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Review Article

Erythropoietin Friend or Foe in Chronic Kidney Disease Anemia: An Analysis of Randomized Controlled Trials, Observational Studies and Meta-analyses

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Abstract

Background: Anemia is a common clinical problem in patients with chronic kidney disease and is associated with increased morbidity and mortality. Erythropoietin is a hormone synthesized in kidney responsible for red blood cell maturation in the bone marrow. It is deficient in majority of patients with advanced kidney disease predisposing to anemia. Therapeutic alternatives are recombinant human erythropoietin (epoietin alfa), darbepoetin, other similar agents all now collectively known as 'erythropoiesis stimulating agents and red blood cell transfusions.

Objective: The aim of this review is to assess that whether Erythropoietin (EPO) treatment is beneficial or harmful in the management of anemia associated with CKD.

Methods: This review is based on randomized controlled trials, observational studies and meta-analyses published between 1989 and 2008 and focusing EPO use in anemia of CKD. Articles were searched in MEDLINE, PubMed, and other electronic databases as well as in online journals. Keywords "Kidney failure, chronic and "erythropoietin" for studies up to 1996, and "epoetin alfa" for subsequent years.

Results: 470 citations were identified in our search. Of these 470 citations, 26 were selected for review.

Conclusion: Randomized controlled trials suggest an association between higher hemoglobin level and improved quality of life but the association with survival is less clear. Observational studies have generally shown increased survival with higher hemoglobin level randomized trials have not shown such benefits. The overall quality of life is improved when anemia is treated with EPO, but aiming for a target value of 13.5 g/dl of hemoglobin per deciliter provided no additional quality-of-life benefit.

Key Words: Chronic kidney disease, Anemia and Erythropoietin.

Abbreviations: QoL: Quality of life, LVH: Left ventricular hypertrophy, LVD: Left ventricular dilatation, LVVI: left ventricular volume index, LVMI: left ventricular mass index, CVE: Cardiovascular events, KPS: Karnofsky Performance Scale, KDQ: Kidney Diseases Questionnaire, SIP: Sickness Impact Profile.

Introduction:

According to The National Kidney Foundation of The United States of America [1] CKD is defined as (1) evidence of kidney damage based on abnormal urinalysis results (e.g., proteinuria, hematuria) or structural abnormalities observed on ultrasound images or (2) an absolute GFR of less than 60 mL/min for 3 or more months. Based on this definition there are five stages. See Table 1.

Table 1: Stages of CKD according to National Kidney Foundation

CKD Stage	Kidney damage	GFR
Stage 1	No kidney damage	>90 mL/min
Stage 2	mild kidney damage	60-90 mL/min
Stage 3	moderate kidney damage	30-59 mL/min
Stage 4	severe kidney damage	15-29 mL/min
Stage 5	Endstage kidney damage	<15 mL/min

Anemia affects 60% to 80% of patients with chronic kidney disease (CKD) and reduces their quality of life. Treatment options are blood transfusion, epoietin alfa and darbepoetin alfa [2] . Anemia of CKD is, in most patients, normocytic and normochromic and primarily caused by depressed production of erythropoietin (EPO), oxidative stress and inflammation, erythropoiesis inhibition and reduction in red blood cell survival [3,4,5] . The other cause of anemia is deficiency of iron. The dialysis patient is in a state of continuous iron loss from gastrointestinal bleeding, blood drawing, and/or, most important with hemodialysis (HD), the dialysis treatment itself. HD patients lose an average of 2 g of iron per year. Thus, iron deficiency will develop in virtually all dialysis patients receiving EPO unless supplemental iron therapy is given orally or intravenously. DRIVE study, a randomized trial study, adds direct evidence that administration of intravenous iron to patients with functional iron deficiency who were on supplemental EPO therapy results in increase in the hemoglobin level [6]. The aim of this review is to assess that whether Erythropoietin (EPO) treatment is beneficial or harmful in the management of anemia associated

with CKD. To address these issues, we have analyzed randomized controlled trials, observational studies and meta-analyses.

Methods:

Search strategy: The search strategy was designed to capture the patient population, suffering from CKD on supplemental erythropoietin (EPO) therapy. Literature search (1989 to 2008) was carried out using MEDLINE, PubMed as well as other electronic databases and in online journals using the keywords "Kidney failure, chronic and "erythropoietin" for studies up to 1996, and "epoetin alfa" for subsequent years.

Selection of studies: All papers identified were English-language, full text papers. In addition, the reference lists of identified relevant articles were also searched. The search was not limited to any specific study design, and we searched for randomized controlled trials (RCTs), observational studies, systemic review and meta-analysis. Citations identified in the literature search were independently screened by author to select potentially relevant articles. The full articles from this list were retrieved and subsequently reviewed by author for inclusion in the systematic review. During selection preference was given to articles published within last five years. Articles were included if they met the following inclusion criteria 1) published in a peer reviewed journal; 2) written in English; 3) reported randomized controlled trials of EPO; 4) observational studies regarding EPO and quality of life; 5) Review articles and meta-analyses about EPO therapy in CKD patients.

Results:

470 citations were identified in search from PubMed, Medline and from other online journals. Of these 470 citations, 444 did not meet the selection criteria and were excluded, leaving 26. Out of 26 citations 11 were RCTs, 10 were observational studies and 5 were reviews and meta-analysis.

Five studies (Parfrey et al[7], Foley et al[8], Furuland et al[9], Drüeke et al[10], and Canadian Erythropoietin Study Group[11]) showed that correction of anemia result in improvement of quality of life, although the singh et al[12] showed such improvement with partial correction of anemia, and no detectable difference in the quality of life was evident in Roger et al[13] study. Five studies Parfrey et al[7], Foley et al[8] and Levin et al[14] and McMahon et al[15] and Roger et al[13] showed that normalization of hemoglobin does not lead to regression of established concentric LV hypertrophy or LV dilation. It may, however, prevent the development of LV dilation. In McMahon et al[15] study the only factor that seemed to predict normalization of LV mass in patients who had LV hypertrophy at study entry was a lower pulse pressure. One study Sikole et al[16] correction of renal anemia can normalize heart morphology and improve heart function. Three studies Besarab et al[17], Drüeke et al[10] and Singh et al[12] demonstrated increased cardiovascular events whereas two studies Drüeke et al[10] and Singh et al[12] also showed progression to dialysis in patients assigned to the highest hemoglobin targets (>13.0 g/dL), compared with <12 g/dL, trial design of three studies was same in respect that both arms were on EPO. In comparison to Drüeke et al[10] and Singh et al[12] studies, in Roger et al[13] study the renal function was not adversely affected in the group randomized to the higher Hb. (Table 2).

Both Phrommintikul et al[18] and Giovanni et al[19] addressed the similar issues, to evaluate the benefits and harms of different hemoglobin (Hb) targets in CKD in their meta-analyses. They reached to similar conclusion, increase in the risk of all-cause mortality in anemic patients with CKD in whom a higher Hb target (in the normal physiological range) is aimed for with treatment with EPO. Such patients are also at an increased risk of arteriovenous access thrombosis and poorly controlled hypertension, which could contribute to the increased risk of mortality.

Table 2: Randomized controlled trials (RCTs)

Study	Study design	Patients enrolled	Parameters observed	Outcomes
Parfrey et al[7]	RCT double blind	596	QoL, LVVI	No change LVVI. QoL improved.
Foley et al[8]	RCT open label	146	QoL, LVH, LVD	QoL improved, No change LVMI
Furuland et al[9]	RCT open label	416	QoL, Safety.	QoL improved.
Drüeke et al[10]	RCT open label	603	CVE, QoL, LVMI, Renal function	QoL improved, No change LVMI.
Canadian Erythropoietin Study Group[11]	RCT double blind	118	QoL .	QoL improved.
Singh et al[12]		1432	CVE, QoL, Renal function	QoL not improved.
Roger et al et al[13]	RCT open label	155	LVMI. Renal function, QoL	No change.
Levin et al[14]	RCT open label	172	LVMI.	No change.
McMahon et al[15]	RCT open label	120	Change in LVMI.	Prevention&↓ in LVMI.
Sikole et al[16]	RCT open label	38	Heart morphology & functions.	Heart function Improved.
Besarab et al[17]	RCT open label	1233	Effects of normal HCT.	↑CVE

Table: 3 Meta-analysis

Meta-analysis	Question Addressed	No of studies included.	Assessed quality of life (QoL).	What measures of quality of life used in these trials.	Were the major gains in QoL seen with EPO.
Phrommintikul et.al[18]	Target Hb and cardiovascular events in CKD.	9	No	_____	_____
Giovanni et al[19]	Evaluate the benefits and harms of different Hb targets in CKD.	19	Yes	KDQ	QoL Improved ↑KDQ
Jones et al[20]	Effects of EPO on clinical efficacy, QoL hospitalizations, and transfusions.	16	Yes	KPS KDQ SIP	QoL improved ↑KDQ ↑ KPS ↓SIP

Furthermore, there seems to be no beneficial effect on left ventricular mass in such patients. There were similarities and differences in inclusion criteria. Both used the trials targeting different Hb concentrations in patients with anemia caused by CKD, majority of trials analyzed were different except 4 trials which were same in both. The difference in inclusion criteria was that Giovanni et. al analyzed two groups of studies: The first group contained studies in which the intervention was to achieve different Hb targets compared (higher *versus* lower Hb targets), both arms were on EPO and trials included individuals with clinical cardiovascular disease. The second group compared EPO treatment with no EPO treatment. The results of these two groups of studies were analyzed separately. In Phrommintikul only one group of studies "EPO treatment with no EPO treatment" was analyzed. Meta-analysis by Phrommintikul et al includes nine RCTs, which enrolled 5143 patients.

In Jones et al[20] meta-analysis both randomized controlled trials and uncontrolled trial were analyzed, all studies were of the "pre/post" design, in that measurements of anemia, quality of life, hospitalizations, and transfusions were taken before and after initiation of EPO therapy. They drew these conclusions from 16 published studies of which 5 were randomized clinical trials. He found that treatment with EPO raised hemoglobin levels, reduced transfusion requirements and improved quality of life. For quality of life outcome in these meta-analysis please review Table 3.

Discussion:

Erythropoietin (EPO) has become an essential part of the management of anemic patients with CKD. It is also used to treat the anemia associated with chemotherapy and other diseases, and it improves quality of life [21,22] . The introduction of EPO in 1989 significantly improved the clinical management of anemia of CKD. By 2005, 99% of incenter hemodialysis patients received EPO treatment for their anemia. EPO dosing has changed dramatically in the past decade and a half; between 1991 and 2005, the mean dose of EPO increased about 4-fold in dialysis patients. Today, EPO therapy is the largest single Medicare drug expenditure totaling $1.8 billion in 2004 (an increase of 17% from 2003) and EPO comprised 11% of all Medicare ESRD costs [23]

EPO and left ventricular hypertrophy. *Randomized vs. Observational studies*. Anemia is a contributing factor in many of the symptoms associated with reduced kidney function. These include fatigue, depression, reduced exercise tolerance, dyspnea. Data from observational studies shows that severe anemia may results in cardiovascular consequences, such as left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction [24]. Left ventricular hypertrophy (LVH) is present in nearly 80% of dialysis patients and is associated with higher rates of cardiovascular events [25.] It is also associated with an increased risk of morbidity and mortality principally due to cardiac disease and stroke [26,27]. As a result, patients with anemia due to CKD are at increased risk of hospitalization, hospital length of stay, reduced quality of life and mortality [28.] Uncontrolled studies suggested that partial correction of anemia with EPO therapy may result in prevention or regression of CHF [29] and LVH [30,31]. Several randomized controlled trials showed that left ventricular hypertrophy was not further improved by a complete correction of anemia compared to only partial correction [7,13,14,15,17.] Robert N Foley et al. randomly assigned 146 patients with either concentric LV hypertrophy or LV dilation to receive EPO to achieve hemoglobin levels of 10 or 13.5 g/dL. He concluded that normalization of hemoglobin does not lead to regression of established concentric LV hypertrophy or LV dilation. It may, however, prevent the development of LV dilation, and it leads to improved quality of life [8.] Partial correction of severe anemia <8 or 9g/dl to mild anemia (10-11 g/dL) likely reduces mortality, but further treatment to higher Hb levels has not been shown to further reduce mortality, and has actually increased mortality. Controlled studies with quality of life (QOL) and left ventricular mass as end points support partial correction of hemoglobin in dialysis patients [11,13,16,32,] The fact that anemic renal failure patients have more LVH than non-anemic renal failure patients does not prove that anemia causes LVH. Vaziri et al in a review mentioned that the real culprits are oxidative stress, inflammation and diminished biological capacity that simultaneously cause treatment-resistant anemia and adverse cardiovascular and other outcomes [33.]

EPO and quality of life: Numerous randomized, controlled trials have demonstrated that EPO significantly raises hemoglobin levels, reduces transfusion requirements, and improves quality of life in anemic patients with chronic renal failure. Lefebvre et al conducted an analysis on data from a multicenter, open-label, prospective study of EPO for anemia in patients with CKD not on dialysis to evaluate the relationship between Hb level and quality of life (QOL). The results showed that the maximal incremental gain in QOL occurred when Hb reached 11 to 12 g/dL. This suggests that treating anemic patients with non-dialysis CKD until their Hb level reaches 12 g/dL will result in the greatest QOL improvement per Hb unit increase [34.]

Randomized vs. Observational studies. Many randomized controlled trials suggest an association between higher hemoglobin level and improved quality of life, physical function, and exercise capacity [7,8,9,35] but the association with survival is less clear. Whereas observational studies have

generally shown increased survival with higher hemoglobin level [36,37,38,39,40] randomized trials have not shown such benefits. The extent anemia of inflammation varies between patients with renal failure. It is this factor that likely explains the following paradox: in observational studies, higher hemoglobin associates with better survival in CKD, while in controlled trials, higher hemoglobin achieved by escalated EPO dosing decreases survival. In the observational studies, those with the higher Hb levels were likely those patients who had the least component of anemia of inflammation, and therefore less resistant to EPO supplementation; they survived better not because they had better hemoglobin, but because they had less burden of inflammatory disease. Anemia of chronic disease is a highly conserved response that is mediated by multiple mechanisms acting in concert to lower the hemoglobin in the face of inflammation, and should be presumed until proven otherwise to be adaptive for most patients who exhibit it. That this is so is supported by the observation that the correction of anemia confers lower survival not only in renal failure, but also in cancer patients and in patients in the critical care unit.

Jones et al. in their very thorough meta-analysis [20] indeed found that treatment with EPO raised hemoglobin levels, reduced transfusion requirements and improved quality of life. Studies have demonstrated that morbidity and mortality rates are lower when hematocrit values are within the Disease Outcomes Quality Initiative (DOQI) target range (33 to 36%) [40]. Ernesto Paoletti et al in their review of observational and randomized studies concluded from the results of observational studies that normalization of Hb in renal patients seems to be associated with further improvement in quality of life and physical activity but with no significant differences in mortality rate, hospitalization rate, and the extent of LVH regression, but the results of randomized trials show that achieving near-normal Hb did not reduce the risk for death from all causes or the risk for cardiac death. The latter risk actually increased slightly, in the group of dialysis patients with normalized Hb concentration [41]. For CKD stage 3 and 4 patients, no improvement seen in CHOIR, but improvements reported in CREATE. There may be reporting bias in CREATE as it was an open label study, and the low target arm had to develop worsening anemia prior to initiating EPO therapy [10,12]

EPO and Cardiovascular Events: Anemia is a common complication of chronic kidney disease. Determination of the appropriate target hematocrit level for patients undergoing hemodialysis continues to be a controversial area [40]. The National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) states when a decision to use EPO is made, some Hgb value in the range of 11 to 12, but no higher than 13 should generally be chosen. [42]. The European Best Practice Guidelines (EBPGs) recommend that most patients with CKD achieve a target hemoglobin (Hb) 11 g/dl to reduce the risk of adverse outcomes [43.]

Randomized vs. Observational studies. Observational studies have shown a strong association between severity of anemia and risk of morbidity and mortality from cardiovascular disease and other causes in CKD patients [36,37,38,39,40]. These findings have been interpreted as evidence for the causal role of anemia in the pathogenesis of adverse outcomes in these patients. On the hand, randomized clinical trials of anemia management revealed either no effect or increased morbidity and mortality in patients assigned to normal hemoglobin Hb targets [10,12,17]. Meta- analyses of randomized clinical trials have shown a significant increase in cardiovascular and all-cause mortality and arteriovenous access thrombosis among patients assigned to the higher than those randomized to the lower Hb targets [18,19]. Meta-analysis of Phrommintikul shows a significantly higher risk of all-cause mortality (targeting a Hb level higher than 12 g/dL results in a 17% increased risk of death compared with target hemoglobin levels less than 12 g/dL), arteriovenous access thrombosis and higher risk of poorly controlled blood pressure in the higher Hb target

group than in the lower target Hb. The incidence of myocardial infarction was much the same in the two groups [18]. Meta-analysis of Giovanni F.M et al shows that on the basis of available randomized, controlled trials, Hb targets of <12.0 g/dL are associated with a lower risk of death in the population with cardiovascular disease and CKD compared with Hb targets of >13.0 g/dL. For every 30 patients treated to an Hb target of <12.0 g/dL compared with an Hb target of >13.0 g/dL, approximately one death is avoided [19]. Two large randomized controlled trials; CREATE [38] and CHOIR [39] demonstrated increased cardiovascular events and progression to dialysis in patients assigned to the highest hemoglobin targets (>13.0 g/dL), compared with <12 g/dL. US Food and Drug Administration (FDA) warned that use of erythropoiesis-stimulating agents (ESAs) increases mortality and morbidity risk. The warning follows publication of studies suggesting that correction of anemia in patients with CKD did not reduce the risk of cardiovascular events and that reaching a target Hb level of >13 g/dL, compared with a target level of 11.3 g/dL, was associated with increased risk of cardiovascular events. FDA said recent studies had found increased risk of death, blood clots, strokes, and myocardial infarctions in patients with chronic renal disease who received ESAs at higher-than-recommended doses that maintained their hemoglobin levels at more than 12 g/dL [44].

EPO and kidney: EPO has been found to interact with its receptor in a large variety of non-haematopoietic tissues, which result into cytoprotective cellular responses, like mitogenesis, angiogenesis, inhibition of apoptosis and promotion of vascular repair through mobilization of endothelial progenitor cells from the bone marrow. In experimental ischaemic and toxic acute renal failure administration of EPO, promotes renoprotection. Preliminary experimental and clinical evidence also indicates that EPO may be renoprotective in chronic kidney disease[22] .EPO is used widely to treat anemia in patients with CKD, but the benefits of EPO use in patients with acute renal failure (ARF) are unclear. In vitro and animal studies suggest that EPO may promote renal recovery and decrease mortality in ARF [45]. Partial amelioration of anemia with low doses of EPO was reported to slow the rate of progression to ESRD in a group of CKD patients [46]. These cellular protection from EPO observed in animal models has not been confirmed in humans, and has been specifically addressed and disproven in large randomized trial. The CREATE study found as a secondary endpoint that early treatment with EPO increased the likelihood of starting dialysis. CHOIR found no reduction in the rate of progression of CKD in patients given more EPO (the higher target arm) compared to the lower target arm [10,12].

EPO for other Indications: In recent years, studies in animals and humans have focused on the use of EPO for other indications. It has been found to play a role in both cardioprotection and neuroprotection. It has effects on the immune system, and can cause regression in hematologic diseases such as multiple myeloma. It may also improve the response of solid tumors to chemotherapy and radiation therapy [21]. Again the cellular protection from EPO observed in animal models has not been confirmed in humans.

EPO and Seizures: Seizures are reported to be a complication of EPO in the product information. However, in a meta-analysis conducted by Giovanni et al showed that treating with EPO may be protective against seizures Lower Hb targets of <95 g/L in individuals who are not treated with EPO are associated with a significantly increased risk of seizures compared with treatment with EPO and Hb values of >100 g/L [19].

EPO and Hypertension: Administration of ESA may be associated with exacerbation of hypertension in about 5% of patients. Robert N. Foley et al in his analysis of observational and randomized studies found that most of the trials that have been reported to date have shown that higher hemoglobin targets lead to higher BP levels and/or greater requirements for antihypertensive therapy, he drew this conclusion from nine randomized trials [47]. The

mechanism of ESA induced hypertension is thought to be related to stimulation of the vascular endothelium by ESA resulting in increased circulating levels of endothelin. Furthermore the increase in hemoglobin associated with ESA therapy may increase blood viscosity resulting in vasospasm. As such routine monitoring of blood pressure is essential in patients treated with ESA [48]. Meta-analysis of Phrommintikul et al showed a significantly higher risk of poorly controlled blood pressure in the higher haemoglobin target group than in the lower target hemoglobin [18] . Giovanni et al meta-analysis showed lower Hb levels of <95 g/L with no EPO treatment are associated with a reduced risk of patients who present with hypertensive episodes. In absolute terms, the risk of developing hypertensive episodes is 16% lower with Hb values <95 g/L compared with Hb >100 g/L. For every seven patients treated to obtain an Hb >100 g/L, one patient will require additional antihypertensive medication [19]

EPO and Access: Normalizing hemoglobin has been associated with a higher incidence of vascular access clotting [40.] Randomized, prospective, open-label trial study of Besarab et al, showed a significantly higher risk of access thrombosis with the higher Hb targe[17]. Meta-analysis of Phrommintikul et al showed a significantly higher arteriovenous access thrombosis in the higher Hb target group than in the lower target Hb [18.]

EPO and Pure Red Cell Aplasia (PRCA): Although rare, administration of ESA may result in formation of anti-erythropoietin antibodies, thereby leading to pure red cell aplasia and erythropoietin resistance [49] In patients in whom ESA doses have been maximized without effect and no other causes can be identified, serum anti-erythropoietin levels and bone marrow biopsy should be performed. If confirmed, erythropoietin administration should be ceased and the patient treated with periodic blood transfusions.

Conclusion: Achieving hemoglobin control over time is a major challenge because of the various physiological factors that influence the response in individual patients and the potential risk for increased mortality, particularly for patients with co morbidities [50]. The association data led to several hypotheses about what anemia was causing e.g. LVH, fatigue, and increased mortality. These hypotheses have been tested in RCT's and in most cases anemia is associated with but does not cause the outcome, such as LVH or mortality. Fatigue is improved somewhat by anemia treatment with EPO, and transfusion frequency is reduced, though the cost is high. In the case of EPO balance is critical. Too little treatment and patients with chronic kidney disease are subjected to a lifetime of exhaustion and blood transfusions. Too much and they could be threatened with an increased risk of death. The overall quality of life is improved when anemia is treated with EPO, but aiming for a target value of 13.5 g of hemoglobin per deciliter provided no additional quality-of-life benefit [12].

Key Points:

- Anemia is associated with bad outcomes; Anemia is nearly universal in advanced renal disease. In these patients, anemia is associated with increased cardiovascular morbidity and mortality, reduced quality of life, and accelerated renal disease progression, though those associations do not necessarily establish causation.
- Treatment of anemia reduces transfusion requirements and improves quality of life in anemic patients with CKD.
- Mortality increases with treatment to higher targets; Recent studies have found an increased risk of death, blood clots, strokes, and myocardial infarctions in patients with chronic renal disease who received ESAs at doses that maintained their hemoglobin levels at more than 12g/dL, leading the Food and Drug Administration to apply a 'black box' warning to the product monographs of licensed ESAs.
- Recent studies support partial correction, not normalization of hemoglobin.
- Current guidelines recommend target of 10-12g/dL.

COMPETING INTERESTS
None Declared

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