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A PROSPECTIVE AND OBSERVATIONAL STUDY OF USE AND FREQUENCY OF VARIOUS ERYTHROPOIETIN (EPO) CONGENERS AND ANALYSING THEIR EFFECTIVENESS IN THREE FORMS: DARBEPOETIN ALFA, EPOETIN ALPHA AND PEGYLATED ERYTHROPOIETIN ON DIALYSIS PATIENTS AT MAX SUPER SPECIALITY HOSPITAL, PATPARGANJ, DELHI

Anamika Singh[1]*, Avijit Majumdar[1], Sanjita Das[1], Satish Chhabra[2], Aditya Jayaraman[2] and Sourabh Bharadwaj[2]

[1]NIET School of Pharmacy, 19, Knowledge Park 2, Greater Noida-201306, UP

[2]Max Super Speciality Hospital Patparganj-110092, Delhi

ABSTRACT

Erythropoietin or EPO is a glycoprotein hormone that controls Erythropoiesis, or red blood cell production. Human EPO has a molecular weight of 34 kDa. Erythropoietin has been shown to exert its effects by binding to the erythropoietin receptor (EpoR). EPO is highly glycosylated (40% of total molecular weight), with half-life in blood around five hours. EPO's half-life may vary between endogenous and various recombinant versions. In this study we will consider following epo on (n=105 patients) 35 patients in each arm. This study compared effectiveness between Darbepoetin alfa, Epoetin alpha and Pegylated Erythropoietin, by calculating their hemoglobin level of the patient on dialysis. A voluntary written consent will be obtained from all eligible patients who fulfill all inclusion criteria and do not meet any exclusion criteria. An average level of Hb for group of patients was recorded as: Darbepoetin alfa (before and after 7.8 and 10.9), Epoetin alfa (before and after 8.6 and 11.7) and Pegylated erythropoietin (Before and after 8.7 and 12.7). Based on the study, and observing the detailed pattern of results produced by various Erythropoietins on various patients, it can be concluded from our study Pegylated Erythropoietin showed the maximum erythropoietin effect followed by Epoetin alpha and Darbepoetin alpha.

Keywords: Erythropoietin, Darbepoetin alpha, Epoetin alpha, Pegylated erythropoietin, Haemoglobin.

INTRODUCTION

In medicine, dialysis (from Greek dialusis,meaning *dissolution*, dia, meaning *through*, and lysis, meaning *loosening or splitting*) is a process for removing waste and excess water from the blood, and is used primarily as an artificial replacement for lost kidney function in people with renal failure. Dialysis may be used for those with an acute disturbance in kidney function (acute kidney injury, previously acute renal failure), or progressive but chronically worsening kidney function - a state known as chronic kidney disease stage 5 (previously chronic renal failure or end-stage renal disease). The latter form may develop over months or years, but in contrast to acute kidney injury is not usually reversible, and dialysis is regarded as a "holding measure" until a can be performed, or sometimes as the only supportive measure in those for whom a transplant would be inappropriate.[1] The kidneys have important roles in maintaining health. When healthy, the kidneys maintain the body's internal equilibrium of water and minerals (sodium, potassium, chloride, calcium, phosphorus, magnesium, sulphate). The acidic metabolism end-products that the body cannot get rid of via respiration are also excreted through the kidneys. The kidneys also function as a part of the endocrine system, producing erythropoietin and calcitriol. Erythropoietin is involved in the production of red blood cells and calcitriol plays a role in bone formation. Dialysis is an imperfect treatment to replace kidney function because it does not correct the compromised endocrine functions of the kidney. Dialysis treatments replace some of these functions through diffusion (waste removal) and ultra filtration (fluid removal).[2-3]

PRINCIPLE

Dialysis works on the principles of the diffusion of solutes and ultra filtration of fluid across a semi-permeable membrane. Diffusion is a property of substances in water; substances in water tend to move from an area of high concentration to an area of low concentration. Blood flows by one side of a semi-permeable membrane, and a dialysate, or special dialysis fluid, flows by the opposite side. A semi permeable membrane is a thin layer of material that contains holes of various sizes, or pores. Smaller solutes and fluid pass through the membrane, but the membrane blocks the passage of larger substances (for example, red blood cells, large proteins). This replicates the filtering process that takes place in the kidneys, when the blood enters the kidneys and the larger substances are separated from the smaller ones in the glomerulus.[4]

Type of Dialysis

- Haemodialysis
- Peritoneal dialysis
- Hemofiltration
- Hemodiafiltration
- Intestinal dialysis

The two main types of dialysis, hemodialysis and peritoneal dialysis, remove wastes and excess water from the blood in different ways.[2] Hemodialysis removes wastes and water by circulating blood outside the body through an external filter, called a dialyzer, that contains a semipermeable membrane. The blood flows in one direction and the dialysate flows in the opposite. The counter-current flow of the blood and dialysate maximizes the concentration gradient of solutes between the blood and dialysate, which helps to remove more urea and creatinine from the blood. The concentrations of solutes (for example potassium, phosphorus, and urea) are undesirably high in the blood, but low or absent in the dialysis solution, and constant replacement of the dialysate ensures that the concentration of undesired solutes is kept low on this side of the membrane. The dialysis solution has levels of minerals like potassium and calcium that are similar to their natural concentration in healthy blood. For another solute, bicarbonate, dialysis solution level is set at a slightly higher level than in normal blood, to encourage diffusion of bicarbonate into the blood, to act as a pH buffer to neutralize the metabolic acidosis that is often present in these patients. The levels of the components of dialysate are typically prescribed by nephrologists according to the needs of the individual patient. In peritoneal dialysis, wastes and water are removed from the blood inside the body using the *peritoneal membrane* of the peritoneum as a natural semi permeable membrane. Wastes and excess water move from the blood, across the peritoneal membrane, and into a special dialysis solution, called dialysate, in the abdominal cavity which has a composition similar to the fluid portion of blood.

Hemodialysis

In hemodialysis, the patient's blood is pumped through the blood compartment of a dialyzer, exposing it to a partially permeable membrane. The dialyzer is composed of thousands of tiny synthetic hollow fibers. The fiber wall acts as the semi permeable membrane. Blood flows through the fibers, dialysis solution flows around the outside of the fibers, and water and wastes move between these two solutions. The cleansed blood is then returned via the circuit back to the body. Ultra filtration occurs by increasing the hydrostatic pressure across the dialyzer membrane. This usually is done by applying a negative pressure to the dialysate compartment of the dialyzer. This pressure gradient causes water and dissolved solutes to move from blood to dialysate, and allows the removal of several litres of excess fluid during a typical 4-hour treatment.

Peritoneal Dialysis

In peritoneal dialysis, a sterile solution containing glucose (called dialysate) is run through a tube into the peritoneal cavity, the abdominal body cavity around the intestine, where the peritoneal membrane acts as a partially permeable membrane. The peritoneal membrane or peritoneum is a layer of tissue containing blood vessels that lines and surrounds the peritoneal, or abdominal, cavity and the internal abdominal organs (stomach, spleen, liver, and intestines).[12] Diffusion and osmosis drive waste products and excess fluid through the peritoneum into the dialysate until the dialysate approaches equilibrium with the body's fluids. Then the dialysate is drained, discarded, and replaced with fresh dialysate. This exchange is repeated 4-5 times per day; automatic systems can run more frequent exchange cycles overnight. Peritoneal dialysis is less efficient than hemodialysis, but because it is carried out for a longer period of time the net effect in terms of removal of waste products and of salt and water are similar to hemodialysis. Peritoneal dialysis is carried out at home by the patient, often without help. This frees patients from the routine of having to go to a dialysis clinic on a fixed schedule multiple times per week. Peritoneal dialysis can be performed with little to no specialized equipment (other than bags of fresh dialysate).

Hemofiltration

Hemofiltration is a similar treatment to hemodialysis, but it makes use of a different principle. The blood is pumped through a dialyzer or "hemofilter" as in dialysis, but no dialysate is used. A pressure gradient is applied; as a result, water moves across the very permeable membrane rapidly, "dragging" along with it many dissolved substances, including ones with large molecular weights, which are not cleared as well by hemodialysis. Salts and water lost from the blood during this process are replaced with a "substitution fluid" that is infused into the extracorporeal circuit during the treatment. Hemodiafiltration is the combining of hemodialysis and Hemofiltration in one process.

Hemodiafiltration

Hemodiafiltration is a combination of hemodialysis and Hemofiltration.

Intestinal Dialysis

In intestinal dialysis, the diet is supplemented with soluble fibres such as acacia fibre, which is digested by bacteria in the colon. This bacterial growth increases the amount of nitrogen that is eliminated in faecal waste. An alternative approach utilizes the ingestion of 1 to 1.5 liters of non-absorbable solutions of polyethylene glycol or mannitol every fourth hour.

MATERIAL AND METHODS

Erythropoietin (EPO) is a glycoprotein hormone that controls Erythropoiesis, or red blood cell production. It is a cytokine (protein signalling molecule) for erythrocyte (red blood cell) precursors in the bone marrow. Human EPO has a molecular weight of 34 k Da. Also called hematopoietin or hemopoietin, it is produced by interstitial fibroblasts in the kidney in close association with peritubular capillary and tubular epithelial tubule. It is also produced in perisinusoidal cells in the liver. While liver production predominates in the fetal and perinatal period, renal production is predominant during adulthood. In addition to Erythropoiesis, erythropoietin also has other known biological functions. For example, it plays an important role in the brain's response to neuronal injury. EPO is also involved in the wound healing process. When exogenous EPO is used as a performance-enhancing drug, it is classified as an erythropoiesis-stimulating agent (ESA). Exogenous EPO can often be detected in blood, due to slight differences from the endogenous protein, for example, in features of modification. Primary role in red blood cell production.[12] Erythropoietin is an essential hormone for red cell production. Without it, definitive erythropoiesis does not take place.

Under hypoxic conditions, the kidney will produce and secrete erythropoietin to increase the production of red blood cells by targeting CFU-E, proerythroblast and basophilic erythroblast subsets in the differentiation. Erythropoietin has its primary effect on red blood cell progenitors and precursors (which are found in the bone marrow in humans) by promoting their survival through protecting these cells from apoptosis.[13] Erythropoietin is the primary erythropoietic factor that cooperates with various other growth factors (e.g., IL-3, IL-6, glucocorticoids, and SCF) involved in the development of erythroid lineage from multipotent progenitors. The burst-forming unit-erythroid (BFU-E) cells start erythropoietin receptor expression and are sensitive to erythropoietin. Subsequent stage, the colony-forming unit-erythroid (CFU-E), expresses maximal erythropoietin receptor density and is completely dependent on erythropoietin for further differentiation. Precursors of red cells, the proerythroblasts and basophilic erythroblasts also express erythropoietin receptor and are therefore affected by it.

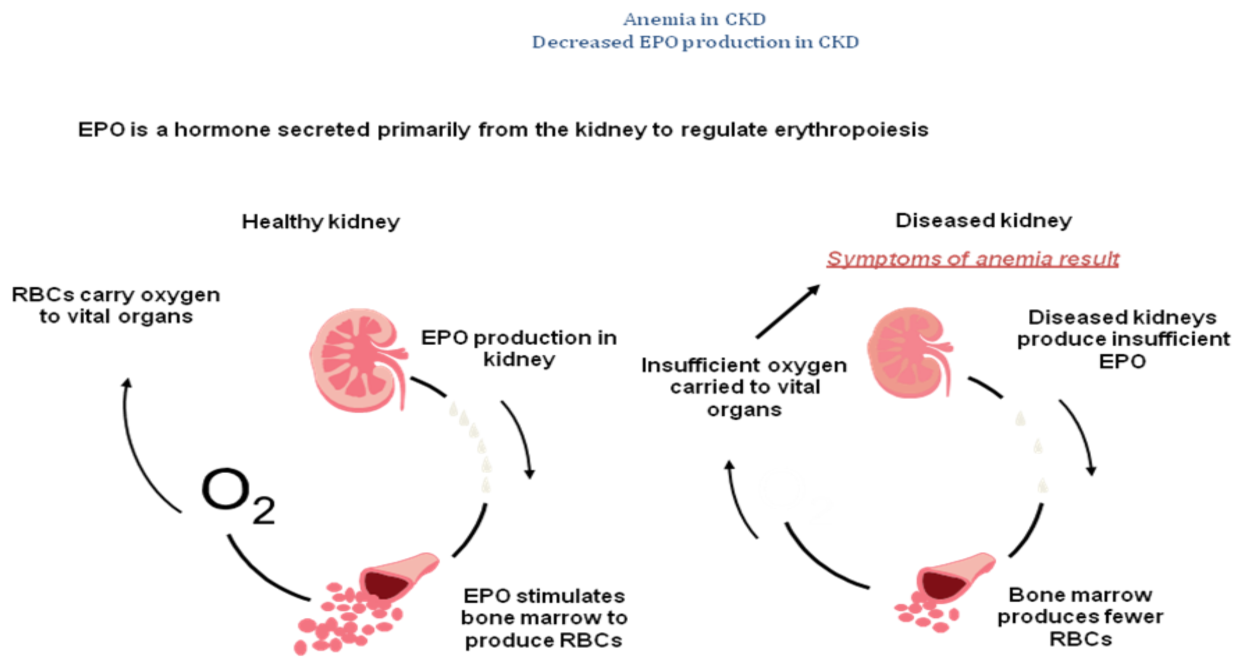

Figure1: Deceased EPO production in CKD

MECHANISM OF ACTION

Erythropoietin has been shown to exert its effects by binding to the erythropoietin receptor (EpoR). EPO is highly glycosylated (40% of total molecular weight), with half-life in blood around five hours. EPO's half-life may vary between endogenous and various recombinant versions. Additional glycosylation or other alterations of EPO via recombinant technology have led to the increase of EPO's stability in blood (thus requiring less frequent injections). EPO binds to the erythropoietin receptor on the red cell progenitor surface and activates a JAK2 signalling cascade. Erythropoietin receptor expression is found in a number of tissues, such as bone marrow and peripheral/central nervous tissue. In the bloodstream, red cells themselves do not express erythropoietin receptor, so cannot respond to EPO. However, indirect dependence of red cell longevity in the blood on plasma erythropoietin levels has been reported, a process termed neocytolysis.[14]

Method

We plan to conduct the study on 105 subjects (35 patients in each arm) who are on Dialysis or planning to get dialysis at Max Super Speciality Hospital, Patparganj, Delhi and fulfil inclusion exclusion criteria to find out the effectiveness of various erythropoietin (epo) congeners is observed by calculating their haemoglobin level before and after the dialysis at 1, 2, and 3rd Months (if possible). A voluntary written consent will be obtained from all eligible patients who fulfil all inclusion criteria and do not meet any exclusion criteria.

After informed consent process collection and documentation of relevant information from subject and his/her medical record will be taken care.

CONCLUSION

Type of Erythropoietin Used

- Darbepoetin Alpha
- Epoetin Alpha
- Pegylated Erythropoietin

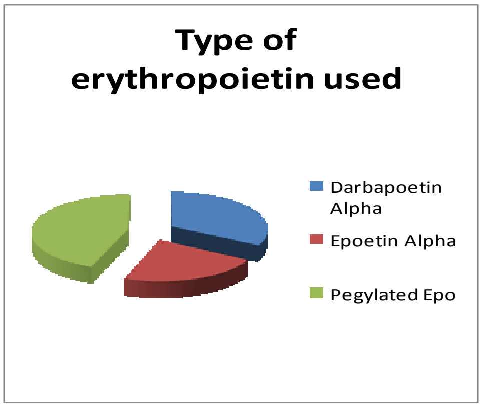

Figure 2: Type of Erythropoietin Used

Table1: Average Hb of patient before and after the treatment of EPO

Erythropoetin	Before	After
Epoietin Alpha	7.8	10.9
Derbepoietin Alpha	8.6	11.7
Pegylated Erythropietin	8.7	12.7

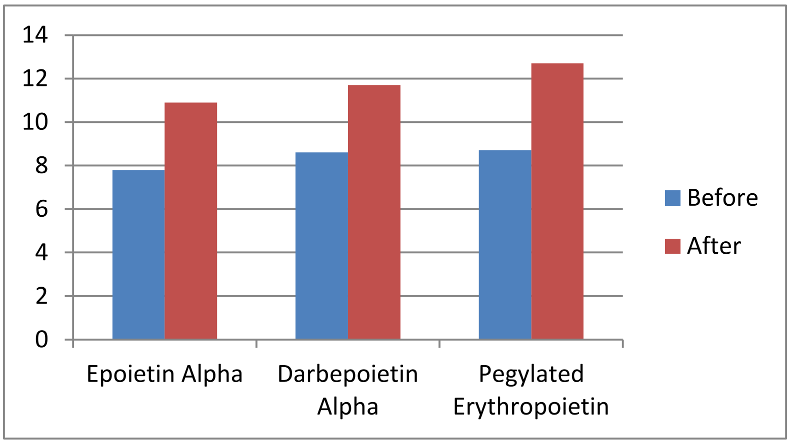

Figure 3: Average Hb of patient before and after the treatment of EPO

An average level of Hb for group of patients was recorded as: Darbepoetin alfa (before and after 7.8 and 10.9), Epoetin alfa (before and after 8.6 and 11.7) and Pegylated erythropoietin (Before and after 8.7 and 12.7). Based on the above study, and observing the detailed pattern of results produced by various Erythropoietins on various patients, it can be concluded from our study Pegylated Erythropoietin showed the maximum erythropoietic effect followed by Epoetin alpha and Darbepoetin alpha. Moreover in comparison epo derivatives that is Pegylated Erythropoietin and Darbepoetin Alpha shows more efficacy as compare to Epoetin alpha.

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Correspondence Author:
Anamika Singh
NIET School of Pharmacy, 19, Knowledge Park 2, Greater Noida-201306, UP

Email: anamika1303@gmail.com

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