseases between the two groups, demonstrated in Table 2, Figure 4.

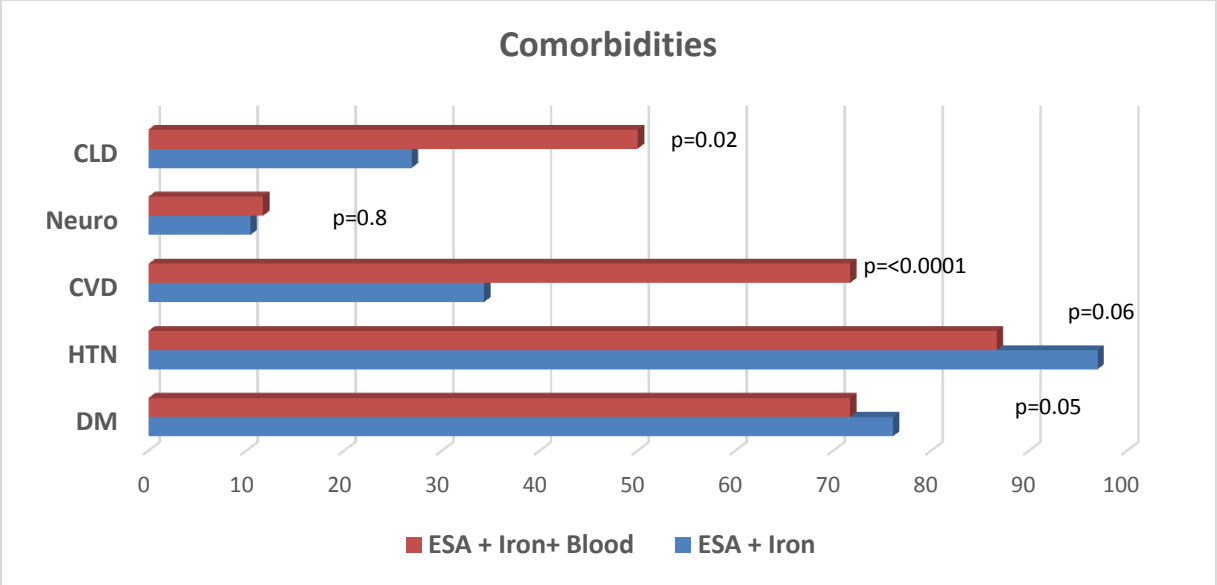


Figure 4: Various comorbidities in patients of both groups

Table 2- Describing the comorbidities of study population

Characteristics	ESA + Iron (n = 67)	ESA + Iron+ Blood (n=60)	p
Comorbidities, n(%)			
Diabetes Mellitus	51 (76.1)	43 (71.7)	0.05
Hypertension	65 (97.0)	52 (86.7)	0.06
Other cardiovascular disease	23 (34.3)	43 (71.7)	<0.0001
Neurological	7 (10.4)	7 (11.7)	0.8
Chronic liver disease	18 (26.9)	30 (50.0)	0.02

We evaluated the dialysis details of all patients irrespective of the group that they belonged. 92.1% were hypertensive and 74.0 % patients were diabetic (Table 3, Figure 5). Details of kidney diseases could be assessed only in 51.3% of patients - 41.5% of these had glomerulonephritis and 29% had renal sclerosis and another 29% had nephrotic syndrome (Figure 6).

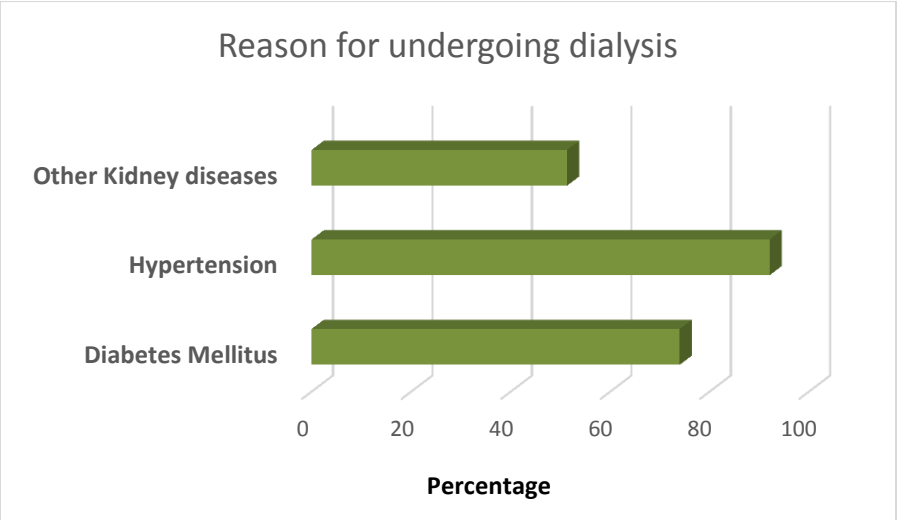
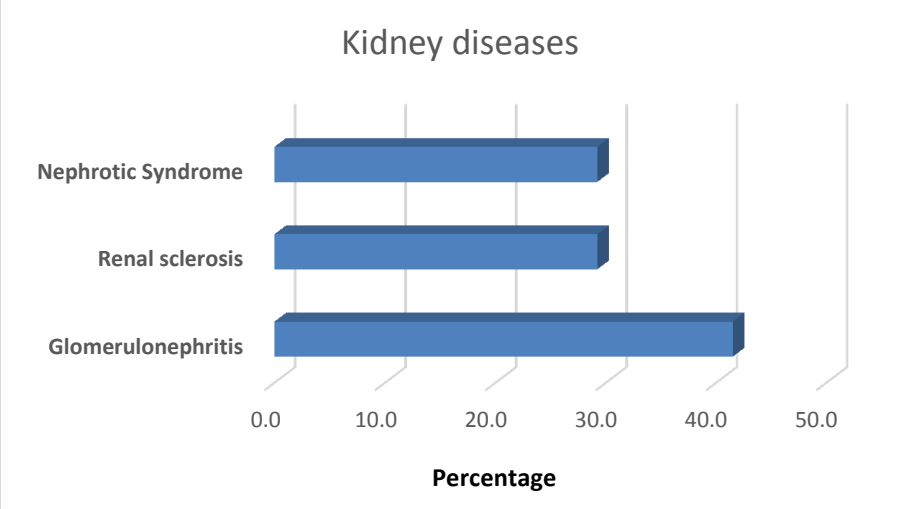


Figure 5: Graphical depiction describing the reasons for undergoing dialysis in patients



Figutre 6: Diagram show the types of kidney diseases in patients

Table 3: Reasons for undergoing dialysis

Characteristics	n (%)
Reason for undergoing dialysis, n(%)	
Diabetes Mellitus	94 (74.0)
Hypertension	117 (92.1)
Kidney diseases	65 (51.2)
Glomerulonephritis Renal sclerosis Nephrotic Syndrome	27 (21.3) 19 (15) 19 (15)
Unknown	62 (48.8)

Patients received ESA+Iron+BT were further categorized under four groups namely cardio vascular disease(CVD) ,elderly patients (>60years), diabetic patients and chronic liver disease (CLD)patients(table 4 ; figure 7).Total number of patients in these category was 60.Out of these 60 patients 37% were elderly. 72% patients were in the categories of CVD and 72% patients were suffering from diabetes and nearly 49% patients were under CLD.

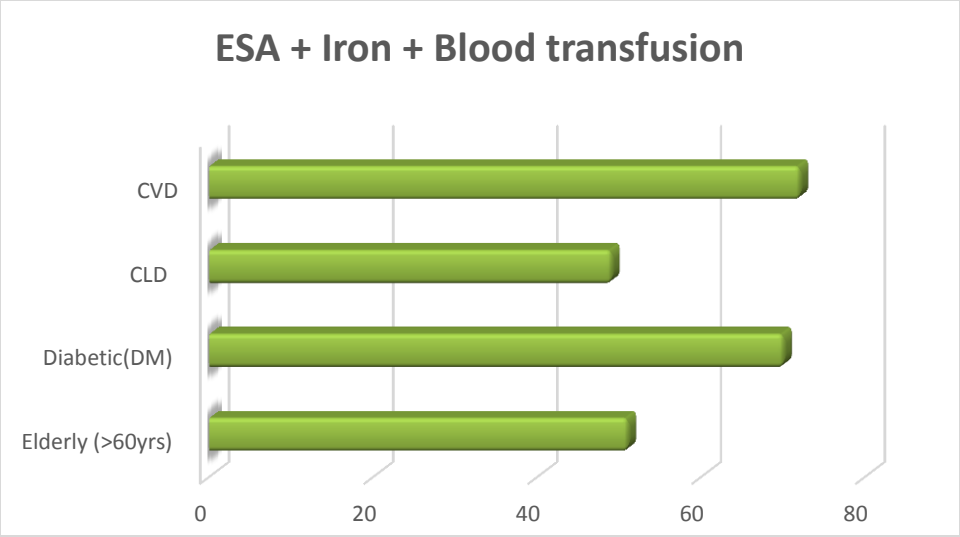


Figure7; Categorization of patient under ESA+iron+BT group

Table 4: Details of ESA+Iron+Blood transfusion

ESA + Iron + Blood transfusion (n=60)			
Elderly patients (>65yrs) n(%)	**Diabetic(DM) n(%)**	**CLD n(%)**	**CVD n(%)**
22 (37)	43(72)	30(50)	43(72)

Majority of patients (57.5%) underwent 3 dialysis per week (Figure 8). 37% of patients were undergoing dialysis for more than 2 years, 23.6% between 1 to 2 years, 29.1% between 6 - 12 months and 10.2% of patients for less than 6 months (Figure 9). Most dialysis (85.8%) were planned dialysis (Figure 10). All dialysis details are described in Table 5).

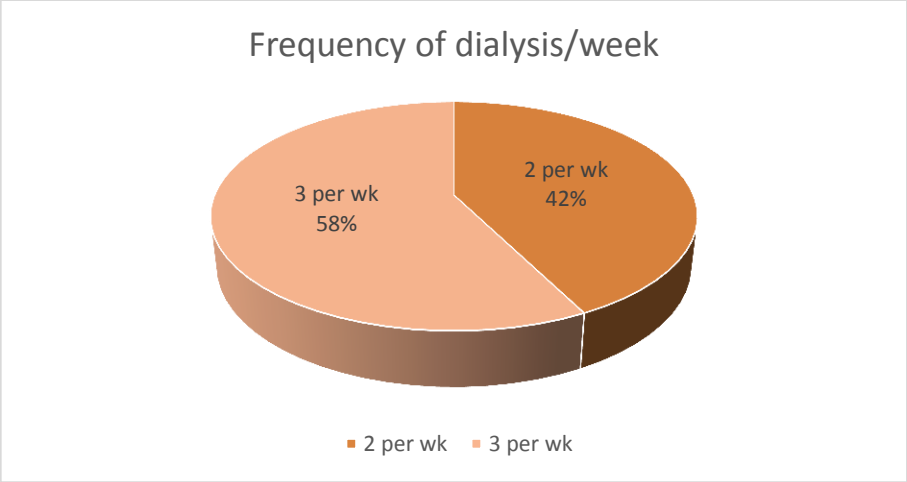


Figure 8: Frequency of dialysis per week in patients

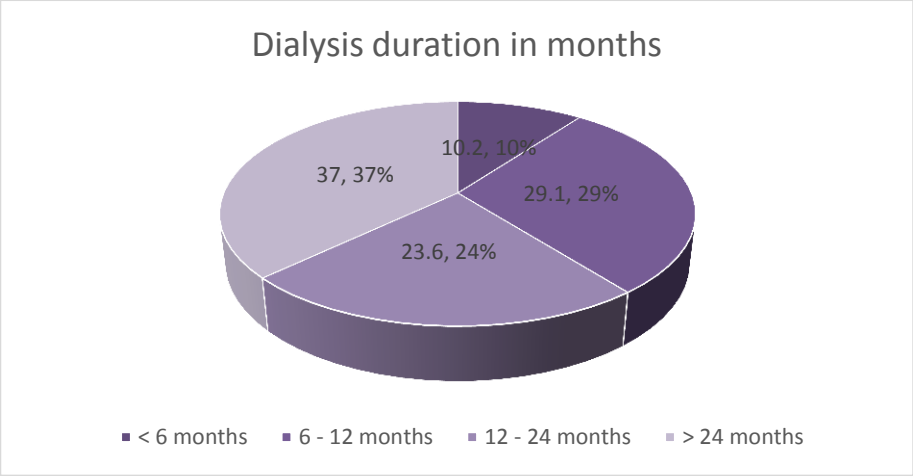


Figure 9: Duration of dialysis in patients

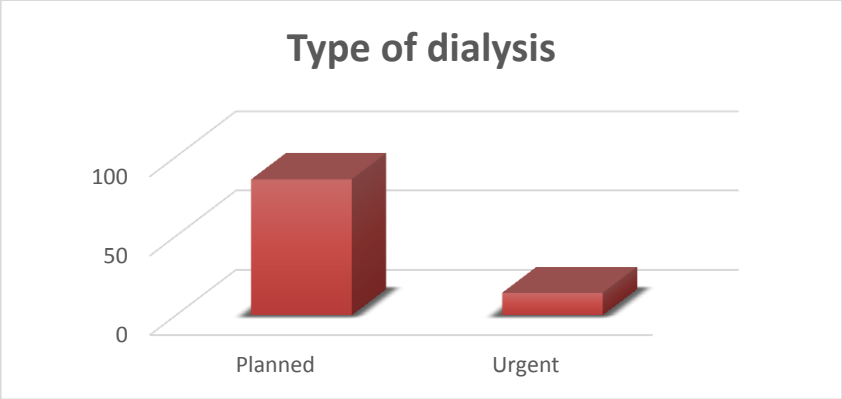


Figure 10: Number of patients underwent planned and urgent dialysis

Table 5: Details of dialysis in patients

Characteristics	**n (%)**
Frequency of dialysis/week, n(%)	
2	54 (42.5)
3	73 (57.5)
Dialysis duration in months, n(%)	
< 6 months	13 (10.2)
6 - 12 months	37 (29.1)
12 - 24 months	30 (23.6)
> 24 months	47 (37)
Type of dialysis, n (%)	
Planned	109 (85.8)
Urgent	18 (14.2)

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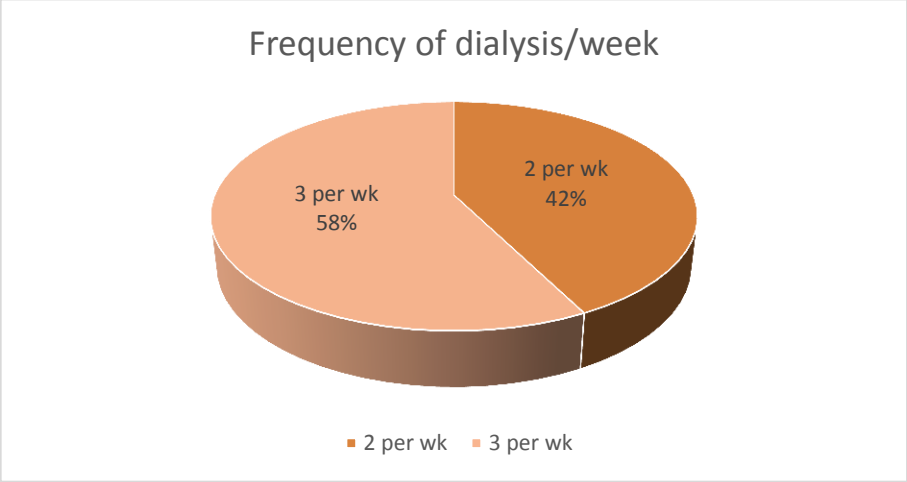


Figure 8: Frequency of dialysis per week in patients

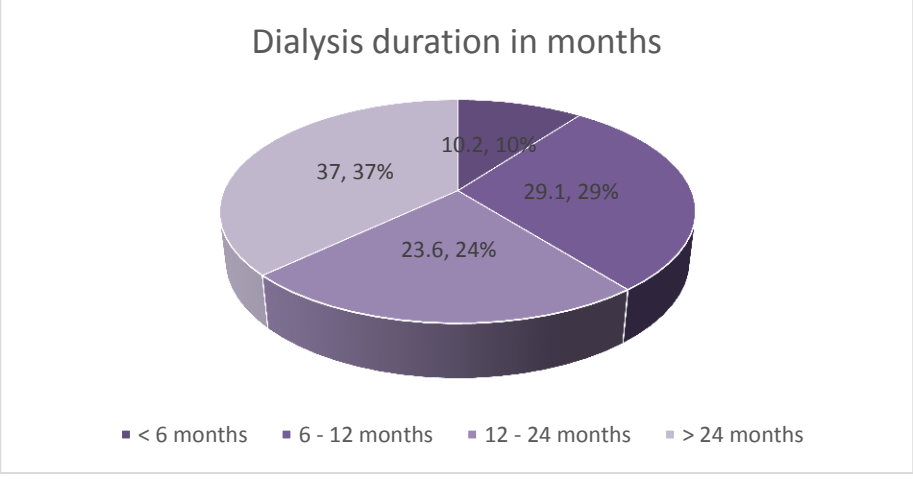
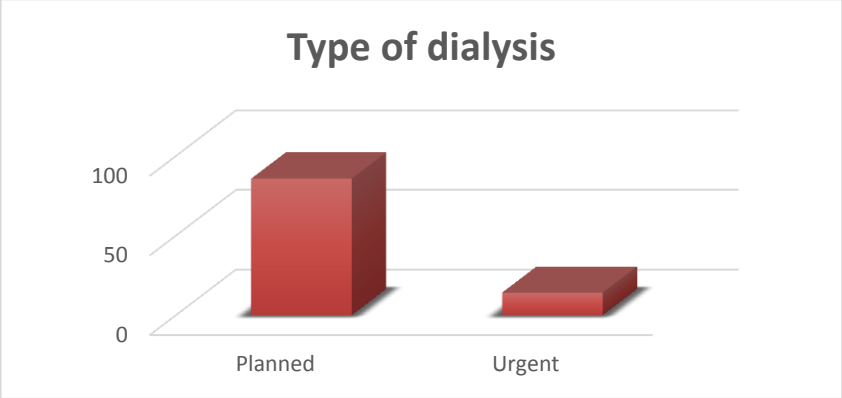


Figure 9: Duration of dialysis in patients



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Type of dialysis, n (%)	
Planned	109 (85.8)
Urgent	18 (14.2)

When the frequencies of dialysis (2/week and 3/week were correlated with the duration of dialysis(table 6 ; figure 11)the findings showed that there are predominantly variations for the patients taking dialysis for a period of 6to 12 months and more than 24months . Patients receiving dialysis for less than 6 months,12to 24 months and greater than 24 months had the similar trend where we observed that higher frequency (3/week)had always greater values than that of the lower one(2/week).However in case of 6 to12 months the trend was absolutely different where we observed that lower frequency of dialysis (2/week) had nearly 2 times greater value than 3/week . This could be possibly due to the patients receiving dialysis 2/week have replaced by 3/week with the progression of disease with a duration of 12 months or more hence in later cases blood transfusion level were increased .However due to less number of sampling statistical analysis was not conducted.

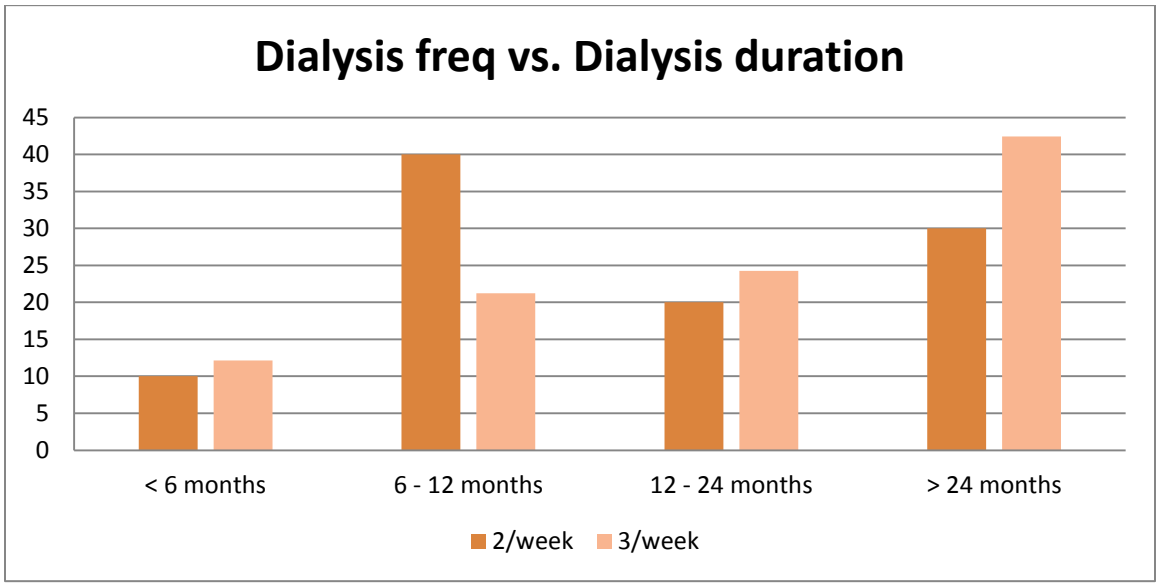


Figure 11; **Relation between frequency of dialysis per week and duration of dialysis in months**

Table 6:Data showing relation between frequency of dialysis per week and duration of dialysis in months

	Duration of dialysis in months(n%)			
Frequency of dialysis/wk n(%)	< 6 months	6 - 12 months	12 - 24 months	> 24 months
2/wk	5(10)	20(40)	10(20)	15(30)
3/wk	8(12.12)	14(21.21)	16(24.24)	28(42.42)

The type, dosage, frequency per week and associated adverse effects with ESA usage was assessed. Majority of patients used Epoeitin alfa (73.2) while 26.8% patients used Darbopoeitin Alfa (Figure 12). We did not find Epoeitin Beta and CERA usage in our study. The mean dosage used Epoeitin alfa was 8580.7 ± 2237.6 International Units. And for Darbopoeitin alfa was 340.6 ± 206.8 International Units. Only 4 adverse effects were noted with usage of Epoeitin alfa group and 3 adverse effects were noted in the Darbopoeitin alfa group. All patients who had adverse effects stated that they had elevation of blood pressure during their treatment. Details of ESA use are described in Table 7.

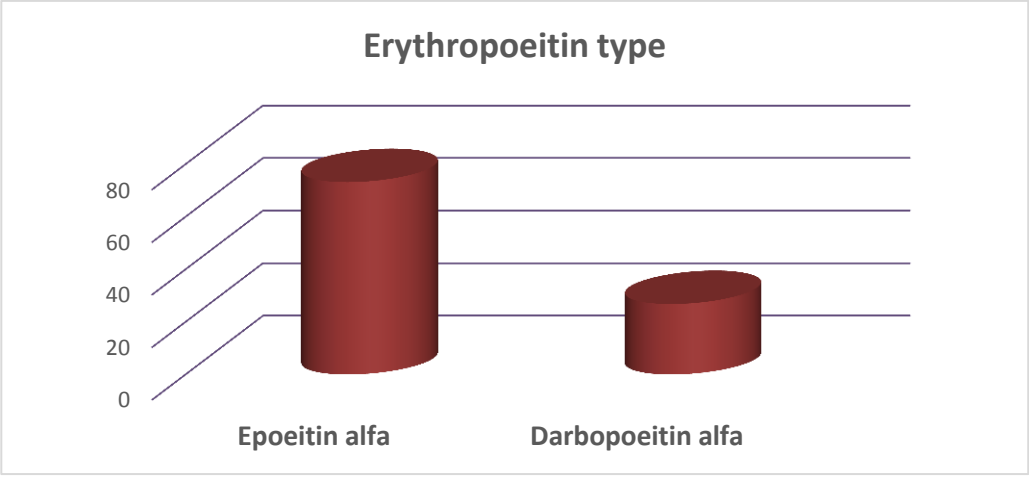


Figure 12: Different types of ESA usage in patients

Table7; Details of ESA use are described

Erythropoeitin type	n(%)	Dosage, mean ± SD	Frequency per week	Adverse effects
Epoeitin alfa	93 (73.2)	8580.7 ± 2237.6	1.8 ± 0.5	4 (4.3)
Darbopoeitin alfa	34 (26.8)	340.6 ± 206.8	1.8 ± 0.7	3 (8.8)

We compared the change in the mean hemoglobin levels in the Epoeitin alfa and Darbopoeitin alfa groups at baseline, 3 months and 6 months after ESA use. The mean hemoglobin steadily increased in both the groups and this increase was statistically significant in both groups. The mean hemoglobin level was also significantly different between the two groups at the end of 6 months (Table 8, Figure 13).

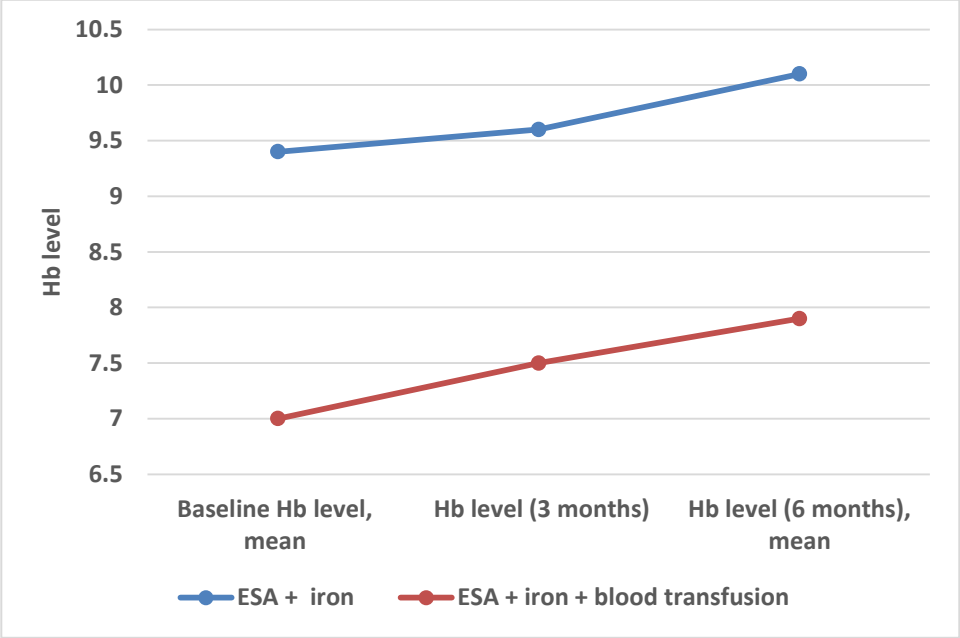


Figure 13: Hemoglobin level in patients during a course of six months from the initial stage of treatment in both type of erthropoeitin use

Table 8 showing type of erthropoeitin use in combination with other hemopoeitic agents

Erythropoeitin + other hemopoeitic agents	n(%)	Baseline Hb level, mean ± SD	Hb level (3 months), mean ± SD	Hb level (6 months), mean ± SD
ESA + iron	67	9.4 ± 1.2	9.6 ± 1.0	10.1 ± 1.3
ESA + iron + blood transfusion	60	7.0 ± 0.8	7.5 ± 1.1	7.9 ± 1.5
P		0.06	0.3	0.005

Hemoglobin level in patients at different duration that is at initial level before beginning the treatment , 3 months after treatment ,and 6 months after the treatment schedules (epoetin alfa +iron , darbepoetin + iron epoetin alfa +iron+BT , darbepoetin + iron+BT) showed that treatment of hemoglobin level improve steadily to the patients received darbepoetin + iron .However epoetin alfa +iron treatment maintained the hemoglobin level even after 6 months the level did not exceed 10mg/dl, epoetin alfa +iron+BT and darbepoetin + iron+BT did not improved the hemoglobin level significantly.compared to the epoetin alfa +iron , darbepoetin + iron patients.(table 9;figure 14)

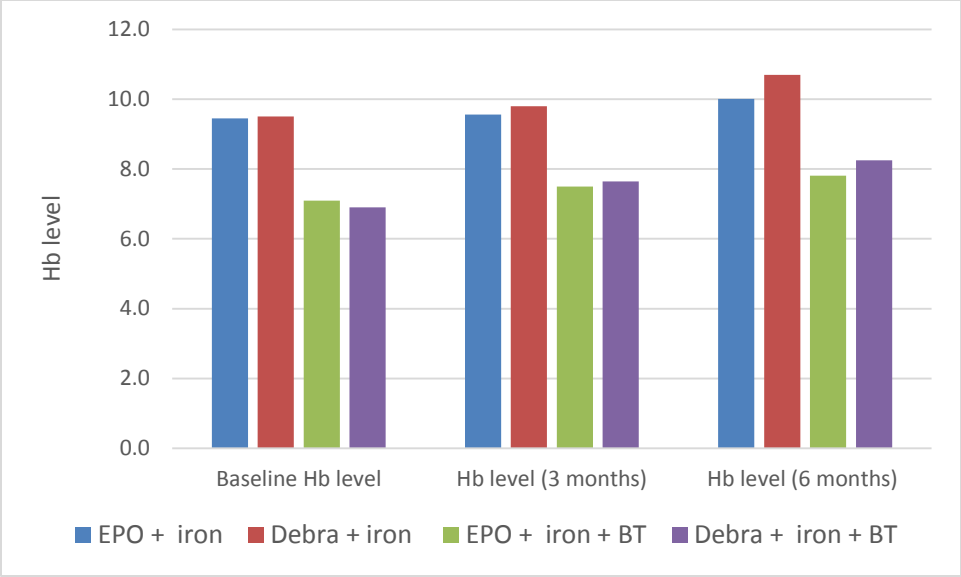


Figure14;Pictorial depiction of data for ESA +iron against hemoglobin(Hb) level

Table9 : data for ESA +iron against hemoglobin(Hb) level

Erythropoeitin + other hemopoeitic agents	**n(%)**	**Baseline Hb level, mean ± SD**	**Hb level (3 months), mean ± SD**	**Hb level (6 months), mean ± SD**
EPO + iron	53(41.37)	9.4 ±1.2	9.56±1	10.0±1.1
Debra + iron	14(9.48)	9.5±1.4	9.8±1.3	10.7±1.8
EPO + iron + Blood trasnfusion	40(34.48)	7.1±1.0	7.5±1.3	7.8±1.6
Debra + iron + Blood trasnfusion	17(14.65)	6.9±0.5	7.6±0.7	8.2±1.4

A comparison was made to see number of patients covered under some kind of insurance, under corporate payment, and the number in self-paid group. In the ESA+Iron group, 35.8% of patients were insurance payed, 25.4% were corporate paid and 38.8% were self paid patients. The corresponding numbers in the ESA+Iron+Blood transfusion group were 36.7%, 25.0% and 38.3%. The payer status did not differ significantly between groups (p=0.9) Table 10, Figure 15).

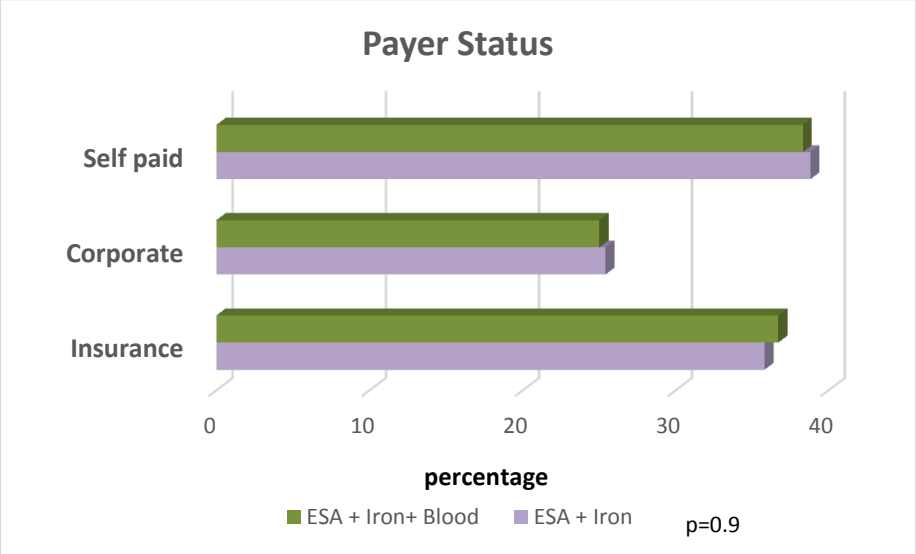


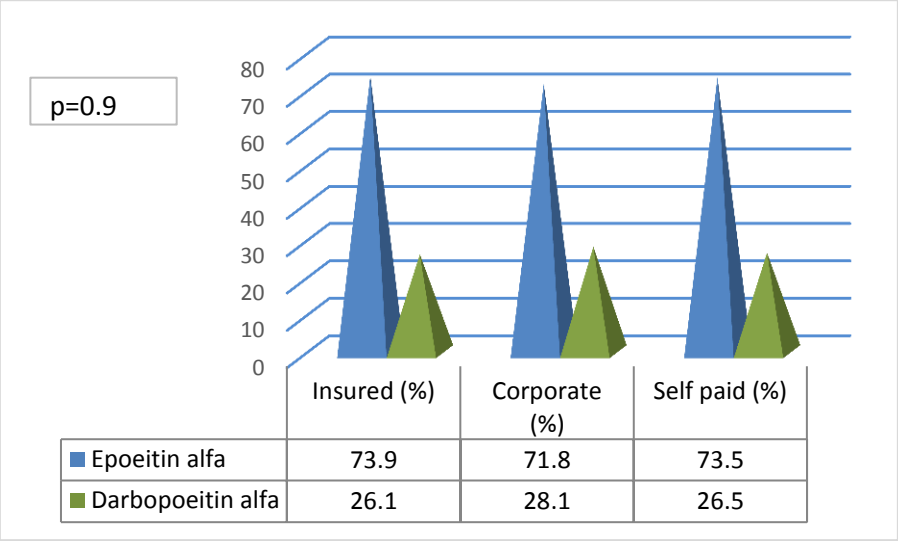
Figure 15: Payer status of patients of both groups

Table 10- Describing the status of payment of the study population

Characteristics	ESA + Iron (n = 67)	ESA + Iron+ Blood (n=60)	p
Payer status, n(%)			
Insurance	24 (35.8)	22 (36.7)	0.9
Corporate	17 (25.4)	15 (25.0)	
Self paid	26 (38.8)	23 (38.3)	

We also assessed whether payer status impacted type of ESA used. Majority of insurance-paid, corporate-paid and self-paid patients were prescribed Epoeitin alfa (73.9%, 71.8% and 73.5%

respectively). There was no significant difference in the usage of either of the ESAs between groups (p=0.9) (Figure 16).



	Insured (%)	Corporate (%)	Self paid (%)
Epoeitin alfa	73.9	71.8	73.5
Darbopoeitin alfa	26.1	28.1	26.5

Figure 16: Diagram showing type of erythropoeitin use according to payer status

DISCUSSION

My study was intended to investigate the pattern of Erythropoietin stimulating agents(ESAs) that is epoetin alfa and darbepoetin alfa use in hemodialysis patients . Data of a total number of 127 patients who received ESAs during the period of study were collected and thus data was correlated with various patients related parameters such as age , sex , comorbidities, level of hemoglobin(Hb) , kinds of diseases they were suffering from, frequency of dialysis they received , duration of dialysis , moderation of dialysis used etc. .Further, patients receive ESAs were also categorized as per their disease condition . The distribution status of payment of the patients population studied here was also correlated with their status of payment such as self paid, paid by insurance, paid by corporate.

Initially when the baseline characteristics of the patients were collected on the basis of type of treatments(ESA+iron) and (ESAs+iron+Blood Transfusion [BT]),it was found that a little higher percentage of patients (statistically not significant) received ESA +Iron+BT. Out of this ,in both the categories of treatments percentage of females were always higher(when two categories of the treatments were compared ,the data showed that enhancement of number of male patients and reduction of number of female patients were more for the patients received ESA+iron+BT). However, the variation of the data is not statistically significant ($p=0.2$)

A significant variation of age group distribution in years was observed. It was observed that more percentage of elderly patients(>65 years) received the treatment ESAs+iron+BT where as less number of patients received ESAs+iron +BT.($p<0.005$).

While investigating comorbidities in the patients,receiving either of the treatments, findings showed that less number of comorbidities such as diabetes , hypertension, neurological diseases were seen in patients receive ESA +iron+BT. However, more diabetic patients received ESA+Iron+BT($p<0.05$) studies have shown that reduced EPO production and anemia happen earlier with diabetes and kidney disease,than those without.That may explain why diabetic patients needed BT in addition to EPO. On the other hand ESA+iron+BT treatments was more common in patients with cardio vascular diseases and chronic liver diseases ($p<0.0001$). Patients with cardio vascular disease received more BT as in these patients the target Hb is higher (ie, >10gm/dl).It is a similar situation with patients with chronic liver disease-these patients need BT as hemoglobin drops due to gastrointestinal bleeding due to ulcer, etc

Another interesting observation depicts a correlation between the frequency of dialysis 2/week or 3/week in patients with the duration of dialysis according to months. Higher frequencies where observed in patients dialyzed for 12 months and above. These could be due to the reason with progression of disease(s) patients need more frequent dialysis.

Here both the treatment type (ESA +Iron and ESA +iron + BT) showed increase of hemoglobin level significantly long term treatment of ESAs showed that darbepoetin increased hemoglobin level slightly more iron EPO. However darbepoetin along with Iron and BT showed more of hemoglobin level than seen in the patients treated with EPO +Iron +BT. In numerous studies darbepoetin has been shown to

equally effective as EPO .My study shows that darbapoetin has slight edge. This will definitely lead to cost saving & less discomfort for the patient.

Compared to the past the pattern of ESA use today shows more use of darbepoetin now days.

CONCLUSION:

CONCLUSION

My study showed that elderly patients had more frequent need for blood transfusion. Erythropoetin & darbapoetin had equal efficacy increasing hemoglobin. However , darbaportin faired slightly better. This was more cost effective and caused less discomfort to patient . Patients with cardiovascular disease needed more blood transfusion as in their case Hb targets are higher . In chance liver disease more blood transfusion were needed as they frequently loose blood from their gut . In general compared to the past there is a pattern of more use of darbapoetin in tertiary care hospital today, irrespective of funding.

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