Anemia among hemodialysis patients; an updated mini-review

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Abstract
Anemia is common in chronic kidney disease (CKD) and has linear relationship with the rate of mortality in CKD patients. There is an increasing proportion of CKD patients and anemia is one of the major complications of this disease which is difficult to manage. In fact, anemia and the factors which hinder the treatment of anemia can be managed by using new hemodialysis (HD) methods such as online hemodiafiltration.

Keywords: Anemia, Hemodialysis, Chronic kidney disease, End-stage renal disease

Introduction
Anemia is one of the common complications of patients with end-stage renal disease (ESRD) who are in need of hemodialysis (HD). There are various reasons for the incidence of anemia in this group of patients. An appropriate HD may decrease the resistance to erythropoietin (EPO) in such patients (1-6).

Materials and Methods
In order to conduct this study, we selected the most relevant articles from different sites like PubMed, Google Scholar, Scopus, Embase, and Web of Science. To select the related articles from these online databases, we searched the databases using some keywords like anemia, hemodialysis, and combinations of the words such as complication of chronic renal failure or end stage renal disease. In this study we used full texts and abstracts of manuscripts that were written in English.

Anemia is common in chronic kidney disease
Anemia is common in chronic kidney disease (CKD) and has linear relationship with the rate of mortality in CKD patients. Even early treatment of anemia cannot decrease some of its complications like cardiovascular diseases (1). In addition to cardiovascular complications, there are also many other complications such as nervous or immune system disorders. Although anemia has serious side effects on many body systems which subsequently affect people's quality of life, the importance of its management and treatment have not been fully understood (7-15). National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF KDOQI) defines anemia in dialysis patients as a hematocrit value less than 33% or a hemoglobin level less than 11 g/dL. One of the important goals of this procedure is to clear and eliminate toxic materials from blood; among them, uremic toxins are one of the harmful materials that have harmful effects on the body. Because of these harmful effects, there is an increase in the utilization of newer HD methods. As an example “high flux HD” (HF-HD) is more efficient than a previous method i.e. low flux HD (LF-HD) (16). In fact, anemia in CKD patients has a linear relationship with the severity of renal function (17). There are several reasons for the incidence of anemia in CKD patients such as the followings entities like; lower production of EPO, insufficient level of iron in the body, and reduced red blood cell (RBC) lifetime (17-20). It has been
found that, the presence of uremic toxins in CKD patients accelerates the speed of cell membrane destruction and also alters cell functioning. On the contrary, lowering the serum levels of these toxins can decrease the rate of injury to the cells (19,20). In addition, the presence of inflammatory cytokines like IL-1, IL-6, and TNF-alpha can lead to the suppression of cell cycle and erythropoiesis, and increase the destruction of RBC. Uremic toxins also exacerbate the severity of micro-inflammation and affect RBC survival. HD may improve erythropoiesis and increase RBC lifetime. Dialysis eliminates and decreases plasma level of waste products in body and subsequently lowers the level of uremic toxins and inflammatory cytokines in CKD patients (21-23).

**Administration of erythropoietin for the treatment of anemia in hemodialysis patients**

Although HD is used as a treatment for ESRD patients and has many benefits for this group of patients, we may bear in mind that HD cannot be used as complete treatment which fully work instead of the kidney, while, there are also some other endocrine functions that cannot be fully performed through HD. One of the problems is body's inability to produce EPO. In order to overcome this problem, it is necessary to utilize some additional therapy methods. One of the modalities for the treatment of anemia in HD patients is the administration of EPO, however, the weak response of the patients to injected EPO is a problem which makes it difficult to manage such patients. There are several reasons for patients' resistance to EPO such as the followings: short time of HD or its low dialysis adequacy, deficiency of iron and other elements that are required for RBC production, high prevalence of infections, and higher rate of inflammatory responses in this group of patients. It is believed that iron deficiency is the major factor among the various factors that take part in patients' resistance to EPO (administered for anemia treatment). However, in patients with adequate iron level – with a normal serum ferritin level –, vitamin B12 and folate deficiency, various micro-inflammatory states like chronic or active infections and other micro-inflammatory states. In addition to the administration of EPO for the treatment of anemia in CKD patients, dialysis is also another treatment method with many benefits. Using HD, waste products and excess water present in the body are removed and eliminated. As a result of the elimination of waste products, patients' health status gets better. However, despite the positive effects of HD and its role in removing waste and excess elements from the blood, this method is associated with some complications. Mortality of HD patients is one of the inevitable complications of this method. Because of mortality during dialysis and considering the other complications of this method, some other strategies have been considered to achieve better results and outcomes while using dialysis. Recently there has been a considerable progress and many improvements in dialysis techniques which have resulted in better treatment outcomes and elimination of toxic material from the body and has decreased the complications of this method. In addition to the improvements made in dialysis techniques, there have been some efforts to modify the duration and frequency of dialysis so that to increase the positive outcomes and to better manage dialysis patients. There are many methods of dialysis, but HD is most common type of dialysis. The major goal of all methods of HD is to remove and eliminate uremic toxins and other wasted elements from the blood. The use of new methods of HD like online hemodiafiltration (which removes larger amounts of waste materials with higher rate of clearance, as compared with other methods) has many positive effects for HD patients. For instance, this method improves the physiological status of patients and decreases mortality rate. Additionally, in this method, a lower rate of resistance to injected EPO was detected. This method has many advantages for the treatment of anemia, because it not only improves the elimination of uremic toxins that suppress bone marrow, but also decreases the rate of inflammation and some endothelial disorders (24-26).

**Administration of supplements for the treatment of anemia in hemodialysis patients**

The use of some drugs for the treatment of anemia in HD patients (for instance the use of erythropoiesis-stimulating agents and iron) can generally reduce the risk of mortality and help to maintain hemoglobin level in the target range between 10 to 12 g/dL. Currently there are two approved erythropoiesis-stimulating agents (ESAs) for treating anemia and stimulating EPO in patients who need dialysis; these two ESAs are epoetin and darbepoetin. Nowadays, new researches have shown that regular and scheduled use of ESA agents can have positive effects on patients and decrease their needs for red blood cell transfusion. As a result, the decreased level of patients' need for blood transfusion can also lower the risk of some common complications of blood cell transfusion like sensitization and infection. This can help to better manage anemia (27,28). Furthermore, intravenous iron therapy in HD patients improves anemia parameters (25-29). However, resistance to ESA is observed in about 15% of such patients, even though they use higher dose of EPO. Resistances to EPO defined by some methods that measure hemoglobin level and administered EPO in these patients. EPO resistance index (ERI: rHuEPO/kg/wk divided by hemoglobin level in g) is one of the methods used for determining patients’ resistance to EPO. It is assumed that, this method is more efficient to detect EPO resistance in HD patients. According to this measurement method, EPO resistance is diagnosed when ERI value goes beyond 0.02 g/kg/wk/g hemoglobin (25).
Treatment of iron deficiency (as one of the important and main causes of resistance) and administration of some elements that have an effect on inflammation and oxidant activity (like ascorbic acid, vitamin E, statins drugs, and L-carnitine) can have positive effects on amelioration of anemia (20-25). Likewise, Chen et al. in their study showed that management of iron level in HD patients can significantly improve their resistance to anemia. They reported that improvement in iron status might result in dramatic changes in patients' response to anemia management (29).

Using a program for anemia management in hemodialysis patients

There are also some programs designed to improve anemia status in such patients; continuous quality improvement (CQI) is one of the programs that has been proved effective in treating anemia in HD patients. The CQI can make it easier to reach higher levels of hemoglobin (Hb) in such patients. On the other hand, researches have shown that lower Hb level has a direct relationship with higher hospitality and mortality rates, hence the use of this useful program for regular management of HD patients can have positive effects and decrease the proportion of complication that commonly happen in HD patients (25-29).

Conclusion

There is an increasing proportion of CKD patients and anemia is one of the major complications of this disease which is difficult to manage. In fact, anemia and the factors which hinder the treatment of anemia can be managed by using new HD methods such as online hemodiafiltration. In addition, adherence to some anemia management programs like continuous quality improvement can augment its effect on anemia correction. Therefore, the use of newer HD methods and better programs can more effectively decrease the complications and improve the health of HD patients.

Authors’ contribution

All the authors contributed equally to the manuscript.

Conflicts of interest

The authors declare no competing interests.

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