Arab Journal of Nephrology and Transplantation. 2014 Jan;7(1):13-19

AJNT

Review

Management of Anemia and other Hematologic Derangements in Patients with Chronic Kidney Disease

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Abstract

Introduction: Chronic Kidney Disease (CKD) has adverse consequences on almost all body systems. The kidney does not function merely as an excretory organ, but participates in normal erythropoiesis, normal bone mineral deposition and blood pressure regulation.

Review: Anemia is prevalent in CKD with known deleterious effects on the car diovascular system. It is mostly due to erythropoietin deficiency, inhibition of erythropoiesis by uremic solutes, and reduction in red blood cell life span. Other possible causes include iron, B12 or folic acid deficiency or blood loss. Dysfunction of the endogenous erythropoietin is usually clinically evident once the glomerular filtration rate (GFR) falls below 20-25 ml/min. Treating anemia of CKD is based on correction of iron deficiency and replacement of decreased erythropoietin production by erythropoietin stimulating agents (ESA). Guidelines recommend targeting hemoglobin levels of no more than 10-12 g/dl since there is evidence of increased mortality and morbidity in patients with higher levels. Increased level of pro-coagulant biomarkers cause enhanced thrombotic activity in CKD patients which promotes ischemic cardiac events while platelet dysfunction leads to bleeding diathesis. If anticoagulation is indicated, low molecular weight heparins (LMWHs) offer certain advantage sbut the dosage needs to be adjusted with increasing grade of renal insufficiency. Antiplatelet agents are effective in averting shunt and catheter thrombosis, but not for avoiding the thrombosis of arteriovenous grafts.

Conclusion: Health related quality of life in CKD patients can be improved by treating anemia. Newly available ESAs and the entry into the market of epoetinbiosimilars are expected to lead to improvements in the management of CKD and its complications.

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Key words: Anemia; CKD; Renal insufficiency;Venous thromboembolism.

The authors declared no conflict of interest

Introduction

Chronic kidney disease (CKD) is known to affect a large proportion of the population worldwide. It can progress to end stage renal disease (ESRD) and lead to serious consequences such as cardiovascular complications and hematological manifestations. These include, but are not limited to, anemia and coagulation dysfunctions [1]. Compromises in kidney function will evidently result in misbalanced homeostasis in the human body. The kidney itself does not function merely as an excretory organ, but has diverse functions in the body such as its participation in normal erythropoiesis, normal bone mineral deposition and blood pressure regulation. Therefore, any suppression of the normal kidney function may dire ctly be translated to other physiological processes, thus resulting inimpairment of multiple organs.

Anemia

Anemia is commonly seen in CKD patients, with a reported prevalence of 47.7% among pre-dialysis patients [2]. Periodic evaluation and monitoring of hemoglobin (Hb) is required for timely interventions. In the early stages of CKD, an annual follow up would be adequate. Patients with moderate or severe CKD need more frequent monitoring due to the increased risk of anemia among these groups. Once patients are maintained on erythropoiesis stimulants, monthly evaluation of Hb becomes essential [3]. Anemia in CKD is mostly due to erythropoietin (EPO) deficiency, inhibition of erythropoiesis by uremic solutes,and reduction in red blood cell life span [4]. Other causes include iron, B12 or folic acid deficiencyor blood loss [5]. It is usually a normochromic normocytic type of anemia.

In normal subjects, plasma EPO levels range from 0.01 to 0.03 Units/ml, these tend to increase to 100 to 1000 folds during hypoxia and anemia. In patients with CKD, production of EPO is impaired, this EPO deficiency is the primary cause of the anemia of CKD [6]. Dysfunction of the endogenous EPO is usually clinically evident once the GFR falls below 20-25 ml/min. Using WHO definitions of anemia, 87% of patients with GFR below 25 ml/min but not yet on dialysis have anemia [5].

Patients with CKD can be iron deficient due to various causes such as occult blood loss from the gastrointestinal tract (GIT) due to platelet abnormalities, frequent phlebotomies and punctures for dialysis. Accordingly, evaluation of serum iron stores, red blood cell count, reticulocyte count, blood smears, assessments for hemolytic anemia and existence of GI bleeding sites should be part of the preliminary work-up of anemia in these patients. Further GI assessments become necessary only when the iron stores remain depleted or there is rapid decline in hemoglobin levels despite adequate replacements with effective iron supplements [7].

Protein energy malnutrition and inflammation are prevalent in dialysis patients. The two conditions are associated with at her osclerosis in a syndrome collectively known as malnutrition- inflammation- atherosclerosis syndrome (MIA syndrome) [8]. Inflammation is aprimary reason for the decreased EPO formation, as it harms the development of erythroblasts and potentiates death of the immature erythroblast. Hepatic production of hepcidin is also induced by this inflammatory process which hinders iron absorption from the GI tract [9]. Hepcidin is expected to be elevated in obese patients; however no excess risk of anemia had been found in the obese. In fact, higher EPO levels had been observed in conjugation with high body mass index (BMI) levels [10]. The reduced oxygen carrying capacity of blood leads to increased blood volume, increased cardiac output and left ventricular hypertrophy (LVH). Even in the early stages of CKD, LVH tends to be more prevalent compared to the general population [11]. In a study by Levin, 45% of patients with CKD and a creatinine clearance of less than 25ml/min were found to have LVH and that prevalence tended to reach 75% by the initiation of the dialysis [12]. Modifiable risk factors for the prevention of LVH such asanemia and high systolic blood pressure tend to worsen with progressive decline in kidney functionand the resulting heart failure can be devastating [13-15]. Anemia is a well-known cause of increased mortality among dialysis and pre-dialysis CKD patients [16]. Likewise, in patients with pre-existing cardiovascular disease (CVD), CKD and the resulting anemia act as additive factors.

Following kidney transplantation, properly functioning kidney grafts are expected to sustain adequate levels of erythropoietin. However, in under-functioning grafts, decreased EPO production can lead to post-transplant anemia, hypoxia and even damage to the allograft itself [17]. Post-transplant pancytopenia, due to uremia and/or hyperparathyroidism with bone marrow fibrosis, had been reported as direct or indirect consequence of chronic allograft dysfunction [18].

The diagnosis of "anemia of CKD" is usually made after excluding other causes of anemia by performing complete evaluation of blood count, reticulocyte count, serum iron, serum ferritin, transferrin saturation (TSAT) and serum vitamin B12. Management of anemia in the early stages of CKD can attenuate further deterioration and reduce the incidence of complications, which may range from cardiovascular diseases to evendeath [19]. Treating anemia of CKD is based on correction of iron deficiency and replacement of decreased EPO production by erythropoietin stimulating agents (ESA).

In pre-dialysis CKD patients, iron deficiency is treated at TSAT<20% and serum ferritin concentration <100ng/ml whereas in patients requiring dialysis, target ferritin levels are >200ng/ml as iron stores are rapidly depleted due to increased consumption during enhanced erythropoiesis [20]. Oral or intravenous (IV) iron administration has been shown to reduce the severity of anemia in CKD patients [21]. Iron supplementation is appropriate in patients whose bone marrow stores are depleted, but who otherwise have an adequate erythropoietic response. However, it is essential to weigh the benefits of iron supplementation against its risks before starting treatment [22]. The route of administration should be decided after taking in account the severity of iron deficiency, availability of venous access, response to previous therapies along with patient compliance and associated costs [23]. Patients given oral iron supplements may not respond adequately due to several factors. These include reduced iron absorption or increased utilization in comparison to the absorptive capacity of iron by oral route [24]. Iron given through the IV route aids in increased efficacy and early replenishment of depleted iron stores [25]. Therefore, in pre-dialysis CKD patients iron therapy through IV route is generally preferred over oral route.

The 2012 guidelines on the management of anemia of CKD by "Kidney disease: Improving global outcomes (KDIGO2012)", recommend conduction of a trial of IV or oraliron if an increase in Hb concentration or a decrease in ESA dose (for those receiving ESA) is desired [23]. The patient should be monitored for 60 minutes

after initiation of infusion of IV iron dextran for signs of anaphylactic reactions [26]. IV administration should be avoided in those with active systemic infections, as iron is a nutrient needed by many pathogens and administration of iron has been shown to lead to impaired control of infections [27]. Excessive administration of IV iron therapy has also been associated with a number of adverse effects. Catalytically active iron had been shown to lead to inflammatory conditions, immune disorders and further progression of renal disease [28].

In 1989, FDA approved recombinant human EPO (epoetinalfa), which along with similar agents now collectively known as erythropoietin stimulating agents (ESA), are being used for the treatment in EPO deficient anemia of CKD [20]. ESAs have revolutionized the treatment of anemia in CKD, improved patients' quality of life, and reduced hospitalization and mortality rates. They significantly diminish transfusion requirements, improve health status and regress cardiovascular complications such as LVH [22]. Epoetinalfa and beta are the two available forms of recombinant DNA-derived erythropoietin (rEPO), which are produced using ovarian cells of Chinese hamster [23]. Although epoetin alpha can easily be self-administered at home, official guidelines recommend supervised intravenous administration at least three times a week for patients on HD. Another formulation, darbepoetin alpha, having longer half-life, is administered once weekly in dialysis patients and usually only once in four weeks in pre-dialysis patients [25]. Initiation of ESA therapy should be guided by close monitoring of Hb levels, ranging from weekly to monthly evaluations. During treatments with the ESA, anti-erythropoietin antibodies can develop leading to neutralization of erythropoietin and pure red-cell aplasia. Once suspected immediate screening for anti-eythropoietin antibodies is advised. Detection of antibodies should be followed by instant discontinuation of the drug. A decrease in the antibody titer is usually observed after halting epoetin administration; immunosuppressive drugs can also be used to speed vanishing of these antibodies. Replacing the drug with other EPO formulations is not advised as cross reaction is expected among the different commercially available recombinant EPO products.

Regardless of the prevalent usage of rEPO, several cases of rEPO resistance or hypo-responsiveness have also been reported [4]. It should be noted that iron deficiency is the most common cause of rEPO hypo-responsiveness and ESA administration would not be sufficient without adequate iron stores being available [26]. However, other causes such as neoplasms, infections, aluminium toxicity and raised parathyroid hormone (PTH) levels should be evaluated to rule out probable causes for a deficient response to ESAs [27]. Continuous erythropoietin Receptor activator (CERA) is a newly developed drug which is under surveillance for its effect in CKD patients with anemia [29]. In pre-dialysis CKD patients CERA once every four week has been proven to maintain stable Hb levels and within required range [30].

Controversy lies in the preferred mode of epoetin administration. Previous studies have reported a more significant increase in Hb concentration on subcutaneous administration [28,31]. As such, subcutaneous administration may represent a more economically feasible option, especially for low-income countries [32]. However, IV route is often preferred for the administration of all ESA forms due to the reported adverse outcome of pure red cell aplasia through subcutaneous route. For peritoneal dialysis patients, subcutaneous or intraperitoneal routes are preferred practical options [33].

Excessive usage of ESAs can be prevented by targeting Hb levels of no more than 10-12 g/dl and treating specific causes of anemia in each patient [22]. Evidence based medicine have suggested increased incidences of mortality and morbidity in patients with higher Hb levels, compared to recommended targets. On the other hand, levels of less than the recommended target hemoglobin are often associated with symptoms. In a double-blind randomized controlled trial (RCT) conducted by the Canadian Erythropoietin Study Group on patients with hemoglobin concentrations less than 9 g/dl, significant differences were observed in the occurrence of physical symptoms (such as fatigue) between placebo group and erythropoietin group [34]. However, no differences in these symptoms were observed between low target Hb (9.5–11 g/dl) and high target Hb (>11 g/d) groups [34].

The superiority of full anemia correction has also been scrutinized in view of the occurrence of adverse events. The Normal Hematocrit Trial, conducted on patients having clinical evidence of congestive heart failure who were undergoing hemodialysis (HD), found that higher hematocrit targets were associated with higher mortality rates [35]. The Canada-Europe trial, conducted on HD patients without symptomatic heart disease, found similar results, with the rates of skeletal pain, surgery, and dizziness being higher in the lower target group, and headache and cerebrovascular events being more frequent in the higher target group [36]. The Cardiovascular Reduction Early Anemia Treatment Epoetinbeta (CREATE) study was an open-label trial that aimed to compare the cardiovascular outcomes of initiation of ESA at an earlier stage than end stage renal disease

(ESRD), between groups having target Hb of 13-15 g/dl and 10.5-11.5 g/dl [37]. There was no significant difference in the combined incidence of adverse events between the two groups, although hypertensive episodes and headaches were more prevalent in the higher target Hb group [37]. In contrast, the Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOIR) study reported a higher incidence of adverse events in higher target Hb group without significant improvements in quality of life [38]. Similar results were produced by the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial, whereby the use of darbepoetinalfa in patients having diabetes, CKD, and moderate anemia did not reduce the risk of death or cardiovascular/renal events, although an increased risk of stroke was observed [39]. The above mentioned trials therefore implicate that full anemia correction may not be advisable in patients having pre-existing cardiovascular or metabolic conditions.

The post-hoc analysis of the TREAT trial revealed a higher mortality rate in patients with a history of malignancy on darbepoetin compared to placebo [39]. Therefore, extreme caution must be exercised in the administration of ESA to patients having an active malignancy [40]. Likewise, administration of ESA in patients with pre-existing hypertension may lead to its aggravation in 5% of the patients due to the stimulation and release of endothelin by the vascular endothelium or due to vasospasm occurring as a result of increased blood viscosity caused by increased Hb levels [41]. Hence, any such event warrants dose adjustment or switching to another agent.

Hemostasis

C-reactive protein, factor VIIc, fibrinogen, interleukin-6, factor VIIIc, D- dimer and plasmin-antiplasmin complex are all increased in patients with CKD [31]. Fibrinogen levels are increased in CKD patients whereas antithrombin-III levels are reduced, coagulation is marked but the fibrinolysis is not enhanced in proportion comparable to the level of elevated coagulation, which leads to increased cardiovascular complications [32]. This has led to the notion that patients with CKD most probably die due to cardiovascular diseases arising out of thrombotic complications [26]. In one study, the prevalence of clinical and subclinical cardiovascular diseases was reported in 64% of patients with elevated serum creatinine [42]. Venous thromboembolism has also been associated with the elevated levels of these factors [43]. In addition, TNFα is increased in inflammatory processes and it has an inverse relation with the GFR. In contrast, TNFα is directly related with the vWF antigen levels. Thus as the GFR increases, both TNFα and vWF increase [44]. In comparison to people with normal kidney function, the relative risk for venous thromboembolism in patients with mild decrease in renal function is 1.28, compared to 2.09 in those with CKD stage 3-4 [45].

In contrast to the higher incidences of prothrombotic events, platelet dysfunction and abnormal interaction between the platelets and the vessel wall also lead to bleeding diathesis in patients with CKD [46]. Platelets dysfunction is responsible for the bleeding tendencies in advanced CKD, which results in hemorrhages at different sites over the body. Intracranial and GI bleeds are quite prevalent in these patients. The use of anticoagulants and their retention in dialysis patients is a probable cause of bleeding complications [7,47]. A defect in glycoprotein GPIb, which serves as a receptor for vWF, is also found in these patients and an inverse relation is observed between serum creatinine levels and the expression of glycoprotein GPIb [34]. Additionally, patients with CKD exhibit decreased platelet activity, in vitro, in response to ADP, tartrate resistant acid phosphatase (TRAP) and C-reactive protein (CRP) as compared to healthy individuals [48]. In dialysis patients, the levels of protein Z (PZ), a vitamin K dependent serine protease inhibitor, and its effect on blocking factor Xa activity remains controversial [35].

Regarding the treatment of thromboembolic disorders in patients with CKD, anticoagulant therapy is inevitably required [36]. The most approved and favored anticoagulant for use in most of the patients with renal insufficiency include unfractioned heparin (UFH). Newer anticoagulants with FDA approval for venous thromboembolism (VTE) prophylaxis and treatment are low molecular weight heparins (LMWHs) and factor Xa inhibitors (e.g., fondaparinux). LMWHs offer the advantage of manageable administration and less need for continuous monitoring [37]. Some of the LMWHs are also indicated in acute coronary syndromes (ACS). All of the newer drugs approved for VTE and ACS are also being used in mild to moderate renal insufficiency. LMWHs, factor Xa inhibitors and direct thrombin inhibitors use renal route for excretion so the dosage needs to be adjusted with increasing grade of renal insufficiency.Decreased clearance (below 30 ml/min) and accumulation of drug may leads to increased bleeding tendency [38]. In moderate or severe cases, anti Xa activity should be evaluated for avoiding bleeding [39].

Antiplatelet agents may also be administered to CKD patients. Aspirin is administered solely and sometimes in combination with warfarin. The other antiplatelet agents used and being studied are ticlopidine, clopidogrel, sulfinpyrazone and dipyridamole. When aspirin is administered in combination with clopidogrel the risk for bleeding is doubled [40]. Antiplatelet agentsare more effective in averting shunt and catheter thrombosis, but

not for avoiding the thrombosis of arteriovenous grafts [40].

Conclusion

Health related quality of life in CKD patients can be improved by treating anemia and other modifiable risk factors for CVD. In addition to the increasing complexity of maintaining Hb levels within narrower margins in CKD patients, the options for treatments are also increasing. Newly available ESAs and the discovery and entry into the market of epoetinbiosimilars, as well as recently identified iron regulatory protein, hepcidin, are expected to exhibit profound results leading to improvements in the management of CKD and its complications [49].

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