Anemia Management and QOL and Frailty in CKD

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Abstract

The strategy to improve health related quality of life (HRQOL) not only renal survival is crucial for chronic kidney disease (CKD) patients. Pathophysiology of anemia is closely associated with heart failure, malnutrition and inflammation which deteriorate HRQOL. Kidney Disease: Improving Global Outcome recommended that the erythropoiesis-stimulating agent (ESA) not be used to maintain Hb concentration above 11.5 g/dL in 2012. Updated systematic reviews for the treatment of anemia and HRQOL outcome mentioned that comparison between baseline Hb < 10 g/dL and partial correction over ≥ 10 g/dL showed the improvement of physical components of HRQOL in dialysis dependent CKD patients. In pre-dialysis CKD patients, aiming for lower Hb target with ESAs not only resulted in better HRQOL but lower healthcare resource utilization than control. However, higher Hb target above 12 g/dL lead to modest improvement of HRQOL with uncertain clinical significance.

Further investigations are required to individualize of the patients that 11.5–13.0 g/dL Hb target is effective for clinically meaningful HRQOL improvement without increasing the risks.

Keywords

Anemia · Cardio-renal-anemia syndrome · Erythropoiesis-stimulating agent · Frailty · Hemoglobin target · Health related quality of life · Malnutrition-inflammation-anemia syndrome · Minimal clinically important difference

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15.1 Introduction

Advanced CKD patients are growing worldwide, furthermore, average life expectancy was extended and elder population has increased in many advanced countries. For example, total number of Japanese patients newly started dialysis are growing to 2600 per million population [1] despite 74 or younger patients who depending renal replacement therapy are decreasing [1]. Therefore, we are forced to construct measures for CKD considering the elderly both pre-dialysis and dialysis dependent. In 2018, the Ministry of Health, Labor and Welfare of Japan released the action plan to overcome of CKD for next 10 years [2]. According to this, the incidence of end stage kidney disease (ESKD) patients starting renal replacement therapy should reduce to 35,000 patients from 40,000 in 2017 by 2028. Additionally, the strategy to improve health related quality of life (HRQOL) is important for CKD patients not only renal survival in the action plan.

15.2 Pathophysiology of Involvement HRQOL in CKD and Anemia

In recent years, the investigations focused on HRQOL are interested in the field of clinical nephrology. Pathophysiology of renal anemia is concerned as the major cause of poor HRQOL in CKD patients but treatable using erythropoiesis stimulating agents (ESA) with or without iron supplementation. Anemia increases circulating plasma volume, cardiac overload, and affected a hypoxic condition of organs. Heart failure and anemia constrict a vessel and renal ischemia via acceleration of a renin angiotensin system. It causes further kidney dysfunction including erythropoietin producing. Consequently, treating renal anemia is possible to break the vicious cycle in cardio-renal-anemia interaction [3, 4].

Metabolic acidosis, overhydration and organ congestion as described above are observed in advanced CKD. Inflammatory cytokines are revealed to affect the hematogenous functions in kidney dysfunction [5–8]. Moreover, dietary restrictions may be performed in order to prevent accumulation of sodium, potassium, phosphate, or urea nitrogen. These restrictions and metabolic disorder are the cause of malnutrition. The inflammation, malnutrition and the iron use interact the hematogenous functions in renal anemia. The role of erythropoietin (EPO) is controlling the apoptosis between maturity from proerythroblast to orthochromatic erythroblast in process of hematogenesis. Hepcidin is controlling whether stimulate iron use or storage in hematopoietic system. Hepcidin is down-regulated in situations where iron utilization proceeds, and in inflammatory conditions hepcidin is increased and iron is channeled into the liver. Steinvinkel advocated those condition as MIA syndrome which affected erythropoietin response in treatment of CKD [9]. Furthermore, the experimental studies revealed the association between uremic toxin such as indoxyl sulfate and myofibroblasts [10, 11] or erythropoiesis [12–14]. Anemia and physical weakness are closely related each other via uremic toxin in CKD patients like this.

In 2001, Fried suggested the definition of frailty in older adults as follows; weight loss, exhaustion, weakness, slow walking speed and low physical activity [15]. The comorbidity is an etiologic risk factor for frailty, and disability is an outcome of frailty. Several studies described anemia was associated to the development of frailty [16]. Ng et al. developed a frailty risk prediction tool including low hemoglobin, eGFR < 60 (ml/min/1.73 m^2), and WBC (×109) ≥6.5, and externally validated using community based two cohorts [17].

Increased white blood cell count is associated to chronic inflammation. Chronic inflammation observed in geriatric patients is known as "inflammaging" with the risks of disability, falls, hospitalization by aging even if without CKD [18]. Inframmaging means that age-related upregulation of the inflammatory response.

Original criteria of frailty was based of biological characteristics, however, the influence of "Inframmaging" should be considered to evaluate the risk of frailty [17, 19]. Therefore, aging and uremic status complicatedly injured the health of elder CKD patients.

15.3 Hemoglobin Target and HRQOL

There have been many reports that anemia deteriorated the physical activity described above, the relationship between hemoglobin concentration and HRQOL has been also evaluated in CKD. HRQOL is consisted with the physical, psychological and social domains of health.

HRQOL is variously evaluated with the instruments to measure the impact of disease and treatment. The medical outcomes study 36-Item Short Form (SF-36) is well known as generic HRQOL tool which can compare across disease. Additionally, KDQ is disease specific QOL tool for kidney disease. It makes difficult to compare directly the HRQOL in outcome studies with different tools. Further concerns is whether the change of HRQOL score is clinically meaningful for the patients or clinician [20]. Minimal clinically important difference was 5–10 points in SF-36, or 0.2–0.5 of effect size in KDQ. In HRQOL evaluation, there are large differences of socio-economic status, healthcare system for end stage kidney disease among the societies [21]. Therefore, the improvement of physical component such as SF-36 vitality, KDQ fatigue, and NHP energy seemed to be major instruments for HRQOL in management of CKD or renal anemia in systematic reviews.

Though the treatment of anemia has contributed to improve morbidity and mortality in CKD both dialysis and pre-dialysis [22–24], Kidney Disease improving Global Outcomes (KDIGO) guideline recommended a target hemoglobin below 11.5 g/L because of cardiovascular event risk in further high target Hb [25]. Those recommendations were based on previous studies that complete correction of anemia did not reduce the risk of cardiovascular events nor HRQOL [26, 27]. After the publication of KDIGO guideline in 2012, practical target Hb was decreased especially in US but little changed in Japan.

The benefit of target Hb range of 11.5–13.0 is controversial because the risk of cardiovascular event in CKD has considerable differences among background of patients such as races, history of CVD or Diabetes.

The incidence of cardiovascular disease was lower in Japanese pre-dialysis CKD patients [26]. It is possible that some individual patients such as younger, without serious comorbidities may bring great wellbeing. Vitality and left ventricular mass index (LVMI) of pre-dialysis patients improved in stratifying Hb 10–11 g/dL, and over 11 g/dL than <10 g/dL reported by Hirakata [27]. Their study had the limitation that darbepoetin was administered every 2 or 4 weeks for higher target Hb but epoetin alfa was need to weekly or every 2 weeks' administration for lower target as conventional methods. For many CKD patients without severe complications, frequent clinical assessment was possible to somewhat affect their QOL beyond LVMI.

Tsubakihara et al. investigated that renal function were preserved in higher hemoglobin group (11.0–13.0 g/dL) than low hemoglobin group (9.0–11.0 g/dL) treated with darbepoetin alfa [28]. Although HRQOL outcome was not included in the study, preserved renal function seems to bring better QOL for advanced CKD patients.

Seven systematic reviews on anemia management and QOL have ever been published.

Clement et al. suggested that Hb target over than 12.0 g/dL did not lead to clinically meaningful improvements of HRQOL in both pre-dialysis and dialysis patients reviewed 11 studies [29]. Collister et al. attempted meta-analysis of 12 pre-dialysis, 4 of dialysis, and 1 both CKD subject to reveal whether the change in HRQOL between baseline and another point was significant by high or low Hb target. They described that ESA treatment of anemia achieving higher Hb level did not show difference in HRQOL, and emphasized the importance of minimal clinically important difference to treat renal anemia and target Hb [30]. They also mentioned that cost-effectiveness consideration in policymakers. Then, economic burden and HRQOL analysis of both dialysis and pre-dialysis setting were published as shown below.

Systematic reviews on maintenance dialysis therapy setting was three [31, 32], Studies in baseline Hb < 10 g/dL and partial correction over ≥10 g/dL showed the improvement of exercise tolerance [31] and fatigue outcomes [32] in dialysis patients by the reviews. Spinowitz et al. highlighted that the economic burden of renal anemia and improvement of HRQOL. In their review, minimal clinically important difference was observed in some studies 11.5–13 g/dL of Hb target. The improvement of HRQOL in higher Hb target resulted in uncertain clinical significance in maintenance dialysis therapy setting [33].

Pre-dialysis setting systematic review was two [34, 35], Gandra identified 14 studies [34]. Ten of them achieved minimal clinically important difference in treated with ESA, one study was not, three studies were not evaluated minimal clinically important difference. They concluded that physical components of HRQOL were improved in pre-dialysis patients.

In 2019, economic burden and HRQOL were also considered in pre-dialysis patients [35].

Untreated anemia leads to lower HRQOL compared with initiating anemia treatment. Furthermore, higher healthcare resource utilization and higher cost were necessary to care in population untreated anemia. Biosimilar ESAs are available to treat renal anemia as a cost-lowering alternative strategy.

15.4 Conclusion

Moderate to advanced CKD patients lose their HRQOL by multiple factors based on the contents described above. One of effective intervention to improve their HRQOL is control of renal anemia and cardiovascular adverse event within safety Hb target.

Nevertheless most physician may consent that therapeutic goal should be based on individual condition with the un-proved benefits in spite of potential risk of higher hemoglobin target as the comment by Wyatt to this systematic review [36]. The individualized therapeutic goals of slightly higher Hb level (11.5–13.0 g/dL) might be considered based on discussion about the risk and benefits. Furthermore, effective and safe medical intervention strategy in CKD with anemia should be further investigated to acquire clinically meaningful change in HRQOL from the point of view both of the patient and the clinician.

Disclosure None.

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